The decision and determinants of adjuvant chemotherapy for stage III colon cancer

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DECLARATION

I confirm that the work presented in this thesis is my own.

ABSTRACT

Introduction: Treatment of stage III colon cancer consists of surgery to remove the tumour followed by 'adjuvant' chemotherapy, which serves to eradicate the microscopic cancer cells that cannot be removed by surgery. Adjuvant chemotherapy could include therapy with a single agent (a fluoropyrimidine) or in combination with a second medication, known as oxaliplatin. Oxaliplatin offers an additional absolute increase of 3-4% in five-year overall survival and 6-7% in five-year disease-free survival. However, it can also result in a condition called peripheral neuropathy (PN), which can persist and influence quality of life. There is no effective prevention or treatment of PN. Therefore, a modest improvement in survival needs to be balanced against a potential risk of persistent neurotoxicity. The focus of this thesis was on stage III colon cancer, to allow for an understanding of the factors that could influence treatment in a setting where the treatment decision is relatively simple. By contrast, settings where more complicated therapy, such as radiotherapy or neo-adjuvant chemotherapy for rectal cancers, may be required adds to the complexity of the decision-making process and the trade-offs to be considered.

Objectives and methods: Four studies were undertaken to investigate determinants of adjuvant chemotherapy among this population of patients. First, a systematic review of the literature to determine the prevalence of PN resulting from treatment with oxaliplatin. Second, secondary data analysis to investigate the role of patients' sex, age, ethnicity, socioeconomic status, and tumour characteristics as determinants of adjuvant chemotherapy and type of chemotherapy received. Third, a qualitative study to investigate how the decision to receive adjuvant chemotherapy and the choice of the type of therapy was made, the nature of the patient-clinician interaction, and what contextual elements may have influenced this interaction. Fourth, a secondary analysis of questions from the National Cancer Patient Experience Survey (NCPES) to determine the extent to which patients perceived being informed about treatment options and side effects, as well as being involved in the treatment decision.

Results: PN is likely to persist among 40% of patients at six months, and between 25-30% at twelve months or longer. Those of older age, of minority ethnic groups, and of lower socioeconomic status were less likely to receive combination therapy than those who were of younger age, White ethnicity, or higher socioeconomic status. Most participants in the qualitative study lacked awareness of treatment options and side effects and did not participate in a decision-making process with the clinician to decide on which treatment to receive. The NCPES showed that those who received combination chemotherapy were less likely to be certain when asked whether they

knew about side effects and future side effects of treatment compared to those who received single therapy.

Conclusion: the decision to receive oxaliplatin for the treatment of stage III colon cancer does not occur through a shared decision-making process. Patients who receive combination chemotherapy are inadequately aware and informed of the likelihood and nature of peripheral neuropathy, which could persist in more than a quarter of patients at least one year after treatment. Group-level variations in the receipt of combination therapy indicates systemic-level inequalities in treatment. A shared decision-making process could increase patients' awareness of their treatment options and side effects and reduce the inequalities that result from provider biases and system-level factors.

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Chapter 1: Background

Colon cancer was the fourth most diagnosed cancer both worldwide and in the United Kingdom (UK) in 2020 (Ferlay et al., 2020). Treatment of this disease depends on the stage at diagnosis (Bromham et al., 2020). Surgery to remove the tumour is highly effective and is often all that is required to treat patients diagnosed at stage I and the majority of those diagnosed at stage II. For those diagnosed at stage III, surgery to remove the tumour is often insufficient, as the disease has spread to the surrounding lymph nodes. Therefore, surgery is routinely followed by chemotherapy, referred to as 'adjuvant chemotherapy', which serves to eradicate the microscopic cancer cells that cannot be removed by surgery. Finally, treatment of stage IV (metastatic disease) is often complex as it may involve multiple modes of treatment (surgery, chemotherapy, radiotherapy) and is usually palliative, i.e., to control the disease, rather than curative.

The cornerstone of adjuvant chemotherapy for stage III colon cancer is a fluoropyrimidine agent. Six months of therapy with a fluoropyrimidine agent has been adopted as the standard regimen for treatment of patients with stage III disease since the 1990s (Rodriguez-Bigas MA, 2003; Wolmark et al., 1999). In 2004, a chemotherapeutic drug known as oxaliplatin was approved by the Food and Drug Administration (FDA) in the USA for use in the treatment of stage III colon cancer in combination with a fluoropyrimidine (National Cancer Institute, 2004). Results from three major Randomised Controlled Trials (RCTs) has shown that treatment with oxaliplatin offers an additional, although relatively modest, absolute benefit in reducing recurrence and increasing survival compared to treatment with fluoropyrimidines only. Currently, the National Institute for Health and Care Excellence (NICE) in the UK recommends that stage III colon cancer patients should be offered either a fluoropyrimidine agent alone or in combination with oxaliplatin (Bromham et al., 2020).

However, treatment with oxaliplatin also causes a condition known as peripheral neuropathy. Acute peripheral neuropathy refers to symptoms that occur during treatment and is experienced by most patients treated with oxaliplatin. Persistent peripheral neuropathy refers to symptoms that persist for several months or years after completion of therapy. Prevalence estimates of persistent peripheral neuropathy have not been consistent across studies, due to variations in study designs, tools used to assess symptoms, and the time points at which assessments were undertaken since treatment completion. However, evidence suggests that persistent symptoms could impact negatively on quality of life (Mols et al., 2014). Currently, there are no known effective pharmacologic or non-pharmacologic interventions for the prevention or

treatment of chemotherapy-induced peripheral neuropathy (Loprinzi, 2017). Therefore, it is important to balance the relatively modest absolute improvement in survival against the potential risk for persistent peripheral neuropathy symptoms. Furthermore, the decision regarding treatment with oxaliplatin is not limited to this trade-off in benefit and risk. The duration of therapy could be an important determinant of the choice of treatment. Statistical evidence supports the use of three months of therapy instead of six months for patients that have certain “low-risk” characteristics of stage III disease, but not for those who have “high-risk” characteristics, although the difference between the two groups could be marginal and current guidelines suggest that this decision should be based on patients’ preference (Lieu et al., 2019). The route of administration may also be a determinant of the choice of treatment. Although oral administration may seem to be an obvious choice, it is possible that some patients may not prefer to ingest a daily pill or would find comfort in frequent hospital visits.

Therefore, the decision to receive adjuvant chemotherapy for stage III colon cancer is a complex one that requires several considerations. This is often the case in the cancer care context whereby treatment choices have implications for patients’ health outcomes and quality of life, evidence on their effectiveness and adverse events lacks certainty, and patients may vary in their judgment on the risks or side effects that they are willing to tolerate. As such, in the last two decades, shared decision-making has become prominent as a model to guide this interaction and has become integral to healthcare planning and delivery, in the UK and elsewhere (Department of Health, 2011; General Medical Council, 2009; Loughlin et al., 2019). Shared decision-making means that clinicians work in partnership with patients to arrive at a treatment decision. It includes providing patients with information in a way they understand, including information on the fact that there are uncertainties associated with their treatment options; listening and responding to their concerns and preferences, including in relation to how different treatment options may influence their lives; and arriving at treatment decisions jointly. As such, shared decision-making safeguards the right of patients to be involved in the decision-making process that determines their treatment, if they wish to do so and to the extent that they wish to be. In addition, it also safeguards against inequalities in healthcare, that is, if treatment decisions are made jointly, we should expect to see only individual-level variations in treatment. Despite its importance in healthcare delivery, it has been shown that shared decision-making is often not implemented in practice (Coulter et al., 2011), and often cancer treatment in general, including treatment with adjuvant chemotherapy for stage III colon cancer, has been shown to differ along demographic and socioeconomic lines, indicating possibly

systemic-level influences on the treatment decision (Boyle et al., 2020). Barriers to implementing shared decision-making occur at multiple and often interacting levels. Time constraint is the most often cited barrier from an organisational or structural perspective. From the clinicians' viewpoint, cited barriers include the perception that they already practice shared decision-making; that shared decision-making require decision-aids and tools, which are often lacking; or that patients do not want to be involved in making healthcare decisions (Joseph-Williams et al., 2017). As for patients, indeed some may prefer that treatment decisions are made by healthcare professionals, but this may be due to feeling unable rather than being unwilling to take part. In addition, the importance of shared decision-making is not limited to who makes the final decision about healthcare. The process of arriving at the decision, regardless of who makes the final decision, is equally if not more important.

The evaluation of the effectiveness of shared decision-making as a model by which treatment decisions are made has been limited by the lack or inconsistency of its implementation, and the variation in the tools and outcomes used to measure it. Tools to measure shared decision making can vary depending on whether outcomes are observer-, patient-, and/or clinician-reported. Despite this variation, however, evidence is suggestive of positive associations with patient-reported affective-cognitive outcomes, quality of life, and improved outcomes for disadvantaged groups (Clayman et al., 2016; Durand et al., 2014; Shay & Lafata, 2015).

Aim and objectives

The aim of this thesis was to understand the determinants of receiving adjuvant chemotherapy, and the type of adjuvant chemotherapy received, among stage III colon cancer patients in the UK. The focus was on the patient, and therefore, I aimed to answer research questions that captured patient-related characteristics and experiences in determining treatment.

The likelihood of benefit from and risks of treatment are both important determinants of the choice of treatment. Evidence on the prevalence and severity of peripheral neuropathy symptoms post-therapy with oxaliplatin was not consistent. Thus, a systematic review was carried out as the first study to determine the prevalence of this adverse effect among this population of patients, and consequently, establish its magnitude and importance as a determinant of adjuvant chemotherapy.

A quantitative study was used to explore the role of patients' sex, age, ethnicity, and socioeconomic status, as well as the size of the tumour and the extent of spread to

adjacent lymph nodes, as determinants of adjuvant chemotherapy and the type of adjuvant chemotherapy that was received. For this study, data from the National Cancer Registry linked to Systemic Anti-Cancer Therapy were used.

Given the uncertainty of the outcomes associated with the use of oxaliplatin, a qualitative study was used to understand, from patients' perspective how the decisions to receive adjuvant chemotherapy and the type of therapy were reached. This included exploring the nature of the interaction between patients and clinicians; factors that were important for patients throughout the decision-making process; and factors that influenced the process.

Finally, another quantitative study was then undertaken to explore the extent to which patients perceived being informed about the availability of treatment options and the benefits and side effects of the treatment they received, using a cross-sectional National Cancer Patient Experience Survey.

Overview

This thesis consists of eight chapters. The first three chapters provide a background and overview of the thesis, a review of the literature, and the conceptual framework, objectives, and methodology that underpin the studies that were carried out. The subsequent four chapters present the four studies that were conducted. The final chapter is dedicated to an integrated discussion of the findings. A more detailed description is as follows:

Chapter 1 – This current chapter provides a brief background on the thesis and its purpose, as well as an overview of the remaining chapters.

Chapter 2 provides a comprehensive review of the literature on the main considerations of the treatment decision relating to the use of oxaliplatin in the treatment of stage III colon cancer, and of oxaliplatin-induced peripheral neuropathy and its impact on quality of life.

Chapter 3 presents the conceptual framework that was used to guide the research questions and objectives of the thesis. It will also present the philosophical position, in terms of epistemology, ontology, and methodology, and describe the methods used for the research.

Chapter 4 presents the systematic literature review that was undertaken to determine the prevalence and severity of persistent peripheral neuropathy symptoms among stage III colon cancer patients after the completion of therapy.

Chapter 5 presents a quantitative analysis of the National Cancer Registry linked to Systemic Anti-Cancer Therapy databases. I explored the association between patient characteristics and the receipt of treatment, as well as the type of treatment received. Variations in treatment between groups, i.e., based on patient-level characteristics, provide an indication for systemic, rather than individual, determinants of therapy.

Chapter 6 presents a qualitative study, which used in-depth narrative interviews with stage III colon cancer survivors to understand the factors, from patients' perspective, that influenced the treatment decision-making process and determined the type of treatment that they received. This study provided an understanding of the determinants of therapy on an individual level.

Chapter 7 offers a quantitative analysis of the National Cancer Patient Experience Survey, which aimed to explore the association between the type of treatment that was received and the extent to which patients perceived being informed about treatment side effects and being involved in the treatment decision.

Chapter 8 an overall discussion that integrates the findings of all four studies, the strengths and limitations of the findings, implications of this work for clinical practice, as well as considerations for further research.

Chapter 2: Literature Review

Colon cancer

Colon cancer is a malignancy that arises from the cells that line the inside of the colon. The disease starts as abnormal cells that take several years to grow and transform into cancer. If left untreated, the cancer cells can grow into the muscle layers, through the bowel wall into the surrounding tissue, and eventually travel via lymph nodes to distant sites in the body. The extent of the cancer can be described in four stages (Roman numerals I, II, III, IV) from least to most severe, depending on the size of the Tumour (T), the spread to nearby lymph Nodes (N), and the spread, or Metastasis to distant sites (M), referred to as the TNM staging system (Sobin, 2009). In very broad terms, in stage I, the cancer has grown into the bowel wall but does not invade through it. At stage II, the cancer does invade through the bowel wall, but does not involve the surrounding lymph nodes. At stage III, the cancer invades into the surrounding lymph nodes. At stage IV the cancer has metastasised (spread to distant sites) (Bruening et al., 2014).

According to the Global Cancer Observatory of the World Health Organisation, colon cancer was the fourth most diagnosed cancer worldwide in 2020 (Ferlay et al., 2020). In the UK, colon cancer was also the fourth most diagnosed cancer and the third most common cause of cancer mortality. With a population of around 66 million people, there were approximately 34 thousand new cases of and 12 thousand deaths from colon cancer in 2020 (Ferlay et al., 2020). The incidence of colon cancer varies across the world. Incidence is higher in Europe, North America, Australia, and New Zealand, compared to South and Central Asia and Africa. This variation in incidence between regions may be due to the interaction of environmental exposures, including dietary differences, with genetic predispositions (Fitzmaurice et al., 2017).

Colon cancer could occur due to a hereditary predisposition; however, most cases arise sporadically. Incidence of sporadic colon cancer increases significantly with advancing age, with higher rates among those over the age of 50 years compared to younger adults, and an increasing rate for each subsequent decade. In Western countries, evidence suggests that incidence of colon cancer is increasing among those who are under the age of 50 years (Araghi et al., 2019). In England, the incidence rate of colon cancer has seen an average annual increase of 8%, from 0.8 in 1993 to 2.8 in 2014 per 100,000 adults aged between 20 to 30 years, and an annual increase of 8.1%

from 2005–2014 for those aged 30 to 40 years, while it remained stable or decreased over the same time periods for those over the age of 50 years (Exarchakou et al., 2019). Race or ethnicity has also been identified as a risk factor for colon cancer. In England, people of non-White ethnicity were shown to have a lower incidence of colorectal cancer compared to White patients between 2001 to 2007 (Ali et al., 2013), and in one region black Afro/Caribbean patients were found to have been diagnosed with colorectal cancer at younger age compared to White British patients between 2000 and 2012 (Askari, Nachiappan, Currie, Latchford, et al., 2017). Other risk factors for colon cancer include inflammatory bowel disease (Yuhara et al., 2011), obesity (Karahalios et al., 2015), diabetes mellitus (Yuhara et al., 2011), consumption of red and processed meat (Wild et al., 2020), smoking (Botteri et al., 2008), and alcohol (Fedirko et al., 2011). In the UK, about 54% of colon cancer cases were found to be attributable to modifiable risk factors (Brown et al., 2018).

Treatment of colon cancer depends on the stage at diagnosis (Bromham et al., 2020). Surgery to remove the tumour is highly effective and is often all that is required to treat patients diagnosed at stage I and the majority of those diagnosed at stage II. For those diagnosed at stage III, surgery to remove the tumour is often insufficient, as the disease has spread to the surrounding lymph nodes. Therefore, surgery is routinely followed by chemotherapy, referred to as ‘adjuvant’ chemotherapy, which serves to eradicate the microscopic cancer cells that cannot be removed by surgery. Treatment of stage IV (metastatic disease) is often complex as it may involve multiple modes of treatment (surgery, chemotherapy, radiotherapy) and is usually palliative, i.e., to control the disease, rather than curative.

Adjuvant chemotherapy for stage III colon cancer

Chemotherapy is a type of systemic therapy for cancer that uses one or more medications, or chemotherapeutic agents, to interfere with the division of and cause damage to cancer cells. The cornerstone of adjuvant chemotherapy for stage III colon cancer is a fluoropyrimidine agent. Six months of therapy with a fluoropyrimidine agent has been adopted as the standard regimen for treatment of patients with stage III disease since the 1990s (Rodriguez-Bigas MA, 2003; Wolmark et al., 1999). In a 2015 meta-analysis of randomised controlled trials and observational studies, five-year survival was found to increase from 49% (95% CI: 23.2–74.8) among those who did not receive post-operative adjuvant chemotherapy to 63.3% (95% CI: 59.3–67.9)

among those who did (Bockelman et al., 2015). There are two types of fluoropyrimidines that could be used as adjuvant chemotherapy: capecitabine or 5-fluorouracil, the latter typically administered with a folinic acid that enhances its effect, known as leucovorin, and is commonly referred to as 5-FU/LV (hereafter 5-FU).

In 2004, a chemotherapeutic drug known as oxaliplatin was approved by the Food and Drug Administration (FDA) in the USA for use in combination with a fluoropyrimidine for the treatment of stage III colon cancer (National Cancer Institute, 2004). Oxaliplatin is a third-generation platinum derivative, best known for its effectiveness in metastatic colon cancer (Giacchetti et al., 2000). Currently, the National Institute for Health and Care Excellence (NICE) in the UK recommends that the options for adjuvant chemotherapy are either a fluoropyrimidine agent alone or in combination with oxaliplatin (Bromham et al., 2020).

As will be discussed in more detail in the next two sections, the addition of oxaliplatin to a fluoropyrimidine agent was shown to offer additional benefit to patients with stage III disease in large multi-centre clinical trials which led to its adoption as standard therapy in this setting. Treatment with oxaliplatin, however, has been shown to cause toxicity in the peripheral nerves and result in a condition called peripheral neuropathy, which can be long-lasting.

Oxaliplatin-induced peripheral neuropathy (OIPN)

One of the main adverse effects that could result from treatment with oxaliplatin is damage to the nerves in the peripheral nervous system, i.e., nerves lying outside the central nervous system (brain and spinal cord), a condition known as peripheral neuropathy (Grothey, 2003). The distribution of the nerve damage is generally bilateral (i.e., affecting both sides of the body) and distal (i.e., affecting parts of the body away from the torso, such as the hands and feet), and can be classified by its underlying pathology, the function disturbed (sensory, motor, autonomic), or by the onset and duration of symptoms (Longmore et al., 2014).

Different terms have been used in the literature to refer to various patterns of symptom onset and duration. Hyper-acute OIPN is used to describe peripheral neuropathy that occurs on day one (≤24 h) of oxaliplatin infusion, in the first cycle of therapy (Tanishima et al., 2017). Acute OIPN refers to symptoms that are experienced during therapy, which generally begin soon after initiating a treatment cycle, but resolve within a few

days between cycles. With cumulative doses of oxaliplatin, symptoms may become progressively more persistent, taking longer to resolve, and at times, not resolving at all between cycles or after treatment with oxaliplatin is complete (Pasetto et al., 2006). Terms such as cumulative, long-term, chronic, or persistent OIPN have been used interchangeably in the literature to describe this pattern of OIPN.

Acute peripheral neuropathy occurs in most patients treated with oxaliplatin (90%) and is characterised by sensory symptoms that are triggered and exacerbated by exposure to cold (Beijers et al., 2014). However, estimates for the prevalence of persistent peripheral neuropathy among stage III colorectal cancer patients resulting from treatment with oxaliplatin are widely variable depending on whether symptoms were assessed by clinicians or reported by patients (the assessment tool used) and the time point at which symptoms were assessed (Beijers et al., 2014; Molassiotis et al., 2019). For example, in the MOSAIC trial, about 15.5% of participants were found to have symptoms of peripheral neuropathy on clinical examination four years after treatment discontinuation (Andre et al., 2009). In another study that used a patient-reported outcome measure, about 60% of patients were found to have lasting neuropathic symptoms interfering with function two years after completion of therapy (Park et al., 2013).

Effect of peripheral neuropathy on patients' lives

Quality of Life (QoL) refers to "the degree to which an individual is healthy, comfortable, and able to participate in or enjoy life events" (Jenkinson, 2020). Therefore, an assessment of QoL is subjective. Some measures assess health related QoL generally. This involves self-reporting on the extent to which ill health influences different aspects of life, such as physical or emotional well-being, the ability to work or engage in social activities, etc, in any population. Others are disease-specific, whereby health-related QoL is assessed among those with a specific condition using a measure that evaluates the extent to which certain characteristics of the condition influence different aspects of life.

A systematic review of the literature published up to 2013 was conducted to assess the association between chemotherapy-induced peripheral neuropathy (CIPN) and quality of life (QoL), and eleven studies that directly investigated this association were included (Mols et al., 2014). The studies included participants who were treated with neurotoxic agents for varying types of cancer, including colon, and were not specific to oxaliplatin. Most studies used one of two measures. One was the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire

Core-30 (EORTC QLQ-C30). This questionnaire assesses a person's functional status in five areas: physical strength (e.g., routine daily activities), role (work productivity, leisure activities, independent living), emotional (e.g., stress, worry, etc.), social (e.g., family life, relationships, community engagement), and cognitive (e.g., concentration, memory, etc.); whether they are experiencing symptoms of: fatigue, nausea and vomiting, pain, dyspnoea (shortness of breath), insomnia, loss of appetite, constipation, diarrhoea, and financial difficulties; and an assessment of global health status (overall health and life quality). The other questionnaire was the Functional Assessment of Cancer Therapy-General (FACT-G), which assesses similar aspects: physical, social, emotional, and functional well-being.

Of the eleven included studies, eight concluded that more CIPN symptoms were associated with reduced quality of life. The quality of the studies was assessed by the authors using a set of 13 predefined criteria, adapted for this topic from quality criteria that have been previously used in the literature. Seven of the eight studies that found an association were of high quality, i.e., met 10 or more of the quality criteria. Four of these seven high quality studies were of prospective design, offering results that were based on comparisons between two groups followed-up over time. Only one study that showed an association was of low quality (met less than 7 of the quality criteria). The remaining three of the 11 included studies did not find an association. One was conducted among children rather than an adult population. The other two were high-quality studies of prospective design. The first included 377 patients with advanced non-small cell lung cancer, and peripheral neuropathy was assessed by physicians rather than self-reported by patients, which may not accurately reflect patients' experience of the condition. The other included 99 ovarian cancer patients and assessed QoL using a general health-related quality of life in patients with cancer (FACT-General), as well as an instrument that evaluates the health-related quality of life associated with chemotherapy-induced neurotoxicity specifically (FACT/GOG-NTX). The study found no difference when using the FACT-General questionnaire between the group that received neurotoxic chemotherapy and were known to have CIPN and those who did not receive chemotherapy, but a significant difference when using the questionnaire specific to neurotoxicity. This indicates that the former is less sensitive to patient-reported symptoms of chemotherapy-induced neurotoxicity, and scales that consist of questions specific to a condition are more effective at detecting its impacts.

Since this review, several other studies published results suggesting that CIPN impacts QoL (measured using the EORTC QLQ-C30 tool) among those treated for cancer with neurotoxic agents. Among 129 women treated for ovarian cancer, 17% had a score of

>50 for CIPN symptoms (on a 0-100 scale, with zero corresponding to none). A higher score of CIPN was associated with lower QoL on all function scales (physical, role, emotional, cognitive, and social) and with lower overall health status. These women also reported more fatigue, nausea and vomiting, pain, dyspnoea, insomnia, loss of appetite, and financial difficulties. These effects were observed up to 12 years after receiving chemotherapy (Ezendam et al., 2014). Similarly, CIPN severity was found to be associated with worse physical, social, and role functioning, global health status, and pain in two studies of 126 and 82 breast cancer patients, respectively (Salehifar et al., 2020; Simon et al., 2017).

Several studies exploring the impact of CIPN on QoL were conducted among stage III colon cancer patients who were treated with oxaliplatin specifically. A single-centre study undertaken in Sweden compared QoL one to eight years after completion of treatment among those who received an oxaliplatin-containing regimen and those who did not (Stefansson & Nygren, 2016). Patients who received oxaliplatin were found to have worse QoL outcomes for almost every function scale and symptom score included in the EORTC QLQ-C30, compared to those who did not receive oxaliplatin. In another study conducted in Finland (Soveri et al., 2019), peripheral neuropathy following oxaliplatin-containing adjuvant chemotherapy was present in 63 of 92 (69%) of participants who were assessed approximately four years after the end of treatment and was found to be significantly associated with decreased physical and role functioning, although not with global health status, emotional, cognitive, or social functioning. In another longitudinal study of 1829 those who received only three-months of oxaliplatin therapy had better scores for all functional and symptom scales, compared to those who received six months of therapy at one, three, and five years of follow-up (Iveson et al., 2018).

Several other studies assessed the influence of oxaliplatin-induced peripheral neuropathy on specific aspects of life, not using a QoL measure. Breedveld-Peters et al. (2020) found that colon cancer survivors who reported higher levels of fatigue or more peripheral neuropathy symptoms were more likely to be dissatisfied with their levels of participation in everyday life (Breedveld-Peters et al., 2020). Another study investigated the impact of oxaliplatin-induced peripheral neuropathy symptoms on breast cancer survivors' perceived ability to work in the first year following treatment (Zanville et al., 2016). The authors found that oxaliplatin-induced peripheral neuropathy symptoms had a significant negative effect on the perceived ability to work after one month of receiving chemotherapy but not after one year. However, an important finding was that the number of symptoms experienced was a predictor of the outcome, in

contrast to findings from studies that investigated the influence of the presence or absence of symptoms or the severity of symptoms instead. Here, the authors argue that although the severity of symptoms may reduce over time, it is possible that several symptoms experienced even mildly could still negatively impact the ability to work. A second important finding was that the type, frequency, severity, and number of symptoms experienced at one month were the same as those experienced at one year. Thus, an improved ability to work at one year is suggestive of survivors' adaptation to the symptoms, rather than improvement in the physical experience of symptoms. This is consistent with evidence suggesting that people have the capability to adapt to health outcomes once they experience them (Stein et al., 2014). Although the most common symptoms of oxaliplatin-induced peripheral neuropathy are sensory in nature, motor symptoms could also occur and persist, and peripheral neuropathy of this nature was found to be associated with a higher rate of falls (Gewandter et al., 2013; Winters-Stone et al., 2017).

Some studies have also looked at variations in the experience of peripheral neuropathy symptoms. For example, some evidence suggests that the burden of peripheral neuropathy symptoms may be higher in those who were obese (Cox-Martin et al., 2017) and those of a younger age group (Wong et al., 2019). In addition, evidence from qualitative studies has shown that people's perceptions of how symptoms may influence daily life varies. Some participants reported that neuropathy symptoms interfered with 'enjoyment of life' (Tofthagen et al., 2011) or the ability to independently perform functions of daily living (Kanda et al., 2017), leading to feelings of frustration, depression, loss of purpose from giving up enjoyable activities, or fear of physical harm from inability to self-care (Kanda et al., 2017) (Tofthagen, 2010). In one study, peripheral neuropathy impacted patients' emotional and physical well-being up to 7 years after treatment with oxaliplatin, affecting their ability to carry out usual activities, and contributing to depressive symptoms and sleep disturbance (Tofthagen et al., 2013).

Prevention and treatment of peripheral neuropathy

Numerous pharmacologic and non-pharmacologic interventions have been studied for the prevention and treatment of chemotherapy-induced peripheral neuropathy (Loprinzi, 2017). Pharmacologic agents investigated for the prevention of neurotoxicity included anticonvulsants (e.g., carbamazepine, oxcarbazepine, gabapentin); anti-depressants (e.g., venlafaxine, amitriptyline); neuroprotective agents (e.g., amifostine, nimodipine); vitamins, minerals, and dietary supplements (e.g., calcium and

magnesium infusions), but none have been shown to be effective (Loprinzi, 2017). As for treatment, duloxetine, an anti-depressant medication, is the only pharmaceutical agent that has shown a small benefit in the treatment of chemotherapy-induced peripheral neuropathy, although the effect was modest. In one RCT of 231 patients, participants receiving duloxetine showed a decrease in mean pain scores and improvement in quality-of-life scores, as well as improvement in tingling and numbness in the feet, but not the hands (Smith et al., 2013). As for non-pharmacologic interventions, there is some evidence suggesting that exercise may offer a potential benefit in preventing peripheral neuropathy and reducing the severity of symptoms (Kleckner et al., 2018; Mols et al., 2015; Streckmann et al., 2014).

As such, the only effective measure for preventing or managing the development of severe symptoms of neuropathy is dose reduction or treatment delay or discontinuation (Loprinzi, 2017). Therefore, the risk of developing potentially long-lasting neuropathy symptoms must be weighed against the benefit of continuing treatment.

Oxaliplatin in the adjuvant setting

Given the potential for oxaliplatin-induced peripheral neuropathy (OIPN) that results from treatment with oxaliplatin and its effect on quality of life, it is therefore important to understand the evidence that justifies its use and influences the treatment decision in the adjuvant setting. To understand the evidence that follows I first define the outcomes used in the evaluation of cancer treatment efficacy.

Cancer-trial survival outcomes for adjuvant therapy

The traditional end point for clinical trials of adjuvant colon cancer treatment was *five-year overall survival* (Sargent et al., 2007), defined as the probability of surviving five years from the date of randomisation into the trial to death from any cause. However, recent trials of adjuvant treatment use *three-year disease-free survival* as the primary endpoint, defined as the probability of surviving three years from the date of randomisation into the trial to cancer recurrence, a second primary cancer of the colon, or death from any cause, whichever occurs first. This revised endpoint was adopted on the grounds of a pooled analysis of nearly 21,000 patients with stage III colon cancer, which found that three-year disease-free survival highly correlated with five-year overall survival (Sargent et al., 2007). However, it has been shown that prolonged survival after recurrence, which has become more common with advances in the detection and treatment of recurrent colon cancer, reduces the association between three-year

disease-free survival and five-year overall survival (de Gramont, 2008). That is, a higher three-year disease-free survival in the treatment arm compared to the control arm does not necessarily mean a higher probability of five-year overall survival. With advances in post-recurrence therapy, both arms could be seen to have similar five-year overall survival (Figure 1). Thus, to detect differences in overall survival between two groups, a longer follow-up period may be required.

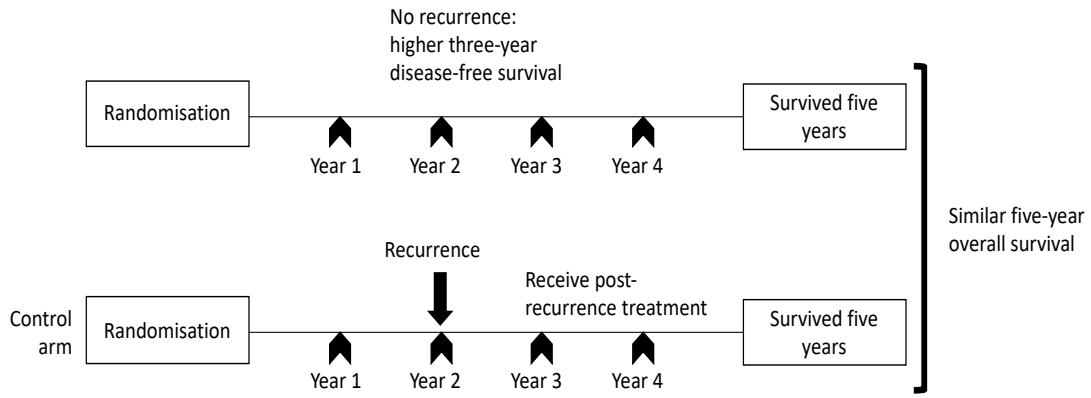


Figure 1 – An illustration of the relationship between three-year disease-free survival and five-year overall survival in the presence and absence of recurrence

Risk of recurrence, or relapse-free survival is another outcome that could be reported to evaluate efficacy. This is considered the most sensitive endpoint for evaluating the need for adjuvant chemotherapy, as it ignores second cancers. However, it is currently not often reported (Punt et al., 2007).

Survival outcomes (disease-free survival, overall survival, and relapse-free survival) could be compared between two groups in two ways: either as a comparison of the survival probabilities, or as a ratio of the reverse of these probabilities, known as the hazard ratio. The survival probability is the probability that a person will 'survive', or not experience an outcome beyond a specified time. For example, three-year disease-free survival of 80% means that a person has 0.8 probability of 'surviving' (not experiencing cancer recurrence, death, or a second primary cancer) beyond three years. The survival probability of one group can be subtracted from the survival probability in another group to obtain an absolute difference between the two groups. The reverse of a survival probability is the probability of a hazard occurring (in this case, death, or recurrence), known as the hazard rate. The hazard rate in one group is divided by that of the comparison group to obtain the hazard ratio, a measure that provides information on the rate of one group relative to the other.

Evidence of oxaliplatin efficacy from randomised controlled trials

The evidence for the efficacy of oxaliplatin in the adjuvant setting comes from three landmark randomised controlled trials (RCTs). The Multicentre International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) was the first trial that found oxaliplatin to have a role in the adjuvant treatment of colon cancer (André et al., 2004; Andre et al., 2009; Andre et al., 2015). This was further supported by results from two other trials, the National Surgical Adjuvant Breast and Bowel Project C-07 (NSABP-C07) (Kuebler et al., 2007; Yothers et al., 2011) and the XELOX in Adjuvant Colon Cancer Treatment (XELOXA) (Haller et al., 2011; Schmoll et al., 2015). The MOSAIC and the NSABP-C07 trials compared treatment with the fluoropyrimidine 5-FU alone to the combination treatment of 5-FU and oxaliplatin (FL-OX), while the XELOXA trial compared 5-FU alone to the combination treatment of capecitabine and oxaliplatin (CAP-OX). Both the MOSAIC and NSABP-C07 trials included participants with stage II and III disease but reported results for each stage separately. The XELOXA trial only included participants with stage III disease.

There are two points to note with regards to the reporting of these trial results. First, the trials reported on disease-free survival, and relapse-free survival but at varying follow-up time points, which limited the ability to make direct comparisons (Table 1). As shown in the table, the MOSAIC trial reported on three-, five-, and ten-year disease-free survival and on three- and six-year overall survival. The NSABP-C07 reported on three-, four- and five-year disease-free survival, on five-year overall survival, and on four-year relapse-free survival. XELOXA reported on three-, four-, five-, six- and seven-year disease-free, overall, and relapse-free survival. The common timepoints between the three trials were only three- and five-year disease-free survival (Table 1).

Table 1 – Time-points (in years) at which each of the outcomes was measured in the three RCTs.

	Disease-free survival					
	3-year	4-year	5-year	6-year	7-year	10-year
MOSAIC	x		x			x
NSABP-C07	x	x	x			
XELOXA	x	x	x	x	x	

	Overall survival				
	3-year	4-year	5-year	6-year	7-year
MOSAIC	x			x	
NSABP-C07			x		
XELOXA	x	x	x	x	

	Relapse-free survival				
	3-year	4-year	5-year	6-year	7-year
MOSAIC					
NSABP-C07		x			
XELOXA	x	x	x	x	x

Second, the Consolidated Standards of Reporting Trials (CONSORT) statement, which sets out recommendations for the reporting of randomised trials, states that trials should report both absolute as well as relative estimates of effect (Schulz et al., 2010). All three trials reported the hazard ratio (relative estimate) accompanied by its uncertainty interval (95% CI) and a test for statistical significance for the difference between the control and treatment groups at all time-points. By contrast, survival probabilities were often reported only as point estimates for the two groups, without uncertainty intervals, an absolute difference between the two groups, or a test for statistical significance for the difference (Table 2, 3). This pattern of reporting indicates that a stronger emphasis was placed on the relative rather than the absolute difference between the treatment and control groups, and thus, presents an incomplete picture of treatment effect. Differences in effect between groups can appear larger in relative compared to absolute terms, which may skew the perception of its magnitude.

Three-year disease-free survival ranged between approximately 65%-67% in the 5-FU group, and between 71%-73% in the FL-OX, a difference of 4%-7%. The confidence intervals around the survival probabilities were only reported by XELOXA, showing overlap between the two groups. It was possible to calculate confidence intervals for the probabilities provided by MOSAIC, which although did not overlap, were of very close proximity (5-FU 65.3%; CI: 62.4%-69.4% and FL-OX 72.2%; CI: 69.5%-76.1%). A similar picture was seen for five-year disease-free survival in both trials. The hazard

ratio for recurrence or death at three-years were similar in all three trials, showing approximately a 20% reduction in the oxaliplatin group compared with the fluoropyrimidine group (Table 2).

Five-year overall survival ranged between 72%-74% in the 5-FU group, and 76%-78% in the FL-OX group, a difference of 2.7%-4.3%. Like three-year disease-free survival, the confidence interval around the survival probabilities was only reported by XELOXA, and was possible to calculate for MOSAIC, both showing overlap between the two groups. The hazard ratio estimated by the XELOXA trial also showed no difference between the two groups, while in the NSABP-C07 trial there was borderline statistical significance. Subsequently, the MOSAIC and XELOXA trials reported a significant 20% reduction in the risk of recurrence or death at six, seven, and ten years. However, for all three estimates the upper bounds of the confidence intervals are high, at 0.97, 0.99, and 0.96, respectively. The absolute difference in the probabilities of survival were similar at six and seven years with 4.2% and 5%, respectively, but was reported to be approximately 8% at ten years. However, the confidence interval around this difference is not reported, and the survival probability estimates also had overlapping confidence intervals (Table 3).

Survival probabilities are the reverse of hazard rates (hazard rates in this case representing recurrence or death). In one pooled analysis of 6,468 patients from the three trials, results were reported in terms of the rate of recurrence or death five years after randomisation (Shah et al., 2016). The cumulative rate of recurrence at five years was 29.4% (95% CI: 28.4%-30.5%) among those who received oxaliplatin compared to 37.3% (95% CI: 35.3%-39.2%) among those who did not. Most of the difference in the rate of recurrence between the two groups, however, occurred during the first year of follow-up, during which the rate of recurrence was 8.5% (95% CI: 7.9%-9.2%) for those who received oxaliplatin, compared to 13.2% (95% CI: 11.9%-14.6%) for those who did not (Table 4). A smaller, but statistically significant difference occurred during the fourth year (Table 4). By contrast, the difference in the cumulative rate of death between the two groups was smaller, with 22.1% (95% CI: 21.1%-23.0%) among those who received oxaliplatin and 26.3% (95% CI: 24.5% to 28.0%) among those who did not. The annual differences between the two groups were also smaller and statistically different only at four years post-therapy (Table 4).

Table 2 – Disease-free survival at different time-points from the three RCTs

		MOSAIC	NSABP-C07	XELOXA
3-year	FU/LV	65.3% (CI not reported; calculated: 62.4%-69.4%)*	67% (not reported)**	66.5% (63.4%-69.6%)
	FL-OX	72.2% (CI not reported; calculated: 69.5%-76.1%)*	73.2% (not reported)**	70.9% (67.9%-73.9%)
	Absolute difference	Not reported; calculated: 6.9%	6.2% (not reported)**	Not reported; calculated: 4.4%
	Hazard Ratio	0.76 (0.62 to 0.92)	0.80 (0.69 to 0.93)**	0.80 (0.69-0.93)
5-year	FU/LV	59.1% (not reported; calculated: 59.4%-62.8%)*	57.8% (not reported)	59.8% (56.4% to 63.1%)
	FL-OX	66.4% (not reported; calculated: 62.9%-70.0%)*	64.4% (not reported)	66.1% (62.9% to 69.4%)
	Absolute difference	Not Reported; calculated: 7.3%	6.6% (not reported)	Not Reported; calculated: 6.3%
	Hazard Ratio	0.78 (0.65 to 0.93; P=0.005)	0.78 (0.68 to 0.90; P < 0.001)	Not Reported
7-year	FU/LV			56% (Cis not reported)
	CAP-OX			63% (Cis not reported)
	Absolute difference			Not Reported; calculated: 7%
	Hazard Ratio			0.80 (0.69 to 0.93; P=0.004)
10-year	FU/LV	59.0% (54.8% to 63.1%)		
	FL-OX	67.1% (63.2% to 71.02%)		
	Absolute difference	Not Reported; calculated: 8.1%		
	Hazard Ratio	0.66 to 0.96; P=0.016)		

*Not reported in the original publication (Andre et al., 2004), but was possible to calculate from a later publication (Andre et al., 2015)
**Survival at three to four years

Table 3 – Overall survival at different time points reported by three trials

		MOSAIC	NSABP-C07	XELOXA
3-year	5-FU	86.6%		84% (not reported)
	FL-OX	87.7%		86% (not reported)
	Absolute difference	Not reported; calculated: 1.1%		Not reported; calculated: 2%
	Hazard Ratio	0.86 (0.66-1.11)		Not reported
5-year	5-FU	71.7% (68.2%-75.2%)	73.8% (not reported)	74.2% (71.3%, 77.2%)
	FL-OX	76% (72.7%-79.3%)	76.5% (not reported)	77.6% (74.7%, 80.3%)
	Absolute difference	4.3% (not reported)	2.7% (not reported)	Not reported; calculated: 3.4%
	Hazard Ratio		0.85 (0.72-1.00; P = 0.052)	0.87 (0.72-1.05; P=0.15)
6-year	5-FU	68.7% (not reported)		
	FL-OX	72.9% (not reported)		
	Absolute difference	Not reported; calculated: 4.2%		
	Hazard Ratio	0.80 (0.65-0.97; P=0.023)		
7-year	5-FU			67% (not reported)
	CAP-OX			73% (not reported)
	Absolute difference			Not reported; calculated: 5%
	Hazard Ratio			0.83 (0.70-0.99; P=0.04)
10-year	FU/LV	59.0% (56.9% to 61.1%)		
	FL-OX	67.1% (65.1% to 69.1%)		
	Absolute difference	Not Reported; calculated: 8.1%		
	Hazard Ratio	0.80 (0.66 to 0.96; P=0.016)		

Table 4 – Annual risk (%) of recurrence and death, by year, among patients with stage III colon cancer obtained (adapted from table by Shah et al., 2016)

	Year 1	Year 2	Year 3	Year 4	Year 5
Recurrence					
5-FU	13.2 (11.9 to 14.6)*	12.2 (10.9 to 13.5)	6.0 (5.1 to 7.0)	3.9 (3.2 to 4.8)*	2.1 (1.6 to 2.9)
5-FU+Ox	8.5 (7.9 to 9.2)*	11.4 (10.7 to 12.2)	5.1 (4.6 to 5.7)	2.6 (2.3 to 3.1)*	2.0 (1.7 to 2.4)
Death					
5-FU	3.4 (2.7 to 4.2)	6.4 (5.4 to 7.4)	6.6 (5.6 to 7.6)*	5.6 (4.7 to 6.6)	4.4 (3.6 to 5.3)
5-FU+Ox	2.9 (2.5 to 3.3)	5.3 (4.8 to 5.8)	5.0 (4.5 to 5.5)*	5.3 (4.8 to 5.9)	4.0 (3.5 to 4.5)

*Statistically significant difference

Evidence of oxaliplatin effectiveness from routine practice

Randomised controlled trials often are conducted in controlled conditions and tend to include participants that are less diverse than the general population. Participants may be younger and healthier than those in clinical practice. Additionally, patients' compliance to treatment, as well as monitoring and careful management of their side effects may also be higher during clinical trials (Batra et al., 2020). Therefore, results from RCTs may offer limited generalisability in terms of effectiveness in routine practice (Tannock et al., 2016), making evidence from population-based observational studies an important complement to that obtained from RCTs (Booth & Tannock, 2014). For example, the three main trials discussed in the previous section included a total of 6,468 patients in both arms. More than 90% of patients included in these trials were of White ethnicity, and more than 80% had low grade tumours (well-differentiated versus poorly differentiated), and a performance status score of zero. Performance status is a score of a patient's ability to perform activities of daily living, without the help of others. The lowest score is zero, indicating normal activity, while the highest score of four indicates being bedridden. To my knowledge, only a few population-based observational studies have been undertaken to evaluate the effectiveness of oxaliplatin-based adjuvant chemotherapy in practice.

The ACCElox registry contains data from 19 countries across Asia-Pacific, Latin America, Middle East, and Africa. Data on 1548 patients were analysed to establish the effectiveness of oxaliplatin-based adjuvant chemotherapy among stage II and III colon cancer patients in clinical practice (Park et al., 2015). The study reported a three-year disease-free survival of approximately 81%, and a three-year overall survival of approximately 95%, figures that were considerably higher than those reported by any of the three main clinical trials discussed earlier. These figures could be explained by the composition of the sample, whereby 27% of patients had stage II disease, and 72% were 65 years or younger. In terms of outcomes, the authors reported three-year overall survival, not the traditional five-year overall survival end point for adjuvant colon cancer treatment (Sargent et al., 2007). Additionally, although disease-free survival was defined as expected (i.e., the probability of survival from the date of first treatment with oxaliplatin to first relapse, new occurrence of colon cancer, or death), the authors reported on disease-free survival only in terms of the proportion of people who did not experience relapse, when it should also include those who experienced a new occurrence of cancer or died from any cause. To clarify, it was reported that disease relapse or recurrence occurred in 18.4% and death occurred in 4.7% of patients. However, the reported disease-free survival appears to have considered only the

former (100%-18.4% = 81.6%). Furthermore, none of the probabilities were accompanied by uncertainty intervals or a test for statistical significance. Finally, the study did not compare those who received oxaliplatin-containing adjuvant chemotherapy to any other group; without a comparison, the reported probabilities do not offer insight into the benefit (or lack of) that could be expected from the addition to oxaliplatin, compared to its absence.

In another study, conflicting results were found depending on the database used. Three-year overall survival among patients who were younger than 75 years of age with stage III colon cancer was compared between those treated with oxaliplatin to those who did not receive oxaliplatin. Data was derived from five data sources in the USA[1] (Sanoff, Carpenter, Martin, et al., 2012). The analysis was adjusted by age, sex, race, comorbidity, marital status, tumour substage, tumour grade, income, and year of diagnosis, using a statistical method called propensity score matching. This means that each treated individual was matched to an untreated individual of similar baseline characteristics to minimise the potential differences between the two groups. Those with the highest and lowest likelihood, or propensity, for receiving oxaliplatin in the oxaliplatin group without a matching individual of similar propensity in the group that did not receive oxaliplatin were omitted. The study found that the use of oxaliplatin was associated with a statistically significant improvement in three-year overall survival in two of the five cohorts examined. The first (SEER-Medicare, n=2458) showed a hazard ratio of 0.70 (95%CI: 0.60, 0.82), while the second (NYSCR-Medicare, n=446) showed a ratio of 0.58 (95%CI: 0.38, 0.90). Results from the remaining three databases (CanCORS, n=272; NYSCR-Medicaid, n=290; and NCCN, n=594), however, did not show a statistically significant improvement between the two groups. Treatment with oxaliplatin was also compared to single therapy among 5,489 patients older than 75 years of age using four of the databases (SEER-Medicare, n=4,226; NYSCR-Medicare,

[1] The Surveillance, Epidemiology, and End Results registry linked to Medicare claims (SEER- Medicare): covers 26% of the US population.

New York State Cancer Registry linked to Medicaid (NYSCR-Medicaid) and Medicare (NYSCR-Medicare): cover the population of New York State

The National Comprehensive Cancer Network (NCCN) Outcomes Database: covers patients treated at eight National Cancer Institute-designated comprehensive cancer centres

The Cancer Care Outcomes Research and Surveillance Consortium (CanCORS): is a population-based cohort study of patients with newly diagnosed colorectal cancer in four geographical regions, five large health maintenance organizations, and 15 Veterans Administration hospitals

n=998; CanCORS, n=121; NCCN, n=144) and no statistically significant difference was found in any. Findings from the largest sample size showed a hazard ratio of 0.84, but with a 95% confidence interval that crossed one (0.69 to 1.04) (Sanoff, Carpenter, Sturmer, et al., 2012).

Conflicting results were also found in two studies from Australia. The first was conducted using data from 434 patients with colorectal cancer obtained from the SESIAHS Clinical Cancer Registry, which covers 17% of the New South Wales population in Australia. The analysis used data adjusted for age, sex, cancer type (colon and rectal), stage (I-IV), and treatment type. The study found no difference in three-year overall survival between those who receive oxaliplatin compared to fluoropyrimidine only regimens (Healey et al., 2013). In contrast, a recent study that used data from 2164 patients with stage III colon cancer obtained from the New South Wales cancer registry, which covers approximately 30% of the Australian population, found that the addition of oxaliplatin provided an overall survival benefit for patients younger than 70 years (HR: 0.44; 95%CI: 0.3-0.6) as well as those older than 70 years (HR: 0.64; 95%CI: 0.5-0.9) (Brungs et al., 2018).

Two other studies reported no significant survival benefit from the addition of oxaliplatin. One was conducted in Taiwan, with data from 14,168 patients in the Taiwan Cancer Registry receiving oxaliplatin and 3,633 receiving single therapy. They used a controlled interrupted time-series analysis to assess the three-year disease-free survival and five-year overall survival rates before (2004–2008) and after (2009–2014) the introduction of oxaliplatin as treatment for stage III colon cancer. Interrupted time series is a quasi-experimental design that offers increased rigour compared to observational studies (Lopez Bernal et al., 2018). It allows examining the change in the trend of an outcome before and after an intervention is introduced within the same group, which minimises selection bias and confounding that result from differences between groups. The addition of a control group comparison also minimises the confounding that can occur from changes over time. In addition, the study also applied propensity score matching to ensure balance in baseline characteristics between the two groups. The study found that the addition of oxaliplatin had no significant impact on either outcome, regardless of age, or number of oxaliplatin cycles. Three-year disease-free survival for patients who did not receive oxaliplatin was found to have improved over time, which may partly explain the nonsignificant benefit seen in comparison to the oxaliplatin group.

Another study compared progression-free survival, as well as cancer and non-cancer related deaths between 178 patients who received a fluoropyrimidine regimen and 90

patients who received oxaliplatin among stage III colon cancer patients who were 65 years or older in Edmonton, Canada (Kim et al., 2014). Progression-free survival was defined as time from first treatment with chemotherapy to disease progression. The study found no statistically significant differences in outcomes between the two groups. Haller et al. found that age was associated with less chemotherapy benefit according to an overall survival hazard ratio of 1.17 (95% confidence interval 1.06 –1.28).

Limitations in findings from routine practice

These conflicting findings could be due to multiple factors. The relatively smaller sample sizes in some of these studies meant that the studies may have been underpowered to detect differences between groups, thereby underestimating the effect of treatment with oxaliplatin. Some studies also used shorter follow-up periods and reported on three-year overall survival, which could also underestimate the effect of treatment. As discussed previously, the traditional endpoint for the effect of therapy using overall survival is five years, and a longer follow-up period beyond five years may be required to detect differences given advances in post-recurrence therapy. Another reason that might result in lack of difference between two groups is a low number of events. Of 268 patients included in the study by Kim et al. (2014), there were 47 recurrences and 46 deaths among those who received a single agent, compared to 16 and 11 among those who received oxaliplatin, respectively. It is also possible that elderly patients included in these studies who received combination therapy were unable to tolerate therapy. As shown by Kim et al. (2014), there were significantly more delays, reductions, discontinuations of treatment among those who were older than 65 years of age on combination therapy. Their stratified analysis showed a five-year overall survival of 80% among those who received more than 75% of their scheduled treatment cycles compared to 64% among those who received less. Therefore, analysis by the intensity of treatment, number of cycles, and dose reductions or delays provides further insights, which were not explored in other studies.

One major limitation that was common to all the studies was the possibility of selection bias, which could overestimate the effect of treatment. This would be introduced into a study if patients receiving oxaliplatin tended to be younger, with fewer comorbidities, and less frail (Kim et al., 2016; van Gils et al., 2012). Several studies undertook propensity score matching, as discussed above, to minimise this bias. However, even with these adjustments, such methods can only account for known measured confounders. For example, although most studies account for comorbidities in their

analysis, medical frailty, i.e., vulnerability to adverse health outcomes, remains unmeasured and therefore unaccounted for (Fried et al., 2004).

Another limitation of these studies is the use of overall survival. The prognosis that is provided by overall survival reflects the real chance of survival for a given individual, because it accounts for both the chance of dying from cancer and from competing causes. For example, for some elderly patients with comorbidities, the chance of dying from other causes may be higher or more imminent than that of dying from their cancer, which reduces the benefit that can be realised from cancer treatment. For these patients, the overall survival probability may provide more insight into how long they could expect to survive than disease-free survival. However, when used in observational studies to compare the effectiveness of a cancer treatment between two groups, bias resulting from unknown causes of death between the groups could occur. Two groups being compared in an observational study (those with and without treatment) are not randomised. Randomisation accounts for both observed and unobserved sources of confounding. Therefore, the two groups could differ in the rate of death from other causes not related to cancer. For example, as discussed earlier, those who receive oxaliplatin could be younger and healthier than those who do not, with lower overall survival among the latter reflecting higher deaths from other causes rather than from the cancer. Although some studies use methods to minimise this selection bias, such as with propensity score matching, there could still be unmeasured confounding. Therefore, higher survival among those who are treated with oxaliplatin, for example, may reflect fewer deaths from other causes rather than fewer deaths from the specific cancer. There are other measures that can be used in survival analysis to isolate the effect of the cancer diagnosis by removing competing causes of death, called net survival. Net survival can complement overall survival by answering questions on the effect of treatment on cancer prognosis, or the probability of survival from the cancer itself, rather than on actual prognosis, which includes competing causes of death. However, this measure requires cause of death information, which is often unavailable or unreliably recorded in cancer registries. Net survival can also be obtained by comparing the survival of individuals with cancer to the expected life expectancy of a comparable group of cancer-free individuals using population life tables, matched on characteristics such as age, sex, race, income level, and geographic area. However, life tables may be unavailable or unreliable in providing an accurate estimate of life-expectancy for a particular group of cancer patients, as they need to represent the varying patterns of mortality in different populations.

Finally, it is also worth noting that in some of the studies discussed above, some of the co-authors were compensated by pharmaceutical companies, particularly Sanofi Aventis, the manufacturer of oxaliplatin. Although conflict of interest was declared and the article were peer-reviewed, industry financing of clinical research is known to introduce biases in results (Chopra, 2003), or more specifically, reporting of results. For example, the study by Sanoff et al. (2012), reported that oxaliplatin was associated with "a trend toward lower mortality" among elderly patients in the SEER-Medicare (HR: 0.84; 95% CI: 0.69-01.04) and NYSCR- Medicare (HR: 0.82; 95% CI: 0.51-1.33) databases. Additionally, that both databases also showed "a 5% absolute improvement" in three-year overall survival. These statements could be misleading to those with limited statistical knowledge. The confidence intervals of the hazard rations clearly cross the value 1.00, indicating no difference. In addition, the test for significance (p-value) was not reported, which most likely would be non-significant. Furthermore, the absolute improvements were reported as percentages without confidence intervals or a test for significance. Given the non-significant hazard ratios, it is likely that the confidence intervals of the survival probabilities would have been overlapping and the test for a difference would therefore also be statistically non-significant.

Treatment duration

Another factor to consider in the treatment decision for adjuvant chemotherapy is the duration of treatment. The risk of developing peripheral neuropathy increases with cumulative doses of oxaliplatin, i.e., the total amount of oxaliplatin given over time in a series of treatment cycles. Therefore, as discussed earlier, the mainstay for preventing the development of neurotoxicity is by reducing the amount of oxaliplatin delivered (Loprinzi, 2017). As such, the International Duration Evaluation of Adjuvant Therapy (IDEA) collaboration prospectively pooled data from six clinical trials[2] of adjuvant therapy for patients with stage III colon cancer to determine whether three months of therapy with FL-OX (5-FU and oxaliplatin) or CAP-OX (capecitabine and oxaliplatin) is as effective (non-inferior) as six months for three-year disease-free survival (Grothey et al., 2018). For non-inferiority to be accepted, it was pre-specified that the upper limit of the 95% confidence interval of the hazard ratio should not exceed 1.12. This cut-off

[2] The six trials were CALGB/SWOG (Cancer and Leukemia Group B/South- west Oncology Group), IDEA France, SCOT (Short Course Oncology Treatment), ACHIEVE (Adjuvant Chemotherapy for Colon Cancer with High Evidence), TOSCA (Three or Six Colon Adjuvant), and HORG (Hellenic Oncology Research Group).

corresponded to a worsening of 2.7% in three-year disease-free survival, which was determined to be clinically acceptable by consensus among the IDEA collaborators.

All patients

The study concluded that for the entire population of stage III colon cancer patients included (12,834 patients), irrespective of type of treatment or tumour characteristics, three months of therapy was not as effective as six months of therapy. This is because the hazard ratio was 1.07, with a 95% CI of 1.00 to 1.15 (P=0.11), which missed the pre-specified non-inferiority upper limit margin of 1.12 by 0.03 (Table 5).

By type of treatment and tumour characteristics

Subgroup analysis to compare the effectiveness of three months to six months was also undertaken by type of treatment (FL-OX or CAP-OX) and tumour characteristics (tumour size and number of lymph nodes). For the type of treatment, the study found that treatment with FL-OX for three months was not as effective as six months (HR: 1.16; 95% CI: 1.06, 1.26). However, treatment with CAP-OX for three months was shown to be as effective as six months (HR: 0.95; 95% CI: 0.85, 1.06) (Table 5). For tumour characteristics, three months of adjuvant therapy was not as effective as six months for any tumour size. For those with T1, T2, or T3 cancers, the upper limit of the 95% confidence interval for the hazard ratio of three months of therapy compared to six missed the pre-specified margin by 0.01 (HR:1.04; 95% CI: 0.96, 1.13). For those with T4 tumours, the result was clearer, yielding a hazard ratio of 1.16 (95% CI: 1.03, 1.31). Similarly for the number of lymph nodes, the results also showed that treatment with three months was not as effective as six months. The hazard ratio was 1.07 (95% CI: 0.97, 1.17) for those with N1 tumours (involving 1-3 nodes), and similarly, 1.07 (95% CI: 0.96, 1.19) for N2 tumours (involving ≥4 nodes), missing the pre-specified non-inferiority margin by 0.05 and 0.07, respectively (Table 5).

By risk group

The authors conducted further exploratory analysis that combined patients into two groups based on both tumour size and number of lymph nodes: low-risk (T1, T2, or T3 tumour size, and N1) and high-risk (T4 and N2). Treatment for three months was as effective as six months for low-risk patients (HR: 1.01; CI: 0.90-1.12) but not for high-risk patients (HR: 1.12; CI: 1.03-1.23) (Table 5). However, although the confidence interval of the hazard ratio for the high-risk group did not fall within the 1.12 pre-specified limit, the three-year disease-free survival was 62.7% (95% CI, 60.8 to 64.6)

with three-months of therapy, and 64.4% (95% CI, 62.6 to 66.4) with six months, an absolute difference of 1.7% and overlapping confidence intervals.

By type of treatment and risk group

In further exploratory analysis, the study also compared the duration of therapy for each of the risk groups by type of treatment. Among low-risk patients, three months of therapy was shown to be as effective as six months of therapy only for those who received CAP-OX, not FL-OX (Table 5).

Summary

In summary, six months of therapy was superior to three months in all patients. However, when stratified by extent of disease and treatment type, three months of therapy was as effective as six months only for the low-risk group who receive CAP-OX.

Table 5 – A summary of the pooled results from the International Duration Evaluation of Adjuvant Therapy (IDEA) collaboration.

		HR (95% CI)	Three-months as effective as six-months of therapy?
All patients		1.07 (1.00, 1.15)	No
By type of treatment	FL-OX	1.16 (1.06, 1.26)	No
	CAP-OX	0.95 (0.85, 1.06)	Yes
By tumour stage	T1, T2, T3	1.04 (0.96, 1.13)	No
	T4	1.16 (1.03, 1.31)	No
By number of lymph nodes (LNs) involved	N1 (1-3 LNs)	1.07 (0.97, 1.17)	No
	N2 (≥4 LNs)	1.07 (0.96, 1.19)	No
By risk group*	Low risk**	1.01 (0.90, 1.12)	Yes
	High risk**	1.12 (1.03, 1.23)	No
By risk group and treatment*			
FL-OX	Low risk	1.10 (0.96, 1.26)	No
	High risk	1.20 (1.07, 1.35)	No
CAP-OX	Low risk	0.85 (0.71, 1.01)	Yes
	High risk	1.02 (0.89, 1.17)	No

*Exploratory analysis, not pre-specified in the protocol
**Low-risk (T1, T2, or T3 tumour size, or N1) and high-risk (T4 or N2)

Regimen

The mode of administration differs for each of the agents included in adjuvant chemotherapy for stage III colon cancer and could therefore be another factor that could determine treatment. The oxaliplatin component is available only as an intravenous infusion (Ibrahim et al., 2004), whether it is combined with 5-FU or with

capecitabine, while the fluoropyrimidine component is available as an intravenous infusion (5-FU) or as oral tablets (capecitabine).

Oxaliplatin is intravenously infused through a cannula that provides access to a peripheral vein in the arm or hand, or a central venous catheter that provides access to a large central vein close to the heart (Devanabanda & Kasi, 2020). A central venous catheter can be placed either directly into the central veins via the chest or indirectly through a peripheral vein in the arm via a Peripherally Inserted Central Catheter (PICC). There are advantages and disadvantages to each of these intravenous access methods. Central lines placed via the chest can cause serious complications, such as perforations to surrounding arteries, veins, or lungs during placement, and a high risk of infections and blood clots, and require regular cleaning and care (Johansson et al., 2013). Although PICC lines were found to have a similar rate of infection compared to central venous catheters in hospitalised patients, they are associated with a lower risk of infections in outpatients (Chopra et al., 2013). For these reasons, central venous catheters are not often used in cancer chemotherapy, and the PICC line has become a popular alternative providing central venous access from a peripheral vein. Extravasation, or leakage, of chemotherapeutic agents from the veins can cause damage to the surrounding tissue ranging from mild inflammation to severe necrosis and is estimated to occur in 0.1–6% of all peripheral intravenous infusions, and in approximately 3% of infusions through central venous access ports (Langer, 2010). Leakage of oxaliplatin has been reported to cause damage or blistering to the surrounding tissue (de Lemos & Walisser, 2005). In this respect, infusion of oxaliplatin through a peripheral vein may offer an advantage as leakage into tissue surrounding peripheral veins is less adverse than into tissue surrounding central veins. One serious complication associated with PICC lines is upper extremity deep venous thrombosis (blood clot forming in the deep veins), which can occur within the first month to two months of its placement (Bhargava et al., 2020). This condition can cause pain and swelling in the arm, and lead to pulmonary embolism (blood clot travelling to and occluding the blood vessels in the lungs), a potentially fatal complication (Heil et al., 2017). PICC lines may also be associated with limitations to lifestyle due to the external device that is placed in the mid-arm. In one study, approximately 15% of PICC lines were removed before the end of therapy due to complications (Bertoglio et al., 2016). However, peripheral venous access also has its disadvantages. Extravasation into the surrounding tissue, which occurs more commonly with cannulas than with central venous catheters (Al-Benna et al., 2013), as well as deterioration of the patient's peripheral veins, lymphangitis (inflammation of the lymphatic system),

thrombosis (occlusion due to blood clots), and vascular pain occur with peripheral venous access (Matsuoka et al., 2019), which may eventually lead to requiring central access.

With CAP-OX, the fluoropyrimidine component (capecitabine) is administered by tablets and oxaliplatin is the only component requiring intravenous access. Therefore, it may be possible to administer oxaliplatin via a peripheral venous cannula. One study that evaluated the use of peripheral veins for oxaliplatin infusion among stage III colon cancer patients who received CAP-OX concluded that it was a feasible mode of administration. The study showed that of 85 patients who started with a peripheral venous access, 81% completed therapy without complications or need for access to a central vein. However, approximately 19% eventually required a central venous access. Reasons cited for these included complications, such as lymphangitis, venous insufficiency (malfunctioning of venous walls and valves causing pooling of blood), pain, and the need to switch from capecitabine to 5-FU, which is also administered intravenously (Lapeyre-Prost et al., 2016). In another study, 59% of the patients developed vascular pain from peripheral venous infusion, although none required a switch to a central infusion or experienced treatment delays (Yoshida et al., 2015).

With FL-OX, the fluoropyrimidine component (5-FU) is administered by intravenous infusion, for a long duration of time (often between 24-46 hours), thus making a peripheral venous cannula less suitable. With FL-OX, an ambulatory pump that can be attached to a patient by a belt and taken home is used (McMillan Cancer Support, 2020). This often requires that the patient return to the hospital for the pump to be disconnected or arrange for a home visit by a district nurse. However, the 5-FU infusion begins at the same time as the oxaliplatin infusion and ends the next day, with no further therapy required for the remainder of the first week as well as the following week (Table 6). In contrast, with the CAP-OX regimen the patient presents to the hospital on one day to receive oxaliplatin by infusion but is required to ingest oral tablets daily for the next two weeks, followed by only one week of ‘rest’ (Table 6). Some cancer patients have been found to prefer receiving chemotherapy in tablet form, while others may prefer to receive it as an intravenous infusion (Eek et al., 2016). However, adherence to oral therapy among cancer patients has been shown to vary and found to be influenced by personal factors such as emotional state, social support, and socioeconomic status (Ruddy et al., 2009). In one study that examined adherence of capecitabine found a self-reported rate of 91% in 161 patients (Kawakami et al., 2015; Winterhalder et al., 2011). Reasons reported for non-adherence included forgetting to take medication, misunderstanding instructions and fear of side-effects.

Finally, another aspect to consider regarding these two regimens is the toxicity profile of each. Both regimens cause similar toxicity, with a few exceptions. Several studies have found that stomatitis (inflammation of the mucous membranes of the mouth) and neutropenia (low count of neutrophil cells, a type of white blood cells that controls infections) are more common with FL-OX regimen, while hand-foot syndrome (redness, swelling, pain, and sometimes blistering of the palms of the hands and soles of the feet) and diarrhoea are more common with CAP-OX (Chintala et al., 2011; Ding et al., 2015; Loree et al., 2018).

Table 6 – Mode of administration and frequency of the flouropyrimidine and oxaliplatin components for FL-OX and CAP-OX

	Week 1	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**
FL-OX (FOLFOX)						
5-FU 24 to 46-hour infusion (Days 1 and 2)	xx		xx		xx	
Oxaliplatin Two-hour infusion (Day 1)	x		x		x	
CAP-OX (CAPOX or XELOX)						
Capecitabine tablet (Day 1-14)	xxxxxxx	xxxxxxx		xxxxxxx	xxxxxxx	
Oxaliplatin Two-hour infusion (Day 1)	x			x		

x – numbers of days in the week that treatment is administered

Summary

Results from three RCTs has shown that treatment with oxaliplatin offers an additional benefit in reducing recurrence and increasing survival compared to treatment with only fluoropyrimidines. However, treatment with oxaliplatin also causes acute peripheral neuropathy in most patients, which could persist for several years. Although prevalence estimates of persistent peripheral neuropathy have not been consistent across studies, evidence suggests that the condition impacts negatively on quality of life. Therefore, it is important to balance the relatively modest absolute improvement in survival against the potential high risk of persistent peripheral neuropathy. This is especially true when the uncertainty intervals around the survival probabilities are considered, as the efficacy of treatment in the population could fall anywhere between the range provided by the confidence intervals. It is also important to consider absolute as well as relative differences in the reduction of risk. Numerically, a relative reduction in risk between two treatment options can appear larger compared to an absolute reduction, which may result in a biased perception of the magnitude of effect. Finally, it is also important to be mindful that although there is evidence to support the biological efficacy of oxaliplatin, its effectiveness in the clinical setting may vary. Treatment under real life conditions varies from treatment that is assessed under controlled conditions, that is, close monitoring and management that occurs in clinical trials. Individuals can also vary in characteristics that could influence their response, adherence to treatment, and tolerability of its side effects. In the three RCTs discussed in this chapter, most patients in both treatment groups were older than 50 years, were of White ethnicity, had a performance status of zero, and had low-grade tumours. These characteristics are not fully representative of all colon cancer patients. Additionally, adverse events from chemotherapy can be higher in certain groups than others, potentially influencing the ability to tolerate treatment. Cardiac disorders, gastrointestinal symptoms, infection, and fatigue, for example, have been shown to be higher among elderly patients, leading to higher presentation and admission to hospital (Brungs et al., 2018) (Hung & Mullins, 2013). Therefore, some individual patients may derive more benefit than others, and some may experience more adverse events than others, depending on their personal and clinical characteristics.

The decision regarding treatment with oxaliplatin is not limited to whether it should be administered. The duration of therapy could be an important determinant of the choice of treatment. Although statistical evidence does not support three months of therapy over six months for all patients, it may be important for every patient to balance the

small margins by which the results missed (or met) the pre-specified non-inferiority criteria against the potentially large reduction in the risk of neurotoxicity. This is particularly true when considering how this cut off was determined, i.e., by consensus among the IDEA collaborators that a worsening of 2.7% in three-year disease-free survival is clinically acceptable. This, however, may not reflect the margin of risk that any individual patient may be willing to accept. As such, the American Society of Clinical Oncology (ASCO) recommends that an offer of treatment duration should be based on level of risk but that the decision should be based on a careful consideration and discussion for all patients, regardless of risk level (Lieu et al., 2019). Finally, the route of administration may also be a determinant of the choice of treatment. Although oral administration may seem to be an obvious choice, it is possible that some patients may not prefer to ingest a daily pill or would find comfort in frequent hospital visits. Additionally, patients' judgment on the risks or side effects that they are willing to tolerate from different types of treatment regimens may vary.

In summary, in the case of adjuvant chemotherapy for stage III colon cancer, several treatment options are available, each with different benefits, risks, and impacts on a patient's physical and psychological wellbeing, resulting in uncertainties in the expected outcomes. As such, the chosen treatment should not only rely on scientific evidence and clinical experience, but also be based on patients' needs, priorities and preferences (Charles et al., 1999; Loughlin et al., 2019).

Chapter 3: Defining this research

In this chapter, I am going to discuss the conceptual framework that guided my research objectives; describe the objectives and the studies that were undertaken to achieve them; and discuss the research paradigm that underpins this thesis. The research paradigm is defined by the ontological and epistemological position that were assumed, and the methodology chosen.

Conceptual framework

Although cancer is a common condition, to my knowledge, there are no theoretical frameworks in the literature that describe determinants of cancer chemotherapy. There is, however, a plethora of models that have described health-seeking behaviours and the choice of healthcare services. Although these models were not developed for choice of therapy in the cancer, some of their underlying theoretical concepts could be applied to this context.

The Health Belief Model is one of the earliest models that aimed to explain the social and psychological determinants of individuals' health-related behaviours (Rosenstock, 1974). It posited that uptake of health services (or adherence to treatment) is a function of people's perceived vulnerability or susceptibility to illness; perceived severity of an illness; perceived benefits as well as costs or barriers of a health-related action; exposure to factors that trigger action (stimulus or cue to action); and self-efficacy, or the confidence in the ability to successfully perform an action. These factors influence individuals' motivation to act or their motivation for which action to take. However, in addition to these factors that influence motivation, the Common Sense Model of Illness Representation emphasises that how people perceive their health threat or illness, in the first place, influences their cognitive and emotional responses, and thus, their health-seeking behaviours (Leventhal et al., 1992). It posits that individuals construct common sense representations of their illness, which result in the procedures (or actions) that are adopted to psychologically cope and manage the illness, and the questions or criteria that are used to appraise the effectiveness of these coping procedures. These representations, coping procedures and evaluative processes are based on the integration of information, memory (formed from prior experiences of illness as well as outcome expectations) and somatic sensation of symptoms. They are also influenced by the individual's experience of the illness (which could reinforce or undermine the representation), their personality traits, and their cultural and

interpersonal interactions with others, such as healthcare professionals, family, or friends.

Other frameworks that provide a sequence of events, or stages, for how people assume the sick role to eventually making choices between different types of health services have been suggested since the 1960s. For example, Schuman was the first to describe logical steps of health-seeking behaviour, which starts with the perception of symptoms until a choice of healthcare facility is made (Suchman, 1965). Igun (1979) proposed a comprehensive model, as shown in Box 1 below, that combined and built on the works of Schuman and several others (Igun, 1979). This model also starts with the experience of symptoms and goes on to describe all the stages that an individual may go through to select a treatment, the role of family or others in their health-seeking behaviours, and that after selection of treatment individuals may also evaluate the effectiveness of their selected treatment.

Box 1 – A descriptive model for the stages in health-seeking (Igun, 1979)

1. Symptoms-experience stage.
2. Self-medication or self-treatment stage.
3. Communication to significant others stage.
4. Assessment of symptoms stage.
5. Assumption of the sick-role stage.
6. Expression of concern stage (by kin and close friends). This is first in sequence but is often simultaneous with the next stage.
7. Assessment of probable efficacy or appropriateness of source of treatment stage. This is first in sequence but is often simultaneous with the next stage.
8. Selection of treatment plan stage.
9. Treatment stage.
10. Assessment or the evaluation of the effects of treatment stage.
11. Recovery and rehabilitation stage.

Finally, there are also frameworks that aimed to articulate determinants, or explanatory variables, that are associated with choice of health care services. For example, Kroeger (1983) proposed that patients' perception of illness (perceived morbidity) interacts with several factors to result in a choice of healthcare (e.g., traditional medicine, modern medicine, pharmaceuticals, or self/no treatment), as illustrated in Figure 2 (Kroeger, 1983). These factors include personal characteristics such as age, sex, ethnicity, socioeconomic status, education level, and one's position in the household and interactions with family and the wider community; disease

characteristics such as cause, duration, severity, and its response to treatment; and characteristics of the health service such as its accessibility, acceptability, quality, communication, and affordability.

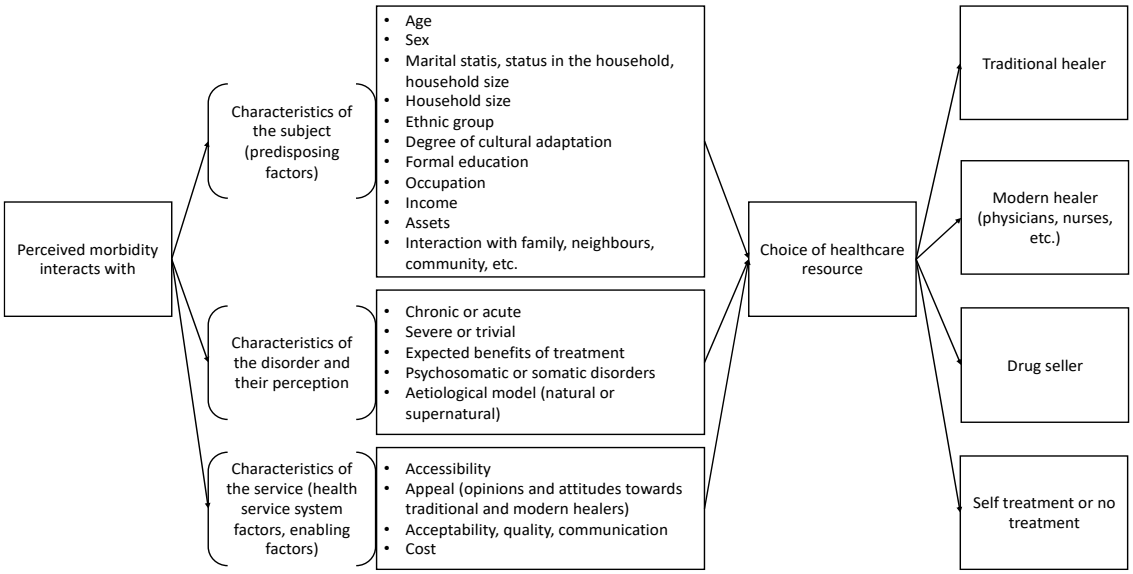


Figure 2 – Reproduced from Kroeger, A. (1983): FIG.1. The choice of healer in relation to various possible explanatory variables

Another framework that appeared in the literature search was one developed by Kelley et al. (2010), which described determinants of medical treatment intensity for patients with serious illness. In addition to patient, disease, and health system characteristics described above, this framework included the role of the physician in determining treatment (Kelley et al., 2010). It recognised that characteristics of the physician, such as age, sex, race, as well as year of graduation, specialty, how and where they were trained, and knowledge, beliefs, attitudes, and explicit or implicit biases (conscious or unconscious perceptions about patients based on certain sociodemographic characteristics), can influence their practice patterns, and thus also play a role in determining treatment. Furthermore, physicians may vary in their ability to stay up to date on the latest diagnostics and therapeutics, which can also influence their practice (Osarogiagbon et al., 2021). Physicians' practice patterns are in turn influenced by local practice patterns and the wider health system context, such as regional supply of medical resources. Kelley et al. (2010) also made explicit that the pathway through which family and patient characteristics could influence treatment is by shaping preferences, which in turn need to be communicated, thereby highlighting the role of communication between patient and physician in determining treatment.

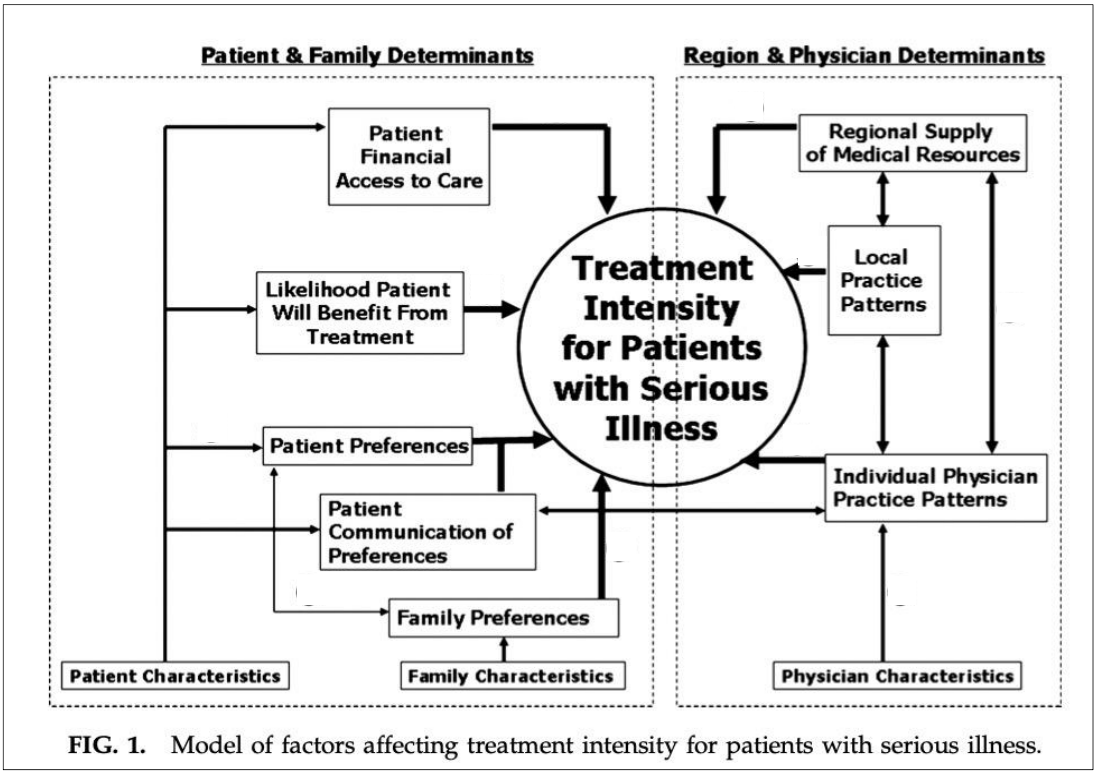


FIG. 1. Model of factors affecting treatment intensity for patients with serious illness.

Figure 3 – Figure from Kelley et al. (2010): FIG.1. Model of factors affecting treatment intensity for patients with serious illness.

A third framework that was identified from the literature was developed by Sundaresan et al. (2016), which aimed to inform the factors that influence access to radiation therapy among cancer patients (Sundaresan et al., 2016). The added value of this framework is that it provided some insights into the cancer treatment context. It included 'referrer level factors', which recognised the role of the physician that refers a cancer patient to more specialised care, and that their personal characteristics, biases, knowledge, communication of a treatment's benefits and adverse effects, and awareness of referral services, are factors that could influence their referral practices. Under consumer level factors, the framework made explicit patients' unmet psychosocial needs as a factor that can impact on utilisation of cancer therapy. It recognised that cancer patients experience psychological distress from diagnosis, need for treatment, and the ways in which their diagnosis and treatment can influence their daily lives, relationships, and work. It also recognised that the current health status or level of co-morbidities can determine whether a patient receives cancer therapy. In addition to patients' perceptions of their disease and the benefits of treatment that were recognised by the previous frameworks, this framework also included patients' perceptions of treatment-related inconveniences, such as the length of time required to receive treatment, and the effect of treatment on their feeling of well-being and quality of life. Finally, regarding service level factors, the framework

highlights the influence of multidisciplinary teams on treatment as they provide multi-specialty experience and knowledge in the management of a patient, and a safeguard against the biases of individual clinicians. The role of a multidisciplinary team will depend on multiple factors, such as the frequency of meetings, composition of specialists, types of cases that are discussed, and the dynamic of the team.

Although availability (presence of health service infrastructure, such as facilities, equipment, and staff), affordability, acceptability, and adequacy (or quality, i.e., effective, and timely) of a medical treatment have been recognised in the frameworks discussed above, this framework presents these factors under the notions of opportunity for and equity of treatment. That is, they determine whether there is opportunity for patients to receive cancer treatment, and whether opportunity is equal among all patients. Although health care in the UK is free at the point of access, Sundaresan et al. (2016) clarifies that affordability could mean more than the direct financial ability to afford a health service. It can include indirect costs such as loss of work productivity or opportunity, loss of time, or cost of outsourcing personal responsibilities such as child-care.

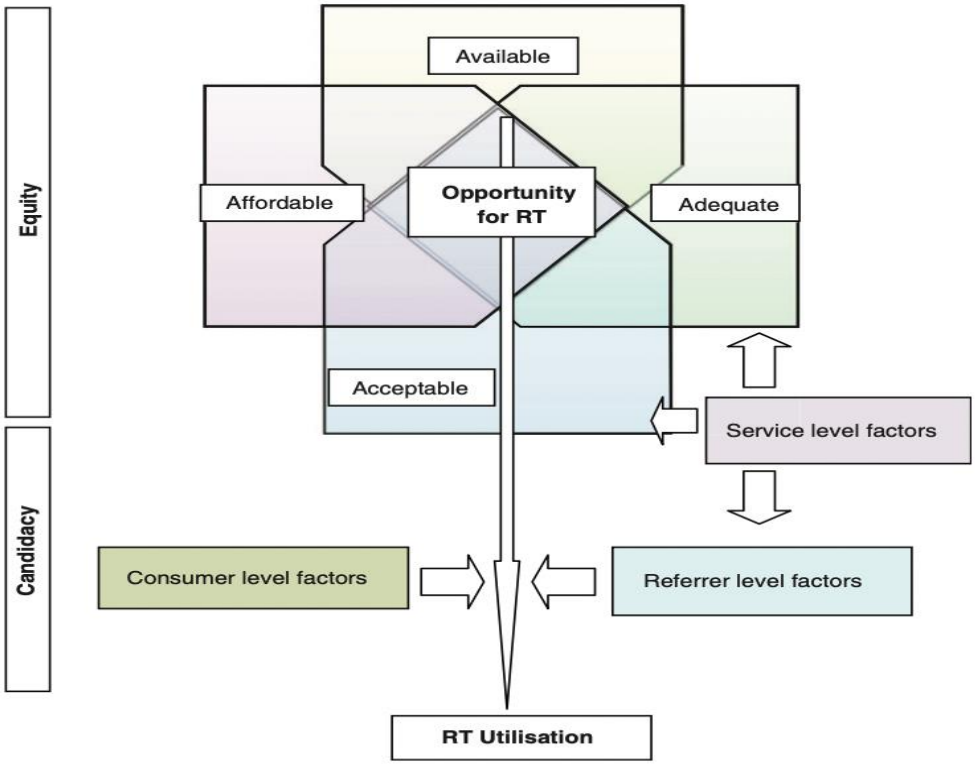


Fig. 1. Conceptual framework for consideration of radiotherapy (RT) access.

Figure 4 – Taken from Sundaresan et al. (2016): FIG.1. Conceptual framework for consideration of radiotherapy access.

As seen by these frameworks, several factors can interact on multiple levels (disease, patient, physician, family, referrer, and system) to determine treatment. However, the decision-making process through which the choice of treatment is made ultimately takes place between patient and physician and is influenced by the nature of their interaction. In the last two decades, shared decision-making has become prominent as a model to guide this interaction and is now considered an integral part of healthcare planning and delivery (Loughlin et al., 2019). In broad terms, shared decision-making is defined as the model by which patients and health professionals work together to reach consensus regarding treatment and care decisions. This is particularly important when several treatment options are available, each with different benefits, risks, and impacts on a patient's physical and psychological wellbeing, resulting in uncertainty in the expected outcomes, and thus, requiring that the chosen treatment is based on patients' needs, priorities and preferences (Charles et al., 1999). A shared decision-making model helps patients develop accurate perceptions about their disease, how they may benefit from or be adversely affected by treatment, the inconveniences it may pose and how it can affect their lives, which would enable them to identify what is important to them. The clinician's role, in turn, is to provide information about the disease and available treatment options, encourage patients to participate in the discussion, and aid them in identifying their needs and priorities and communicating their preferences.

Although I was unable to identify one theoretical framework that explains determinants of cancer chemotherapy choice, the concepts from the models discussed above, although overlapping to a large extent, were also complementary. As such, Figure 5 introduces a conceptual framework that combined the concepts of the abovementioned frameworks and guided my research.

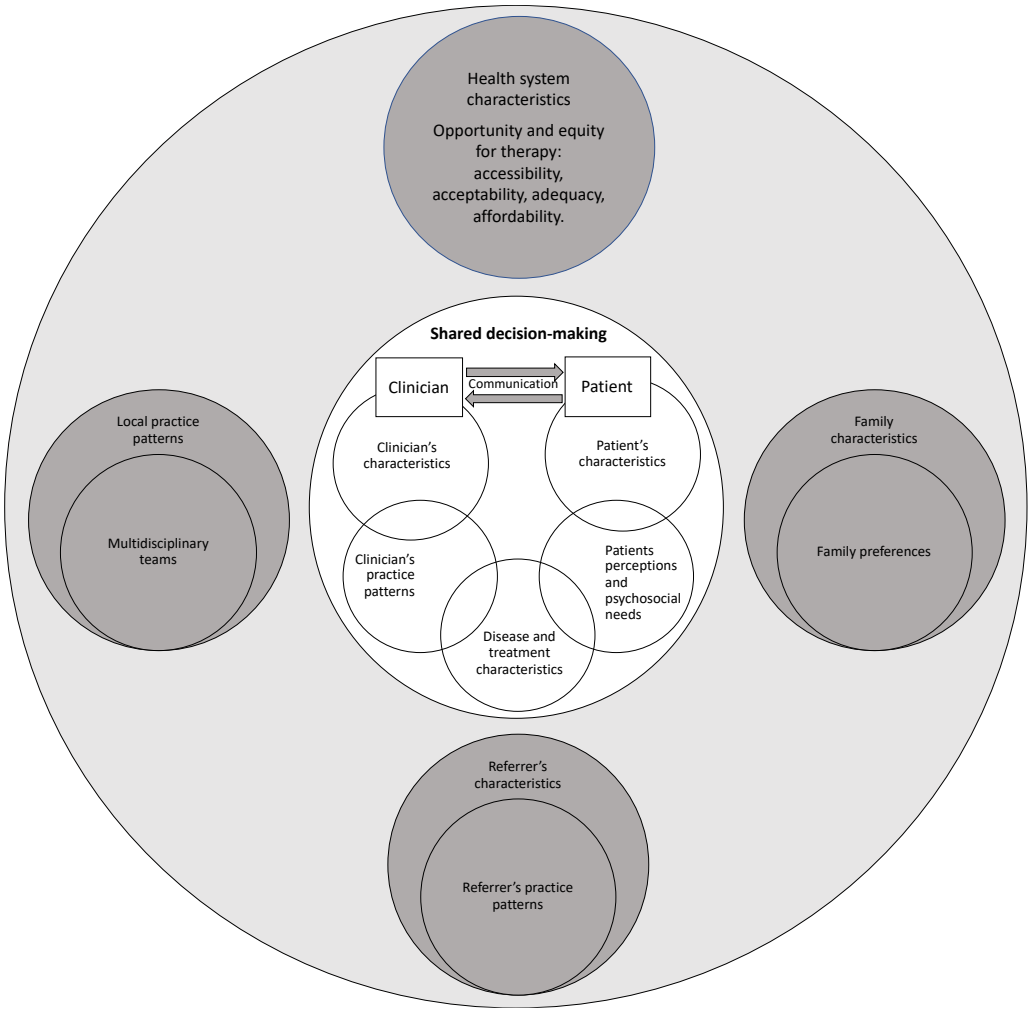


Figure 5 – Conceptual framework for the determinants of chemotherapy among cancer patients

The Research Paradigm

As outlined above, four studies were undertaken for this thesis. In this section I discuss the ontology, epistemology, methodology, and the overall philosophical paradigm that underpins this research.

Ontology, Epistemology, and Methodology

The word paradigm was first used to refer to a set of common beliefs, values, and techniques that are shared by a community of scientists (Kuhn, 1970). Guba (1994) posited that it is a model or approach to research that is defined by three dimensions: ontology, epistemology, and methodology (Guba & Lincoln, 1994).

Ontology refers to the "study of being" and asks the question "what is reality?". It is concerned with how researchers define reality or articulate their beliefs about what

exists in the world and what can be investigated. With ontology, there are essentially two basic positions to what reality could be: realism or relativism. Realism posits that there is a single truth about what exists in the world, while relativism considers that reality is created or perceived by individuals, such that no one 'true' reality exists, instead, it is relative to how individuals experience it at any given time and place. Epistemology is the "study of knowledge" and asks, "how is knowledge acquired?". It is concerned with articulating the nature of the knowledge that can be acquired about reality and how researchers will uncover this knowledge. With epistemology, there are also essentially two basic positions: objectivist or subjectivist. The objectivist position assumes that we can acquire knowledge by measuring it with reliable tools, while the subjectivist position argues that reality, and knowledge, are constructed within social structures or are a matter of interpretation or perspective. The third dimension that constitutes the research paradigm is the methodology, which is concerned with choosing a procedure to produce or acquire valid knowledge about what exists in the world that is appropriate for the ontological and epistemological positions that are assumed. As such, the philosophical paradigm within which a researcher operates depends on the ontological and epistemological views that they hold; it clarifies the purpose of the research, the methodology that should be adopted to acquire knowledge, and consequently, the methods, or tools, that should be used in the quest for knowledge (Guba & Lincoln, 1994).

Positivism is a research paradigm that is underpinned by a realist ontology and an objectivist epistemology (Hughes & Sharrock, 2016). Therefore, research in this paradigm is undertaken with the assumption that knowledge exists independent of the researchers, instruments, or personal ideas or thoughts, and that the world is comprised of elements or events that can be empirically observed and objectively quantified. Thus, the goal is to uncover the universal laws that govern how the world works and fill the gaps in our knowledge. The research methodology within this paradigm follows the scientific method in that it is based on testing hypotheses with empirical data, manipulating and measuring variables, and applying statistical analysis to make conclusions. As such, it relies on the use of highly standardized quantitative tools that are valid and reliable, i.e., instruments that measure what they are intended to measure accurately and can produce the same results consistently when used on repeated occasions. The rigour of research in this paradigm is therefore judged by the validity and reliability of its instruments and the replicability and generalisability of its findings (Tolley et al., 2016).

In contrast to positivism, constructionism and interpretivism are underpinned by relativist ontology and a subjectivist epistemology (Crotty, 1998; Hughes & Sharrock, 1997). Research in these paradigms posits that phenomena and behaviours cannot be observed objectively, and the 'real world' is not independent of human activity. Interpretivism, emphasises that meaning is interpreted by individuals: our own experiences and interpretations of what we observe play a critical role in understanding society. Constructionism shares the view of interpretivism but adds that meaning is also constructed through language and individuals' interactions with each other and with their wider social context. The methodologies used in this paradigm follow an exploratory approach to derive meaning and gain understanding of social phenomena in the contexts within which they occur, rather than relying on objective measurement (Tolley et al., 2016). Therefore, qualitative tools such as interviewing, participant observation, or ethnographic and phenomenological research are used, which allow discovery and are sensitive to context. The rigour of research in this paradigm is not judged by the same standards as quantitative tools. Instead, Lincoln & Guba suggested that rigour in qualitative methods is judged using the concept of 'trustworthiness', which is defined by four elements: credibility, which refers to confidence in the truth of the study's findings; transferability, which refers to how applicable the findings are to similar situations or populations; dependability, refers to findings that could be repeated and consistent with findings by others; and confirmability; which means the extent to which the findings are based on neutrality and free of potential bias. Specific strategies to achieve trustworthiness of qualitative studies include use of multiple methods or data sources, detailed descriptions of context and prolonged engagement with participants, audit trails that highlight the steps undertaken during analysis, and inquiry audits (Guba & Lincoln, 1981; Lincoln & Guba, 1986). In addition to specific strategies, others have argued that using valid and reliable verification strategies during the research process is equally important (Morse et al., 2002). They emphasised that qualitative research should be based on an iterative process that allows the researcher to move back and forth between the design, implementation, and analysis of the study to ensure coherence and enable the researcher to identify and correct errors and biases in the development and analysis of a study (Morse et al., 2002).

Post-positivism is a third paradigm that sits between positivism and social constructionism/interpretivism. Post-positivism takes from positivism with the notion that an objective reality exists in the world but differs in that it acknowledges that this reality cannot be observed or measured objectively. Post-positivism recognises that

theories and the background knowledge and values of individuals introduce biases into their observations, and that measurement tools are imperfect and introduce error. Therefore, the understanding and knowledge that we gain of the world is incomplete and probabilistic, requiring multiple methods, both quantitative and qualitative, to minimise these biases and errors.

Stemming from the post-positivist position is critical realism (Bhaskar, 2010). This position assumes that reality consists of three elements: the empirical, which contains the events that are observed or experienced; the actual, which contains all events independently of whether they are observed; and the real, which contains all the mechanisms and structures that generate or cause events. Both positivism and constructionism or interpretivism operate in the realm of the empirical, aiming to uncover a reality that can only be observed or experienced (Wuisman, 2005). Critical realism operates in the realm of the real. It is concerned with uncovering the causal mechanisms that can explain the relationship between events. However, it recognises that these mechanisms arise within a given context, and act as tendencies that are relative, rather than absolute universal laws, whereby social structures shape individuals' knowledge, behaviours, and actions, and in turn, individual agency also changes social structures. Critical realism, therefore, theorises about possible tendencies between social events and seeks empirical evidence to establish whether the relationship exists within a given context.

Lastly, unlike the positions discussed thus far, pragmatism is an approach that does not aim to define the nature of reality or how it can be uncovered. Instead, it is based on the notion that research can focus on the practical understanding of real-world problems, and that research data is analysed and interpreted to generate knowledge that would lead to useful and practical consequences, such as improved quality of life, or provision of more effective health services (Bishop, 2015; Cornish & Gillespie, 2009; Yardley & Bishop, 2008). As such, research in this paradigm asks questions on how a certain theory or model works in practice, why it may or may not work as expected, and what the resulting outcomes are, to identify ways in which practice can be improved. Research that assumes this position requires the use of any method or a combination of methods, qualitative or quantitative, to answer the research question in the best possible way.

'Multiple methods' and 'mixed-methods' research

There has been little clarity and much debate on what the terms multiple methods (or multi-method) and mixed-methods research mean conceptually or methodologically.

Some argue that these are two different approaches to research, while others have used the terms interchangeably. However, in recent years, efforts have been made to clarify these terms and move this debate forward (Anguera et al., 2018).

In an article written in 2017, the editors of the Journal of Mixed Methods Research distinguished between multiple methods and mixed-methods research (Fetters & Molina-Azorin, 2017). They stated that multi-method research "can include two or more exclusively qualitative approaches, Qual plus Qual, two or more quantitative approaches, Quan plus Quan, or a combination of qualitative and quantitative approaches, Qual plus Quan, hence mixed methods research". Therefore, they defined multiple methods as the use of any two methods, while mixed methods as one type of multi-method where both qualitative and quantitative methods are used.

More recently, Anguera et al. (2018) conducted a narrative review of the literature that explored the various ways in which multi-method and mixed-methods research had been described by other scholars (Anguera et al., 2018). The distinction that they proposed lies not only in the type of methods used, but also in the time at which the integration of the different types of data takes place. They defined mixed-methods research as containing "qualitative and quantitative components that must be integrated to ensure the mixing of the information they carry". This is largely aligned with Creswell & Plano Clark's emphasis that mixed-methods research should include a 'mixing' of qualitative and quantitative methods (Creswell & Clark, 2017). Thus, integration of qualitative and quantitative data is required in mixed-methods research as the purpose is to gain a deeper understanding of the same research objective. On the other hand, multi-method research was defined as one where a specific methodology in an empirical study is used to address each of the research questions that are related to an overall research goal. Other ways of describing multi-method research includes one where the different methods used in the research are "not integrated until inferences are being made" (Johnson et al., 2007), or one where more than one method is conducted "rigorously and complete in itself" in one research project (Morse, 2003). Thus, because of the different methods used to answer different research questions, integration is not a requirement of multi-method research.

This thesis

In this thesis, I did not aim to uncover a reality that is independent of human experience or one that is only defined by human experience, and therefore I did not assume a positivist, or constructionist/interpretivist position. Instead, I adopted a critical realist approach. The purpose of the research was to explain the mechanisms, or

tendencies, that determine treatment in the context of adjuvant chemotherapy among stage III colon cancer patients in the UK, including the extent to which individual agency and the wider systemic structures influence this decision. It is credible to argue that this thesis also takes a pragmatist approach. I placed greater emphasis on applying the methods that worked best to answer my research questions and understanding the process by which treatment decisions in this context were made, to identify what could be improved for the better well-being of patients. I used multiple methods in four empirical studies to achieve the objectives set out in the previous section.

First, as discussed earlier, peripheral neuropathy could be one of the most important determinants of whether a patient chooses to receive adjuvant chemotherapy with oxaliplatin. Therefore, I conducted a quantitative synthesis of evidence from systematically reviewed literature on the prevalence of this condition specifically among stage III colon cancer patients who received oxaliplatin.

The second study was a quantitative analysis of the national longitudinal Cancer Registry data, linked to the national Systemic Anti-cancer Therapy data to explore whether there are variations in the use of adjuvant chemotherapy on a systematic level. That is, whether it varies between groups based on socio-demographic characteristics.

For the fourth study I used qualitative in-depth narrative interviews to understand the process that leads to receiving adjuvant chemotherapy among stage III colon cancer patients from patients' perspective, and the factors that influence this process. For this study, the interviews served as accounts of patients' experiences within the broader context relating to personal circumstances and the healthcare system.

The fourth study was a quantitative data analysis using data from the National Patient Experience Survey (NCPES) to explore how those who receive combination therapy perceive the quality and quantity of information they receive about their treatment options and side effects, as well as how they perceived their involvement in the decision-making process.

Each study was designed, conducted, and analysed separately and independently using the techniques traditionally associated with each data type (methods used are discussed in more details in each corresponding chapter). Each study answered a different research question, allowing for an understanding of the overall research goal at different levels. Inferences were made based on the findings of all four studies in the final chapter of this thesis, *Chapter 8: Discussion*.

It is worth noting that, in retrospect, the third (qualitative) and the fourth (quantitative study using NCPES data) studies related to each other in ways that exhibited features of a mixed-methods study, although it was not intended as such.

A mixed-methods study is defined by its design and purpose. The design of mixed-methods research is determined by the timing and emphasis of its qualitative and quantitative components. That is, whether the components were conducted simultaneously or sequentially, and whether they are of equal importance or if one weighs more than the other. Regarding purpose, Greene et al. discussed five different purposes of mixed methods research. Those are development, expansion, triangulation, complementarity, and initiation. Development refers to using results from the first method to inform the development, or the design, of the second method. Expansion refers to using different methods to investigate different phenomena, thereby extending the breadth and depth of the research. The remaining three are somewhat related in that methods with complementary strengths and weaknesses are used for different purposes: to gain a more complete understanding of complex phenomena (complementarity), to obtain convergence or confirmation of findings (triangulation), and to uncover divergence in the findings (initiation).

In terms of design, the second (qualitative) and third (quantitative) studies were conducted sequentially, with greater emphasis placed on the qualitative component. This is because the qualitative component provided a broader picture and illuminated several elements of the decision-making process with detailed accounts, while the quantitative component mainly focused on specific aspects to this process, i.e., information provision and involvement. In terms of purpose, the findings from the quantitative study confirmed, or converged, with those of the qualitative study.

Chapter 4: Prevalence of oxaliplatin-induced peripheral neuropathy among colorectal cancer survivors: a systematic review

Introduction

Accurate measurement of the burden of permanent side effects resulting from cancer therapy is critical for improving the quality of life of cancer survivors. It can inform the development and use of support and health services or inform the decisions new patients and their treating clinicians must make.

As discussed in Chapter 1, peripheral neuropathy is a common side effect to treatment with oxaliplatin, used in adjuvant chemotherapy for stage III colon cancer. Acute symptoms, which last a few days after oxaliplatin administration but resolve between cycles, are experienced by most patients (Beijers et al., 2014). As treatment continues, the accumulating doses of oxaliplatin may result in more severe symptoms that persist between cycles and could also persist for years after completion of therapy (Beijers et al., 2014). Persistent peripheral neuropathy has been shown to interfere with activities of daily living and influence quality of life (Mols et al., 2014). However, estimates for the long-term prevalence of this condition among stage III colon cancer patients resulting from treatment with oxaliplatin vary widely depending on whether symptoms were assessed by clinicians or reported by patients and time point at which symptoms were assessed (Beijers et al., 2014; Molassiotis et al., 2019).

Assessment of chemotherapy-induced peripheral neuropathy

There are three main approaches to assess the presence of chemotherapy-induced peripheral neuropathy (CIPN): physiological, clinical, and patient-reported. Measurement scales could be based on any one of these approaches or could use a combination.

Physiologic measures assess nerve function and include methods such as electrodiagnostic tests that measure the electrical activity of muscles and nerves such as electromyography and nerve conduction velocity. However, their use to determine the presence (or absence) of peripheral neuropathy may be inappropriate as they may be costly, time-consuming, and impractical (Forsyth et al., 1997; Cavaletti et al., 2003),

and more importantly, can underestimate the severity of the symptoms that patients experience (Dunlap & Paice, 2006).

Clinical measures rely on clinicians' physical examination of patients, and patients' response to the clinical examination, while patient-reported measures assess patients' experience of symptoms, without an examination by a clinician. There are numerous clinical scales and patient-reported outcome measures that have been identified in the literature (Curcio, 2016; Griffith et al., 2010; Haryani et al., 2017; Sasane et al., 2010).

One of the most widely used measure of peripheral neuropathy is the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), which consists of sensory and motor symptom subscales. However, since CIPN is typically sensory in nature, empirical studies often report on the sensory subscale only. Similar measures include the Eastern Cooperative Oncology Group (ECOG), World Health Organization Common Toxicity Criteria for Peripheral Neuropathy, and Ajani criteria (Ajani et al., 1990; Miller et al., 1981; Oken et al., 1982). These scales categorise neuropathy into four to five ordinal grades, where 0 indicates no symptoms, and four/five indicate paralysis or debilitating paraesthesia (an abnormal sensation, typically tingling or pricking). Although these measures rely on both a physical examination as well as how patients respond to the examination, these tools mainly emphasise clinical judgement rather than patient experience. Additionally, the use of such ordinal categories may be limited in their ability to be responsive to or detect small and cumulative changes in impairment over time, which is characteristic of CIPN (Cavaletti et al., 2006). Furthermore, there may also be inter-observer disagreement in grading the severity of symptoms, which was demonstrated for the CTCAE scale, indicating that it may be useful as a screening tool for choosing which patients need a neurological examination rather than for providing a true evaluation of the extent and severity of CIPN (Cavaletti et al., 2010; Postma & Heimans, 2000; Postma et al., 1998). For example, grade-II of the CTCAE scale (Appendix 1) indicates symptoms that interfere with instrumental activities of daily living while grade-III indicates symptoms that interfere with self-care activities of daily living; it is not clear how a distinction between instrumental symptoms and self-care symptoms is judged.

Patient-reported outcome measures rely entirely on patient report. These measures vary in the extent to which they include questions about symptoms, severity, activity limitations, and psychosocial impact. For example, the Chemotherapy-Induced Peripheral Neuropathy Survey (CIPNS-32) and Assessment of Peripheral Neuropathy (APN) scales both include questions about the "bothersomeness" of symptoms, while others do not. Thus, no single patient-reported outcome measure is comprehensive in

capturing all the ways in which peripheral neuropathy symptoms could interfere with patients' daily lives (Sasane et al., 2010).

Prevalence of peripheral neuropathy

To my knowledge, two systematic reviews have been published that have attempted to quantify the severity and duration of chemotherapy-induced peripheral neuropathy (CIPN) among cancer patients.

The first was a systematic review of studies published between 2003 and 2012 that aimed to estimate prevalence of CIPN resulting from treatment with oxaliplatin specifically at least twelve months after completion of therapy. It also aimed to examine whether there was an association between developing CIPN and oxaliplatin administration in terms of its treatment schedule, total cumulative dose, and dose intensity (Beijers et al., 2014). Studies were included only if information on both those aspects were available (prevalence of oxaliplatin-induced peripheral neuropathy (OIPN) assessed after at least twelve months of follow-up, as well as oxaliplatin administration). The search was done using two databases: PubMed and Cochrane, and fourteen studies met the eligibility criteria. All included studies used the CTCAE tool their assessment of peripheral neuropathy. However, studies varied in sample size (from 16 to approximately 2000), stage of cancer (II, III, and IV), and time point at which assessment of symptoms took place (twelve months to 8 years), and therefore, a summary estimate of prevalence was not possible. The study concluded, however, that any degree of OIPN (grades one to three) persisted in many patients after at least twelve months of follow-up. Grade-I and grade-II symptoms ranged between 12.5%-46%, while grade-III ranged from zero to 5% at twelve months. Grade-I symptoms were found in nearly 38% and 12% after two years and four years of follow up, respectively, while grade-III was found in 12.5% and 0.7%, as reported by two of the included studies.

Another systematic review of studies published up to 2013 was undertaken to assess the prevalence of CIPN resulting from any neurotoxic treatment for any type of cancer (Marta Seretny et al., 2014). Of the 31 studies included, 12 were specific to colorectal cancer and treatment with oxaliplatin. Of those, however, only one assessed neuropathy at twelve months after completion of treatment (Attal et al., 2009), while the remaining made the assessment at less than six months. Only 18 patients were assessed by Attal et al. (2009), 30% of which received oxaliplatin for metastatic cancer. They reported that 44% and 22% had symptoms of grades two and three, respectively.

Aim and objectives of this study

As discussed previously (Chapter 1), treatment with oxaliplatin for stage III colon cancer may offer only a relatively modest absolute improvement in survival compared to the fluoropyrimidine component alone, and thus, should be balanced against the potential risk of persistent peripheral neuropathy. Therefore, the treatment decision for this population of patients may differ from that in the palliative (metastatic) setting, or for that of other cancer and neurotoxic treatment types. Neither of the two reviews discussed above have been comprehensively or adequately conducted to allow for a clear estimate on the prevalence of peripheral neuropathy among this population group. Additionally, neither review attempted to summarise prevalence estimates by the type of measure used. It is worth noting that the reviews undertaken by Seretny et al. (2014) and Beijers et. Al. (2014) overlapped in only one study. This may be because Beijers et al. (2014) searched only two databases and restricted inclusion to studies that also reported on details of oxaliplatin administration, while Seretny et al. (2014) restricted the search to prospective designs and used narrow search terms.

As such, in this study, a systematic review of the literature was carried out to determine the prevalence of persistent peripheral neuropathy among stage III colon cancer survivors, at different long-term timepoints following completion of therapy, and by the assessment measure used. Therefore, this review provided an update to the published reviews by including studies that have been published since 2013. Furthermore, the search consisted of broad search terms on seven databases to ensure comprehensiveness, and there were no restrictions on study design or on the availability of information for outcomes other than the outcome of interest.

Methods

This study was registered on PROSPERO (https://www.crd.york.ac.uk/prospero/); registration number: CRD42019156476.

Search strategy

I started with very broad search terms using the CoCoPop mnemonic (condition, context, and population) to determine the inclusion criteria, as proposed by Munn et al. (2015) for reviews assessing prevalence data (Munn et al., 2015). The search was not limited by study design, and the outcome of interest (in this case prevalence of peripheral neuropathy) was not specified, as prevalence can be reported in a variety of ways without being explicitly stated as such.

Condition

The condition of interest in this review is persistent peripheral neuropathy. Due to the lack of agreement in the literature on how to best define and measure persistent peripheral neuropathy, I specified inclusion of all studies that assessed symptoms of sensory or motor neuropathy experienced at least six months after the end of treatment with oxaliplatin, regardless of the tool used. Peripheral nerves take between six to eight weeks to recover from mild forms of injury and three to six months to recover when 20-30% of the axons are damaged (Menorca et al., 2013). Therefore, symptoms persisting beyond six months may indicate that full recovery may be protracted or unlikely due to extensive nerve damage.

Context

The search was focused on studies that assessed patients who underwent adjuvant chemotherapy after resection of the tumour. Only the term “adjuvant” was used in the search to capture all its uses in phrases such as adjuvant chemotherapy, adjuvant therapy, adjuvant treatment, or the adjuvant setting. I also listed all possible adjuvant therapy options explicitly (for example, FOLFOX, CAPOX, etc.)

Population

The study is focused on those who receive oxaliplatin for stage III colon cancer. Although adjuvant chemotherapy can also be used in the treatment of high-risk stage II disease, it is not a standard treatment that is offered routinely for those patients due to uncertainty regarding its benefit (Simillis et al., 2020). Those with stage IV disease also receive adjuvant chemotherapy, however, this is provided for palliative rather than

curative intent. Therefore, treatment for stage II and IV may vary considerably in its administration from that for stage III.

I used all variants of the phrase “colorectal cancer” to comprehensively identify studies on colon cancer patients and avoid missing those that combine both colon and rectal cancer patients. Terms included “cancer of the colon” as well as “colon or colorectal cancer, neoplasm, malignancy, carcinoma, or tumour”. Synonyms for stage III were identified as: Stage III, Dukes C, stage-three, third stage, “locally invasive”, “locally advanced”, or variants of non-metastatic (i.e., without metastasis, not metastasised). Such broad synonyms would capture stages one and two of the disease as well since both could be described as locally invasive or non-metastatic. However, studies on stage one would be unlikely to appear with the combination of the “adjuvant” context, while those on stage II would be excluded by screening.

Data sources

The following seven databases were searched on 5 September 2019:

Medline (Ovid), EMBASE(Ovid), PsychINFO, Scopus, Web of Science, CINAHL, and the Cochrane library. A hand search of the references of included studies were checked for relevance.

Search terms

Search terms were derived from several sources, including two known reviews in the area (Beijers et al., 2014; M. Seretny et al., 2014), and were then refined through an iterative process for each of the databases in consultation with a trained librarian (Burke R, face-to-face appointment) at the London School of Hygiene and Tropical Medicine (LSHTM). The search strategy was validated by checking that references from the two reviews and other known studies were captured. The search terms used for each database are shown in Appendix 2.

Study selection

All abstracts were screened independently by two reviewers (myself and Nasser Fardousi, a colleague at LSHTM). The full texts of potentially eligible studies were evaluated by applying the inclusion and exclusion criteria, defined a priori based on research objectives, as shown in Table 7. Final inclusion of studies into the review was done by agreement of both reviewers. Discrepancies were resolved by discussion.

Duplicate studies were removed using 12 steps on the EndNote reference manager, as advised by a trained librarian at LSHTM (Falconer, 2018).

Table 7 – Inclusion and Exclusion criteria for study selection

Criteria	Included	Excluded
Outcomes	Prevalence of OX-IPN, at least six months after end of treatment among stage III colon cancer patients who receive adjuvant chemotherapy containing oxaliplatin	Studies that investigate the incidence of peripheral neuropathy assessed during treatment only. Qualitative studies
Source type	Research articles	Book chapters Audio/video reports Blog posts Social media/media articles Guidance documents Agency reports Conference abstracts or posters Commentaries/opinions /editorials/protocols
Quantitative Study design	Any	NA
Time-period	> 1994 (10 years before Oxaliplatin was approved for use as therapy in stage III CRC, to incorporate trials that led to this decision)	< 1994
Participants/ population	Studies with patients over 16 years of age Studies of patients with colon cancer Studies that include patients with stage III disease (those with resected primary tumour and spread to lymph nodes only).	Patients under 16 years of age Colon cancer patients of stage I, stage II, or stage IV disease. Colon cancer patients with unresectable or metastasised disease (spread to distant organs) Patients of rectal cancer only, not involving the colon. Patients of other cancer types. Peripheral neuropathy due to treatment other than oxaliplatin.
Language	All for which an English abstract is available.	Sources for which no English abstract is accessible

Data extraction

Data was extracted into Microsoft Excel for the following variables that were identified a priori:

- Source identifiers
    - Lead author
    - Publication year
    - Title
    - Publication Journal
- Study characteristics
    - Date of recruitment
    - Country in which the study took place
    - Setting of data collection
    - Study design
    - Sample size
- Participant characteristics
    - Age
    - Gender
    - Any other socioeconomic indicators such as ethnicity, income or education level, employment, or marital status, etc.
- Outcomes of interest
    - Prevalence of peripheral neuropathy at least six months after end of treatment and for different severity levels
    - Assessment tool used

Quality assessment

Typically, in conducting the critical appraisal of studies included in systematic reviews, the tool used to assess the quality of each individual study will depend on the design of the study (X. Zeng et al., 2015). However, since prevalence data can be obtained from different study designs, and sometimes as a secondary objective in a larger study, I used a critical appraisal tool that specifically assesses the quality of prevalence data, transcending the design of the study from which the data is obtained (Munn et al., 2015; Munn et al., 2014). This tool assesses the quality of prevalence data based on nine criteria (shown in Box 1 below).

For an assessment of adequate sample size (third criterion), Munn et al. (2014) suggested using the following formula (Naing et al., 2006):

$N = Z^2P(1-P) / d^2$

Where:
N= sample size
Z= Z statistic for a level of confidence
P= Expected prevalence or proportion (to be determined from previous literature)
d= precision (if 5%, d= 0.05)

The estimate of prevalence (P) that was used in the formula was obtained by using results from the review conducted by Beijers et al. (2014). Prevalence of grades one and two was reported to range between 12%-46%. The lower limit 0.12 (12%) yielded a sample size of 162, while 0.46 (46%) yielded a sample size of 381. Therefore, a sample ranging between 162 to 381 participants may be adequate to obtain an estimate of prevalence for grades one and two. Estimates for grade-III ranged from 0.7%-12%, and so 0.01 (1%) was used (rounded up from 0.7). The recommended level of precision to be used for a prevalence (P) of less than 0.1 (10%) is half of the prevalence (P) estimate to be used (Naing et al., 2006). Therefore, for 0.01 (1%), a precision level of 0.005 was used in the formula, which resulted in 1,521. However, when a review is carried out in an area of scientific uncertainty, such as this case, it is important to combine all available evidence in an aim to resolve this uncertainty regardless of the sample size, and so it would be inappropriate to exclude smaller studies (Turner et al., 2013).

There is no single recommended approach to determine the overall quality of a study for inclusion or exclusion using this quality assessment tool. Instead, the inclusion or exclusion of a study is based on the reviewer's judgment. For this review, it was predetermined that a study is of adequate quality if it meets five essential criteria: that the sample frame is appropriate to address target population; study participants sampled in an appropriate way; study subjects and setting described in detail; valid methods were used for the identification of the condition; the condition measured in a standard, reliable way for all participants. The remaining four criteria regarding sample size (number 3), data and statistical analysis (numbers 5 and 8), and response rate (number 9) were not considered essential criteria. This is because the synthesis in this review was not based on the data or statistical analysis conducted in the study, rather, prevalence was estimated from each study using the number of participants that constituted the numerator and denominator. Although management of low response rate is an important quality criterion, under or over estimation of prevalence due to low response rate can be discussed as a limitation and was not considered a basis for

exclusion. Finally, as discussed above, studies were included regardless of sample size.

Box 2 – Critical appraisal criteria for the assessment of the quality of prevalence data

1. Was the sample frame appropriate to address the target population?
2. Were study participants sampled in an appropriate way?
3. Was the sample size adequate?
4. Were the study subjects and the setting described in detail?
5. Was the data analysis conducted with sufficient coverage of the identified sample?
6. Were valid methods used for the identification of the condition?
7. Was the condition measured in a standard, reliable way for all participants?
8. Was there appropriate statistical analysis?
9. Was the response rate adequate, and if not, was the low response rate managed appropriately?

Analysis and reporting of results

Tables were used to present a summary of included articles by the elements of source, study, and participant characteristics defined above.

A meta-analysis of the prevalence of peripheral neuropathy (the outcome of interest) was possible for studies that used the Common Terminology Criteria for Adverse Events of the National Cancer Institute (henceforth CTCAE). This was done for each time point that assessment took place, and for each level of severity (*described in more detail in the Results section*). Forest plots were used to display how prevalence estimates varied between studies and over time.

A meta-analysis of prevalence was also possible for studies that used the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Chemotherapy-Induced Peripheral Neuropathy 20 module (henceforth CIPN-20). This was also done for each time point that assessment took place, level of severity, and symptom assessed by the tool (*described in more detail in the Results section*). The results of this analysis were summarised into tables.

Several of the studies included for meta-analysis used small sample sizes and reported extremely small (skewed) proportions of prevalence. When this is the case, it is recommended that transformation to a normal distribution is applied using the double arcsine transformation method (Barendregt et al., 2013). A random effects model using

the Restricted maximum likelihood method (REML) was used to calculate the weighted summary proportion with its 95% confidence interval, as well as the proportions and the corresponding 95% confidence intervals of the included studies. Heterogeneity was assessed using the I^2 test.

For the remainder of the studies that used different assessment tools or used different ways of reporting their findings, it was not possible to combine the findings quantitatively. Instead, a narrative synthesis was conducted, whereby the findings of studies were summarised and explained using text. Authors were contacted for more information twice where a study met the inclusion criteria but data on prevalence of peripheral neuropathy was not clear or not reported.

Results

The search yielded 3072 studies and 26 met the inclusion criteria after title, abstract and full text screening. However, two of the studies used the same database, and so only the one with more detailed analysis was used, thus leaving a total of 25 studies for inclusion.

Deviation from pre-specified inclusion and exclusion criteria: Stage of disease and type of cancer

Of 25 studies, only one study recruited participants with stage III disease exclusively. The remaining studies included a mix of patients diagnosed with stages II, III, and IV, only three of which reported on each stage separately allowing extraction of the data relevant to stage III. Therefore, the total number of studies from which it was possible to obtain estimates for stage III specifically was four. Due to this small number, a decision was made to include mixed-stage studies if stage III patients constituted more than 50% of the sample. Three studies did not meet this condition and were excluded from the analysis (Soveri et al., 2019; Tofthagen et al., 2011; Ventzel et al., 2016).

Of the remaining 22 studies, nine recruited participants with colon cancer, while the remaining 13 studies included colorectal cancer patients. Similar to stage, a decision was made to include studies of colorectal cancer patients if participants with colon cancer made up more than 50% of the sample. All but four studies met this condition. In the nine included studies that met the criteria of at least 50% of colon cancer patients, the authors further specified that those who received other types of chemotherapy or pre-operative chemotherapy were excluded. This provided confidence that colorectal and colon cancer patients in these studies did not receive different treatments and thus, received similar treatment despite having different tumour types. A flow diagram of study selection is shown in Figure 6.

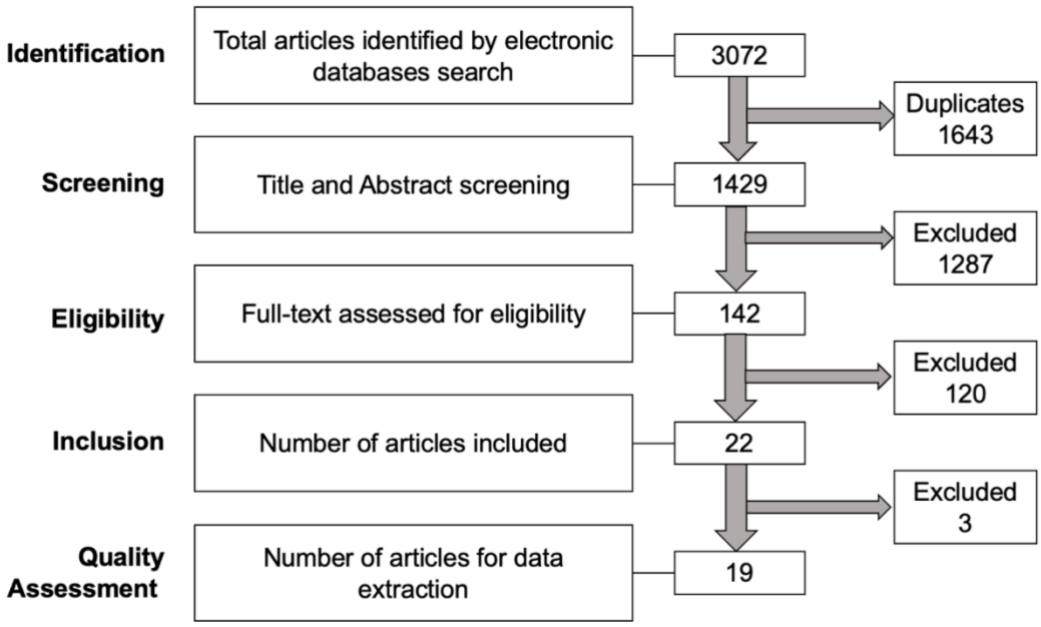


Figure 6 – Flow-diagram of the stages of study selection

Quality Assessment

Fifteen studies did not meet one of the essential criteria due to the mixed-stage sample, which meant that sample frame was not appropriate to address the target population. However, as discussed above, a decision was made to include those studies if most of the sample was of the target population.

Of 22 studies that met the inclusion criteria, three studies did not meet one or more of the remaining essential criteria requirements and were subsequently excluded from the analysis. Data was extracted from 19 studies (Figure 6). In one study, there was no adequate description of the setting; it was not possible to determine the time point at which peripheral neuropathy assessment took place since randomisation or end of treatment (Allegra et al., 2009; Jeon et al., 2011). For the third, there was no adequate description of study participants, and several assessment tools were described in the methods but there was no explanation on how the findings were summarised into a score or how to interpret the results, therefore a valid method was not used for the identification of the condition (Kokotis et al., 2016). Authors of these studies did not respond to requests for more information.

Overview of assessment tools used in included studies

Eleven studies assessed PN using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) scale, and seven used the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-

CIPN twenty-item scale (CIPN-20) (Table 8). As discussed in the *Methods* section, pooling to derive a summary estimate of prevalence was possible for studies that used each of these tools and are reported separately in the following sections.

Three studies used the Functional Assessment of Cancer Therapy/Gynaecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx) questionnaire, and one used the Neurologic Symptom Score (NSS) (Table 8). It was not possible to derive a summary estimate from these, however, and results are reported in the *Narrative Synthesis* section.

Further description of each of these tools is provided in the corresponding sections.

Table 8 – Tools used in included studies to assess peripheral neuropathy

Author	CTCAE	CIPN20	FACT GOG-NTx	Other
(André et al., 2004)	✓			
(Land et al., 2007)	✓		✓	
(Lee et al., 2009)	✓			
(Storey et al., 2010)	✓			
(Park et al., 2011)	✓	x		NSS
(Kidwell et al., 2012)			✓	
(Vatandoust et al., 2014)	✓			
(Park et al., 2015)	✓			
(Padman et al., 2015)	✓	x		
(Pachman et al., 2015)		✓		
(Mols et al., 2015)		✓		
(Dault et al., 2016)	✓			
(Stefansson & Nygren, 2016)		✓		
(Zimmerman et al., 2016)		✓		
(Tanishima et al., 2017)	✓			
(van Erning et al., 2015)		✓		
(Kim et al., 2018)	✓	✓		
(Iveson et al., 2018)			✓	
(Wesselink et al., 2018)		✓		

x – Tool was used to assess peripheral neuropathy, but results were not reported in a form that allowed extraction

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) assessment tool

Eleven of the included studies carried out peripheral neuropathy assessment using the CTCAE (Table 8). The CTCAE is a clinical assessment scale that consists of two subscales to assess sensory and motor symptoms. To date, there are five versions of the CTCAE (version 1 to 4.03, Appendix 1). The versions are similar in their classification of peripheral neuropathy, with only one difference. The first classified the condition into three severity grades, while in subsequent versions a fourth category was added. Grade-I is defined as tingling and prickling sensation and/or loss of deep tendon reflexes, and grade-IV constitutes disabling or permanent sensory loss that interferes with function, and/or paralysis. Severity grades for each of the versions of this tool are summarised in Appendix 1.

Study characteristics

The year of publication of the included studies ranged from 2004 to 2018, and the recruitment period ranged from 1998 to 2014 (Table 9). Participants were recruited from multiple centres in six studies, and from a single centre in five. The studies were conducted in a wide range of countries. Three were from Australia, one trial recruited participants from across the United States, and one was conducted in each of Canada, Japan, Korea, and Scotland. One multi-centre trial recruited participants from a wide range of countries, mainly in Europe, while another multi-centre trial recruited from five Asian countries: China, Hong Kong, Korea, Taiwan, Thailand. Finally, one used data from the Adjuvant Colon Cancer with Eloxatin (ACCElox) registry (Table 9). This registry was established to assess the management of patients with early-stage colon cancer treated with 5-FU and oxaliplatin (Eloxatin) in the adjuvant setting from countries that did not participate in the MOSAIC or the NSABP-C-07 clinical trials. Those were 19 countries across Asia-Pacific, Latin America, the Middle East, and Africa but were not explicitly listed.

Three studies were interventional studies with prospective follow-up (Table 9). Two were randomised controlled trials, while the third was a non-randomised single arm study. The primary objective in those studies was to determine the effect of oxaliplatin on disease-free survival. Assessment of peripheral neuropathy was undertaken as a secondary objective. The remaining eight studies were observational; four examined medical records of patients who completed treatment with oxaliplatin retrospectively, while the other four conducted prospective follow-up. The assessment of peripheral neuropathy was the primary objective in these studies.

The number of participants recruited at the start of these studies ranged from 24 to 1548 participants (Table 9) However, the sample sizes from which an estimate of prevalence was derived varied due to varying number of patients that were available for assessment at later time points *(sample sizes for each estimate of prevalence at different time points are noted in the forest plots).*

Five of the studies excluded patients with pre-existing peripheral neuropathy, while the other six did not, although one excluded patients with other pre-existing conditions that are risk factors for peripheral neuropathy (Table 9).

Table 9 – Characteristics of studies that used the CTCAE tool to assess peripheral neuropathy

Author, Publication year	Study design	Exclusion of patients with peripheral neuropathy (PN)	Recruitment period	Starting sample size	Setting	Country
Andre, 2004	Interventional RCT with prospective follow-up	No; but exclusion of patients with possible risk factors for PN: prior chemotherapy, immunotherapy, or radiotherapy.	1998-2001	1108	Multi-centre; 146 participating centres	19 countries: Australia, New South Wales; Austria; Belgium; Denmark; France; Germany; Greece; Hungary; Israel; Italy; Netherlands; Norway; Poland; Portugal; Singapore; Spain; Sweden; Switzerland; United Kingdom
Land, 2007	Interventional RCT with prospective follow-up	Yes, patients with CTCAE grade-II or higher	2000-2001	1068	Multi-centre; explicit number not reported	United States of America
Lee, 2009	Interventional non-randomized, single arm trial with prospective follow-up	Yes, patients with CTCAE grade-I or higher	2004-2006	159	Multi-centre; explicit number not reported	Five Asian countries: China, Hong Kong, Korea, Taiwan, Thailand
Storey, 2010	Retrospective review of medical records	No	2006-2007	87	Multi-centre; Patients under the care of the ECC, sole provider of specialist cancer services to 1.5 million people	Southeast Scotland, UK

Park, 2011	Prospective observational study	Yes, patients who received other neurotoxic chemotherapy, or had pre-existing neuropathic symptoms or baseline abnormalities in nerve function.	2002-2008	24	Single Centre; Department of Medical Oncology, Prince of Wales Hospital	Australia
Vatandoust, 2014	Retrospective questionnaires sent to patients who completed treatment with oxaliplatin	No	Not reported	27	Two centres; Queen Elizabeth Hospital, Lyell McEwin Hospital	Australia
Padman, 2015	Retrospective review of medical records	No	Not reported	25	Single centre; Department of Medical Oncology, Flinders Medical Centre	Australia
Park, 2015	Prospective observational study	Yes, patients with sensory neuropathy	2006-2008	1548	Multi-centre; ACCElox registry	19 countries from Asia-Pacific Latin America the Middle East and Africa
Dault, 2016	Prospective observational study	No	2012-2013	29	Single Centre; Centre hospitalier universitaire de Sherbrooke	Canada
Tanishima, 2017	Retrospective review of medical records	No	2010-2014	47	Single centre; National Hospital Organization Osaka Minami Medical Center	Japan

Kim, 2018	Prospective observational study	Yes, patients with a history of peripheral neuropathy, alcohol abuse, prior exposure to neurotoxic agents, or degenerative neurological disorders	2009-2012	69	Single centre; National Cancer Centre	Korea
*Reported on stage III patients separately and only this information was extracted						

Patient characteristics

All included studies reported on sex and age. None reported on any other socioeconomic characteristics, except for two that reported on race. One consisted of all White participants, while the other had participants of mixed Asian ethnicities.

The median age was reported in most studies, ranging from 55 to 68. Female participation was generally lower than male participation, with only two studies having an approximately equal distribution (Table 10).

Three studies reported results by stage, allowing extraction of stage III data (Storey, 2010; Dault, 2016; Tanishima, 2017). Of the remaining, seven studies included participants with stage II disease, while two studies included participants with stage IV disease. The proportion of patients with stage III disease made up most of the participants in the mixed studies, ranging from 58 to 77% (Table 10).

Table 10 – Characteristics of patients in studies that used the CTCAE assessment tool

Author, Publication year	Women	Median age	Mean age	Age range	Race	Stage II	Stage III	Stage IV
Andre, 2004	44%	61	-	19-75	-	40%	60%	-
Land, 2007	45%	59	-	69% < 65 years	-	29%	71%	-
Lee, 2009	45%	55	55	20–74	Chinese 68% Korean 24% Thai 8% Other 0.6%	28%	72%	-
Storey, 2010	39%	61	-	25-79	-	-	100%	-
Park, 2011	38%	62	60	41–78	-	-	58%	42%
Vatandoust, 2014	33%	66	-	48–80	-	-	70%	30%
Padman, 2015	23%	68	-	58–79	-	-	68%	32%
Park, 2015	43%	58.4	57	18–89	-	27%	73%	-
Dault, 2016	42%	66	-	43–84	White 100%	-	100%	-
Tanishima, 2017	51%	-	65	-	-	-	100%	-
Kim, 2018	49%	-	53	-	-	23%	77%	-

Time of peripheral neuropathy assessment

Data from the included studies were synthesised according to three time points, depending on follow-up since completion of therapy with oxaliplatin: at six months, twelve months, or 'long-term' (Table 11). The long-term time point includes studies of varying follow-up durations, so it was not possible to group these based on a specific time-point.

Table 11 – Summary of the time points at which assessment of peripheral neuropathy took place for each included study

Time of assessment	Author, Publication year
Six months (six studies)	Andre, 2004; Land, 2007; Lee, 2009; Storey, 2010; Park, 2015; Kim, 2018
Twelve months (seven studies)	Andre, 2004; Land, 2007; Lee, 2009; Storey, 2010; Park, 2015; Kim, 2018; Tanishima, 2017
Long term (six studies)	
18 months	Andre, 2004
27 months (Approx. 2 years)	Land, 2007
10 – 67 months (Median 25 months; approx. 2 years)	Park, 2011
20 to 11six months (Median 37 months; approx. 3 years)	Vatandoust, 2014
18 months	Padman, 2015
16–28 months (Median 22 months; approx. 2 years)	Dault, 2016

Six studies follow-up patients to six and twelve months after completion of therapy (André, 2004; Land, 2007; Lee, 2009; Storey, 2010; Park, 2015; Kim, 2018), with an additional study that undertook only twelve-month follow-up (Tanishima, 2017), making up a total of seven studies with twelve-month follow-up (Table 11).

At long-term follow-up, Andre et al. (2004) and Padman et al. (2015) followed-up participants to 18 months after completion of therapy, while the remaining three studies followed-up participants approximately one to nine years (Table 11).

Grades of severity

Incomplete reporting was considerable among the included studies. Ideally, each included study should contribute information on four severity grades, for each of the time points at which assessment took place. However, this was not the case. For example, at six months follow-up, we would ideally know the number of patients experiencing each of grades one, two, three, and four from all studies that assessed

peripheral neuropathy at that time point. However, only three studies reported on grades one and two, and five studies reported on grade-III. The number of studies that contributed to the summary estimate of each grade and at each time point is shown in Table 12. The data extracted from all studies for each grade and at each time point is shown in Appendix 3.

The total number of people who experienced peripheral neuropathy symptoms (of all grades), was obtained either from direct reporting by the authors, or from calculating the sum of the number of patients for each of the severity grades.

Grade-IV was reported by ten of thirteen studies. Of a total sample of 4891 patients from these studies, 19 people had grade-IV during therapy (0.40%), and there was no report of grade-IV severity at any of the later follow-up times (six months, twelve months, or long-term). Therefore, grade-IV is not featured in any further reporting in this study.

Table 12 – A summary of the data provided by studies that assessed peripheral neuropathy using the CTCAE for each grade of severity and at each time point

	Six months				**Twelve months**				**Long-term**			
	Any	**I**	**II**	**III**	**Any**	**I**	**II**	**III**	**Any**	**I**	**II**	**III**
Andre, 2004	*	*	*	*	*	*	*	*	*	*	*	*
Land, 2007	*				*	*	*	*				
Lee, 2009				*				*				
Storey, 2010	*	*	*	*	*	*	*	*				
Park, 2011									*	*	*	*
Vatandoust, 2014									*	*	*	*
Park, 2015	*			*	*			*				
Padman, 2015									*	*	*	*
Dault, 2016									*	*	*	*
Tanishima, 2017					*							
Kim, 2018	*	*	*	*	*	*	*	*				
Number of studies contributing data	5	3	3	5	6	4	4	6	5	5	5	5

Heterogeneity of results

There was a considerable amount of heterogeneity between individual studies. However, due to the large number of estimates (three grades of severity and any grade of severity at three time points), it was impractical to report values from each individual study. Therefore, estimates were pooled despite the heterogeneity for the purpose of providing a manageable summary of the results, and therefore, results should be

interpreted with caution. The pooled estimates, as well as prevalence estimates from each of the individual studies are shown in the forest plots. The small number of studies precluded a formal moderator analysis to determine the source of heterogeneity, but this was explored descriptively.

Peripheral neuropathy of "any grade" of severity

Six studies followed-up participants to six months and seven to twelve months. However, it was not possible to extract data for peripheral neuropathy of any grade from Lee et al. (2009) as they only reported on grade-III. For long-term follow-up, it was possible to estimate the proportion of people experiencing peripheral neuropathy at all levels of severity from all six studies in this group (Table 12).

The proportion of people with peripheral neuropathy (of any grade) was 0.57 (CI: 0.41, 0.72) at six months and 0.33 (95%CI: 0.28, 0.38) at twelve months (Figure 7, Figure 8). For long-term follow-up, the point estimate is higher at 0.56, however, the confidence interval around this estimate overlaps with the estimates of the previous time points (95%CI: 0.27, 0.83) (Figure 9).

There was considerable heterogeneity in the prevalence of peripheral neuropathy among the studies included at six months. Two large studies reported a similarly lower prevalence relative to the rest: Park et al. (2015) with 0.39 (95%CI: 0.37 to 0.41; n=1548) and Andre et al. (2004) with 0.41 (0.38 to 0.44; n=1058), compared to Kim et al. (2018) with 0.81 (95%CI: 0.68 to 0.93; n=36), and Land et al. (2007) with 0.70 (95%CI: 0.67 to 0.73; n=1235). The study by Land et al. (2007) is similar in study design and sample size to the two studies that reported a lower prevalence; therefore, it is unlikely that the heterogeneity in these findings is moderated by these factors. It is possible that the administration of oxaliplatin differed between the studies resulting in the differences in estimates, however, the reporting on this varied and therefore it is not possible to comment on this.

By contrast, the heterogeneity observed among the studies included at twelve months could be due to sample size. Three studies with a large sample size reported a similar prevalence ranging from 0.25-0.29, with mostly overlapping confidence intervals. Another three studies that reported higher prevalence (95%CI: 0.35, 0.47 and 0.64) were of considerably smaller sample size and lacked precision with wider confidence intervals.

At the long-term follow-up, the most precise estimates were from Andre et al. (2004) who reported a prevalence of 0.24 (95%CI: 0.21-0.26) from a sample of 967. The

remaining studies had smaller sample sizes ranging from 10 to 27, and prevalence from these studies was higher, ranging from 0.50 to 0.79, with wide and overlapping confidence intervals, although none overlapped with the largest study.

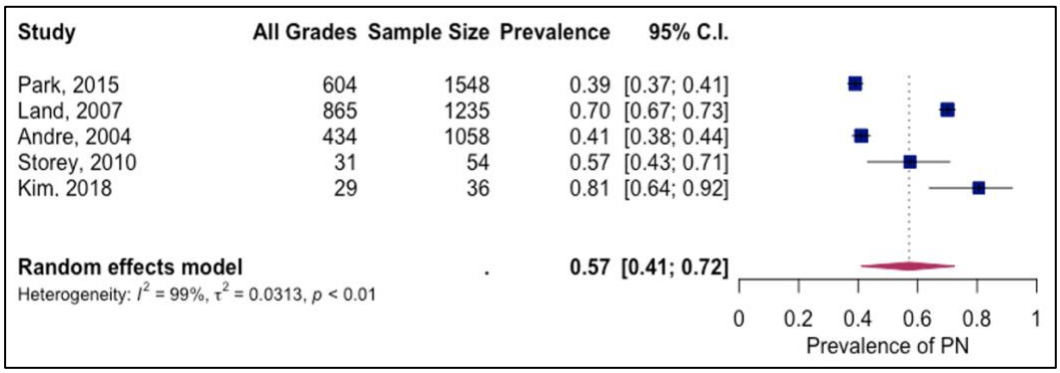


Figure 7 – Prevalence of any grade peripheral neuropathy at six-month follow-up

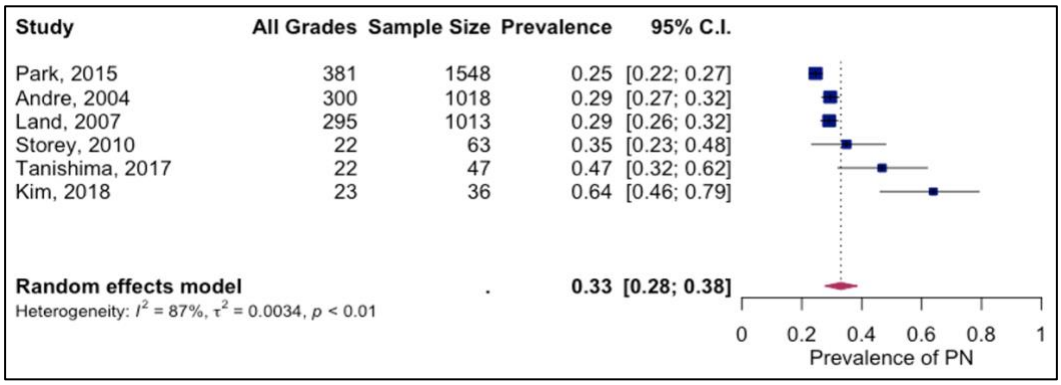


Figure 8 – Prevalence of any grade peripheral neuropathy at twelve-month follow-up

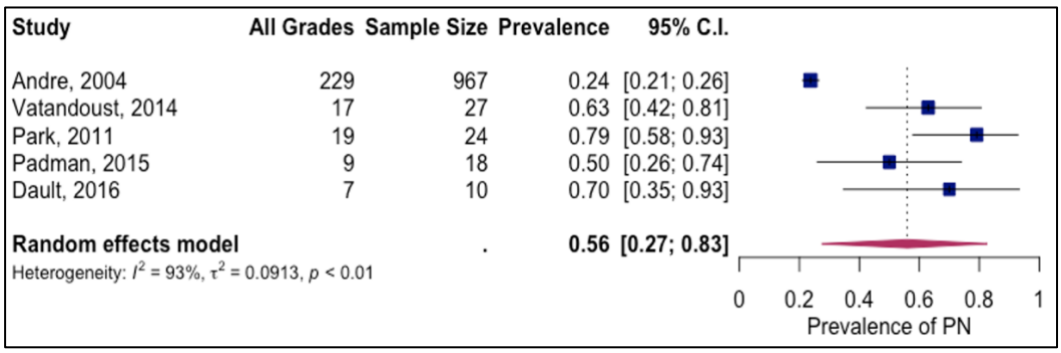


Figure 9 – Prevalence of any grade peripheral neuropathy at long-term follow-up

Peripheral neuropathy of Grade-I

The proportion of people who had peripheral neuropathy of grade-I was synthesised from three of seven studies at six-month, four of eight for twelve-month, and all six studies at long-term follow-up (Table 12).

The proportion of people with grade-I peripheral neuropathy was 0.38 (95%CI: 0.26, 0.51) at six months, 0.21 (95%CI: 0.16, 0.30) at twelve months and 0.24 (95%CI: 0.16, 0.33) at long-term follow-up (Figure 10, Figure 11, Figure 12).

The heterogeneity in the results was highest at twelve months. The proportion of patients with grade-I peripheral neuropathy at twelve months was identical in two of the studies at 0.24 (95%CI: 0.21, 0.27), both of which had over a thousand patients designed as RCTs with prospective follow-up. The two other studies were of cohort design and considerably smaller sample size. The proportion of grade-I peripheral neuropathy was 0.05 (95%CI: 0.01, 0.12) of 63 patients by Storey et al. (2010), who conducted a retrospective review of medical records, while the prospective follow-up of 36 patients by Kim et al. (2018) reported a prevalence of 0.50 (95%CI: 0.34, 0.66).

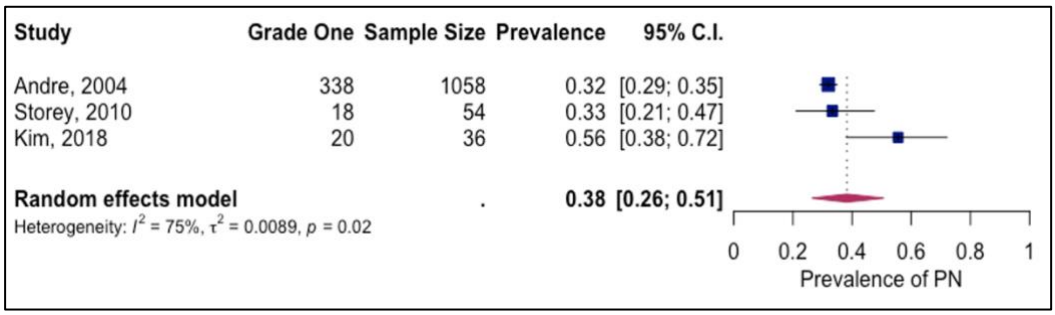


Figure 10 – Prevalence of grade-I peripheral neuropathy at six-month follow-up

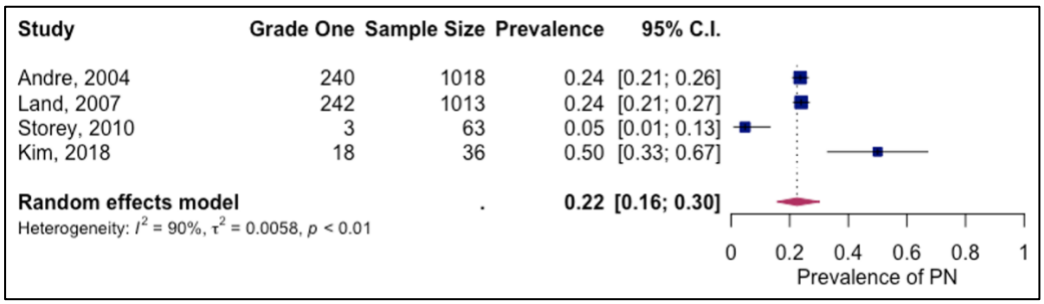


Figure 11 – Prevalence of grade-I peripheral neuropathy at twelve-month follow up

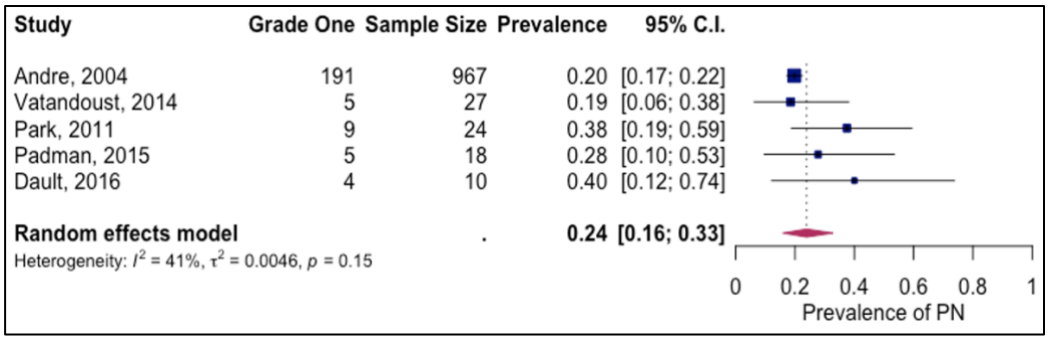


Figure 12 – Prevalence of grade-I peripheral neuropathy at long-term follow up

Peripheral neuropathy of Grade-II

The proportion of people who had peripheral neuropathy of grade-II was synthesised from three of six studies at six months, four of seven at twelve months, and all six of the long-term group (Table 12).

The proportion of people with grade-II peripheral neuropathy was 0.08 (95%CI: 0.06, 0.10) at six months and 0.04 (95%CI: 0.03, 0.05) at twelve months (Figure 13, Figure 14). At long-term, the summary estimate was 0.17 (95%CI: 0.04, 0.35), but the confidence interval around the estimate is very wide and overlaps with previous time points, indicating a lack of evidence of difference between the estimate at long-term and the previous time points (Figure 15).

Studies included at six and twelve months were mainly in agreement with similar point estimates of prevalence and no evidence of heterogeneity, although the two smaller studies lacked precision with wide confidence intervals.

There was considerable heterogeneity among studies in the long-term group. The largest study reported a prevalence of 0.03 with high precision (95%CI: 0.02, 0.05). Although Padman et al. (2015) reported a similar estimate (0.06; 95%CI: 0.00-0.27), it had a wide confidence interval that overlapped with the remaining three studies in this group who reported higher estimates ranging from 0.20 to 0.33, with wide and overlapping confidence intervals.

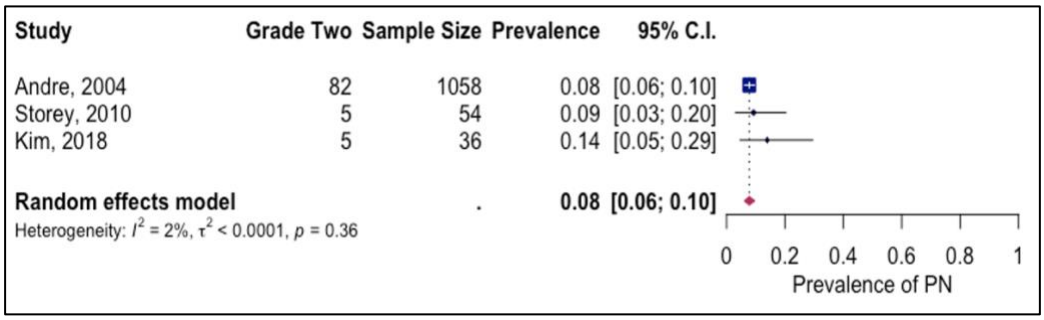


Figure 13 – Prevalence of grade-II peripheral neuropathy at six-month follow-up

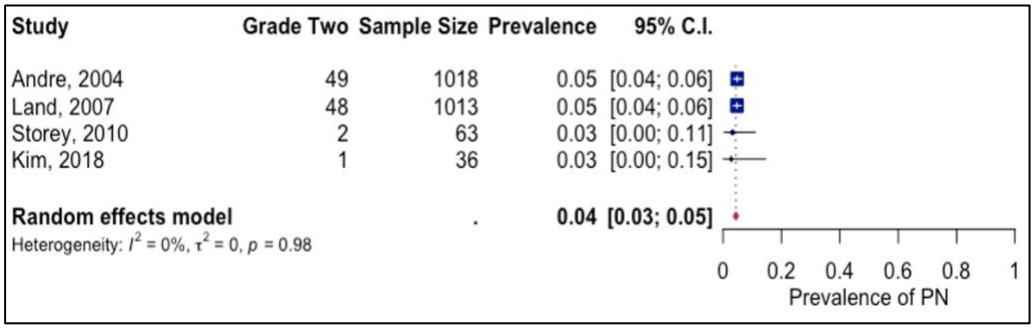


Figure 14 – Prevalence of grade-II peripheral neuropathy at twelve-month follow-up

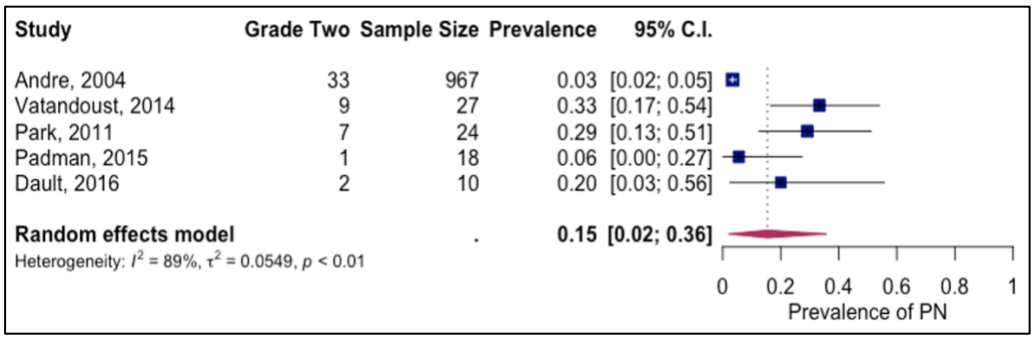


Figure 15 – Prevalence of grade-II peripheral neuropathy at long-term follow-up

Peripheral neuropathy of Grade-III

The proportion of people who had peripheral neuropathy of grade-III was synthesised from five of six studies at six-month, six of eight at twelve-month, and all six studies at long-term follow-up (Table 12).

Park et al. (2015) reported the total number of people who had grade-III or higher at six and twelve months, without making a distinction between grades 3 and 4. However, based on findings from other studies, an assumption was made that the number of people experiencing grade-IV severity was either zero or too small to result in a significant difference. Thus, the number they reported was included in the synthesis for grade-III.

The proportion of people with grade-III was 0.05 (95%CI: 0.01, 0.11) at six months, 0.02 (95%CI: 0.00, 0.04) at twelve months (Figure 16, Figure 17). The estimate at long-term was 0.07 (95%CI: 0.01, 0.18) but with wide confidence intervals that overlap with the previous time points (Figure 18).

There was high heterogeneity in the studies at all time points. The two largest studies included in the synthesis at six months showed different findings with confidence intervals around the estimates that did not overlap (Figure 16). A prevalence of 0.08 (95%CI: 0.06, 0.09) was estimated from Park et al. (2015), while an estimate of 0.01 (95%CI: 0.01, 0.02) was obtained from Andre et al (2004). An estimate closer to Andre et al. was obtained from the study by Lee et al. (2009), which had a relatively smaller sample size of 159 patients (0.01; 95%CI: 0.00, 0.04). The other two small studies (n= 54 and n=36) reported higher estimates of 0.15 and 0.11, respectively, but lacked precision with confidence intervals that overlapped with the other studies.

At twelve months, the two largest studies (Andre et al., 2004 and Land et al., 2007) showed similar findings, with overlapping confidence intervals. However, the two smaller studies (Storey et al., 2010 and Kim et al., 2018) showed higher estimates, with wide confidence intervals that did not overlap with the larger studies (Figure 17).

At long-term follow-up, estimates varied from 0.01 with high precision due to a large sample size (Andre et al., 2004), to 0.17 with wide confidence intervals (Padman et al, 2015). All confidence intervals in this group overlapped with each other, except for the study by Andre et al. (2004) (Figure 18).

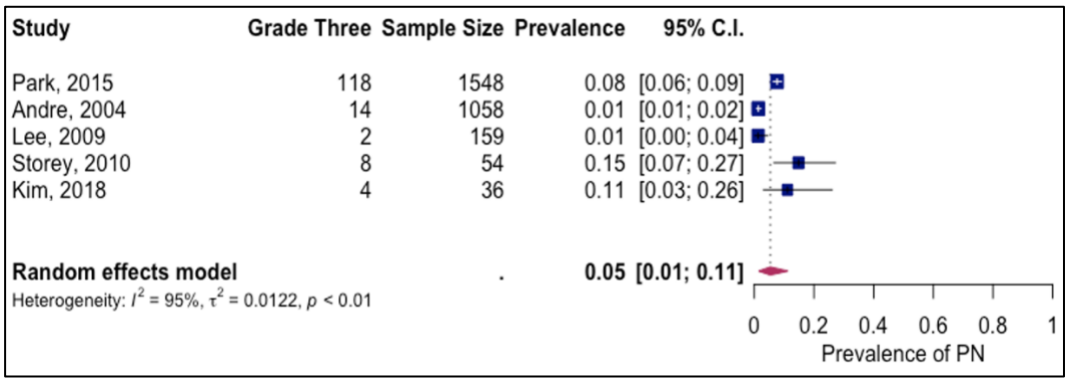


Figure 16 – Prevalence of grade-III peripheral neuropathy at six-month follow-up

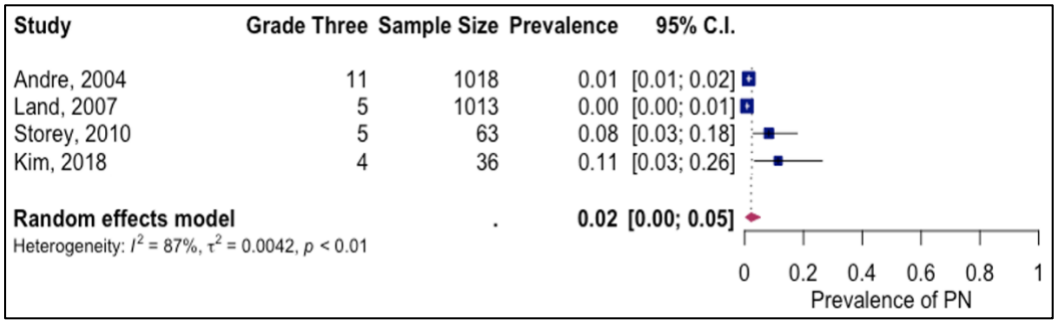


Figure 17 – Prevalence of grade-III peripheral neuropathy at twelve-month follow-up

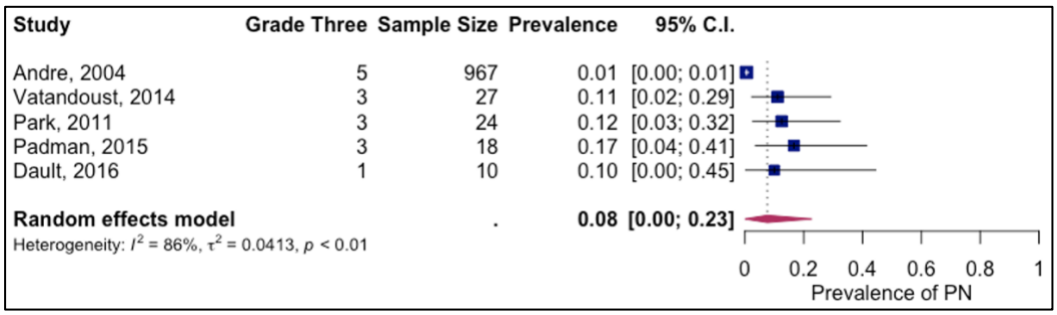


Figure 18 – Prevalence of grade-III peripheral neuropathy at long-term follow-up

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Chemotherapy-Induced Peripheral Neuropathy 20 module (CIPN-20)

The CIPN20 questionnaire includes 20 questions on nine sensory, eight motor, and three autonomic symptoms. The answer for each question can vary on a scale of “not at all”, “a little bit”, “quite a bit”, or “very much” (Appendix 1).

Evidence suggests that hearing loss (item 9), as well as the autonomic scale items assessing orthostatic hypotension (item 18), blurred vision (item 19), and erectile dysfunction (item 20) are less relevant to CIPN, and a reduced version with 16 items was proposed as a more clinically relevant assessment tool (Lavoie Smith et al., 2013). Therefore, the focus in this analysis was on 16 clinically relevant questions.

Study characteristics

Nine studies used the CIPN-20 in the assessment of peripheral neuropathy; however, data was extracted from seven. Park et al. (2011) and Padman et al. (2015) used CIPN-20 to assess the significance of patients’ symptoms but did not report on the number of people that experienced each of the symptoms and so it was not possible to extract data from these articles for this analysis.

The year of publication ranged from 2015 to 2019. Recruitment period ranged from 2007 to 2015 in The Netherlands, USA, Sweden, and Korea. Two studies recruited patients from a single centre, two recruited from multiple centres and the remaining three studies used cancer patient registries to identify their sample. Sample sizes ranged from 12 to 353. Four studies followed-up oxaliplatin-receiving patients prospectively while three were of cross-sectional design. A summary of the characteristics of the included studies is shown in Table 13. Zimmerman et al. (2016) conducted a trial that tested the addition of Venlafaxine to combination therapy with oxaliplatin for the prevention of neuropathy, compared to placebo. The trial found no difference between the two arms; thus, the full sample was included in this analysis.

Table 13 – Characteristics of the studies that assessed peripheral neuropathy using the CIPN-20 tool.

Author, Publication year	Study design	Starting sample size	Recruitment	Setting	Country
Beijers, 2015	Cross-sectional	200	2007-2009	PROFILES registry (Patient Reported Outcomes Following Initial Treatment and Long-Term Evaluation of Survivorship), linked to the Netherlands Cancer Registry	The Netherlands
Pachman, 2015	Prospective follow-up	353	2010-2012	Patient data from North Central Cancer Treatment Group trial N08CB	USA
Stefansson, 2016	Cross-sectional	65	2004-2011	Single Centre	Sweden
Zimmerman, 2016	Prospective follow-up	14	2012-2014	multi-centre	USA
vanErning, 2017	Cross sectional	12	2013-2014	PROFILES registry	The Netherlands
Kim, 2018	Prospective follow-up	36	2009-2012	Single centre	Korea
Wesselink, 2018	Prospective follow-up	165	2012-2015	Multi-centre	The Netherlands

Patient characteristics

The mean age of patients ranged from 53 to 67 years. In one study, only those over 70 years of age were included. There was an approximately equal distribution of males and females in five studies, while in another two females made up 36 and 42% of the sample (Table 14).

Patients with stage III disease were exclusively recruited in one study only, while for the remainder there was a mix of stage II and IV. However, patients with stage III disease made up most of the participants in the mixed studies, ranging from 51 to 84% (Table 14).

Table 14 – Characteristics of patients in studies that used the CIPN-20 assessment tool

Author, Publication year	Women	Mean age	Age range	Stage II	Stage III	Stage IV
Beijers, 2013	43%	66	-	10%	84%	2%
Pachman, 2015	52%	56	-	19%	75%	6%
Stefansson, 2016	51%	64	41-77	25%	70%	4%
Zimmerman, 2016	48%	58	-	-	62%	38%
vanErning, 2017	50%	-	All patients were > 70	-	100%	-
Kim, 2018	49%	53	-	23%	77%	0
Wesselink, 2018	36%	64	60-68	8%	74%	10%

Time of peripheral neuropathy assessment

Data from the included studies were categorised into three time points: assessment that took place at six-month, twelve-month, or long-term follow-up. Studies that made up the long-term time point differed in the length of time since completion of treatment, which ranged from one to nine years (Table 15).

Table 15 – Time of peripheral neuropathy assessment for included studies that used the EORTC QLQ-CIPN20

Time of assessment	Author, Publication year
Six months (four studies)	Pachman, 2015; Zimmerman, 2016; Wesselink, 2018; Kim, 2018
Twelve months (four studies)	Pachman, 2015; Zimmerman, 2016; Kim, 2018; vanErning, 2017
Long-term	
1 to 5 years (median 4.2 years)	Beijers, 2015
18 months	Pachman, 2015
18 months	Zimmerman, 2016
2 – 8 years	Stefansson, 2016

Heterogeneity of results

Assessment of peripheral neuropathy at different time points (six-month, twelve-month, and long-term follow-up) and two categories (any level of severity or severe) yielded five time point and severity combinations to report on: any and severe symptoms at six-month follow-up; any and severe symptoms at twelve-month follow-up; and severe symptoms at long-term follow-up. For each of these groups, each individual study reported on 16 symptoms. Therefore, although there was a considerable amount of

heterogeneity between individual studies, it was impractical to report values from individual studies, for all symptoms, at each time point, and for two categories. Instead, like the approach taken for the CTCAE, estimates were pooled despite the heterogeneity for the purpose of providing a manageable summary of the results. For some symptoms, although the test for heterogeneity yielded small values, the 95% confidence intervals around the I^2 estimate were still wide, indicating uncertainty.

Ideally, each included study should contribute information on the proportion of patients that experienced symptoms on three severity levels (a little bit, quite a bit, and very much), for each of the time points at which assessment took place. However, this was not the case. Like the CTCAE tool, incomplete reporting limited the number of studies that could be synthesised to obtain a summary estimate of prevalence for each of the severity levels at each time point (Table 16).

Four studies assessed peripheral neuropathy using CIPN-20 at six months. Three of these provided a breakdown of results by mild (“a little bit”) and severe (“quite a bit” and “very much”), which allowed the estimation of the prevalence of more severe experiences (Table 16).

Similarly, four studies assessed peripheral neuropathy at twelve months, and a breakdown of results by severity was provided by two (Table 16).

Finally, five studies assessed peripheral neuropathy at long-term. However, all reported the number of people experiencing severe symptoms and did not report on “a little bit”. Therefore, it was only possible to determine the total number who experienced severe symptoms at long-term follow-up, and not the total number of people with symptoms (Table 16).

Table 16 – A summary of the data provided by studies that assessed peripheral neuropathy using CIPN-20 for each level of severity and at each time point

	Six months		Twelve months		18 months		Long term	
	Any	**Severe**	**Any**	**Severe**	**Any**	**Severe**	**Any**	**Severe**
Mols, 2015								*
Pachman, 2015	*		*		*			
Stefansson, 2016								X
Zimmerman, 2016	*	*	*	*	*	*		
vanErning, 2017			*					
Kim, 2018	*	*	*	*				
Wesselink, 2018	*	*						
Soveri, 2019								*
Number of studies contributing data	4	3	4	2	2	1	0	3

x – Stefansson et al. contributed data for 4 questions, the estimates for the remaining questions were obtained from 2 studies

Several studies reported a breakdown of the CIPN20 results by severity level, allowing for an estimation of prevalence of more severe symptoms, defined as those experienced by patients “quite a bit” or “very much”. Three studies reported on level of severity at six months, two at twelve months, and five at the long-term time point (Table 16). One of the five studies in the long-term category, however, reported on only four of the CIPN20 items, not all. Therefore, the estimates of the remaining 12 questions were pooled from four studies.

Peripheral neuropathy symptoms at six and twelve months

Six months

At six months of follow-up, estimates of prevalence of peripheral neuropathy symptoms of any level of severity were derived from four studies, while estimates of prevalence of severe symptoms were derived from three.

Prevalence of peripheral neuropathy of any level in the upper limbs ranged from 0.11 (0.07-0.15) for the inability to distinguish between hot and cold to 0.48 (0.40-0.56) for numbness in the fingers or hands, although tingling of fingers and hands was at a similarly high prevalence (0.46; CI: 0.26-0.67) (Table 17). A similar pattern is seen for the lower limbs, where numbness (0.52; CI: 0.35-0.68) and tingling (0.41; CI: 0.17-

0.67) were the most common symptoms experienced in the toes or feet, and difficulty using the pedals (driving) was least common 0.07 (0.02, 0.14) (Table 17).

Several other symptoms had relatively high point estimates, and confidence intervals that overlapped with those of tingling and numbness in both the upper and lower limbs. Namely for the upper limbs, those were difficulty manipulating small objects (0.29; 95% CI: 0.10-0.53), weakness in the hands (0.29; 95% CI: 0.15-0.45), and difficulty writing (0.21; 95% CI: 0.14-0.30). For the lower limbs, symptoms such as weakness in the legs (0.23; 95% CI: 0.14-0.34), difficulty feeling the ground (0.20; 95% CI: 0.08-0.37), and cramps in feet (0.17; 95% CI: 0.08-0.29) (Table 17).

The symptoms felt most severely at six months follow-up were also tingling (0.17; 95% CI: 0.03-0.37) and numbness (0.10; CI: 0.03-0.20) in the hands, as well as in the feet, with 0.15 (95% CI: 0-0.5) and 0.16 (95% CI: 0.04-0.35), respectively (Table 18).

There was considerable heterogeneity in estimates between studies, however, with considerable overlap in the confidence intervals. Generally, the two studies with a small sample size of 36 patients each (Zimmerman et al., 2016; Kim et al., 2018) produced comparably lower estimates than the two larger studies (97 and 165 patients). For many of the symptoms the confidence intervals around the estimates produced from the two smaller studies crossed zero compared to the two larger studies (Table 18).

Twelve months

At twelve months follow-up, the prevalence of peripheral neuropathy symptoms in the upper limbs again ranged from 0.11 for both the inability to distinguish between hot and cold (95% 95% CI: 0.03-0.20) and cramps in the hands (95% CI: 0-0.32) to 0.48 (0.20-0.76) for tingling and 0.36 (0.16-0.59) for numbness in the fingers or hands (Table 19). For the lower limbs, difficulty driving was again the least commonly experienced symptom (0.09; 95% CI: 0.02-0.20), while tingling (0.43; 95% CI: 0.18-0.70) and numbness (0.40; 95% CI: 0.20-0.62) of the toes or feet were most common (Table 19). Several other symptoms had relatively high point estimates, and confidence intervals that overlapped with those of tingling and numbness in both the upper and lower limbs. Like findings at six months, those were namely weakness in the hands (0.21; 95% CI: 0.04-0.45), difficulty manipulating small objects (0.21; 95% CI: 0.07-0.41), and difficulty writing (0.16; 95% CI: 0.07-0.27), and cramps in the feet (0.17; 95% CI: 0.05-0.33). A pooled prevalence of 0.16 was estimated for weakness of the feet with a confidence interval that crosses zero (95% CI: 0.00-0.44). However, of the four studies from which

this estimate was derived, the largest study with a sample size of 92 produced an estimate of 0.37 (0.27 to 0.47) (Table 19).

There were only two studies that reported on severe symptoms experienced at twelve months, and as such the estimates were not pooled (Table 20). The two studies reported similar estimates of prevalence all with overlapping confidence intervals and a lower limit of zero, except for one, which was an estimate of 0.39 (0.16 to 0.61) for tingling in the fingers or hands by Zimmerman et al. (2016).

Table 17 - Prevalence of symptoms of any severity in the upper and lower limbs assessed at six months follow-up using the CIPN-20

Symptom	Kim 2018 (N=36)	Pachman 2015 (N=97)	Wesselink 2018 (N=165)	Zimmerman 2016 (N=36)	Pooled effect	I^2
Upper Limbs						
Tingling in fingers or hands	0.08 (0.01 to 0.17)	0.56 (0.48 to 0.64)	0.61 (0.53 to 0.68)	0.64 (0.48 to 0.80)	0.46 (0.26-0.67)	93% (85-97%)
Numbness in fingers of hands	0.53 (0.36 to 0.69)	0.53 (0.45 to 0.61)	0.49 (0.41 to 0.57)	0.31 (0.16 to 0.46)	0.48 (0.40-0.56)	51% (0-84%)
Shooting or burning pain in fingers or hands	0.06 (0.00 to 0.13)	0.17 (0.11 to 0.23)	0.21 (0.14 to 0.27)	0.11 (0.01 to 0.21)	0.15 (0.10-0.21)	51% (0-84%)
Difficulty distinguishing between hot and cold water	0.03 (0.00 to 0.08)	0.14 (0.08 to 0.19)	0.13 (0.08 to 0.18)	0.08 (0.00 to 0.17)	0.11 (0.07-0.15)	32% (0-75%)
Cramps in hands	0.03 (0.00 to 0.08)	0.17 (0.11 to 0.23)	0.21 (0.14 to 0.27)	0.08 (0.00 to 0.17)	0.13 (0.06-0.21)	72% (19-90%)
Difficulty holding a pen making writing difficult	0.19 (0.07 to 0.32)	0.24 (0.17 to 0.31)	0.29 (0.22 to 0.36)	0.08 (0.00 to 0.17)	0.21 (0.14-0.30)	64% (0-88%)
Difficulty manipulating small objects with your fingers	0.28 (0.13 to 0.42)	0.34 (0.26 to 0.41)	0.58 (0.51 to 0.66)	0.03 (0.00 to 0.08)	0.29 (0.10-0.53)	95% (90-97%)
Difficulty opening a jar or bottle because of weakness in hands	0.08 (0.00 to 0.17)	0.36 (0.28 to 0.44)	0.48 (0.40 to 0.56)	0.22 (0.09 to 0.36)	0.29 (0.15-0.45)	90% (76-95%)
Lower Limbs						
Tingling in toes or feet	0.08 (0.00 to 0.17)	0.63 (0.55 to 0.71)	0.68 (0.61 to 0.76)	0.25 (0.11 to 0.39)	0.41 (0.17-0.67)	96% (92-98%)
Numbness in toes or feet	0.58 (0.42 to 0.74)	0.63 (0.55 to 0.71)	0.62 (0.55 to 0.70)	0.19 (0.07 to 0.32)	0.52 (0.35-0.68)	88% (73-95%)
Shooting or burning pain in toes or feet	0.06 (0.00 to 0.13)	0.22 (0.15 to 0.29)	0.32 (0.25 to 0.39)	0.06 (0.00 to 0.13)	0.16 (0.06-0.29)	87% (70-95%)

Difficulty standing/walking because of difficulty feeling the ground	0.11 (0.01 to 0.21)	0.25 (0.18 to 0.32)	0.42 (0.34 to 0.49)	0.06 (0.00 to 0.13)	0.20 (0.08-0.37)	91% (80-96%)
Cramps in feet	0.11 (0.01 to 0.21)	0.26 (0.19 to 0.33)	0.28 (0.22 to 0.35)	0.03 (0.00 to 0.08)	0.17 (0.08-0.29)	85% (62-94%)
Difficulty walking because feet drop downwards	0.03 (0.00 to 0.08)	0.14 (0.09 to 0.20)	0.18 (0.12 to 0.24)	0.03 (0.00 to 0.08)	0.10 (0.04-0.18)	75% (32-91%)
Difficulty climbing stairs or getting up out of a chair because of weakness in legs	0.08 (0.00 to 0.17)	0.31 (0.24 to 0.39)	0.32 (0.25 to 0.39)	0.17 (0.04 to 0.29)	0.23 (0.14-0.34)	77% (38-92%)
Difficulty using the pedals	0.03 (0.00 to 0.08)	0.12 (0.06 to 0.17)	0.13 (0.08 to 0.19)	0	0.07 (0.02-0.14)	77% (38-92%)

Table 18 - Prevalence of severe symptoms severity in the upper and lower limbs at six months follow-up using the CIPN-20

Symptom	Kim 2018 (N=36)	Wesselink 2018 (N=165)	Zimmerman 2016 (N=36)	Pooled effect	I^2
Upper Limbs					
Tingling in fingers or hands	0.06 (0.00 to 0.13)	0.33 (0.26 to 0.40)	0.14 (0.03 to 0.25)	0.17 (0.03-0.37)	88% (68-96%)
Numbness in fingers of hands	0.11 (0.01 to 0.21)	0.17 (0.11 to 0.23)	0.03 (0.00 to 0.08)	0.10 (0.03-0.20)	68% (0-91%)
Shooting or burning pain in fingers or hands	0.06 (0.00 to 0.13)	0.07 (0.03 to 0.10)	0.06 (0.00 to 0.13)	0.06 (0.03-0.10)	0% (0-90%)
Difficulty distinguishing between hot and cold water	0.03 (0.00 to 0.08)	0.04 (0.01 to 0.07)	0.03 (0.00 to 0.08)	0.03 (0.01-0.06)	0% (0-90%)
Cramps in hands	0	0.05 (0.02 to 0.09)	0	0.01 (0.00-0.07)	61% (0-89%)
Difficulty holding a pen making writing difficult	0.03 (0.00 to 0.08)	0.11 (0.06 to 0.16)	0	0.04 (0.00-0.13)	78% (28-93%)
Difficulty manipulating small objects with your fingers	0.06 (0.00 to 0.13)	0.25 (0.19 to 0.32)	0	0.08 (0.00-0.30)	93% (83-97%)
Difficulty opening a jar or bottle because of weakness in hands	0	0.15 (0.10 to 0.21)	0.03 (0.00 to 0.08)	0.05 (0.00-0.18)	87% (61-95%)
Lower Limbs					
Tingling in toes or feet	0.06 (0.00 to 0.13)	0.44 (0.37 to 0.52)	0.03 (0.00 to 0.08)	0.15 (0.00-0.50)	96% (91-98%)
Numbness in toes or feet	0.14 (0.03 to 0.25)	0.31 (0.24 to 0.38)	0.06 (0.00 to 0.13)	0.16 (0.04-0.35)	87% (62-95%)
Shooting or burning pain in toes or feet	0.06 (0.00 to 0.13)	0.12 (0.07 to 0.17)	0	0.05 (0.00-0.15)	79% (32-93%)

Difficulty standing/walking because of difficulty feeling the ground	0.06 (0.00 to 0.13)	0.13 (0.08 to 0.18)	0	0.05 (0.00-0.16)	80% (38-94%)
Cramps in feet	0	0.10 (0.06 to 0.15)	0	0.02 (0.00-0.12)	84% (52-95%)
Difficulty walking because feet drop downwards	0.03 (0.00 to 0.08)	0.04 (0.01 to 0.06)	0	0.02 (0.01-0.05)	0% (0-90%)
Difficulty climbing stairs or getting up out of a chair because of weakness in legs	0.03 (0.00 to 0.08)	0.09 (0.05 to 0.13)	0.03 (0.00 to 0.08)	0.06 (0.03-0.11)	19% (0-92%)
Difficulty using the pedals	0.03 (0.00 to 0.08)	0.03 (0.00 to 0.06)	0	0.02 (0.00-0.04)	0% (0-90%)

Table 19 - Prevalence of symptoms of any severity in the upper and lower limbs assessed at twelve months follow-up using the CIPN-20

Symptom	Kim, 2018 (N=36)	Pachman, 2015 (N=92)	vanErning, 2012 (N=12)	Zimmerman, 2016 (N=36)	Pooled effect	I^2
Upper Limbs						
Tingling in fingers or hands	0.11 (0.01 to 0.21)	0.64 (0.54 to 0.73)	0.50 (0.22 to 0.78)	0.69 (0.54 to 0.84)	0.48 (0.20-0.76)	92% (84-96%)
Numbness in fingers of hands	0.14 (0.03 to 0.25)	0.57 (0.47 to 0.67)	0.42 (0.14 to 0.70)	0.36 (0.20 to 0.52)	0.36 (0.16-0.59)	87% (68-95%)
Shooting or burning pain in fingers or hands	0.06 (0.00 to 0.13)	0.14 (0.07 to 0.21)	0.08 (0.00 to 0.24)	0.14 (0.03 to 0.25)	0.11 (0.07-0.17)	0% (0-85%)
Difficulty distinguishing between hot and cold water	0.03 (0.00 to 0.08)	0.13 (0.07 to 0.20)	0.33 (0.07 to 0.60)	0.08 (0.00 to 0.17)	0.11 (0.03-0.20)	61% (0-87%)
Cramps in hands	0.06 (0.00 to 0.13)	0.29 (0.20 to 0.38)	0.25 (0.01 to 0.49)	0	0.11 (0.00-0.32)	90% (77-96%)
Difficulty holding a pen making writing difficult	0.08 (0.00 to 0.17)	0.20 (0.12 to 0.27)	0.42 (0.14 to 0.70)	0.08 (0.00 to 0.17)	0.16 (0.07-0.27)	64% (0-88%)
Difficulty manipulating small objects with your fingers	0.08 (0.00 to 0.17)	0.29 (0.20 to 0.38)	0.58 (0.30 to 0.86)	0.08 (0.00 to 0.17)	0.21 (0.07-0.41)	84% (59-94%)
Difficulty opening a jar or bottle because of weakness in hands	0.06 (0.00 to 0.13)	0.43 (0.33 to 0.53)	0.33 (0.07 to 0.60)	0.11 (0.01 to 0.21)	0.21 (0.04-0.45)	90% (76-95%)
Lower Limbs						
Tingling in toes or feet	0.11 (0.01 to 0.21)	0.63 (0.53 to 0.73)	0.58 (0.30 to 0.86)	0.47 (0.31 to 0.64)	0.43 (0.18-0.70)	91% (80-96%)
Numbness in toes or feet	0.39 (0.23 to 0.55)	0.61 (0.51 to 0.71)	0.42 (0.14 to 0.70)	0.19 (0.07 to 0.32)	0.40 (0.20-0.62)	85% (64-94%)
Shooting or burning pain in toes or feet	0.08 (0.00 to 0.17)	0.21 (0.13 to 0.29)	0.17 (0.00 to 0.38)	0.03 (0.00 to 0.08)	0.11 (0.03-0.22)	67% (4.6-89%)

Difficulty standing/walking because of difficulty feeling the ground	0.08 (0.00 to 0.17)	0.25 (0.16 to 0.33)	0.25 (0.01 to 0.49)	0.03 (0.00 to 0.08)	0.13 (0.03-0.28)	78% (41-92%)
Cramps in feet	0.08 (0.00 to 0.17)	0.32 (0.23 to 0.41)	0.25 (0.01 to 0.49)	0.08 (0.00 to 0.17)	0.17 (0.05-0.33)	79% (44-92%)
Difficulty walking because feet drop downwards	0.06 (0.00 to 0.13)	0.16 (0.09 to 0.24)	0	0.22 (0.09 to 0.36)	0.11 (0.04-0.21)	61% (0-87%)
Difficulty climbing stairs or getting up out of a chair because of weakness in legs	0.06 (0.00 to 0.13)	0.37 (0.27 to 0.47)	0.42 (0.14 to 0.70)	0	0.16 (0.00-0.44)	93% (86-97%)
Difficulty using the pedals	0.03 (0.00 to 0.08)	0.12 (0.06 to 0.19)	0	0.25 (0.11 to 0.39)	0.09 (0.02-0.20)	71% (17-90%)

Table 20 - Prevalence of severe symptoms in the upper and lower limbs assessed at twelve months follow-up using the CIPN-20

Symptom	Kim 2018 (N=36)	Zimmerman 2016 (N=18)
Upper Limbs		
Tingling in fingers or hands	0.06 (0.00 to 0.13)	0.39 (0.16 to 0.61)
Numbness in fingers of hands	0.03 (0.00 to 0.08)	0.06 (0.00 to 0.16)
Shooting or burning pain in fingers or hands	0.03 (0.00 to 0.08)	0.06 (0.00 to 0.16)
Difficulty distinguishing between hot and cold water	0	0.06 (0.00 to 0.16)
Cramps in hands	0	0
Difficulty holding a pen making writing difficult	0.06 (0.00 to 0.13)	0
Difficulty manipulating small objects with your fingers	0.06 (0.00 to 0.13)	0.06 (0.00 to 0.16)
Difficulty opening a jar or bottle because of weakness in hands	0	0
Lower Limbs		
Tingling in toes or feet	0.08 (0.00 to 0.17)	0.11 (0.00 to 0.26)
Numbness in toes or feet	0.11 (0.00 to 0.21)	0
Shooting or burning pain in toes or feet	0.03 (0.00 to 0.08)	0.06 (0.00 to 0.16)
Difficulty standing/walking because of difficulty feeling the ground	0.03 (0.00 to 0.08)	0
Cramps in feet	0.03 (0.00 to 0.08)	0
Difficulty walking because feet drop downwards	0.03 (0.00 to 0.08)	0
Difficulty climbing stairs or getting up out of a chair because of weakness in legs	0.03 (0.00 to 0.08)	0
Difficulty using the pedals	0.03 (0.00 to 0.08)	0

Peripheral neuropathy symptoms at long-term follow-up

Several symptoms were experienced severely at the long-term time point. The most prevalent symptoms at long-term follow-up were tingling (0.28; 95% CI: 0.18-0.40), numbness (0.21; 95% CI: 0.09-0.36), and burning or shooting pain (0.14; 95% CI: 0.05-0.26) in the toes or feet (Table 21). Other symptoms in the lower limbs included weakness (0.08; 95% CI: 0.05-0.12) and cramps (0.07; 95% CI: 0.01-0.16) in the feet. Estimates from both Beijers (2015) and Stefansson (2016) were higher and with overlapping confidence intervals compared to Zimmerman et al. (2016) who reported lower estimates, almost all of which except for one had confidence intervals that crossed zero (Table 21).

Only two studies reported on symptoms in the upper limbs, therefore results were not pooled. A prevalence of 0.14 (95% CI: 0.10-0.19) and 0.28 (95% CI: 0.11-0.44) for tingling in the fingers or hands were estimated from Beijers et al. (2015) and Zimmerman et al. (2016), respectively. All other estimates for the upper limbs from Zimmerman et al. (2016) crossed zero. Other estimates for the upper limbs from Beijers et al. (2015) included weakness in the hands 0.10 (95% CI: 0.06-0.14) trouble with small objects (0.09; 95% CI: 0.05-0.13), cramps (0.05; 95% CI: 0.02- 0.08), numbness (0.06; 95% CI: 0.02-0.09) and burning (0.04; 95% CI: 0.01-0.07).

Table 21 – Prevalence (95% CI) of severe symptoms of peripheral neuropathy (experienced "quite a bit" or "very much") at long-term follow-up

Symptom	Beijers 2013 (N=200) Median 4.2 years	Stefansson 2016 (N=65) 2 to 8 years	Zimmerman 2016 (N=29) 18 months	Pooled effect	I^2
Upper Limbs					
Tingling in fingers or hands	0.14 (0.10 to 0.19)	-	0.28 (0.11 to 0.44)	0.19 (0.08-0.33)	66%
Numbness in fingers of hands	0.06 (0.02 to 0.09)	-	0.10 (0.00 to 0.21)	0.06 (0.02-0.10)	14%
Shooting or burning pain in fingers or hands	0.04 (0.01 to 0.07)	-	0.03 (0.00 to 0.10)	0.04 (0.01-0.07)	0%
Difficulty distinguishing between hot and cold water	0.03 (0.00 to 0.05)	-	0.03 (0.00 to 0.10)	0.02 (0.00-0.05)	0%
Cramps in hands	0.05 (0.02 to 0.08)	-	0	0.03 (0.00-0.09)	49%
Difficulty holding a pen making writing difficult	0.03 (0.00 to 0.05)	-	0	0.02 (0.00-0.04)	0%
Difficulty manipulating small objects with your fingers	0.09 (0.05 to 0.13)	-	0	0.04 (0.00-0.17)	79%
Difficulty opening a jar or bottle because of weakness in hands	0.10 (0.06 to 0.14)	-	0.10 (0.00 to 0.21)	0.10 (0.06-0.14)	0%
Lower Limbs					
Tingling in toes or feet	0.29 (0.23 to 0.36)	0.38 (0.27 to 0.50)	0.14 (0.01 to 0.26)	0.28 (0.18-0.40)	67%
Numbness in toes or feet	0.18 (0.13 to 0.23)	0.37 (0.25 to 0.49)	0.10 (0.00 to 0.21)	0.21 (0.09-0.36)	82%
Shooting or burning pain in toes or feet	0.12 (0.08 to 0.17)	0.26 (0.15 to 0.37)	0.03 (0.00 to 0.10)	0.14 (0.05-0.26)	80%
Difficulty standing/walking because of difficulty feeling the ground	0.09 (0.05 to 0.13)	-	0	0.04 (0.00-0.17)	79%
Cramps in feet	0.09 (0.05 to 0.12)	0.15 (0.07 to 0.24)	0	0.07 (0.01-0.16)	76%

Difficulty walking because feet drop downwards	0.03 (0.01 to 0.06)	-	0	0.02 (0.00-0.05)	6%
Difficulty climbing stairs or getting up out of a chair because of weakness in legs	0.09 (0.05 to 0.13)	-	0.03 (0.00 to 0.10)	0.08 (0.05-0.12)	0%
Difficulty using the pedals	0.01 (0.00 to 0.03)	-	0	0.01 (0.00-0.03)	0%

Narrative synthesis

The Functional Assessment of Cancer Therapy/Gynaecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx) questionnaire

The FACT/GOG-Ntx measures sensory symptoms (numbness and discomfort in hands and feet, difficulty feeling the shape of objects), motor symptoms (general weakness, Difficulty walking, Difficulty buttoning buttons, joint pain/muscle cramps), auditory problems (difficulty hearing, buzzing/ringing in ears), and cold-induced pain in hands and feet. The responses can vary on a five-point scale: “not at all,” “a little bit,” “somewhat,” “quite a bit,” and “very much” (Appendix 1).

Three studies reported assessment of peripheral neuropathy using the FACT/GOG-NTx questionnaire. However, differences in reporting precluded synthesis of the results into summary estimates. The study by Land et al. (2007) reported on the total number of people experiencing symptoms “quite a bit” or “very much” for each of the twelve questions in the FACT/GOG-NTx individually. Kidwell et al. (2012) did not report on each of the questions individually. Instead, the FACT manual proposes that the twelve items in the FACT/GOG-NTx questionnaire can be summed to a score that can range from 0 to 48 and thus, Kidwell et al. reported on the mean score for the twelve items combined. Iveson et al. (2018) used a version of the FACT/GOG-NTx that only has four questions instead of twelve. It asks about numbness or tingling in the hands and the feet, as well as on discomfort in the hands and the feet. They reported the total number of patients experiencing symptoms “quite a bit” or “very much” for all four questions combined.

Study characteristics

All three studies that used the FACT/GOG-NTx tool undertook an assessment of neurotoxicity on a subsample of patients recruited to large randomised controlled trials.

Land et al. conducted a prospective follow-up of 189 patients who participated in the NSABP C-07 at six, twelve, and eighteen months. The primary objective of the trial was to assess the effect of oxaliplatin on disease free survival. Kidwell et al. (2012) also reported on a cross sectional sample of 353 patients who took part in the NSABP C-07, at a median of 6 years (range from 4.2 to 8.6 years) from random assignment to the trial (Table 22).

Patients in the NSABP C-07 were recruited from multiple centres across the United States from 2000 to 2002. The trials excluded patients who had prior history of peripheral neuropathy of grade-II or higher as assessed by the CTCAE.

Iveson et al. (2018) prospectively followed-up 2871 patients who took part in the IDEA trial at one, three, and five years. The primary objective of the trial was to test the effectiveness of three months of therapy with oxaliplatin compared to six months. Patients were recruited from multiple centres from six countries between 2008 to 2013. Patients were excluded based on multiple criteria that assessed health status, such as cellular count (number of red or white blood cells) or renal impairment, defined for the primary objective of the study, but not based on peripheral neuropathy (Table 22).

Table 22 - Characteristics of the studies that assessed peripheral neuropathy using the FACT/GOG-NTx questionnaire

	Inclusion	Exclusion	Study design	Starting sample size	Recruitment	Setting	Country
Land, 2007	Patients with stage II or III colorectal cancer undergone resection with curative intent.	Patients with clinically significant peripheral neuropathy (National Cancer Institute Common Toxicity Criteria version 2.016 grade-II or higher) were excluded.	Prospective follow-up (The PRO study: the first 400 patients from the NSABP C-07 trial)	395 (189 combination therapy and 206 single therapy)	2000-2001	Multi-centre	USA
Kidwell, 2012	Patients with stage II or III colorectal cancer undergone resection with curative intent. Survived at least 3 years after study entry and had been in contact with institutional staff within the prior two years.	Patients with clinically significant PSN (National Cancer Institute Common Toxicity Criteria version 2.016 grade-II or higher) were excluded.	Cross-sectional assessment of the PRO study participants	353 patients who participated in NSABP C-07 trial.	2000-2002	Multi-centre	USA

Iveson, 2018	Patients with stage II or III colorectal cancer undergone resection with curative intent. A normal CT scan of the chest, abdomen, and pelvis. WHO performance status 0 or 1, adequate organ function, and life expectancy of greater than 5 years with reference to non-cancer related diseases.	Multiple criteria defined for the primary objective of the study.	Interventional RCT with prospective follow-up	2871 patients who took part in the IDEA trial	2008-2013	Multi centre; 244 participating centres	Six countries: UK, Denmark, Spain, Sweden, Australia, and New Zealand

Patient characteristics

Studies reported on age, with a mean or median that ranged between 57 to 65 years. There was a smaller proportion of women compared to men in all three studies. Kidwell et al. (2012) did not explicitly report on the characteristics of the cross-sectional sample they included in their study but stated that their sample was representative of the NSABP C-07 trial. Most patients included in each study were with stage III disease, ranging from 69-82%, the remainder having stage II disease (Table 23).

Table 23 - Characteristics of patients of three studies that used the FACT/GOG-Ntx

Author, Publication year	Women	Median age	Mean age	Age range	Stage II	Stage III	Stage IV
Land, 2007	41%	-	57	22-77	31%	69%	0
Kidwell, 2012*	45%	59	-	-	29%	71%	0
Iveson, 2018	39%	65	-	58-70	18%	82%	0

*Patient characteristics were not explicitly reported; patients included in the study were representative of the NSABP C-07 participants.

Findings

Land et al. (2007) undertook an assessment of patients at three time points: six, twelve, and eighteen months of follow-up (Table 24). The most prevalent symptoms among those who received combination therapy at all time points were numbness or tingling in the hands with 0.17 (95%CI: 0.13, 0.24) at six months, 0.08 (95%CI: 0.05, 0.13) at twelve months, and 0.07 (95%CI: 0.01, 0.06) at 18 months. Numbness and tingling were also the most prevalent symptoms in the feet at all time points with 0.17 (95%CI: 0.12, 0.23) at six months, 0.10 (95%CI: 0.07, 0.16) at 12months, and 0.14 (95%CI: 0.04, 0.12) at 18 months (Table 24). The overlapping confidence intervals around the estimates indicates that there may be no difference in the prevalence of some symptoms compared to others or a difference over time.

Table 24 – The prevalence (95% CI) of symptoms assessed by the FACT/GOG=Nx12 at six, twelve, and eighteen months as reported by Land et al. (2007)

	Six months	Twelve months	18 months
Feet numb/tingling	0.17 (0.12, 0.23)	0.10 (0.07, 0.16)	0.14 (0.04, 0.12)
Hand numb/tingling	0.17 (0.13, 0.24)	0.08 (0.05, 0.13)	0.07 (0.01, 0.06)
Foot discomfort	0.10 (0.07, 0.15)	0.04 (0.02, 0.08)	0.08 (0.00, 0.02)
Hand/foot pain in cold	0.08 (0.05, 0.13)	0.05 (0.03, 0.09)	0.07 (0.02, 0.07)
Joint pain/muscle cramps	0.07 (0.04, 0.12)	0.04 (0.02, 0.08)	0.04 (0.01, 0.05)
Difficulty hearing	0.02 (0.01, 0.05)	0.03 (0.01, 0.06)	0.04 (0.01, 0.06)
Hand discomfort	0.09 (0.05, 0.13)	0.03 (0.01, 0.07)	0.03 (0.01, 0.06)
Difficulty feeling shapes	0.06 (0.04, 0.11)	0.02 (0.01, 0.05)	0.02 (0.01, 0.05)
Feeling weak all over	0.03 (0.01, 0.06)	0.02 (0.01, 0.05)	0.02 (0.01, 0.05)
Ringing ears	0.02 (0.01, 0.05)	0.01 (0, 0.04)	0.02 (0.02, 0.08)
Difficulty walking	0.02 (0.01, 0.05)	0.02 (0.01, 0.05)	0.00 (0.04, 0.12)

The study also reported the odds of experiencing symptoms “somewhat,” “quite a bit,” or “very much” compared with “a little bit” or “not at all” between those who received combination therapy with oxaliplatin and those who received single therapy at 18 months follow-up (Table 25). There was a significant difference between the two groups for three of the symptoms, mostly in the feet. At 18 months follow-up, those who received oxaliplatin had five times the odds of experiencing numbness or tingling in the feet (95% CI: 1.95, 12.85), four times the odds of experiencing discomfort in the feet (95% CI: 1.47, 11.74), and almost three times the odds of experiencing hand or foot pain when exposed to cold (95% CI: 1.08, 7.08).

The authors also reported the change in the mean NTX-12 score from baseline. However, they proposed that for a change in the mean score between two time points (i.e., from baseline) or two groups (treatment vs. control) to be considered clinically significant, the difference should be of at least four points, referring to that as in the mean score. A change in at least four points was considered the “minimal clinically important difference”. The study showed that compared to baseline, 40% of patients in the combination therapy group experienced a clinically significant worsening of their mean NTX-12 score at six months, and 31% at 18 months.

The study by Kidwell et al. (2012) reported on a cross-sectional sample of 353 patients from both treatment groups who had participated in the NSABP-C-07 trial. They assessed peripheral neuropathy at a median of six years (range from 4.2 to 8.6 years) from random assignment to the NSABP-C-07 trial. Like Land et al. (2007), Kidwell et al. (2012) reported on the odds of experiencing symptoms between the two groups. They

found that those who received oxaliplatin had two times the odds (95% CI: 1.15-3.48) of experiencing numbness or tingling in the hands, and almost three times the odds of experiencing numbness and tingling in the feet (OR: 2.78; 95% CI:1.59-4.85) than those who received single therapy (Table 25).

Table 25 - The odds of experiencing symptoms "somewhat", "quite a bit" or "very much" compared

	Land et al. (2007)	Kidwell et al. (2012)
	Odds Ratio at 18 months	Odds Ratio at median of 6 years (Range: 4.2-8.6 years)
Feet numb/tingling	5.00 (1.95, 12.85)	2.00 (1.15, 3.48)
Foot discomfort	4.15 (1.47, 11.74)	-
Hand/foot pain in cold	2.77 (1.08, 7.08)	-
Hand numb/tingling	-	2.78 (1.59, 4.85)

They also compared the mean and median NTX-12-scores of those who received single therapy to those who received combination therapy and found statistically significant differences of 1.8 in the mean and 2 in the median between the two groups. However, these differences did not meet the minimal clinically important difference criteria discussed above, and the authors did not consider this difference to be clinically significant.

In addition to the cross-sectional sample of 353 patients, Kidwell et al. (2012) also reported on a longitudinal sample of 92 patients from both treatment groups, for whom compared changes in the mean and median NTX-12 score at six, twelve, and eighteen months as well as at a median of 7 years (ranging from 5.5 to 8.1 years) from randomisation. The authors only reported a qualitative summary of their findings stating that differences in the mean and median NTX-12 scores between the two treatment groups were only significant at six months follow-up. For the 12- and 18-month time points, there were overlapping confidence intervals in the scores of both groups, while the mean changes in the scores from baseline were the same at long-term follow-up.

Iveson et al. used a version of the FACT/GOG-NTx that included only 4 questions instead of 12 (Appendix 1). The authors reported on the total number of patients who answered "quite a bit" or "very much", for all four questions combined, at one, three, and five years of follow-up. This was a trial that aimed to establish the effectiveness of receiving three months of treatment with oxaliplatin compared with six months, and the presence of neurotoxicity was compared between these two groups. The proportion of

people who experienced peripheral neuropathy in the three-month treatment group was about half of that in the six-month treatment group, at all three time points. However, the prevalence of peripheral neuropathy symptoms in the hands and feet experienced "quite a bit" or "very much" was still 16% five years of follow-up, even after only three months of treatment with oxaliplatin (Table 26).

Table 26 – The percentage of people who experienced peripheral neuropathy "quite a bit" or "very much" at one, three, and five years post therapy with three months of oxaliplatin compared to six months.

	Six-month group	Three-month group
One year	34%	14%
Three years	32%	15%
Five years	29%	16%

Neuropathy Symptom Score (NSS)

In the study by Park et al. (2011), peripheral neuropathy was assessed using the CTCAE (reported under the CTCAE section) as well as the Neuropathy Symptom Score (NSS) (Park et al., 2011). The NSS consists of 17 items categorised into symptoms of muscle weakness, sensory disturbance, or autonomic (Appendix 1). Sensory symptoms can either be described as negative (difficulty identifying objects in mouth, difficulty identifying objects in hands, or unsteadiness in walking) or positive (numbness or pain).

In this study, each of the negative (subset IIA) and positive (subset IIB) symptoms in the NSS was given a score of one if present, adding up to a total of five. Patients were assessed at two years post-treatment with oxaliplatin. About 21% of patients did not have any symptoms, while 42% had a score of one mostly reflecting numbness, 33% had a score of 2, and 4% had a score of 3.

Discussion

In this study, a systematic review of the literature was undertaken to determine the prevalence of persistent peripheral neuropathy among those who were treated with oxaliplatin for stage III colorectal cancer, at different times of follow-up and for each measurement tool used.

Summary and interpretation of Findings

Findings from studies that used the CTCAE showed that the proportion of people with any grade peripheral neuropathy was 57% at six months, and about 33% at twelve-month follow-up. It is likely that former is an overestimate, as the confidence interval around the pooled estimate was wide, and two studies of large sample sizes (above 1000 participants) tended to have a similar lower estimate of prevalence around 40%. By contrast, at twelve-month follow-up the confidence interval around the pooled estimate was narrower, and three studies of a large sample size (above 1000 participants) reported similar prevalence ranging from 25-30%, thus giving higher confidence in the pooled estimate.

The pooled estimate for the long-term follow up was nearly 56%, which is also likely to be an overestimate. However, the wide confidence interval around this pooled estimate overlaps with that of twelve months, indicating that the estimates from these two time points may not be different. In addition, the prevalence estimates from Andre et al. (2004) (which included the largest sample size of 967 participants) was also about 25% at 18 months. Therefore, it is possible that the prevalence of symptoms does not reduce greatly beyond twelve months.

Symptoms of grade-II (interfere with function but not activities of daily living) was shown to be at 4% by twelve months, and 15% in the long-term follow-up. The latter is also likely to be an overestimate, given the wide confidence interval. However, the lower limit of the confidence interval is 2%, and the proportion from the study with the largest sample size of 967 participants was also 2%, suggesting that symptoms of grade II peripheral neuropathy do persist beyond twelve months. Symptoms of grade-III (interfere with daily living) severity were shown to be at 2% and 8% by twelve months and long-term follow-up, respectively. The confidence intervals around these estimates cross zero, so it is possible that symptoms of grade-III severity do not persist beyond six months, while those of grade-I and grade-II severity do.

Findings from the CIPN-20 tool provided insight into the type of symptoms that could persist after completion of therapy. Tingling and numbness in both the upper and lower limbs were the most experienced symptoms at six- and twelve-month follow-up.

Tingling and numbness in the lower limbs were the most common symptoms that persisted “quite a bit” or “very much” at long-term follow up in 28% and 21% of patients, respectively. Other symptoms experienced at this level included shooting or burning pain in toes or feet (14%), difficulty climbing stairs or getting out of a chair because of weakness in legs (8%), and cramps in the feet (7%). Only two studies provided estimates for symptoms in the upper limbs at long-term follow-up. Both were consistent in their finding that tingling was the most common symptoms that persisted “quite a bit” or “very much” at a prevalence of 28% after 18 months, and 14% at a median of 4 years of follow up. Further findings from one study showed that weakness, difficulty manipulating small objects, numbness, cramps, and shooting or burning pain may still be found in 4-10% of patients up to four years after completion of therapy. At long-term follow-up, only the number of patients that experienced symptoms “quite a bit” or “very much” were reported. Data on those who experienced mild symptoms (“a little bit”) was not available from any of the studies at the long-term follow up group, which indicates that the total number of patients experiencing symptoms of any level could be higher.

These findings from the CIPN-20 tool lend support to the findings from the CTCAE tool, that the prevalence of peripheral neuropathy symptoms of any grade or level could range from approximately 7% to 50% depending on the symptoms experienced, and that some symptoms, primarily numbness and tingling, could persist for several years. The finding that some symptoms persist at long-term follow-up are experienced “quite a bit” or “very much” supports the prevalence of grades two and three assessed by the CTCAE tool at long-term follow-up, and as such, reduces the likelihood that the prevalence of grade-III is zero as suggested by the lower limit of the confidence intervals.

Further support to these findings comes from three studies that used the FACT/GOG-NTx tool. Two of the studies reported that symptoms of tingling and numbness in the hands and feet were of highest prevalence compared to others. Synthesis of studies that used this tool also found that those who received combination therapy were at significantly higher odds of experiencing these symptoms compared to those who received single therapy at 18 months of follow-up, as well as at long-term (range from 4.2 to 8.6 years). Iveson et al. (2018) reported prevalence of tingling and numbness symptoms, experienced “quite a bit” or “very much” was at 29% after five years of

follow-up for those who received six months, and at 16% even for those who only received three months of therapy.

Linking findings to the wider literature

The findings reported here are consistent with the systematic review undertaken by Beijers et al. (2014), which concluded that oxaliplatin-induced peripheral neuropathy of any grade persisted in many patients after at least twelve months of follow-up, with the majority being mild to moderate (grades one and two). However, their conclusion was based on examination of individual, rather than pooled, estimates. The prevalence of neuropathy after twelve months of follow up varied between the studies included in that review from 0.6% to 46% for grades one and two and from zero to 5% for grade-III. In this study, more precise estimates were possible for grades one and two. Of 14 studies that were included in the review by Beijers et al. (2014), six did not meet the eligibility criteria for this review. Three were studies of patients with stage IV disease, one included patients with gastric cancer, while the stage of colorectal cancer and the time point of assessment were not clear in another two, respectively. Therefore, this study provides estimates of prevalence that are more applicable to stage III patients specifically.

The findings of this study are also consistent with a recent, large, multicentre, cross-sectional study that was conducted in 16 French centres, which assessed the prevalence of peripheral neuropathy among colorectal cancer patients during the five years after the end of oxaliplatin treatment (Selvy et al., 2020). It found that among all 406 patients assessed with the CIPN-20 tool, prevalence of peripheral neuropathy was approximately 40% during the first year, reducing to around 27% by the fifth year. Likewise, this analysis also provided an indication that there is little change in the prevalence of symptoms beyond twelve-month follow-up.

One study explored the distress that could result from symptoms of peripheral neuropathy, and showed that tingling and numbness, although more frequent, are not perceived to be as distressing to patients as other symptoms such as cold sensitivity, difficulty with balance, or pain (Tofthagen, 2010). It is therefore important to consider the less frequent but potentially more distressing symptoms. This study has shown that other symptoms of notable prevalence included difficulty manipulating small objects in the hands, as well as weakness and cramps in the hands and feet, which seemed to persist “quite a bit” or “very much” at long-term follow-up. This highlights the shortcomings of the CTCAE tool in comparison to the CIPN-20, as it does not distinguish individual symptoms or their level of severity as experienced by the patient.

On the other hand, although the CIPN-20 provides insight into patients' experience of the symptoms, it is not clear to which extent these symptoms may interfere with function or with daily living.

Strengths and limitations

Although stage III patients constituted most of the samples, almost all studies assessed a mix of patients. Three studies were mixed with stage IV patients, one of which provided separate analysis that allowed extraction of only stage III disease. The separate analysis gave insight into the pattern among stage IV patients compared to adjuvant patients. It reported that adjuvant-treated patients were more affected with oxaliplatin-induced peripheral neuropathy (35%) than palliative-treated patients (16%) after twelve months. Therefore, for other studies where separate analysis was not possible, the inclusion of palliative patients may have resulted in an underestimation of prevalence in the adjuvant population.

Prevalence could also be under or over-estimated depending on the dose and number of cycles of oxaliplatin, or the type of therapy received (oxaliplatin with 5-FU or with capecitabine). It is well established that peripheral neuropathy is associated with higher cumulative doses of oxaliplatin. Survivors who are assessed for symptoms at long-term time points may be those with less severe disease, and therefore have been treated less aggressively, resulting in less neurotoxicity. As Kidwell et al. (2012) noted, most patients assessed in their study had less than 4 positive nodes, and therefore better prognosis (Kidwell et al., 2012). It is possible that these patients did not receive high doses of oxaliplatin, explaining the lack of difference between the two groups (single vs. combination therapy) observed by Kidwell et al. (2012). This is important because on the other side of this position we may find patients who had had more aggressive disease who may have been treated with higher doses of oxaliplatin, resulting in higher incidence and prevalence of peripheral neuropathy, but did not survive long enough to participate in this or similar long-term studies. These patients are important to consider because it is possible that they spent what remained of their lives experiencing unpleasant symptoms that may have influenced their daily living.

The prevalence of oxaliplatin-induced peripheral neuropathy could also be overestimated depending on the presence of pre-existing risk factors for neuropathy. Only five studies excluded patients with pre-existing neuropathy, and none excluded patients with diabetes mellitus. Peripheral neuropathy is a common complication of diabetes, with a prevalence estimated to be between 6% and 51% in this population (Hicks & Selvin, 2019). Patients who had diabetes may have developed peripheral

neuropathy due to their condition during follow-up. Therefore, the possibility that some cases of long-term sensory neuropathy observed in the included studies could be due to, or are exacerbated by, other causes cannot be ruled out.

Incomplete reporting was considerable among the included studies. Ideally, each included study should contribute information on all grades of severity and all items in a questionnaire to allow pooling of estimates. This may not be possible due to limitations imposed by scientific journals on word count, but data should be made available as supplementary material. The variability in reporting made data extraction difficult and limited the number of studies that could be synthesised to obtain a summary estimate of prevalence for different grades of severity at different time points. In addition, many of the authors who were contacted with a request for data either did not respond to the request or were unable to provide data due to time constraints or the long duration since the study was conducted.

The studies differed considerably in sample size, study design, and follow-up time. Therefore, one limitation of this study is that it was not possible to examine the effect of these characteristics due to the small number. This heterogeneity also meant that pooling of the estimates was not appropriate. However, due to synthesis of data at multiple levels of severity, and for time points and symptoms, it was impractical to report on individual studies, although every effort was made to describe this information where it was most relevant. As such, the results are most useful in demonstrating patterns in the condition and providing approximate rather than accurate estimates and should be interpreted with caution.

Conclusions and recommendations

In summary, this systematic review showed that a large proportion of patients treated with oxaliplatin for stage III colon cancer experience mild symptoms at six- and twelve-months post therapy, mainly of numbness and tingling in the hands and feet. The prevalence of oxaliplatin induced peripheral neuropathy seems to decrease between six and twelve months of follow up. By contrast, there seems to be little change in the estimates, indicating no or slow improvement in symptoms, beyond twelve months post therapy. Although no firm conclusions can be drawn regarding prevalence of more severe symptoms beyond twelve months, a considerable proportion of patients might experience certain symptoms, namely tingling and numbness, “quite a bit” or “very much” several years after completion of therapy. This provides support that the prevalence of grade-III neuropathy, which interfered with activities of daily living, as assessed by the CTCAE tool is unlikely to be at zero.

This review offered insight into what could be expected in terms of the severity and duration of this adverse effect from treatment with oxaliplatin for stage III colon cancer. This is useful in the clinical setting when a discussion and evaluation of risks and benefits should take place between patients and clinicians to decide on treatment. However, the limited ability to make firm conclusions on prevalence indicates that a standardised classification and measurement of chemotherapy-induced peripheral neuropathy, and larger prospective studies with adequate sample sizes are necessary to allow for consistent and accurate assessment of this side effect and a better understanding of its risk factors.

Chapter 5: Variations in the receipt and type of adjuvant chemotherapy among stage III colon cancer patients in England

Introduction

Survival from many types of adult cancers has been steadily improving over time, but it may still vary between groups (Arnold et al., 2019). Certain biological, physiological, or genetic predispositions may result in differences in cancer incidence, aggressiveness, or response to treatment (Toral Gathani et al., 2021; Glare, 2005; Klimosch et al., 2013; Watanabe et al., 2001). Environmental exposures as well as lifestyle and dietary factors can also play a role. This includes exposures to infectious agents, such as in the case of the human papillomavirus and cervical cancer; exposure to poor air quality, radiation, or chemical agents such as aromatic amines that may cause bladder cancer; or lifestyle and dietary choices such as alcohol, smoking or obesity (Murphy et al., 2019). However, there are also demographic and psychosocial factors that can result in differences in survival (Mirosevic et al., 2019). Socioeconomic inequality in cancer survival has been shown to occur worldwide as well as in the UK (Benitez-Majano et al., 2016; Dalton et al., 2019; Exarchakou et al., 2018; Ito et al., 2014; Møller et al., 2012; Stanbury et al., 2016). Cancer survival could also vary by other characteristics such as age, race, sex and comorbidities, and patterns are likely to differ depending on cancer type (Lamkaddem et al., 2017; Sogaard et al., 2013; C. Zeng et al., 2015).

These observed disparities in cancer survival between groups are due to factors related to either diagnosis or treatment. Some groups may experience delayed diagnosis resulting from screening non-attendance, delays in presentation with symptoms, or delays in referrals from primary care (Hayes et al., 2021; Niksic et al., 2015; Woods et al., 2006). For example, it has been shown that for some cancers, such as breast and colorectal, individuals of minority ethnic groups are less likely to get screened (Ponce et al., 2004; Smith- Bindman et al., 2006). A systematic review that included 22 studies of colorectal or lung cancer showed that emergency presentation, which is an indication of advanced disease, was more likely in women and those of older age, or higher deprivation (Mitchell et al., 2015). In addition to delayed diagnosis, however, there may also be differences in the receipt of or adherence to appropriate treatment between groups.

Differences in healthcare services related to diagnosis or treatment could be due to interactions between patient, healthcare professional, and health system factors. For example, those of lower socioeconomic status, ethnic minorities, or older age have been shown to have low health literacy, a factor which is known to reduce patients' engagement with healthcare services and could lead to disparities in health outcomes (Berkman et al., 2011; Protheroe et al., 2009; Sudore et al., 2006). Those from deprived areas could also lack access to good quality health facilities or availability of time or transportation to attend appointments. Differences between groups could also be associated with healthcare professional characteristics or explicit or implicit biases towards certain patient groups. Clinicians have been shown to be less likely to discuss diagnosis and prognosis and spend less time with older compared to younger patients. Additionally, clinical care and treatment has been shown to vary by healthcare professional characteristics such as race, sex, specialty, and degree of experience (McKinlay et al., 2002; Shackelton-Piccolo et al., 2011). Finally, variations in healthcare can also be associated with the organisation, location, or practice culture within healthcare facilities (Curoe et al. 2003, Kralewski et al. 2005, Shackelton et al. 2009; Burgess et al. 2010, Stepanikova et al. 2012).

In the context of stage III colon cancer, adjuvant chemotherapy has been shown to be highly effective in increasing survival compared to surgery alone (Bockelman et al., 2015). Clinical guidelines recommend that all patients with stage III colon cancer should receive adjuvant chemotherapy after surgical resection of the tumour (Bromham et al., 2020). However, treatment with adjuvant chemotherapy for stage III colon cancer has been shown to differ along similar demographic and socioeconomic lines as survival.

In the USA, Chagpar et al. (2012) investigated adjuvant chemotherapy use among 53,127 stage III colorectal cancer patients treated between 2003-2007 identified in the National Cancer Database. The study found that underuse of adjuvant chemotherapy was associated with increasing age and comorbidity score, and lack of private insurance (R. Chagpar et al., 2012). A later analysis of approximately 75,000 patients who were pathologically diagnosed with stage III colon cancer between 2006-2013 and identified from the same database, found similar results (Schroder et al., 2019). The authors compared those who received adjuvant chemotherapy with those who did not, based on patient characteristics such as age, gender, type of insurance, race, and comorbidity; clinical characteristics such as tumour site, extent of resection, surgical margin, readmission within 30 days of surgery; and type of facility. The study found that over a quarter of patients (27%) did not receive chemotherapy. Those who were older

in age, black, and who had more comorbidities had lower odds of receiving chemotherapy. Those with positive surgical margins, underwent resection of adjacent organs, or were re-admitted within 30 days of surgery also had lower odds of receiving chemotherapy. Chemotherapy receipt was also found to vary by the type of insurance and the region of the United States, but not by income or education level, or the site (left of right of the colon) or size of the tumour. Although the authors investigated variation of adjuvant chemotherapy by several clinical characteristics, the receipt of therapy could also vary depending on the number of lymph nodes involved, which was not considered in this study. In Canada, a study that analysed 772 stage III colon cancer patients from the Alberta Cancer Registry found that only 50% of patients diagnosed between 2002-2005 received adjuvant chemotherapy, with age being the strongest predictor for not receiving therapy, after adjustment for comorbidities (Winget et al., 2010). This study, however, did not consider the number of positive lymph nodes. In another study that used the Ontario Cancer registry and included approximately 2800 patients, those who were older, with comorbidities, living in low-income areas, and with increased post-operative length of stay were found to be less likely to receive adjuvant chemotherapy (Booth et al., 2016).

In a study that included 29,044 stage III colon cancer patients diagnosed between 2009-2014 in The Netherlands, 2009-2013 in Belgium, 2009-2014 in Sweden found that the rate of receiving adjuvant chemotherapy varied between the three countries: 61% in The Netherlands, 68% in Belgium, and 55% in Sweden (Babaei et al., 2018). Administration of adjuvant chemotherapy decreased significantly with increasing age in all three countries. In Sweden, women were more likely to receive adjuvant chemotherapy than men, while the opposite was true in Belgium.

To date, there has been only one study that has explored variation in the use of adjuvant chemotherapy for stage III colon cancer in England (Boyle et al., 2020). The study reported that about 40% of 11,932 stage III colon cancer patients diagnosed between 2014 to 2017 did not receive adjuvant chemotherapy. The use of adjuvant chemotherapy significantly reduced with age, and increased with higher deprivation group, fewer comorbidities, better performance status, better pre-surgical physical status (American Society of Anaesthesiologists (ASA) grade), after adjustment for all other factors. Those who had an elective or laparoscopic resection, more advanced disease (T3/T4: tumour that penetrates the bowel wall, or N2: more than 3 lymph nodes involved) and did not have an unplanned readmission were also more likely to receive chemotherapy. The extent of disease for this study was identified from the pathology staging information available in the National Bowel Cancer Audit data

(NBOCA). However, although pathological diagnosis of stage is based on the examination of the tumour tissue and lymph nodes, using only the pathological diagnosis may not comprehensively identify all those with stage III disease. For example, metastasis, which would indicate stage IV disease, may be diagnosed more accurately clinically through imaging studies than through pathologic sampling. Therefore, someone who is classified as having stage III disease using pathologic diagnosis, may also show signs of metastasis using clinical diagnosis. Benitez-Majano proposed an algorithm that is based on clinically logical assumptions, taking into account three sources of diagnosis (pathologic, clinical, and integrated) found in the national cancer registry to identify the stage of disease (Benitez-Majano et al., 2016). This will be used to identify stage III colon cancer patients in this study.

None of the above-mentioned studies investigate variation in the type of adjuvant chemotherapy received, i.e., single or combination, and evidence on this is very limited in the literature. One study analysed 1,035 stage III patients registered in the Puerto Rico Central Cancer Registry-Health Insurance Linkage Database who had undergone resectional surgery between 2008–2012. Receiving oxaliplatin was associated with age of less than 70 years, dual Medicare/Medicaid insurance, and those diagnosed in 2008 compared to later years, and was not associated with sex, marital status, comorbidity, region, primary tumour location, or tumour grade (Ortiz-Ortiz et al., 2018). In another study that used the Surveillance, Epidemiology and End Results (SEER)-Medicare linked database to analyse 4106 stage III colon cancer Medicare patients found that those living in less urban regions 42% less likely to receive combination chemotherapy compared to those who live in big cities (Panchal et al., 2013). The SEER registry covers approximately 35% of the US population, and Medicare data covers insured patients aged 65 years or older, therefore, limiting their representativeness.

This study uses the national cancer registry data linked to SACT to explore variations in the type of adjuvant chemotherapy (single or combination therapy) received among stage III colon cancer patients in England, by patient-level characteristics including age, sex, deprivation group, ethnicity, year of diagnosis, size of tumour, and number of lymph nodes involved. The study also explores variations in the receipt of adjuvant chemotherapy by the same patient and clinical characteristics. As discussed above, the study by Boyle et al. (2020) is the first and only study to examine stage III-specific variations in treatment in England. Thus, the findings of the existing study will be compared to the findings of this current study to test its replicability and strengthen the evidence base.

Methods

Data sources and management

This analysis was undertaken within the Inequalities in Cancer Outcomes Network (ICON) (https://icon.lshtm.ac.uk), to which I am affiliated through one of my supervisors, Professor Bernard Rachet at the London School of Hygiene and Tropical Medicine.

The data used for this analysis is routinely collected population-based data. As secondary users of the ICON are not required to seek participant consent, and statutory approvals are in place to use the data. The data are stored on a non-connected secure computer in a secure room protected by codes and passwords. The data extract was anonymised and copied to a folder on the ICON drive and made available for my use.

Ethical approval for this study was obtained from the London School of Hygiene and Tropical Medicine (Ref: 15081).

National Cancer Registry

The cancer registry consists of three data tables, which provide information on patient demographic characteristics, cancer diagnoses, and treatment, and is linked to vital status information from the Office of National Statistics (ONS).

The three cancer registry data tables (patient, tumour, treatment) were linked to create one data table.

Eligibility and Exclusions criteria

The study population comprised adults older than 15 years of age registered as being diagnosed with a primary, malignant, and solid neoplasm of the colon, at stage III of the disease, in England. Cases of a primary, malignant, and solid neoplasm of the colon were identified based on the behaviour (behaviour code 3, which is the code for malignant), morphology (morphology codes for adenocarcinoma), and topography codes (Table 27) of the International Classification of Disease for Oncology (ICD-O-3) (Organization, 2013). Cases of stage III of disease were identified using an algorithm that will be described in more detail below.

Table 27 - ICD-O-3 Topography code (anatomical site) for colon cancer

C18.0	Caecum - Ileocaecal valve
C18.1	Appendix
C18.2	Ascending colon
C18.3	Hepatic flexure
C18.4	Transverse colon
C18.5	Splenic flexure
C18.6	Descending colon
C18.7	Sigmoid colon - Sigmoid (flexure), Excl.: rectosigmoid junction (C19)
C18.8	Overlapping lesion of colon
C18.9	Colon, unspecified - Large intestine NOS

Several data quality checks were carried out on the cancer registry data to identify ineligible records, and records that should be excluded from analysis (Li et al., 2014). Missing values for date of birth, date of diagnosis, last known vital status are considered indicators of poor data quality. Thus, only records with complete data for these variables were eligible for analysis.

Exclusions from these eligible records were performed based on diagnosis by death certificate only, missing or invalid values for sex, and invalid sequences of dates for date of birth, date of diagnosis, and date of last known vital status. For example, if the date of diagnosis preceded the date of birth the record was excluded. Age at diagnosis was derived from the difference between the date of diagnosis and the date of birth, and those younger than 15 years of age were also excluded from the analysis.

Tumour count

Patients may develop multiple tumours because of the same cancer diagnosis, defined as tumours arising at the same site and within 6 months of each other. To avoid including the same patients in the analysis twice, only the tumour with the earliest date of diagnosis was retained. Patients may also have multiple tumours because of a different cancer diagnosis, defined as tumours arising at a different site or more than six months of each other; those records were also excluded. This was because the decision was made to focus the analysis on exploring variations in adjuvant chemotherapy of stage III colon cancer when the treatment decision is not complicated by considerations of a second cancer diagnosis.

Patients who had multiple tumours were identified and excluded as follows.

The cancer registry contains a number that reflects a count of every tumour assigned to a patient's unique identifier (Patient ID), regardless of site or date of diagnosis. A tumour count was derived manually by counting of all unique tumour identifiers (Tumour IDs) assigned to each unique Patient ID, within the data that were available to us. The cancer registry's tumour count was compared to the derived tumour count. Only those with a tumour count that matched the cancer registry tumour count were retained. When the two counts did not match, it was assumed that this was due to one of the following two scenarios, and those patients were excluded from analysis:

1- That the first tumour of the same cancer diagnosis was diagnosed within the six months prior to the time period of the data that is available to us. However, since it was not possible to determine the date of the first tumour, those patients were excluded.

2- That the cancer registry tumour count is reflecting a tumour that is not of the same cancer diagnosis, either because it was diagnosed in the same site more than 6 months prior to the time period of the data available to us or diagnosed at a different site which would indicate metastasis or a second primary tumour.

Systemic Anti-Cancer Therapy (SACT)

Data on SACT consists of six separate data tables: patient, tumour, regimen, cycle, drug detail, and outcome. The SACT database provides detailed information on systemic anti-cancer therapy from all NHS England chemotherapy providers for the treatment of malignant diseases. The National Cancer Registration and Analysis Service (NCRAS) at Public Health England began receiving data from NHS trusts in April 2012. It did not become mandatory for NHS trusts to provide data until April 2014, and this was not achieved by all NHS trusts until July 2014, although the data was assessed as being adequate for most purposes from 2013 onwards (Bright et al., 2020).

The six SACT data tables were first linked together, using the different unique identifiers of each table. The complete SACT data was then linked to the cancer registry based on patient and tumour unique identifiers (i.e., Patient ID and Tumour ID). This is to ensure that the treatment information obtained from the SACT data corresponds to both the patient and the tumour included in the study.

Patients with and without a SACT record were identified and explored. Those who did not have a SACT record were assumed to not have received systemic anti-cancer therapy. Among those with a SACT record, those who received adjuvant chemotherapy

were identified, and the type of therapy received was categorised. Patients were grouped into those who received capecitabine or 5-flourouracil (monotherapy), those who received capecitabine or 5-flourouracil in addition to oxaliplatin (combination therapy), and those who did not receive either of these regimens (other therapy).

Definitions

Stage III colon cancer

Staging of colon cancer is based on the Union for International Cancer Control TNM classification of malignant tumours. The TNM classification is used to classify malignant tumours by the anatomical extent: the extent of the primary tumour (T), the presence and extent of metastases to regional lymph nodes (N), and the presence of distant metastases (M) (Sobin, 2009). The TNM classification for colon cancer is shown in Table 28.

Table 28 - TNM classification for colon cancer

Tumour (T)		Nodes (N)		Metastasis (M)	
Tx	No description of the tumour's extent is possible because of incomplete information.	**Nx**	No description of lymph node involvement is possible because of incomplete information.	**M0**	No distant spread is seen
Tis	In situ: The cancer involves only the mucosa and has not grown beyond the inner muscle layer (muscularis mucosa)	**N0**	No cancer in nearby lymph nodes.	**M1**	The cancer has spread to 1 distant organ or set of distant lymph nodes
T1	The cancer has grown through the inner muscle layer and extends into the submucosa	**N1**	Cancer cells are found in or near 1 to 3 nearby lymph nodes		
T2	The cancer has grown through the submucosa and extends into the outer muscle layer (muscularis propria)	**N2**	Cancer cells are found in 4 or more nearby lymph nodes		
T3	The cancer has grown through the muscularis propria and into the outermost layers of the colon but not through them and has not reached any nearby organs or tissues.				
T4a	The cancer has grown through the outermost lining of the intestines (serosa)				
T4b	The cancer has grown through the wall of the colon and is attached to or invades into nearby tissues or organs				

The cancer registry database contains information on stage, grouped into three categories. First, "Clinical stage" is stage obtained clinically, before treatment, from

physical examination or imaging tests; “Pathological stage” is stage obtained from histopathological assessment of the primary tumour, regional lymph nodes, or distant metastases; and a third category referred to as the “integrated stage”. To our knowledge, there is no literature that describes how this third category is derived and no clarification from the holders of the data was provided. It may be that this category is assigned by clinical leads who combine clinical, imaging, and pathological data to derive it (UKACR and NCIN Symposium, 2011). For each of these categories, an overall stage as well as the individual T, N, and M components are recorded. The total is 12 variables that provide staging information.

On exploration of these variables, it was not clear how the overall stage was derived for any of the three categories (clinical, pathological, or integrated). For example, we would expect a patient with T1, N0, and M0 to have an overall stage I disease. However, the recorded overall stage did not correspond to the recorded individual TNM components of their category.

Therefore, a previously developed hierarchical algorithm was used to derive an overall stage, using information from all 12 stage variables, in addition to a 13th variable found in the cancer registry that contained information on the number of lymph nodes involved (Benitez-Majano et al., 2016).

Stage III colon cancer can take any value of T. The extent of metastasis to the regional lymph nodes (N) is what distinguishes stage III from stages I and II. Therefore, for stages I and II, there is no spread to regional lymph nodes (N0), while for stage III there is (N1 or N2).

The extent of metastasis to distant sites (M) is what distinguishes stage III from stage 4. For stage III, there is no distant metastasis (M0), while for stage IV metastasis to other sites has occurred (M1).

The focus of this study is stage III colon cancer; therefore, the algorithm was used to determine lymph node involvement (N) and distant metastasis (M) components of the TNM classification, regardless of the size of the tumour (T).

First, assumptions were made on how to treat the values that each of the N and M components as well as the overall stage found in the data can hold. These assumptions and decisions are shown in Appendix 4.

Then, new N and M components were derived based on a hierarchy that was used for the different types of information, given that information could come from three categories.

For the M component, the positive value of either the clinical or the pathological categories was given priority. That is, if either one was positive, regardless of the value of the other, then the derived M was assumed to be positive. The integrated M component was used only when the clinical and pathological components were missing. This hierarchy is illustrated in Figure 19.

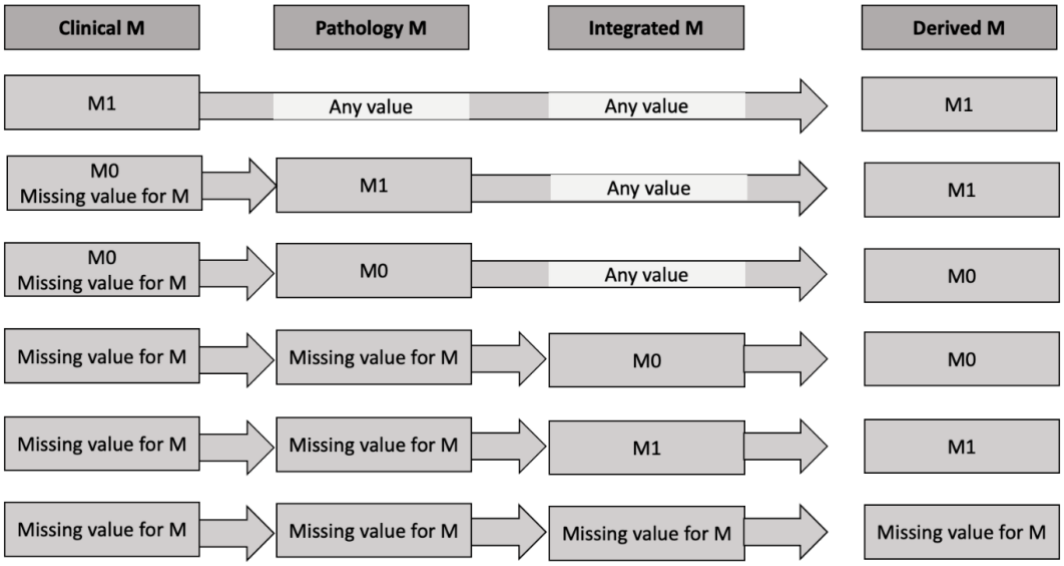


Figure 19 - Deriving extent of metastasis (M) based on a hierarchy of metastasis information coming from three categories available in the cancer registry

For the N component, priority was given to the pathological category regardless of the value of the others. For example, if the pathological N component was positive (N1 or N2) or negative (N0), that was the value given to the derived N. When information from the pathological category was missing, then the clinical category was used. Finally, when information from both categories was missing, the integrated category was used. The cancer registry also includes information on the number of lymph nodes that were found to be positive from those that have been resected during surgery. In the case that data on the N component was missing in all three categories, this variable was used to determine N, as shown in Figure 20.

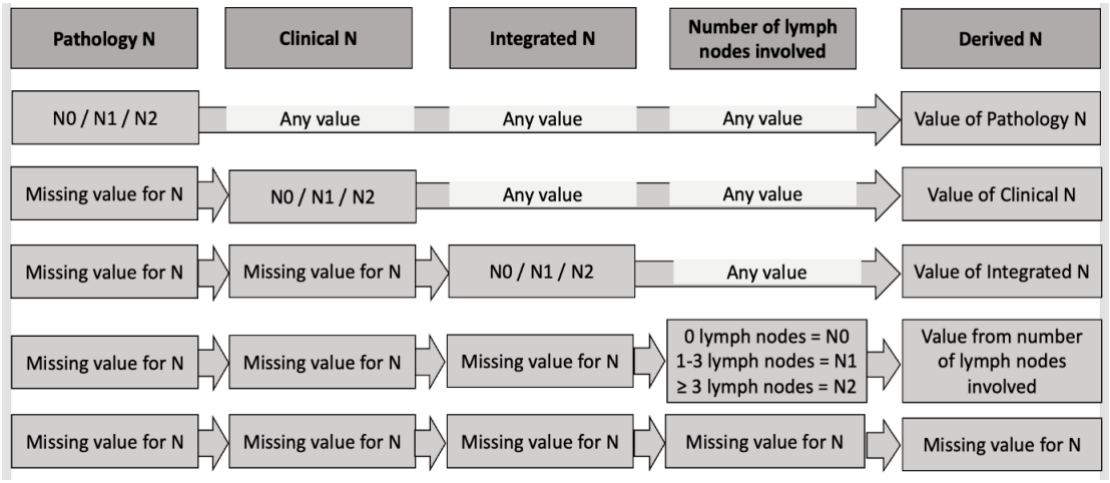


Figure 20 - Deriving extent of lymph node involvement (N) based on a heirarchy of lymph node involvement information coming from four categories available in the cancer registry

This algorithm allowed the identifications of stages I and II combined (difference between stages I and II depends on tumour size (T), which was not determined for this purpose), stage III, and stage IV based on the TNM classification system as shown in Table 29.

Table 29 – Derived overall stage from the derived extent of metastasis (M) and the derived extent of lymph node involvement (N)

Derived M		Derived N		Derived overall stage
M0	+	N0	=	Stage I or II
M0	+	N0 / N1 / N2	=	Stage III
M1	+	N0 / N1 / N2 / Missing	=	Stage IV
M0	+	Missing	=	Missing
Missing	+	N0 / N1 / N2 / Missing	=	Missing

For some patients, information on the N and M components was not recorded for any of the three staging categories, and it was not possible to derive stage in this way. As mentioned previously, the cancer registry also includes an overall stage for each of the three categories. Therefore, for those records where it was not possible to derive the N and M components as described above, overall stage was used instead. The overall stage from the pathological category was given priority, followed by clinical, then integrated, as shown in Table 30.

Table 30 – Using information from the overall stage of the three stage categories when it was not possible to derive metastasis and lymph node involvement

Derived M	Derived N	Pathology overall stage	Clinical overall stage	Integrated overall stage	Derived stage
Missing		III	Any	Any	III
		Missing	III	Any	III
		Missing	Missing	III	III
		Missing	Missing	Missing	Missing

Size and extent of tumour (T)

The size of the tumour among stage III patients was derived to allow comparisons in the receipt and choice of adjuvant chemotherapy based on the extent of tumour invasion. For this analysis, tumour size of T1 and T2 were combined into one category while T3 and T4 remained in their separate categories. This decision was made because as described in Table 28, tumour of T1 and T2 extent are localised to the colon and have not yet penetrated the bowel wall, while those of T3 and T4 extent have penetrated the bowel wall or reached adjacent organs, respectively. Like the number of lymph nodes, pathological diagnosis took priority over both clinical and integrated categories, followed by clinical diagnosis when pathological was missing, then the integrated diagnosis when both were missing, as shown in Figure 21.

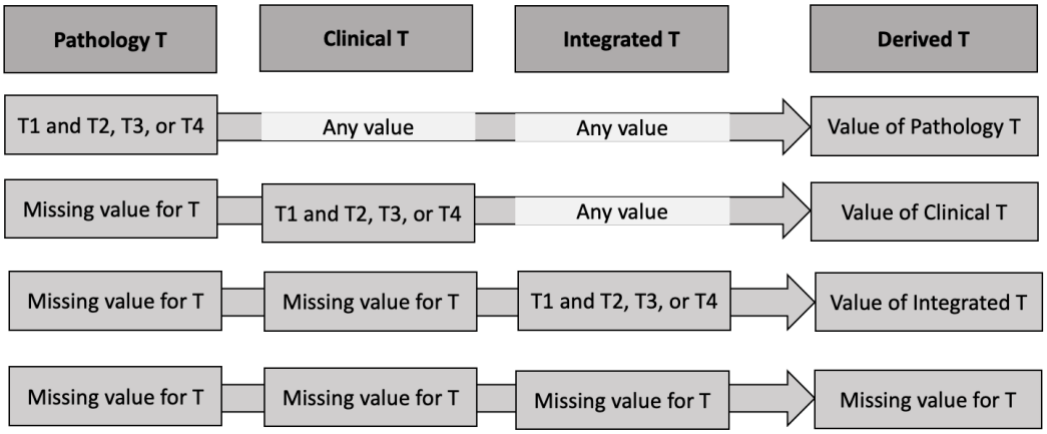


Figure 21 - Using information from the pathology, clinical, and integrated size of the tumour to derive overall size

Adjuvant chemotherapy

Adjuvant chemotherapy means chemotherapy received after surgery to excise the tumour. Therefore, it was necessary to first identify those who underwent resectional surgery, and second, to identify chemotherapy received after surgery.

Resectional surgery

Information on excisional surgery was derived using the cancer registry, by identifying the relevant codes of the Classification of Intervention and Procedures of the Office of Population Censuses and Surveys (OPCS), a standard classification of procedures done in National Health Service (NHS) hospitals in England (NHS Digital). To identify which OPCS codes are relevant for resectional surgery of the colon, two sources were used. First, excisional surgery codes for colon cancer that were listed in a standard operating procedure published by Public Health England (Public Health England, 2018). This was then compared and complemented by the resectional surgical codes identified by Benitez-Majano (Benitez Majano et al., 2019) through a comparison with list of codes from the Lancet Oncology Cancer Surgery Commission by Sullivan et al. (Sullivan et al., 2015). The OPCS codes used to identify patients who underwent resectional surgery for colon cancer are listed in Appendix 5. This list excludes codes for procedures that do not explicitly involve removal of the primary tumour and excludes procedures that are specific to early-stage tumours.

Chemotherapy after surgery

To identify those who received chemotherapy after surgery, the date of surgery, obtained from the cancer registry, was compared to the starting date of the chemotherapy regimen, obtained from SACT. A starting date is recorded in SACT for every regimen received by a patient. As such, only the date of the first regimen was retained to be compared to the date of surgery. Those whose date of surgery was after the date of the first regimen were identified and excluded, and only those who received chemotherapy within the first four months of the date of surgery were included.

Deprivation

There are seven distinct domains, or indices of deprivation, that are obtained from the Ministry of Housing, Communities and Local Government to measure relative levels of deprivation in small areas in England, called the Lower-layer Super Output Areas (LSOA) (Ministry of Housing). The LSOAs are administrative geographical areas established to improve reporting of small area statistics. Patients were assigned to one of 32,844 LSOAs based on their postcode of residence at the time of diagnosis. Each LSOA has a population of approximately 1500 people.

The seven indices of deprivation are: income; employment; health deprivation and disability; education, skills training; crime; barriers to housing and services; and living environment. All seven indices are also combined and weighted to form an overall measure of deprivation called the Index of Multiple Deprivation (IMD).

For each of these indices, each LSOA receives a score on the continuous scale (from 1 to 100) and is ranked to indicate its position relative to others based on this score. A rank of 1 is the most deprived and a rank of 32,844 is the least deprived. The LSOAs were grouped into quintiles based on this rank, from least (group 1) to most deprived (group 5).

Each of the seven distinct indices as well as the combined IMD are ecological measures of deprivation, i.e., they are used to classify the relative level of deprivation of the LSOAs where individuals reside, not the level of deprivation of the patients themselves on an individual level.

For this analysis, the income index score was used as a marker of deprivation instead of the combined IMD. The income index measures the proportion of the population with low income in each LSOA. The IMD was not used because one of the indices that make up the IMD is health deprivation and disability, and the primary outcomes of this study, i.e., variation of receipt and type of chemotherapy, are features of access to

healthcare. Due to the likely correlation between the income index and the remaining six indices, only the income index was used as a predictor in the analysis.

There have been several iterations of these indices of deprivation over the years, and as such, the appropriate version was used to classify the LSOAs where patients resided at the time of their diagnosis. For this study, the 2015 version provided information to determine the relative deprivation of the LSOAs where patients who were diagnosed between 2011 to 2015 resided, while the 2019 version was used for those diagnosed from 2016 onwards.

Statistical Analysis

The distribution of stage and the presence or absence of a SACT record was explored for all colon cancer patients diagnosed between 1995-2017, to confirm the time period with the best data quality to include in the analysis. Patients diagnosed between 2012-2017 with stage III disease were identified and extracted for further analysis.

Demographic and clinical characteristics of those who had treatment was compared to those who did not have treatment among stage III colon cancer patients. Frequency tables were used to describe the distribution of receipt of treatment by the demographic characteristics age, gender, year of diagnosis, and deprivation group. The distribution was also explored for three clinical characteristics: the size of the tumour (T), the number of lymph nodes (N), and time between diagnosis and death within the first year. Logistic regression was used to obtain crude and adjusted odds ratios (ORs). The strength of the association between each level of the exposures with the outcome was tested with the Wald Test, while the strength of the overall association between the two variables was tested with the Likelihood Ratio Test (LRT). Demographic and clinical characteristics were then compared between those who received monotherapy (capecitabine or 5-Flourouracil) and combination therapy (capecitabine or 5-fluorouracil and oxaliplatin). Frequency tables were used to describe the distribution of each type of therapy by the same demographic and clinical characteristics, and logistic regression was used to obtain crude and adjusted odds ratios (ORs).

Results

The population of interest

There were 451,129 patients registered in the national cancer registry between 1995-2017 with the ICD-O-3 code C18.0-C18.9, indicating a tumour in the colon. After applying the eligibility and exclusion criteria to identify those with a primary, malignant, and solid neoplasm of the colon, and excluding based on diagnosis by death certificate only; missing or invalid values for sex; missing values for age; those younger than 15 years; invalid sequences of dates for date of birth, date of diagnosis, and date of last known vital status; a total of 438,052 patients remained. The cancer registry tumour count was compared to the derived tumour count as described in the methods section. Patients whose derived tumour count did not match the cancer registry tumour count were excluded, and a total of 311,848 patients remained.

As expected from published reports of the cancer registry and the SACT database, information on both stage and treatment was not adequate for analysis or available until 2012 (Bright et al., 2020). The hierarchical algorithm used to determine the extent of disease resulted in four categories: stages I or II, stage III, stage IV, or missing stage. Distribution of stage by time period of diagnosis showed that between 25 to 44% of patients diagnosed before 2012 were missing information on stage. By contrast, only 10% of patients diagnosed between 2012-2017 were missing this information (Figure 22). Likewise, the analysis confirmed that a SACT record was not available for any patient diagnosed from 1995-2005, and available for only 3% of patients diagnosed between 2006-2011. By contrast, 68% of those diagnosed between 2012-2017 had a SACT record.

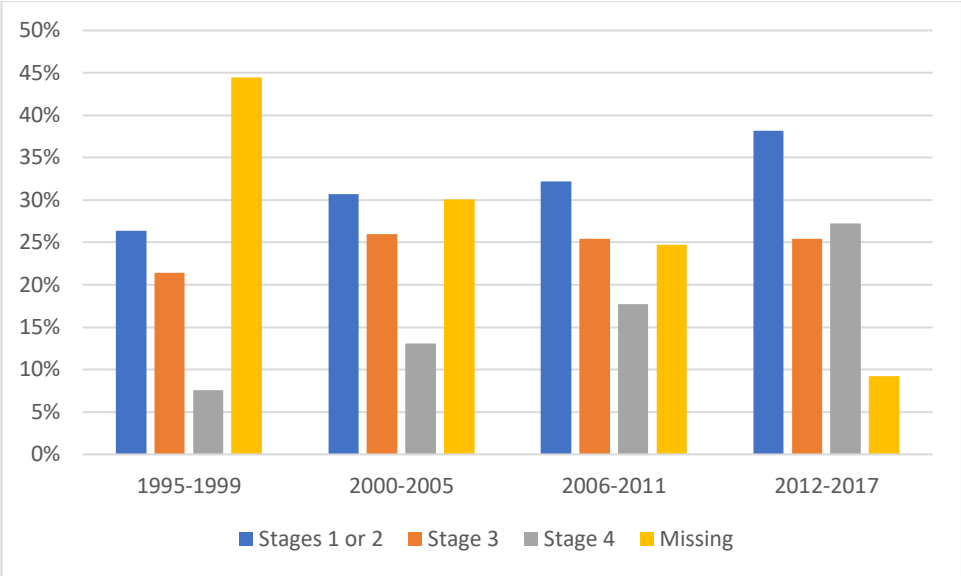


Figure 22 – Distribution of stage by time period of diagnosis

Period of diagnosis 2012-2017

In total, there were 132,628 colon cancer patients registered in the cancer registry between 2012-2017 before applying the eligibility and exclusion criteria. After applying the eligibility and exclusion criteria as described above, a total of 90,827 patients diagnosed from 2012-2017 were available for analysis.

Stage III colon cancer

Of the 90,827 patients diagnosed between 2012-2017, there were 23,105 (25.4%) patients diagnosed with stage III colon cancer, classified, and identified by the stage derived from the algorithm described in the methods. Of those, 19,604 (84.8%) patients were identified as having undergone resectional surgery using the PCOS codes specified.

Distribution of adjuvant chemotherapy among stage III colon cancer patients

Of 19,604 patients with stage III colon cancer who underwent resectional surgery to remove the tumour, 12,011 (61.3%) received chemotherapy. Of those, 1422 (11.8%) patients received chemotherapy either before resectional surgery to remove the tumour or more than four months after, and these were excluded from the analysis. The total was 18,182 patients included for analysis, 10,589 (58.2%) of which received adjuvant chemotherapy, defined as chemotherapy within four months after resectional surgery (Figure 23).

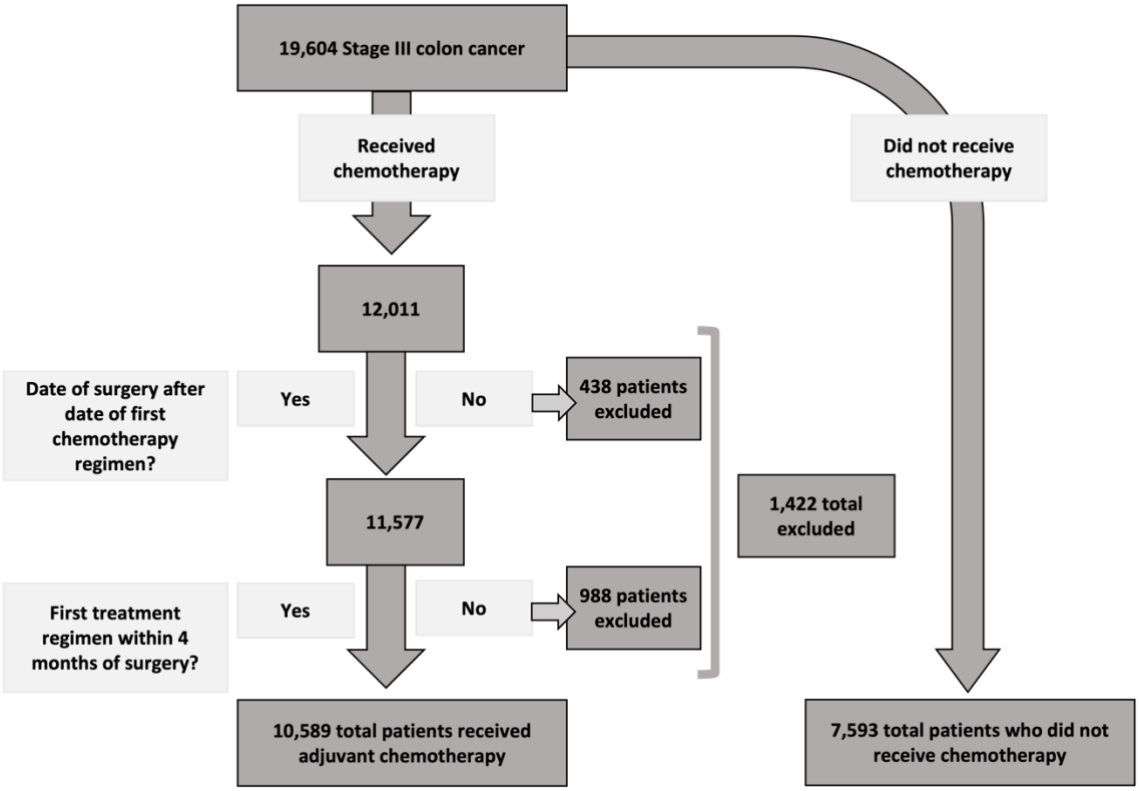


Figure 23 - Identification of stage III colon cancer patients who did and did not receive adjuvant chemotherapy

The distribution of adjuvant chemotherapy among stage III colon cancer patients was explored by age, sex, deprivation group, ethnicity, year of diagnosis, tumour size (T), number of lymph nodes involved (N), and days from diagnosis to mortality and compared between those who received adjuvant chemotherapy and those who did not (Table 31).

The receipt of adjuvant chemotherapy was associated with age. The mean age for those who received adjuvant chemotherapy was 63 years compared with 75 years for those who did not. Among those who were younger than 65 years, the percentage of patients who received adjuvant chemotherapy was between 77-79% and decreased with every subsequent age category. Only 14% of patients aged over 80 received therapy. This was supported by strong evidence that the odds of having a SACT record after adjustment decreases after 65 years of age ($p < 0.001$). Those who were between 70-75 years had about 32% lower odds of having a SACT record compared to those between 65-70 (OR: 0.68; CI: 0.60,0.76), and the odds decreased further with every subsequent age category (Table 31).

Distribution by deprivation showed that receiving adjuvant chemotherapy was associated with a lower deprivation group. Among those in the most deprived group, 55% of patients had a SACT record compared to 61% among the least deprived. There

was strong evidence that those in the most deprived group had approximately 26% lower odds of receiving adjuvant chemotherapy than those in the least deprived group, after adjusting for all other variables (OR: 0.74; CI: 0.66,0.84, $p < 0.001$) (Table 31).

As for ethnicity, 61% of minority ethnic groups patients received adjuvant chemotherapy compared to 58% of White patients. After adjusting for all other factors in logistic regression, there was evidence to suggest that those in the minority ethnic groups had 24% lower odds of having a SACT record compared to those of White ethnicity (OR: 0.76; CI: 0.64,0.89, $p < 0.001$). Similarly, those who were missing information on ethnicity had 36% lower odds of having a SACT record compared to those of White ethnicity (OR: 0.64; CI: 0.54,0.74, $p < 0.001$) (Table 31).

The percentage of patients who received adjuvant chemotherapy increased with every subsequent year since 2012. In 2012, only 44% of patients had a SACT record. This increased to 57% in 2013, reaching 63% by 2017. There was strong evidence to suggest that patients had lower odds of having a SACT record in 2012 and 2013 compared to 2015, however, there was no difference between 2014, 2016, or 2017 compared to 2015 (Table 31).

In terms of the clinical characteristics of the tumour, there was evidence to suggest that receiving adjuvant chemotherapy varied by both an increasing size of the tumour ($p < 0.001$) and an increasing number of lymph nodes involved ($p < 0.001$). A very small percentage of patients (0.12%) had missing information on the size of the tumour, and 1.7% had missing information on the number of lymph nodes. There was no evidence that the presence or absence of a SACT record was associated with missing information on lymph nodes. However, there was some evidence to suggest that those with missing information on size have a 74% lower odds of having a SACT record, although the confidence intervals for this estimate was wide due to the small sample size (OR: 0.26; CI: 0.09, 0.76, $p = 0.013$).

Table 31 –Receipt of adjuvant chemotherapy by age, sex, deprivation group, year of diagnosis, size of tumour, and number of lymph nodes involved

	Did not receive adjuvant chemotherapy		Received adjuvant chemotherapy						
	Count (n=7,593)	**%**	**Count (n=10589)**	**%**	**Total (row)**	**Crude OR (95% CI)**	**Adjusted OR* (95% CI)**	**Wald Test**	**LRT**
Age									**< 0.001**
< 50 years	317	21.5%	1160	78.5%	1477	1.33 (1.15,1.55)	1.26 (1.08,1.48)	0.004	
50-60	536	21.1%	2001	78.9%	2537	1.36 (1.20,1.55)	1.28 (1.12,1.46)	< 0.001	
60-65	518	22.6%	1769	77.4%	2287	1.24 (1.09,1.42)	1.25 (1.09,1.43)	0.002	
65-70	740	26.7%	2030	73.3%	2770	*1 (reference group)*			
70-75	1007	34.8%	1886	65.2%	2893	0.68 (0.61,0.76)	0.68 (0.60,0.76)	< 0.001	
75-80	1460	53.9%	1250	46.1%	2710	0.31 (0.28,0.35)	0.31 (0.28,0.35)	< 0.001	
>80	3015	85.9%	493	14.1%	3508	0.06 (0.05,0.07)	0.06 (0.05,0.07)	< 0.001	
Sex									**0.942**
Male	3784	40.0%	5670	60%	9454	*1 (reference group)*			
Female	3809	43.6%	4919	56.4%	8728	0.86 (0.81,0.91)	1.00 (0.93,1.07)	0.942	
Deprivation									**< 0.001**
Least deprived	1595	39.5%	2447	60.5%	4042	*1 (reference group)*			
2	1701	40.7%	2479	59.3%	4180	0.95 (0.87,1.04)	1.02 (0.91,1.13)	0.773	
3	1595	43.0%	2113	57%	3708	0.86 (0.79,0.95)	0.88 (0.79,0.98)	0.022	
4	1434	42.0%	1977	58%	3411	0.90 (0.82,0.99)	0.89 (0.80,1.00)	0.048	

Most deprived	1268	44.6%	1573	55.4%	2841	0.81 (0.73,0.89)	0.74 (0.66,0.84)	< 0.001	
Ethnicity									**< 0.001**
White	6852	41.8%	9526	58.2%	16378	*1 (reference group)*			
Minority ethnic groups	342	38.7%	542	61.3%	884	1.14 (0.99,1.31)	0.76 (0.64,0.89)	< 0.001	
Missing	399	43.4%	521	56.6%	920	0.94 (0.82,1.07)	0.64 (0.54,0.74)	< 0.001	
Year of diagnosis									**< 0.001**
2012	1655	55.6%	1324	44.4%	2979	0.51 (0.46,0.56)	0.43 (0.38,0.48)	< 0.001	
2013	1209	43.3%	1584	56.7%	2793	0.83 (0.75,0.92)	0.80 (0.71,0.91)	< 0.001	
2014	1134	39.2%	1757	60.8%	2891	0.98 (0.88,1.09)	1.01 (0.89,1.15)	0.847	
2015	1191	38.8%	1879	61.2%	3070	*1 (reference group)*			
2016	1170	37.1%	1981	62.9%	3151	1.07 (0.97,1.19)	1.07 (0.95,1.21)	0.266	
2017	1234	37.4%	2064	62.6%	3298	1.06 (0.96,1.17)	0.98 (0.87,1.11)	0.747	
Size of tumour									**< 0.001**
T1 or T2	560	38.5%	894	61.5%	1454	*1 (reference group)*			
T3	3758	40.7%	5470	59.3%	9228	0.91 (0.81,1.02)	1.16 (1.02,1.32)	0.028	
T4	3259	43.6%	4219	56.4%	7478	0.81 (0.72,0.91)	1.31 (1.14,1.50)	< 0.001	
Missing	16	72.7%	6	27.3%	22	0.23 (0.09,0.60)	0.26 (0.09,0.76)	0.013	
Number of lymph nodes									**< 0.001**
N1	5200	43.8%	6677	56.2%	11877	*1 (reference group)*			
N2	2282	38.1%	3715	61.9%	5997	1.27 (1.19,1.35)	1.46 (1.34,1.58)	< 0.001	
Missing	111	36.0%	197	64%	308	1.38 (1.09,1.75)	1.20 (0.91,1.59)	0.187	

*Odds Ratios mutually adjusted for age, sex, deprivation, ethnicity, year of diagnosis, size of tumour and number of lymph nodes

Exploratory analysis of ethnicity

There was a slightly larger number of patients with missing information on ethnicity than the number of patients in minority ethnic groups, and those with missing information on ethnicity showed reduced odds of receiving adjuvant chemotherapy. This prompted an exploratory analysis to determine which factors might be associated with missing ethnicity data. The presence or absence of ethnicity information was explored by age, sex, deprivation group, year of diagnosis, size of tumour, number of lymph nodes, and time between diagnosis and mortality.

There was evidence to suggest that higher odds of missing information on ethnicity was associated with older age, women, higher deprivation, earlier (2012-2014) as well as most recent year of diagnosis (2017), but not with size of the tumour or number of lymph nodes (Table 32).

Table 32 – Exploratory analysis of factors associated with missing ethnicity data among stage III colon cancer patients

	Crude OR (95% CI)	Adjusted OR (95% CI)*	P-value for adjusted OR
Age			< 0.001*
< 50 years	1.57 (1.22,2.02)	1.64 (1.27,2.12)	< 0.001
50-60	1.25 (0.99,1.58)	1.29 (1.02,1.62)	0.033
60-65	1.05 (0.82,1.34)	1.06 (0.83,1.36)	0.635
65-70	*1 (reference group)*		
70-75	0.94 (0.74,1.19)	0.90 (0.71,1.14)	0.364
75-80	0.71 (0.55,0.92)	0.63 (0.49,0.82)	< 0.001
>80	0.66 (0.51,0.84)	0.51 (0.39,0.66)	< 0.001
Sex			0.013
Male	*1 (reference group)*		
Female	0.82 (0.72,0.94)	0.84 (0.74,0.97)	0.013
Deprivation			0.04
Least deprived	*1 (reference group)*		
2	0.88 (0.72,1.06)	0.89 (0.73,1.08)	0.228
3	0.93 (0.76,1.13)	0.92 (0.75,1.12)	0.4
4	0.84 (0.68,1.03)	0.81 (0.66,1.00)	0.047
Most deprived	0.78 (0.62,0.97)	0.72 (0.57,0.90)	0.004
Year of diagnosis			< 0.001
2012	0.46 (0.35,0.58)	0.43 (0.33,0.55)	< 0.001
2013	0.58 (0.46,0.73)	0.57 (0.45,0.72)	< 0.001
2014	0.74 (0.60,0.92)	0.74 (0.60,0.93)	0.008
2015	*1 (reference group)*		
2016	0.85 (0.69,1.05)	0.85 (0.69,1.04)	0.120
2017	0.82 (0.67,1.01)	0.81 (0.66,0.99)	0.043
Size of tumour			0.618
T1 or T2	*1 (reference group)*		
T3	1.01 (0.79,1.31)	1.07 (0.83,1.39)	0.601
T4	1.07 (0.83,1.39)	1.16 (0.89,1.51)	0.280
Missing	0.93 (0.12,6.99)	0.91 (0.12,6.92)	0.925
Number of lymph nodes			0.785
N1	*1 (reference group)*		
N2	0.98 (0.85,1.13)	0.97 (0.84,1.12)	0.672
Missing	1.16 (0.72,1.88)	1.14 (0.70,1.85)	0.607

*Odds Ratios mutually adjusted for age, sex, deprivation, ethnicity, year of diagnosis, size of tumour and number of lymph nodes

Type of adjuvant chemotherapy received for stage III colon cancer

The type of adjuvant chemotherapy was explored among 10,589 stage III colorectal cancer patients who were identified as having received chemotherapy. There were 8,750 patients who received either single or combination adjuvant chemotherapy. Of these, 22.3% of patients received single therapy with either capecitabine or 5-Fluorouracil, and 60.4% received combination therapy of a fluoropyrimidine with oxaliplatin. A group of 547 (5.2%) patients received oxaliplatin only, not in combination with capecitabine or 5-fluorouracil, and 93 (0.9%) patients received other types of treatment and did not receive any of the three standard adjuvant chemotherapy medications (capecitabine, 5-Fluorouracil, or oxaliplatin). Details of the type of therapy received was missing for 11.3% of patients. The distribution of the type of therapy is shown in Table 33.

Among those who received single therapy, approximately 83.5% did not receive any additional treatment, and 16.5% received other medications. Among those who received combination therapy, there was an approximately equal distribution between those who received additional treatment and those who did not (Table 33). In absolute terms, 32.6% more patients received additional treatment among those who received combination chemotherapy compared to those who received single therapy. A list of treatments received in addition to both single and combination adjuvant chemotherapy is presented in Appendix 6.

Table 33 – Distribution of patients by the type of adjuvant chemotherapy received

Adjuvant chemotherapy	With additional treatment	Without additional treatment	Total
Monotherapy	389 (16.5%)	1,970 (83.5%)	2,359 (100%)
(Fluoropyrimidine)			22.3%
Combination	3,140 (49.1%)	3,251 (50.9%)	6,391 (100%)
(Fluoropyrimidine + oxaliplatin)			60.4%
Oxaliplatin only	408 (74.6%)	139 (25.4%)	547 (100%)
			5.2%
Other treatment only			93
			0.9%
Missing			1,199
			11.3%
Total # of patients			**10,589 100%**

Of 8,750 patients who received single or combination therapy, the distribution of the type of adjuvant chemotherapy was explored by age, sex, deprivation group, ethnicity, year of diagnosis, size of the tumour and number of lymph nodes involved (Table 34). There was strong evidence to suggest that the type of therapy varied by age, sex, deprivation, size of the tumour, and number of lymph nodes involved, after mutual adjustment. The evidence suggesting that type of therapy varied by year of diagnosis is mainly driven by the decreased odds of receiving combination therapy in 2012 compared to 2015. Finally, there was weak evidence (p=0.056) to suggest that type of therapy varied by ethnicity, which seems to be mainly driven by higher odds of receiving combination therapy for those with missing data on ethnicity compared to those of White ethnicity.

The mean age for those who received combination therapy was 61 years compared with 71 years for those who received monotherapy. Among those who were younger than 50 years of age, 92% of patients received combination therapy. The percentage of patients who received combination therapy decreased significantly for each subsequent age category, reaching approximately 81%, 63%, 40%, and 21% for those between 65-70, 70-75, 75-80, and above 80 years of age, respectively. There was strong evidence to support this association after adjusting for all other factors ($p < 0.001$) (Table 34).

There was strong evidence to suggest that women had 0.86 (95%CI: 0.77,0.95) the odds of receiving combination chemotherapy compared to men. Among women, approximately 72% received combination therapy and 28% received single therapy, while among men it was 74% and 26%, respectively (Table 34).

Among those who were least deprived, 75% received combination therapy, compared to 69% among the most deprived, a difference of 6%. There was strong evidence to suggest that the odds of receiving combination therapy decreased with increasing deprivation group ($p < 0.001$). Those from the most deprived group had half times the odds of receiving combination therapy compared to the least deprived group (OR: 0.5, CI: 0.42,0.59, $p <0.001$) (Table 34).

Among those diagnosed in 2017, 76% received combination therapy compared to 72% of patients diagnosed in 2015. There was strong evidence to suggest that those diagnosed in the year 2017 had 1.25 times the odds of receiving combination therapy compared to those diagnosed in 2015 (OR: 1.25; CI: 1.06,1.49, $p < 0.001$) (Table 34).

Most patients of White, minority ethnic groups, and those with missing information on ethnicity received combination therapy, with 72%, 80%, and 70% of patients,

respectively. There is some evidence to suggest that those with missing information on ethnicity have 1.34 (CI: 1.02,1.76; p = 0.03) times the odds of receiving combination therapy compared to White patients, but no evidence to suggest that there is a difference in the type of therapy received by White and minority ethnic groups (Table 34).

Finally, there was evidence to suggest that those with the largest tumour size of T4 classification and those with N2 classification for lymph nodes involvement had 30% (OR: 1.30; CI: 1.07,1.59; p = 0.008) and 50% (OR: 1.5; 1.34,1.69; p < 0.001) greater odds of receiving combination therapy compared to those with T1 or T2 and those with N1, respectively (Table 34).

Table 34 – Type of adjuvant chemotherapy by age, sex, deprivation group, year of diagnosis, size of tumour, and number of lymph nodes involved

	Single therapy		Combination therapy					
	Count n=2,359	**%**	**Count n=6,391**	**%**	**Total (row)**	**Crude OR (95% CI)**	**Adjusted OR (95% CI)***	**P values for adjusted OR**
Age								**< 0.001**
< 50 years	77	8%	890	92%	967	2.76 (2.12,3.59)	2.88 (2.20,3.75)	< 0.001
50-60	214	13%	1427	87%	1641	1.59 (1.32,1.92)	1.63 (1.34,1.97)	< 0.001
60-65	218	14.9%	1247	85.1%	1465	1.37 (1.13,1.65)	1.39 (1.15,1.68)	< 0.001
65-70	320	19.3%	1341	80.7%	1661	*1 (reference group)*		
70-75	583	36.9%	995	63.1%	1578	0.41 (0.35,0.48)	0.40 (0.34,0.47)	<0.001
75-80	612	60.3%	403	39.7%	1015	0.16 (0.13,0.19)	0.15 (0.12,0.18)	<0.001
>80	335	79.2%	88	20.8%	423	0.06 (0.05,0.08)	0.06 (0.04,0.07)	<0.001
Sex								**0.005**
Male	1206	25.7%	3484	74.3%	4690	*1 (reference group)*		
Female	1153	28.4%	2907	71.6%	4060	0.87 (0.79,0.96)	0.86 (0.77,0.95)	0.005
Deprivation								**<0.001**
Least deprived	508	25%	1526	75%	2034	*1 (reference group)*		
2	542	26.6%	1493	73.4%	2035	0.92 (0.80,1.06)	0.89 (0.76,1.04)	0.134
3	459	26.6%	1264	73.4%	1723	0.92 (0.79,1.06)	0.83 (0.70,0.97)	0.023
4	447	27.2%	1196	72.8%	1643	0.89 (0.77,1.03)	0.73 (0.62,0.86)	<0.001
Most deprived	403	30.6%	912	69.4%	1315	0.75 (0.65,0.88)	0.50 (0.42,0.59)	<0.001
Ethnicity								**0.056**
White	2178	27.7%	5674	72.3%	7852	*1 (reference group)*		
Minority ethnic groups	93	19.8%	377	80.2%	470	1.55 (1.23,1.96)	1.16 (0.89,1.52)	0.257
Missing	88	20.6%	340	79.4%	428	1.48 (1.16,1.88)	1.34 (1.02,1.76)	0.034
Year of diagnosis								**< 0.001**
2012	203	25.4%	597	74.6%	800	1.12 (0.92,1.35)	0.99 (0.80,1.23)	0.931
2013	296	25.7%	857	74.3%	1153	1.10 (0.93,1.31)	1.08 (0.89,1.31)	0.435
2014	414	29.1%	1011	70.9%	1425	0.93 (0.79,1.09)	0.89 (0.75,1.07)	0.221
2015	453	27.6%	1189	72.4%	1642	*1 (reference group)*		

2016	537	29.8%	1265	70.2%	1802	0.90 (0.77,1.04)	0.86 (0.72,1.01)	0.071
2017	456	23.7%	1472	76.3%	1928	1.23 (1.06,1.43)	1.25 (1.06,1.49)	0.009
Size of tumour								**0.033**
T1 or T2	225	30.1%	523	69.9%	748	*1 (reference group)*		
T3	1238	27.4%	3287	72.6%	4525	1.14 (0.96,1.35)	1.24 (1.02,1.49)	0.028
T4	896	25.8%	2578	74.2%	3474	1.24 (1.04,1.47)	1.30 (1.07,1.59)	0.008
Missing	3	100%	0	0%	3			
Number of lymph nodes								**< 0.001**
N1	1626	29.4%	3903	70.6%	5529	*1 (reference group)*		
N2	692	22.6%	2370	77.4%	3062	1.43 (1.29,1.58)	1.50 (1.34,1.69)	< 0.001
Missing	41	25.8%	118	74.2%	159	1.19 (0.83,1.71)	1.09 (0.73,1.63)	0.683
*Odds Ratios mutually adjusted for age, sex, deprivation, ethnicity, year of diagnosis, size of tumour and number of lymph nodes								

Exploratory analysis of ethnicity

Those with missing information on ethnicity showed higher odds of receiving combination therapy compared to White ethnicity, which prompted an exploratory analysis to determine the factors that might be associated with missing ethnicity data among those who received adjuvant chemotherapy. The presence or absence of ethnicity information was explored by age, sex, deprivation group, year of diagnosis, size of tumour, number of lymph nodes, and time between diagnosis and mortality.

There was strong evidence to suggest that missing ethnicity data among this group of patients was associated with the 2012 and 2013 years of diagnosis, after mutual adjustment for all other factors (Table 35). There is very weak evidence to suggest lower odds of having missing information on ethnicity among women compared to men. However, the upper limit of the OR confidence interval is 1.00, and therefore should be interpreted with caution.

Table 35 - Exploratory analysis to determine factors associated with missing ethnicity data among stage III patients who received adjuvant chemotherapy

	Crude OR (95% CI)	Adjusted OR (95% CI)*	P-value
Age			**0.10**
< 50 years	1.42 (1.02,1.98)	1.37 (0.98,1.91)	0.06
50-60	1.05 (0.77,1.43)	1.02 (0.75,1.39)	0.90
60-65	*1 (reference group)*		
65-70	0.87 (0.62,1.21)	0.87 (0.62,1.21)	0.41
70-75	0.86 (0.62,1.19)	0.87 (0.63,1.22)	0.42
75-80	0.67 (0.45,1.00)	0.73 (0.48,1.11)	0.14
>80	0.88 (0.53,1.47)	1.00 (0.58,1.71)	0.99
Sex			**0.056**
Male	*1 (reference group)*		
Female	0.83 (0.69,1.02)	0.82 (0.68,1.00)	0.056
Deprivation			**0.30**
Least deprived	*1 (reference group)*		
2	0.88 (0.66,1.18)	0.88 (0.65,1.18)	0.38
3	1.22 (0.91,1.62)	1.20 (0.90,1.61)	0.20
4	0.97 (0.72,1.32)	0.94 (0.69,1.29)	0.71
Most deprived	1.03 (0.74,1.41)	0.99 (0.72,1.38)	0.97
Year of diagnosis			**< 0.001**
2012	0.37 (0.22,0.60)	0.36 (0.22,0.60)	< 0.001
2013	0.42 (0.28,0.63)	0.41 (0.27,0.62)	< 0.001
2014	0.82 (0.60,1.11)	0.83 (0.61,1.14)	0.24
2015	1 (reference group)		
2016	0.80 (0.60,1.07)	0.80 (0.60,1.07)	0.13
2017	0.92 (0.70,1.22)	0.91 (0.69,1.20)	0.50
Size of tumour			**0.109**
T1 or T2	*1 (reference group)*		
T3	1.36 (0.90,2.04)	1.40 (0.93,2.10)	0.11
T4	1.47 (0.97,2.22)	1.53 (1.01,2.33)	0.05
Number of lymph nodes			**0.139**
N1	*1 (reference group)*		
N2	0.87 (0.71,1.07)	0.83 (0.67,1.02)	0.07
Missing	0.60 (0.25,1.48)	0.64 (0.26,1.57)	0.32
*Odds Ratios mutually adjusted for age, sex, deprivation, ethnicity, year of diagnosis, size of tumour and number of lymph nodes			

Discussion

In this study, I have explored variation in the use of adjuvant chemotherapy and the type of therapy received among stage III colon cancer diagnosed between 2012-2017 in England, using national cancer registry and SACT data.

Summary and interpretation of findings

Among stage III colon cancer patients, those of older age and who live in more deprived areas have lower odds of undergoing adjuvant chemotherapy, and among those who do, lower odds of receiving combination therapy. Adjuvant chemotherapy receipt was not found to differ between men and women; however, women were found to have lower odds of receiving combination therapy compared to men. For ethnicity, those of minority ethnic groups as well as those with missing information on ethnicity were less likely to receive adjuvant chemotherapy than those of White ethnicity. By contrast, those with missing information on ethnicity were more likely to receive combination therapy. Those patients with more advanced disease (defined as those with larger tumour size and higher number of lymph nodes involved) were more likely to receive therapy compared to those with tumours of smaller size or a lower number of lymph nodes involved, and it was also more likely that they received combination therapy. Finally, adjuvant chemotherapy was shown to be less likely in 2012 and 2013 compared to later years, and combination therapy was more likely in 2017 compared to earlier years.

Variation in adjuvant chemotherapy

The analysis undertaken showed that 58% of colon cancer patients at stage III disease diagnosed between 2012-2017 received adjuvant chemotherapy within 4 months of surgery. After mutual adjustment, those who were younger than 65 years of age; in the least deprived group; and have more advanced disease, represented by larger tumour size (T3 or T4) and a higher number of lymph nodes involved (N2) had higher odds of receiving adjuvant chemotherapy compared to those older than 70 years of age, in the most deprived group, and with less advanced disease (T1 or T2 and N1), respectively. There was no variation in treatment by sex. To my knowledge, the study by Boyle et al. is the only other that explored variation in adjuvant chemotherapy use among stage III colon cancer patients in England (Boyle et al., 2020). The findings of the current study were consistent with Boyle et al. (2020) who also reported that approximately 60% of those diagnosed between 2014-2017 received adjuvant chemotherapy in England.

They also reported that adjuvant chemotherapy was more likely among patients younger than 60 years of age, those of higher socioeconomic status and with more advanced disease. Boyle et al. found that treatment varied by these factors even after controlling for performance status, pre-surgical physical status (American Society of Anaesthesiologists (ASA) grade), type of resection (elective or laparoscopic compared to emergency surgery), and unplanned hospital readmission. One limitation of the analysis undertaken here is that data on hospital episode statistics, from which this information would be obtained, was not available to use at the time of the analysis. This precluded the ability to control for these factors. Nonetheless, the similarities in the findings between this study and the findings by Boyle et al. strengthen the evidence base and confidence in the observed patterns.

The findings of this study are also consistent with the wider literature outside the UK. Regarding age, several studies from the United States have shown that the likelihood of receiving adjuvant chemotherapy decreases with older age (Ryaz Chagpar et al., 2012; Lima et al., 2011; Sanoff, Carpenter, Sturmer, et al., 2012; Sanoff & Goldberg, 2007). Similar to Boyle et al. (2020), Merkow et al. (2013) also controlled for comorbidities and post-surgical complications, factors that could confound this association, and found that patients older than 75 years of age had nearly 5.5 times the odds of not receiving adjuvant chemotherapy compared to those who were 55 or younger (Merkow et al., 2013). The presence of an association after controlling for these strong potential confounders indicates that the underuse of chemotherapy in the older patients may not be due to the presence of co-morbidities or poorer surgical outcomes.

Regarding socioeconomic status, a recent systematic review and meta-analysis showed that people with stage III colon cancer of lower socioeconomic position are less likely to receive adjuvant chemotherapy than those of higher socioeconomic position (Konradsen et al., 2020). The systematic review included 27 studies published between 1990 and 2019. Meta-analyses were performed on each of the socioeconomic indicators found in the included studies. It showed that the odds of receiving adjuvant chemotherapy was lower for those who had public or no insurance compared to those who have private insurance; those who earned low income compared to those with high income; those of lower socioeconomic index, measured on individual or area level, compared to a higher socioeconomic index; and those with lower education level compared to patients with higher education level. Poverty, however, was not found to be associated with receiving adjuvant chemotherapy. In other studies, other outcomes related to adjuvant chemotherapy were also found to vary based on socioeconomic

status. Winget et al. (2010) found that patients who live in areas of low-income were found to have a higher risk of not meeting an oncologist compared to those living in high-income areas (Winget et al., 2010).

In addition to variation by age, deprivation group, and extent of disease, the analysis undertaken in this study showed that those of White ethnicity were more likely to receive adjuvant chemotherapy than ethnic minority groups. To my knowledge, in the UK, there are no studies that have explored ethnic variation in the receipt of chemotherapy for colon cancer regardless of stage, and studies investigating cancer treatment by ethnicity are scarce in general, regardless of cancer type. Those that have been conducted, however, have shown variations by ethnicity. For breast cancer, Black African women were shown to be the least likely to have a record of surgery or hormone therapy, but most likely to receive chemotherapy compared to White women (Jack et al., 2009). In another study, non-White women were shown to be less likely to undergo immediate reconstruction after resectional surgery for breast cancer than White women (Jeevan et al., 2010). In other research, however, among men with prostate cancer, management did not differ by ethnicity (Evans et al., 2010; Jack et al., 2010), and surgical management of early breast cancer was found to be similar in all women, regardless of ethnicity (T Gathani et al., 2021). Ethnic variations in other aspects relating to cancer, such as stage at diagnosis or uptake of screening has also been shown. For example, one study found that those of Black African or Caribbean ethnicity were more likely to undergo emergency surgery for colorectal cancer, indicating more advanced disease (Askari, Nachiappan, Currie, Bottle, et al., 2017). Analysis of a large database showed that Black women of African or Caribbean heritage living in England and Wales were more likely to present with stage III or IV breast cancer than White British women and less likely to have their cancer detected through screening (Brennan, 2017).

Outside the UK, several studies have shown ethnic variations in therapy for colon cancer. In the Netherlands, a study that explored ethnic differences in treatment and survival for colon cancer found that patients of Moroccan origin were significantly less likely to receive adjuvant chemotherapy than Dutch or other Western patients (Lamkaddem et al., 2017). In New Zealand, those of Maori, Asian, and Pacific ethnic groups were less likely to receive chemotherapy and less likely to receive chemotherapy in a timely manner compared to New Zealand Europeans (Lao et al., 2020). Studies conducted in the US have also shown that among those being treated on Medicare, ethnic minority groups are less likely to receive surgery, chemotherapy, and radiation for colon cancer than those of White ethnicity (Popescu et

al., 2016). By contrast, in one study of a military hospital in the US that offered equal access to healthcare for all military personnel regardless of insurance status showed that there was no evidence of treatment delays for black compared to White patients (Eaglehouse et al., 2020). However, comparisons between countries should be interpreted carefully with consideration for their differing social, political, and healthcare contexts.

Those with missing data on ethnicity were also found to be less likely to receive adjuvant chemotherapy compared to those of White ethnicity. The exploratory analysis showed that missing ethnicity data was associated with older age, higher deprivation, and all years of diagnosis except 2015 and 2016. Therefore, it is likely that those who had missing information on ethnicity were less likely to receive adjuvant chemotherapy due to their age or deprivation status. Completeness of ethnicity data in the cancer registry only started to improve since 2012 (Henson et al., 2020), which may explain missing ethnicity information for earlier years (2012-2014) compared to later years (2015-2016). However, the reasons for missing information on ethnicity in 2017 is less clear.

Variation in the type of adjuvant chemotherapy

This study also explored variations in the type of adjuvant chemotherapy received by stage III colon cancer patients, and showed that among those who receive adjuvant chemotherapy, approximately 22% received single therapy and 60% combination therapy. The odds of receiving combination therapy were higher for those who were younger than 65 to 70 years, in the least deprived group, those with more advanced disease (indicated by larger tumours (T3, and T4) and a higher number of lymph nodes involved (N2)), with missing data on ethnicity, and those diagnosed in 2017.

To my knowledge, there are no studies that have investigated variations in the type of adjuvant chemotherapy received for stage III colon cancer in the UK, and only a few have investigated this elsewhere. In The Netherlands, 47% of the patients received oxaliplatin-based chemotherapy while 13% received non-oxaliplatin-based chemotherapy and 40% received no chemotherapy, lower percentages compared with this study. The findings of this study are consistent with a study done in Puerto Rico, where receiving oxaliplatin was also found to be associated with age less than 70 years, and Medicaid insurance (the latter a type of insurance that is an indicator of lower socioeconomic status), and those diagnosed in 2008 compared to later years. However, it was not found to be associated with sex, marital status, comorbidity, region, primary tumour location, or tumour grade (Ortiz-Ortiz et al., 2018). In another

study in the US, those living in less urban regions were 42% less likely to receive combination chemotherapy compared to those who live in big cities (Panchal et al., 2013).

Sanoff et al. (2012) investigated oxaliplatin use among those older and younger than 75 years of age with resected stage III colon diagnosed between 2004 and 2007 registered in three databases in the US[3] (Sanoff, Carpenter, Sturmer, et al., 2012). They found that the proportion of patients over 75 years of age who received oxaliplatin varied widely, with 28% in NYSCR-Medicare, 42% in SEER-Medicare, and 61% in NCCN. In this study, approximately 34% of those over 75 years of age received oxaliplatin, which is closer to that found in the NYSCR-Medicare and SEER-Medicare. Medicare is a federal health insurance scheme for people who are 65 or older. It is possible that the similarities seen in the proportion found of this study, and those of the Medicare population is because the National Health Service in England and the Medicare insurance scheme are both governments funded while the NCCN database represents those with private medical insurance. This indicates that government guidelines on how older patients are treated may play a role.

Explaining variations in treatment

It is likely that the decrease in receiving adjuvant chemotherapy with age is due to oncologists' as well as patient factors. Older patients could be more likely to refuse therapy when recommended to them (Couture et al., 2005; El Shayeb et al., 2012). Evidence from a study conducted in the US suggested that older patients prioritise preserving their memory, cognitive function, and quality of life over prolonged life when choosing a treatment option (Dhakal et al., 2021). Oncologists may also want to avoid treatments that could result in potential toxicities in older patients. One study that surveyed surgeons and oncologists found that physicians agree with guidelines to recommend adjuvant chemotherapy for young and healthy patients with stage III colon cancer. However, for older patients and those with comorbidities, they differed widely on their recommendations, indicating that treatment decisions for these groups are not solely guided by guidelines (Keating et al., 2008). This may be especially true for those

[3] The Surveillance, Epidemiology, and End Results registry linked to Medicare claims (SEER- Medicare): covers 26% of the US population.

New York State Cancer Registry linked to Medicare (NYSCR-Medicare): cover the population of New York State

The National Comprehensive Cancer Network (NCCN) Outcomes Database: covers patients treated at eight National Cancer Institute-designated comprehensive cancer centres

who also suffer from comorbidities, as they may be more likely to experience adverse outcomes from treatment, or that the severity of their comorbidities places them at higher risk of mortality before any benefit from treatment can be realised. Evidence suggests that comorbidities are often a reason why clinicians may not offer therapy to older patients (van Erning et al., 2015). However, several studies discussed earlier have taken comorbidities into account in their analysis, and age appears to be an independent factor to not receiving adjuvant chemotherapy. Treatment with 5-FU has been shown to be effective in older patients, with little difference in toxicity compared to their younger counterparts (D'Andre et al., 2005; Fata et al., 2002; Gill et al., 2004). Therefore, exclusion from receiving adjuvant chemotherapy with a single agent should not be based on age alone (Jessup et al., 2005; Wildes et al., 2010). With regard to combination therapy, effectiveness has also been shown among older adults (Lund et al., 2020). However, toxicity from oxaliplatin has been shown to increase with increasing age. In one study, a pooled analysis of individual data from four trials that used FOLFOX for treatment of patients with colon cancer (both from the metastatic and adjuvant setting) was carried out to compare the effectiveness and toxicity of FOLFOX by age. The study found that there was no difference in the effectiveness of FOLFOX, however, severe hematologic toxicity (neutropenia and thrombocytopenia) and severe nausea or vomiting and fatigue were significantly increased with age (McCleary et al., 2013). Therefore, from a clinical point of view there may be justification for older patients not to be offered combination therapy with oxaliplatin.

Variation in receiving adjuvant chemotherapy by deprivation group could be due to multiple factors. There is evidence to suggest that those living in areas of low income were less likely to have adjuvant chemotherapy recommended to them by oncologists (El Shayeb et al., 2012). Those of lower socioeconomic status are disproportionately more likely to experience poorer health status and a higher number of comorbidities than those of higher socioeconomic status, and comorbidities have been shown to be an important mediator between socioeconomic status and cancer survival (Frederiksen et al., 2009). Thus, it is possible that those from a higher deprivation group are less likely to have chemotherapy, and especially combination therapy, recommended to them due to comorbidities. However, there is evidence to suggest that combination therapy with oxaliplatin is still effective regardless of comorbidities (Haller et al., 2012). El Shayeb at al. also showed that those living in areas of low income were less likely to accept adjuvant chemotherapy when recommended to them (El Shayeb et al., 2012). Another study from the US also found that colon cancer patients with Medicaid, indicating lower socioeconomic status, were more likely to refuse curative surgery for

early disease, and more likely to refuse adjuvant chemotherapy for stage III disease (Kaltenmeier et al., 2020). Evidence suggests that better social support and wider social links lead to health seeking behaviours, timely diagnosis and treatment, and better survival (Woods et al., 2006). However, those of lower socioeconomic status have been found to have low social links, which has been shown to be associated with inequalities in healthcare and health outcomes (Uphoff et al., 2013).

Reasons for variations in adjuvant chemotherapy by ethnicity are less clear due to the scarcity of research that has explored this among colon cancer patients, or in the context of oncology treatment more generally. Some research suggested that lack of information or understanding of health information, or health literacy, could be more prevalent among ethnic minorities, leading to reduced uptake of treatment. In one study of patients who have multiple myeloma, ethnicity was associated with knowledge deficits about chemotherapy (Arber et al., 2017). In other research, patients of ethnic minority groups were found to have lower engagement with information about colon cancer screening compared to White British patients (Ghanouni et al., 2017), and ethnic differences in the uptake of screening was shown to be mediated through knowledge (Lo et al., 2015). This could be due to difficulty in interpreting written information, or in communication with healthcare professionals. In one study, limitations posed by written English was among the reasons for low colorectal cancer screening uptake across South Asian faith groups (Palmer et al., 2015). In another study, health and social care staff expressed difficulties and challenges they found in caring for patients from black and ethnic minority groups at all stages in the care pathway, including at diagnosis and during treatment. They reported their inability to communicate with some patients, which resulted in difficulties in establishing a good relationship. They also reported difficulties in working with interpreters or family members who could be reluctant to translate difficult information (Richardson et al., 2006). In one study from the Northwest region of England, the Chinese population was found to be underusing cancer prevention and tertiary services due to lack of awareness and understanding, as well as dissatisfaction and lack of confidence in these services. A large proportion of this population was found to be considering using healthcare abroad (Conway et al., 2014). Therefore, it is possible that factors lead to patients from ethnic minorities travelling elsewhere for treatment, such as countries where they may have relatives or perceive healthcare to be better.

In research outside the UK, African Americans tended to be doubtful of their diagnosis, treatment, and prognosis, less satisfied in their communication with healthcare professionals, and more likely to believe that healthcare professionals would expose

them to unnecessary risks (Jacobs et al., 2006; Jones et al., 2017). This population has also been shown to be more likely in general to refuse chemotherapy for stage III disease than those of White ethnicity (Kaltenmeier et al., 2020), surgery for early-stage pancreatic cancer (Tohme et al., 2018) and chemotherapy for early-stage lung cancer (Williams et al., 2012), even after accounting for comorbidities and socioeconomic status.

In a scoping review of barriers to screening among ethnic minorities, beliefs and attitudes such as fatalism and the perception that screening may be unnecessary were some of the drivers for low uptake of screening (Crawford et al., 2016). It is possible that these attitudes could play a role in the treatment context as well leading to refusal of treatment, or choosing alternative treatment, such as traditional medicine (Goss et al., 2014). In a study among black and south Asian population in the UK, about 20% participants believed that treatment, especially surgery, caused the cancer to spread (Lord et al., 2012).

Among those who received chemotherapy, those of unknown ethnicity were more likely to receive combination chemotherapy. This is a difficult finding to explain. It is possible that people of White ethnicity may be more likely to be identified as such by the hospital staff who record this information, and so if information on ethnicity is missing it is possible that those patients were of mixed backgrounds that were more difficult to identify. It is also possible that those missing information of ethnicity received combination chemotherapy due to more advanced disease and were more likely to die with incomplete hospital records.

Reasons that could underlie variation by extent of disease are also unclear. Treatment with single therapy is considered standard for treatment of patients with stage III disease since the 1990s and is found to be highly effective and strongly associated with increased survival (Bockelman et al., 2015). Therefore, it would be expected that everyone diagnosed at stage III should be offered treatment with at least single therapy regardless of the extent of disease. It is possible that patients may refuse treatment for various reasons, however this would most likely occur on individual basis, and less likely to be observed on group-level. It is possible that those with less advanced disease are those diagnosed through screening, and thus, are older in age and less likely to receive adjuvant chemotherapy for reasons discussed above. It is also possible that those patients are incidentally diagnosed with colon cancer following investigation for other conditions, and thus could have severe or multiple comorbidities, which also makes them less likely to receive chemotherapy. Further research is needed to understand this pattern. By contrast, combination therapy was more likely in

those with more advanced disease, which indicates more aggressive treatment for those patients.

Those with missing data on ethnicity were found to have higher odds of receiving combination therapy compared to White patients. Missing ethnicity data was associated with the 2012 and 2013 years of diagnosis, which can be explained by incomplete data collection in those earlier years, as discussed previously. However, missing data on ethnicity was not associated with any other factors, which makes an interpretation of reasons why this group had higher odds of receiving combination therapy difficult.

Those diagnosed in 2012-2013 were found to have lower odds of receiving adjuvant chemotherapy compared to later years. This may possibly reflect the incompleteness of SACT at that time, as it only became mandatory for NHS trusts to submit data from 2014 onwards (Bright et al., 2020). However, it is less clear why those diagnosed in 2017 had higher odds of receiving combination therapy. It may be that results of the IDEA trial, which showed that 3 months of therapy with oxaliplatin may be as effective as six months of therapy for those with less advanced disease, had an influence on clinical practice during that time (Grothey et al., 2018). Clinicians may have been encouraged to treat more patients with combination therapy for a shorter duration to avoid the side effects associated with oxaliplatin.

Finally, regarding sex, although there was no difference in the receipt of adjuvant chemotherapy between men and women, women were less likely to receive combination therapy. The reason for this is also less clear. A recent review of sex-related differences in colorectal cancer incidence, screening uptake, routes to diagnosis, cancer stage and survival in the UK has shown that there were no differences between the proportions of males and females diagnosed at stages III disease (White et al., 2018). Although it is possible that females have less advanced stage III disease at time of diagnosis (smaller tumour size or number of lymph nodes involved) and thus, do not require aggressive treatment with combination therapy, the study has also shown that females diagnosed at stage III disease had lower survival than males. This indicates that females may be undertreated with combination therapy compared to males.

Strengths and limitations

A strength of this study is that to my knowledge, it is the first study in England to investigate variations in the type of chemotherapy received by stage III colon cancer patients, which could have important influences on health outcomes, including quality

of life and survival. Another strength is that this study used the cancer registry data, which provided a large representative cohort of patients with stage III colon cancer receiving care from the National Health Service in England. The SACT data provided data on chemotherapy captured directly by the service providers. Linkages of these two datasets facilitated a comprehensive analysis and validation of the data.

One limitation of this study is that the hospital episode statistics dataset, which contains details of all admissions, emergency attendances and outpatient appointments at NHS hospitals in England, was not available to use at the time of the analysis. This precluded exploration of variation in treatment by other clinical factors such as comorbidities, and factors related to surgery such as pre-surgical status, type of surgery, and surgical complications; or hospital-level factors. Boyle et al. (2020) showed that therapy was more likely in those that had fewer comorbidities, better performance status, better pre-surgical physical status, who underwent laparoscopic or elective surgery, and who did not have unplanned hospital readmissions; and reported that hospital-level factors were non-significant. It would be important to explore the influence of these factors on the type of treatment received.

Although data completeness for stage and ethnicity at NCRAS has vastly improved since 2012 (Henson et al., 2020) a proportion of patients still had missing information on disease stage and ethnicity. The use of the staging algorithm described in the methods section, which considered the clinical and integrated categories of stage that were available in the cancer registry data in addition to the pathological stage, did not lead to the identification of more stage III cases compared to those that were included by Boyle et al. (2020). Although the total number of patients included in this analysis was higher (18,182 compared to 11,932), this was mainly due to the inclusion of those who were diagnosed in the years 2012 and 2013. The number of patients diagnosed between 2014 to 2017 was 12,410 which is not largely different to the 11,932 patients identified by Boyle et al. (2020) for the same years of diagnosis. Some of the additional patients identified through this algorithm may have been misclassified as stage III. However, several steps undertaken for this analysis reduced the likelihood of misclassification occurring. First, only those who underwent major resectional surgery were included, as identified by the OPCS codes. Codes for procedures identified as minor, non-resectional, or only performed for early-stage disease were excluded. This step removed those who may have early-stage disease and were misclassified as stage III. This step also excludes those who may have been at an advanced stage of disease for whom surgery was not appropriate. Second, only those who received chemotherapy within four months after undergoing surgery were included in the

analysis. This step excluded those who may have had more advanced disease and required chemotherapy to reduce the extent of the disease before surgery was possible. It also excluded patients who may have had more advanced disease or more complicated surgery due to advanced disease, that would have delayed the start of their chemotherapy.

Misclassification due to the use of area-level indicators of socioeconomic status is another possible limitation of this study. An area-level indicator was used because no individual-level indicators are available. Therefore, on an individual level, some patients may not belong to the deprivation group that they were classified to base on their area of residence.

Finally, the completeness of SACT depends on prescriptions of treatment that are recorded electronically. However, oral chemotherapy has been shown to have less ascertainment of electronic registration that other forms of cancer therapy. Therefore, it is possible that some patients who received single therapy with capecitabine (an oral form of the fluoropyrimidine component of adjuvant chemotherapy for stage III colon cancer) may have been misclassified as having not received any therapy.

Conclusions and recommendations

Difference in the receipt of adjuvant chemotherapy and the type of regimen reflects possibly complex interactions between patient, healthcare professional, and healthcare system characteristics. It warrants further investigation to examine the underlying reasons for these differences among the different groups. Patient choice is an important factor that could influence the use of chemotherapy. Further understanding of the social, cognitive, or psychological factors that could be associated with patients of certain characteristics that determine their choices would enable efforts that aim to correct perceptions and attitudes or address barriers. For example, in one study conducted in the US among colon cancer patients, those who were of older age, a non-White race/ethnicity, lived without a life partner, and had stage II disease were more likely to refuse surgery, a decision they know could reduce their survival (Rapp et al., 2019). Similarly, healthcare professional-level factors such as implicit or explicit biases towards certain patient characteristics, or poor communication skills could also play a role. Further investigation would enable training for healthcare professionals to help them identify and correct their own attitudes and assumptions when interacting with different groups of people, better patient-clinician communication to identify different health and social needs, and better shared decision-making regarding treatment that considers preferences of patients and their relatives. In addition, it is also important to

investigate system-level factors, such as the role of interpreters and how that may influence the care that ethnic minority patients receive or examining current health and social care services to better respond to the complex health and social needs of some groups, such as elderly patients or those from deprived backgrounds. For example, it is uncertain whether lower rates of treatment with oxaliplatin observed among elderly patients represent justified clinical judgement, or undertreatment brought about by lack of clinical guidance, healthcare professional biases, or lack of social support that could lead elderly patients to decline this treatment. Therefore, efforts should include the generation of a better evidence base and guidelines for the treatment of elderly patients or those with comorbidities, better social support for those who lack social networks and are particularly vulnerable. It is also important to use routinely collected data in the cancer registry and systematic anti-cancer therapy databases to determine how differences in treatment may influence mortality or survival outcomes among cancer patients in practice compared to results from randomised controlled trials. It is also important to collect data on factors that may mediate the differences in treatment observed between groups and conduct statistical analysis to establish their significance.

Chapter 6: Patients' perspectives on the decision-making process for adjuvant chemotherapy for stage III colon cancer

Introduction

In the UK, the National Health Service's (NHS) constitution set forth the rights of patients, as well as their families and carers, to make choices about their management, be given information about these choices, and be involved in discussions and decisions about their care (Department of Health and Social Care, 2012 updated 2021).
The General Medical Council (GMC), the professional regulatory body for all doctors in the UK, also declared that clinicians should work in partnership with patients, listen and respond to patients' concerns and preferences, provide information in a way they understand, and respect their rights to discuss treatment and care options and reach decisions with their doctors jointly (General Medical Council, 2009). These requirements are features of a shared decision-making model.

In cancer care in particular, several factors necessitate a shared decision-making process. First, cancer treatment is complex, and treatment choices have serious implications for patients' health outcomes and quality of life. Second, evidence for many treatment options tends to be limited, with many uncertainties regarding effectiveness and adverse events. Third, cancer patients differ in how they weigh the risks and benefits and make trade-offs between different treatment attributes. In the context of adjuvant chemotherapy for colorectal cancer, NICE's current guidelines for the management of stage III colon cancer asserts that "the choice of adjuvant treatment should be made jointly by the individual and the clinician responsible for treatment after an informed discussion between the clinician and the patient; this discussion should take into account contraindications and the side-effect profile of the agent(s) and the method of administration as well as the clinical condition and preferences of the individual" (National Institute for Health and Care Excellence, 2020).

Shared decision-making models

The principles of shared decision-making date back to the 1970s (Veatch, 1972) but was loosely defined as a concept until Charles et al. proposed a conceptual framework consisting of four criteria to characterise it (Charles et al., 1997). They used early-stage

breast cancer as an example, but the framework was not developed specifically for the oncology context (Charles et al., 1997). Nevertheless, it aimed to define the type of patient and clinician involvement in making a single treatment decision in the context of a life-threatening disease, where several treatment options were available. First, that shared decision-making requires at least two people to participate in the decision-making process, the patient, and the physician. However, it also recognised that at times it may involve more than two people as patients are often accompanied by others (Hirpara et al., 2016), and several physicians could be involved in the management of an illness. Second, that the physician and the patient are taking the necessary steps to ensure that participation occurs. This means that a physician should signal to the patient that their participation is important, aid the patient in uncovering their values and preferences, provide information on possible options and their attributes, and ensure that the information is understood. The patient also has a role in making their willingness to participate known, acknowledging, and discussing their values, asking questions to clarify what is not known, deliberating options, and expressing their preferences. Third, that it is necessary for information to be exchanged, that is, patients providing information about what is important to them to aid physicians in identifying the appropriate options, and physicians providing information on the available options and their benefits and risks. Finally, those involved in the decision-making process should agree on a final decision, implement it, and share responsibility for its outcome. Later, the framework was revisited to acknowledge the dynamic nature of decision making, in which they discussed that the approach adopted at the start of a medical encounter may change during the course of the interaction (Charles et al., 1999). The framework had limitations in that it was mostly prescriptive, which meant that some aspects did not adequately reflect what occurs in practice. For example, it conceptualised the clinician as the primary source of information and technical knowledge required for making the decision. However, in practice, patients arrive at the oncology consultation with some knowledge already gained from other healthcare workers, such as surgeons and nurses, or from accessing health information from the wide range of sources available to them. One study that included 1,841 patients of prostate, colorectal and lung cancer found that almost 70% of patients obtained information from at least one source in addition to medical staff. Sources of information varied and included the internet, books, support groups, scientific articles, organisations, as well as family members and friends (Walsh et al., 2010).

Another model for shared decision-making is based on the PrOACT decision making model, which was first developed by Hammond, Keeney, and Raiffa in 1999

(Hammond et al., 2015). Gregory et al. (2011) conducted a study to examine communications between clinicians and patients about choices concerning the use of prescription medications in the primary care setting in the US and applied the PrOACT model to describe and made recommendations to improve this process. The model starts with defining the Problem context, clarifying Objectives, identifying treatment Alternatives, differentiating between the Consequences of alternatives, and addressing Trade-offs between alternatives. The Problem context is defined as the context of the interaction between patient and clinician. That is, whether both patient and clinician are open to and expecting a dialogue about the treatment decision, or if the expectation is for the clinician to provide treatment based on their experience and judgement. Most patients who prefer to engage in dialogue will require help from their physicians to understand and evaluate their condition and treatment and need to take an active role in making this known to their clinicians. Thus, clinicians have a responsibility to be aware of their framing and presentation of the diagnosis and treatment choices, as that may influence patients' perceptions. It is also important that both patients and clinicians explicitly state their objectives from treatment, some of which might overlap, while others may vary in their relative importance. Those are defined as the expectations or concerns that they may have regarding treatment. For patients, this may include gaining benefit, avoiding side-effects, or reducing worry, time, inconveniences, and costs of treatment. For the clinician, this may include ensuring that the patient benefits from, is not harmed by, and is adherent to treatment. However, for patients to be able to express their objectives and concerns regarding treatment, they must have enough knowledge about their own condition and emotional state. For common conditions patients may already have a good amount of knowledge, while for more complex diseases or treatments, the clinician becomes one of the main sources of information. Additionally, clinicians have a responsibility to help patients in asking questions that demonstrate interest in understanding patients' objectives and help them clarify what these might be. It is also important for clinicians to present and for patients to consider all available treatment alternatives in terms of their benefits and consequences relative to each other and to the option of no receiving any treatment as well. Information on the consequences of treatment includes information on all its possible impacts, not only in terms of benefits and risks such as side effects, but also on whether or how it might have demands on their emotional state, family members, or time. In addition, there are uncertainties associated with the available alternatives and their consequences, which should also be recognised, discussed, and understood. Therefore, these uncertainties or probabilities in outcomes requires sensitivity to patients' numerical abilities and therefore, attention to the ways in which they are framed and presented. This

knowledge of the consequences of treatment is not only acquired from scientific sources, but are also from the effects experienced by patients, and therefore, feedback from patients is required. However, each treatment option may be associated with many consequences, making the presentation of all impractical. Therefore, clinicians should aid patients in recognising which consequences require their attention and which don't, guided by patients' objectives and their health status. Finally, to reach a decision, patients and clinicians should engage in an analysis of trade-offs between options. However, it's important to recognise that making trade-offs may require multi-dimensional comparisons, which can induce cognitive biases or heuristics, or emotional responses that could influence the decision process. Therefore, patients should be aided to make trade-offs that are guided by the dimensions that are most important to them, and for information to be presented in a way that simplifies and allows for these comparisons to be made, perhaps by using tools such as tables to present the choices and their attributes.

Shared decision-making models in oncology

A recent systematic review (Bomhof-Roordink, Fischer, et al., 2019; Bomhof-Roordink, Gartner, et al., 2019) of 40 shared decision-making models found that only two models were developed specifically for oncology care. The first built on and incorporated concepts from shared decision-making models found in review of the literature published between 2008-2013 (Kane et al., 2014). However, the review was not systematic, and the methods used, including the search strategy, and the inclusion and exclusion criteria, were not well described. The second was informed by empirical data collected for the specific purpose of informing a shared decision-making model (Bomhof-Roordink, Fischer, et al., 2019). One strength of this framework is that data was collected from a wide range of participants that included current cancer patients, oncologists, nurses, researchers, and the public. Another important feature of this model is that it also recognises that the shared decision-making process takes place during as well as outside of consultations. During consultations, this framework reiterates the conditions described by Charles et al. (1997). Oncologists explain that options are available and that there is a choice to be made; emphasise that the patient's opinion is important; explicitly invite patients to be involved; provide information about the disease and the benefits and harms of all options; ensure that the patient understands the information provided; and get to know their patients to help them identify the issues that are important to them. The patients' responsibilities are to ask questions to clarify issues that they do not understand; be open in expressing their thoughts, feelings, and concerns; consider the information being provided, as well as

what is important to them. Different to other models, however, is that this model makes explicit that oncologists and patients spend time outside the consultation thinking about treatment choices: oncologists may identify the possible treatment options appropriate for patients before the consultation, and a large part of deliberation process may occur in the patient's home, with their family and friends. By making explicit time outside the consultation, the model highlights that decision making in cancer treatment may require at least two consultations to allow for deliberation to take place between the first meeting during which information is exchanged, and a subsequent meeting during which a decision could be made. It also acknowledges that time is needed to allow for a relationship to build between patient and clinician. This is important because when making a recommendation for treatment, the clinician should consider the knowledge they gain about the patient, which requires time to develop.

Evaluation of shared decision-making

To date, however, empirical evidence to support the value of patient participation in medical decisions has been inconsistent. The evaluation of shared decision-making is limited by two issues: the measurement tools available and the outcomes measured. First, several instruments have been developed for this purpose, which may take a patient, clinician, and/or observer view (Scholl et al., 2018). However, agreement between scores of patients, clinicians, and observers regarding the same consultation is poor. Second, there are a wide variety of outcomes that have been used in the evaluation of shared decision-making.

Two systematic reviews were carried out to synthesise the evidence on the effectiveness of shared decision-making. The first was a review that included 39 studies and found that in total there were 97 outcome assessments made by these studies. The array of outcomes that were assessed were grouped into three categories: 50 assessments of affective-cognitive outcomes, 27 assessments of behavioural outcomes, and 20 assessments of health outcomes (Shay & Lafata, 2015). Affective-cognitive outcomes were those that related to how patients perceived or felt about the decisions they made or the process through which a decision was reached, such as their satisfaction, understanding, or level of trust in the decisions made, their interactions with clinicians, or in the information they received. Behavioural outcomes were those that related to the course of action that patients took, such as the choices they made, whether they adhered to treatment, or uptake of other health behaviours such as diet or stress management. Finally, health outcomes included quality of life, as well as physiological or symptom reduction measures. The measured outcomes varied

between patient, observer, or clinician reported. In total, a positive association was found between shared decision-making and 42 (43%) of the 97 assessments made. Studies that used patient-reported measures (regardless of outcome category) and those that assessed affective-cognitive outcomes (regardless of the source of reporting) were most likely to be positively associated with shared decision-making. Of all health outcomes assessed, five were found to be associated with shared decision-making, all of which were patient reported. These were general health, discomfort, symptom improvement, general medical improvement, and depressive symptoms.

Another systematic review (Clayman et al., 2016) was conducted around the same time but included a far larger number of studies. In this review, increased participation in shared decision-making was shown to be associated with at least one positive outcome in five (50%) of ten included RCTs. By contrast, in non-randomised studies, increased participation was associated with at least one positive outcome in 78 (74%) of 105 studies. For all outcomes across all studies, the results varied by study design. In cross-sectional studies, shared decision-making was associated with 129 (61%) of 212 outcome assessments, while in longitudinal and choice studies nearly three-quarters of outcomes did not show an association with participation.

Although neither review showed conclusive evidence for the value of SDM, the results are suggestive of some beneficial effect that should not be dismissed, especially when considering the wide variety of measures used and the outcomes assessed that precluded direct comparisons. Shay and Lafata (2014) showed a positive impact of patient-reported shared decision-making on affective-cognitive outcomes, which is an important finding on its own. Similarly, Clayman et al. (2015) found a positive association of increased participation with at least one outcome in most of the included studies. Furthermore, a narrative synthesis and meta-analysis that evaluated the effect of shared decision-making interventions on disadvantaged groups and health inequalities found that shared decision-making improved outcomes for disadvantaged patients compared to those from a higher literacy or socioeconomic group (Durand et al., 2014). The synthesis also showed beneficial effects of shared decision-making on some cognitive outcomes. Similarly, another systematic review assessing the effect of shared decision-making on quality of life found weak but suggestive evidence of a positive association (Kashaf & McGill, 2015).

Implementation of shared decision-making

In the UK, although shared decision-making is an important part of healthcare delivery, it is often not implemented in practice (Coulter et al., 2017; Joseph-Williams et al.,

2017). Additionally, the National Institute for Health and Care Excellence's (NICE) only recently published specific guidelines for incorporating shared decision-making in routine clinical practice (Carmona et al., 2021). Furthermore, several challenges to implementation of shared decision-making in the UK context has been described, mainly from clinicians' perspective (Joseph-Williams et al., 2017). First, that limited time and resources were an important challenge to the implementation of shared decision-making. For this, organisational leadership in the implementation of shared decision-making is essential. Clinicians need to see this as an organisational priority and a shared responsibility, rather than as an initiative that imposes on their time and workload. Second, clinicians may think that they already practise shared decision-making by involving patients in decisions about their care, which highlights the importance of increasing their understanding that shared decision-making entails additional components such as communicating risk and exploring patients' priorities and preferences. Furthermore, some clinicians may also think that shared decision-making requires decision support tools. However, it is unrealistic and impractical for every decision to have a decision support tool, and at the heart of shared decision-making is the information exchange and communication that occurs between patient and clinician, with or without a decision support tool. Finally, there may also be a perception among clinicians that patients prefer to defer decision making to them. Indeed, research suggests that patients may prefer to assume a passive role in the decision-making process and defer treatment decisions to clinicians (Damm et al., 2014). The shared decision-making model developed by Bomhof-Roordink (2019), as discussed above, does not prescribe who should make the final decision on treatment. Some participants who took part in the development of the model believed that patients should explicitly make the decision, as it concerns their body and life. Others thought that while patients may not explicitly make the decision, they do so implicitly with their right to refuse or accept the recommended course. There was agreement that the oncologist has the ultimate responsibility of making the decision when the patient does not wish to do so (Bomhof-Roordink, Fischer, et al., 2019). Individuals with cancer who participated in decision-making at their preferred level reported higher satisfaction with the decision and lower levels of depression (Hotta et al., 2010; Vogel et al., 2009), while those with discordance between desired and actual roles reported lower physical and emotional quality of life (Atherton et al., 2013). Therefore, it is crucial to allow people to choose to what extent they want to actively engage in decision making and explicitly elicit, rather than assume, their preference for the role in the decision-making process (Cranley et al., 2017). However, there is evidence to suggest that patients' preference for assuming a passive role might be due to their perception that they lack

necessary knowledge, the healthcare professional is too busy to answer questions, or that it is not appropriate (Sanders & Skevington, 2003). The process of shared decision-making, whereby patients are informed, involved, and their preferences clarified, may be more important than who makes the final decision (Edwards & Elwyn, 2006), and therefore, it is also crucial to acknowledge the importance of providing information and supporting deliberation even when a patient does not wish to make the final decision.

Aim and objectives of the study

As discussed in Chapter 1 of this thesis, there are two options for adjuvant chemotherapy treatment of those with stage III colon cancer: a fluoropyrimidine alone or in combination with oxaliplatin. The latter is associated with uncertainties in its survival benefit as well as potential for permanent symptoms of peripheral neuropathy. It is not known how the decision to receive adjuvant chemotherapy, and specifically oxaliplatin-containing therapy, which may be associated with a trade-off between benefits and risks is reached. The aim of this study was to gain an in-depth understanding of the decision-making process from patients' perspective. Specifically,

- how and to what extent were patients aware of their treatment options;
- how and to what extent were they informed about the benefits and risks of their treatment options;
- how and to what extent were their preferences and priorities elicited and considered.

Additionally, this study aims to explore what factors were most important to patients in the decision-making process, and what contextual factors outside of their inter-personal interaction with the oncologist might have had an influence on this process.

Methods

Ethical approval

Ethical approval was granted by the ethics committee of the Department of Psychological Sciences, Birkbeck University (reference number: 171885).

Study design

Data was collected using in-depth narrative interviews, with the support of an interview topic guide. First, patients were encouraged to “tell their story”, starting from diagnosis until the end of their chemotherapy treatment. By telling their story, patients would reveal the context of receiving adjuvant chemotherapy from their perspective, and the factors that have influenced their experience, both before and after starting chemotherapy. The interview topic guide was used to guide the probing questions into the decision-making process around chemotherapy specifically, after the patients told their story, to ensure that certain questions of interest regarding chemotherapy were not missed. The interviews were conducted over the telephone to allow for recruitment of participants from different geographical locations across the UK, thus capturing a wide range of experiences.

Population

Individuals diagnosed with stage III colon cancer, who underwent surgery to remove the tumour and may or may not have received adjuvant chemotherapy after surgery. Participants had to be adults aged 18 years or older and speak English. There were no other restrictions by any other characteristics.

Recruitment and informed consent

An advertisement was posted on online forums and/or newsletters of the following charities and support organisations: Bowel Cancer UK and Beating Bowel Cancer (two organisations that merged in January 2018), the National Cancer Research Institute’s Consumer Forum, Bowel Research UK, Southeast Cancer Help Centre, and Colostomy UK. The advertisement described the study and invites individuals of the population of interest to participate in a telephone interview (Appendix 7).

Those interested in participating were given a choice to contact the researcher by telephone or e-mail. Potential participants who used the telephone were asked whether they preferred to be provided with information about the study verbally on the

telephone, or by receiving a participant information sheet (PIS) by e-mail (Appendix 8). All preferred the latter, and the PIS was sent by e-mail. The PIS was prepared in accordance with the Participant Information Sheet Preparation Guidance of the Health Research Authority (NHS Health Research Authority, Updated 2019). Participants were asked to read the PIS, and if still willing to take part, to respond with suggested dates and times of availability for the interview.

On the day of the interview, consent was taken verbally as per the consent sheet (Appendix 9) and recorded. Participants provided their full names, the date of the interview, and were asked to agree or disagree with the statements that were read to them. The consent, which contained identifying information, was recorded separately from the remainder of the interview, during which potentially identifiable information (such as names of places or first names of people) may have been used but were changed in the transcripts.

Analysis

Thematic analysis was used to analyse the data collected for this study, following an inductive approach, allowing for themes to be derived from the data. With thematic inductive analysis, patterns in meaning were identified from the interview transcripts, and were grouped into themes and sub-themes according to similarities.

Analysis began alongside data collection allowing for an iterative process. Findings and emerging ideas of each phase of analysis refined data collection, and the data that was collected led to the re-organisation of themes and sub-themes (Figure 24).

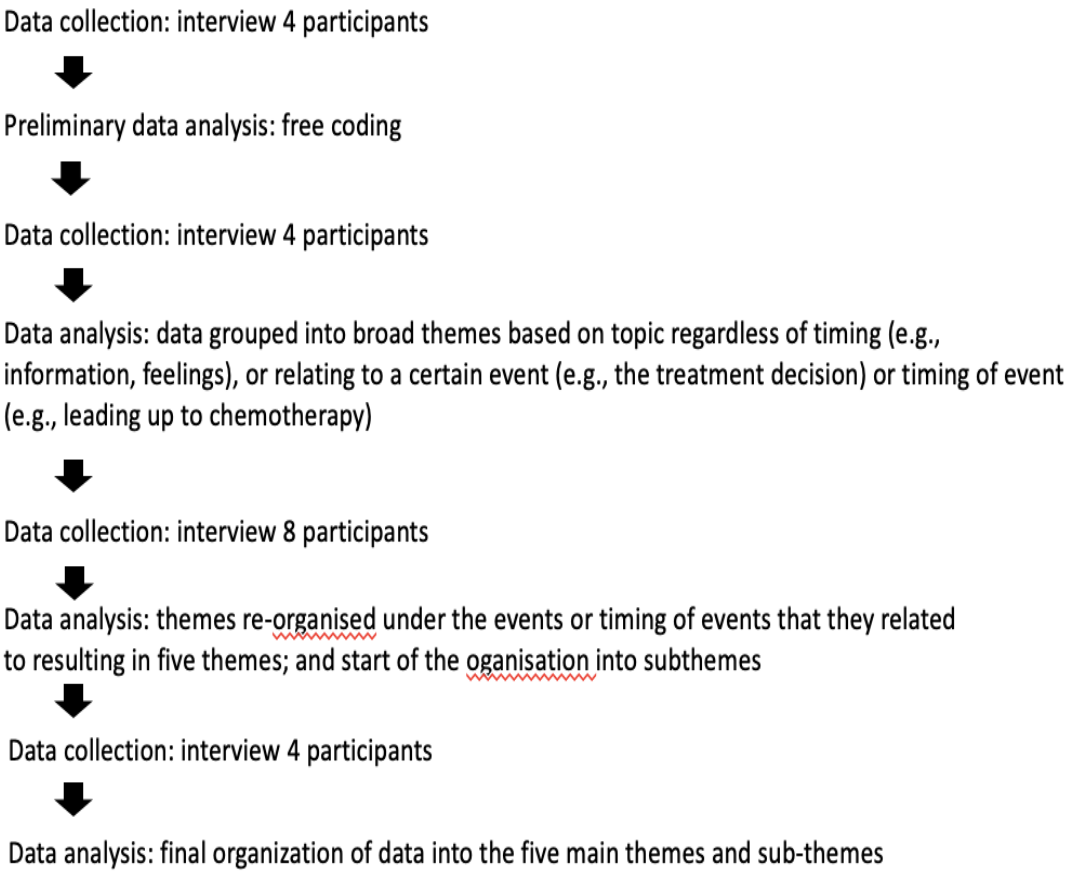


Figure 24 - A flow diagram illustrating the iterative process between data collected and data analysis

Data analysis followed four main stages: immersion, coding, categorising, and creation of themes (Green & Thorogood, 2014; Green et al., 2007).

Immersion in the data was achieved through repeated listening of the audio-recordings and transcription of the dialogue, slowly becoming aware of recurrent ideas and patterns in meaning. Once transcribed, repeated reading of the transcripts ensured detailed examination of the interview as a whole.

Coding was undertaken using NVivo 12, whereby segments of text that related to particular points were labelled or grouped into a descriptive category, giving rise to ‘free codes’. This means that the codes were non-hierarchical and did not have any connections to each other. The audit trail which shows the progression of data analysis from free codes to themes and subthemes is shown in Appendix 10.

As more transcripts were added and coded, free codes that were conceptually similar were organised into broader categories. Some were grouped based on the topic that they related to, while others were grouped based on events or timing of events. For example, how patients interacted with their family, regardless of the reason, were all

grouped under the heading “Family”; how they felt about different aspects of their experiences, regardless of what this related to, were all grouped under the heading “Feelings”; all accounts of information received, regardless of what they relate to, were grouped under the heading “information”, etc. On the other hand, events that took place prior to treatment with chemotherapy were grouped under the heading “leading up to chemotherapy”; and events that took place at the time of the treatment decision or factors that related to how the treatment decision was made were grouped under the heading “the treatment decision” (See *Main themes (based on topic and events or timing of events)* in Appendix 10).

As analysis continued, categories that were initially grouped based on topic were re-organised to fit under either the timing at which they took place, or the event that they related to. For example, information or feelings related to diagnosis, interactions with surgeons, and family-related history or events that occurred before treatment were all re-organised under the theme “leading up to chemotherapy”, while information or feelings that related to the treatment decision itself, interactions with oncologists were re-organised grouped under “the treatment decision”. The result was five main emerging themes. First, events or factors that took place “leading up to chemotherapy”. Second, factors that related to “the treatment decision”. Third, factors relating to “the wider context” around the treatment decision. The fourth theme was on “time”, and the fifth theme consisted of feelings or events experienced “post-therapy” (see *Main themes (based on events and timing of events)* in Appendix 10).

In the final stages of analysis, two of the themes were re-named to better reflect their content. The theme “leading up to chemotherapy” was renamed into “the pre-treatment context”, while the theme “time” was re-named into “Time: a double-edged sword”, to reflect both positive and negative influences of the passage of time before and during treatment. In addition, the categories under each of the main five themes were re-organised into sub-themes. The final organisation of the data into themes and sub-themes are reflected in the *Results* section and are shown in five corresponding figures in the *Final themes and sub-themes* section in Appendix 10.

This analysis contributed to the overarching paradigm of this thesis, which assumes a critical realism lens, by providing an in-depth exploration of the mechanisms that led to the decision to receive or decline adjuvant chemotherapy for stage III colon cancer, and the contextual factors that influenced this process. This included uncovering patient-level knowledge, perceptions, emotions, and behaviours, that played a role in their interaction with their healthcare professionals, as well as how factors relating to

healthcare professionals and their wider healthcare system and social context may have influenced them.

Results

Description of participants

In total, 31 individuals expressed interest in participating, however, eight did not respond after sharing the information sheet, and three were not eligible for inclusion: two were diagnosed with stage-II disease and one was diagnosed with rectal cancer. Twenty interviews were conducted, transcribed, and analysed.

Table 36 shows the characteristics of the included participants. The participants included six males and 14 females, aged 33 to 75, from various regions of England and Scotland as shown in the map below. All participants were of White, British ethnicity. Four participants described their income level as high, thirteen described it as middle, and three said it was low. Two participants did not hold educational qualifications, while for the remaining participants' the highest level of educational attainment varied between A-levels, professional, university, and master's degrees. Three participants were single, while the remaining were married and had children.

The year of diagnosis ranged from 2010 to 2019. At the time of the interview, fifteen participants had completed therapy and five were still receiving treatment.

Sixteen participants received adjuvant chemotherapy that included oxaliplatin. Of those, two were changed to single therapy in the early stages of treatment due to severe acute peripheral neuropathy symptoms and did not develop persistent symptoms. Of the remaining fourteen, eight had persistent symptoms at the time of the interview, three had acute symptoms only and recovered, and the other three were still receiving treatment at the time of the interview but were experiencing acute symptoms.

Four participants received single therapy: one refused treatment with oxaliplatin and chose single therapy (60 years old), while the other three were not offered oxaliplatin (74, 63, 75 years of age).

Table 36 – Characteristics of participants

	Gender	Type and duration of therapy	Neuropathy at time of interview?	Completed therapy at time of interview?
1	Female	Combination, 6 months	Yes	Yes
2	Female	Combination, 6 months	Yes	Yes
3	Female	Combination, 6 months	Yes	Yes
4	Female	Combination, 6 months	Yes	Yes
5	Female	Combination (Reduced from 6 to 4 months)	Yes	Yes
6	Male	Refused oxaliplatin	No (did not receive oxaliplatin)	Yes
7	Female	Single, 3 months	No (did not receive oxaliplatin)	Yes
8	Female	Combination, 4 months	Acute symptoms*	No
9	Male	Combination, 6 months	Acute symptoms*	No
10	Female	Combination, 3 months	Acute symptoms*	No
11	Male	Single, 6 months	No (did not receive oxaliplatin)	Yes
12	Female	Combination, 3 months	Acute symptoms	Yes
13	Male	Combination, 3 months	Yes	Yes
14	Female	Combination, 6 months (Switched to single)	No (stopped oxaliplatin)	Yes
15	Male	Single, 6 months	No (did not receive oxaliplatin)	Yes
16	Female	Combination, 6 months	Acute symptoms*	No
17	Female	Combination, 6 months	Yes	Yes
18	Female	Combination, 4 months	Acute symptoms only	Yes
19	Male	Combination, 6 months	Yes	Yes
20	Female	Combination, 3 months (Switched to single)	Acute symptoms only	Yes

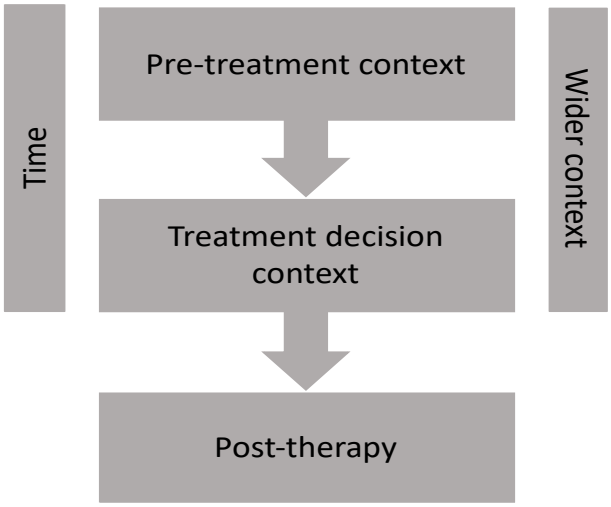
*Treatment not completed; long-term effects not yet known

Map 1 - Location of participants

Emerging themes

The first four themes grouped the factors that may influence the decision-making process in relation to the pre-treatment context, the treatment decision context, the wider context surrounding the treatment decision, and time as a ‘double edged sword’. The fifth theme was also based on timing of events, however, was not related to factors that may influence the decision-making process. Instead, the fifth themes related to post-therapy, offered a retrospective insight into the feeling about the decision and a description experiencing peripheral neuropathy post-therapy. Figure 25 offers a depiction of how the themes related to each other.

Figure 25 – Conceptual depiction of the relation between the five main themes



The pre-treatment context

Analysis of the data has shown that several factors may have had an impact on some participants’ ability to contemplate chemotherapy prior to being referred to an oncologist. These factors related to diagnosis, the surgery that they underwent to remove the tumour, as well as family- and life-related events.

Diagnosis

Reaction to diagnosis

Almost all participants reported feeling shocked by their diagnosis and fearing that their disease will ultimately lead to death. For those who were not diagnosed by screening, the way the diagnosis was reached also had an emotional impact in addition to the diagnosis itself. For example, those whose symptoms were repeatedly dismissed by

the GP and their referral delayed expressed anger. One such participant ultimately experienced severe symptoms that led to an emergency presentation and reported deterioration of her mental health status.

> *"…I think I was in shock I couldn't believe what happened"*
>
> *Participant 2*

> *"…and at the time I felt quite a lot of anger I think both at myself for not really thinking that it could be cancer but also for my GP for not referring me for a colonoscopy or at least some other tests sooner than they had."*
>
> *Participant 10*

Only one participant reported that the diagnosis did not cause him emotional distress, and therefore, was able to think about his condition and began arranging his family's affairs immediately after his diagnosis.

> *"I certainly suffered no anxiety or anything like that. It was clear that it was a 50-50 chance of me living 5 years, so I needed to make some adjustments. I'm very pragmatic and I certainly wasn't scared or anything."*
>
> *Participant 6*

Some patients expressed that their perceived health status pre-diagnosis contributed to their feelings of shock, and even bewilderment, at their diagnosis. Some perceived themselves to be healthy or making healthy lifestyle choices, while others expressed that they experienced no prior symptoms.

> *"I was really fit for a 65-year-old. I was vegetarian. Non-smoker. Exercised. Ideal weight. No family history at all of cancer. In fact, both my parents lived to be in their 90s. So, I sat there feeling really,*

really, healthy, surrounded by people that look really ill and it was it was quite upsetting."

Participant 20

"…the fact that it was a malignant tumour near the cecum and that I would need to have surgery, which was rather a shock because I had virtually no symptoms that I was aware of…"

Participant 7

Another way that some patients reacted to their diagnosis was through disregard and "denial" (Participant 5), and by focusing on their daily lives and routine activities.

"Q: During the two months when you were waiting [for chemotherapy] you didn't have another discussion with the doctor or tried to discuss it further with your family or friends?

Participant: No, no I didn't, I didn't. All I wanted to do was trying to get back to a normal life […] my husband and I took my mother away for a week before I started my chemo, so we had, I had something to look forward to which was different and enjoyable. So, I didn't really think anything about it until the day of the first day I had to go in and have it"

Participant 1

"I just carried on as normal, I remember we picked the green apples off the tree, and I made jam, and I cleared up some chores because my son and his wife were going to come and stay"

Participant 5

One participant described how she received her cancer diagnosis, which may have also had a negative influence on her emotional state at the time, while another participant described delays in receiving the diagnosis, which may have also heightened his anxiety.

"…the only thing that I was sort of a bit upset about in the early stage is that when I was in [name of hospital] and got given the diagnosis of cancer it was in the worst room possible, it was like a really small room with no windows, it was so small that the surgeon and the Macmillan nurse were sitting on the bed and my friends and I were

sitting on chairs directly opposite them and our knees were almost touching, that's how bad the room was"

Participant 8

"…I was then sent for an MRI scan, and all of this was quite long waiting times for the scans, and it was only through me really, really, pestering and the colorectal surgeon also pestering the radiology department that we managed to get the scans within a week"

Participant 10

Information on diagnosis

Characteristics of the tumour such as stage, grade, and differentiation are typically provided to patients in a pathology report. Several participants reported that the pathology reports that they received were not discussed, and the stage of disease or its implications were not explained by a healthcare professional. As a result, when asked for the characteristics of the tumour, many did not know and some of those who were able to find this information from their pathology reports did not understand it. In one account, there was a discrepancy between the classification system that was presented and explained in the written information material and the system that was used in the pathology report. This caused confusion and distress for both the patient and other members of his family and may have provoked an emotional response that could have been avoidable.

"…we got the letter, it said Dukes C stage III T4, and I automatically thought that that was stage IV, because obviously the piece of paper, this was one of the confusing things, because we were given leaflets before the pathology results which explained the TNM staging system but then our pathology results paperwork came through and it was with the Dukes' staging system. So, we were given two completely separate pieces of paperwork […] we automatically assumed that we were misinformed again and the tumour itself had actually been upgraded to a T4, and that was over the weekend, so we had a really, really, bad weekend […] and on the pathology results also said the EMVI although I'm still really not clear what that is"

Participant 9

"…I think I just made a mistake of not asking the stage of the cancer, I think that was my naivety, I just took it as oh it was cancer it hasn't

spread and I just never gave it a thought that the staging of the cancer would have an effect on the chemo that I took, but that was just my, we just never thought"

Participant 16

"…well when I asked about the size of the tumour I was told that it was irrelevant and that it was where it was that was more important and eventually it was the oncologist who said to me, because I think I asked my surgeon three times, and eventually I asked the oncologist and he said, he was very good, he said it's your information and I will get you the pathology report which he did, it was so complicated but at least it said there in the report I think it was a 4 1/2 cm tumour and so he was quite good in that you know, he said that it's your information, it's your body"

Participant 10

Surgery

Most participants said that their need for adjuvant chemotherapy was first indicated by the surgeon who resected the tumour. The surgeon can judge the need for chemotherapy from the size of the resected tumour and the presence of cancer cells in adjacent lymph nodes. Thus, participants were referred from the surgical to the oncology team already anticipating that they will likely need adjuvant chemotherapy. Some surgeons, however, only suggested the need for adjuvant chemotherapy and referred further discussions to the oncology specialist, while others made strong recommendations for further treatment with adjuvant chemotherapy and provided more detail on the type of therapy that should be received.

"…the surgeon didn't give me any clues as to chemotherapy just that I should go see the oncologist and she would explain it all."

Participant 3

"…it's actually my surgeon who said you're going to be having chemotherapy. So, he actually said that to me in the hospital when I was first diagnosed, we're going to take this out, and then you're

going to have chemotherapy and I was like, okay, that's what is going to happen."

Participant 2

Patients trust the clinicians that attend to them, including the surgeons that operate to remove the tumour. Therefore, information received from surgeons can have a lasting impact and influence the ways in which patients might think or feel about their treatment.

"…I went to see the oncologist […] which came frankly as a bit of a surprise and disappointment because I think somehow naïvely, I trusted the surgeon when he said he got all the cancer that he got all the cancer. So again, that was another shock really, I never considered you know sort of cell level cancer."

Participant 11

"…I saw the surgeon and his first words to me were you are not going to die and me and my husband we both hung onto those words, and I thought well if Mr. X said that I'm not then I'm not, and I came away very reassured"

Participant 5

One participant reported declining the surgical procedure that was recommended by the surgeon, which carried a risk of permanent chronic pain, and instead, knowingly opted for a procedure that resulted in a permanent stoma (Participant 6). Discussions with the surgeon about different surgical options increased his awareness of the options for chemotherapy and his subsequent involvement in discussions relating to that with the oncologist.

In addition to the interactions with the surgeon, the surgery itself may be a factor that could have an influence on patients. Several participants reported that they were still coping with having a stoma or with complications of surgery at the time of their first meeting to discuss chemotherapy with an oncologist.

"…dealing with the stoma took any thought or any concern about the chemo coming up away from me"

Participant 1

"…he said you tend to sort of react to chemotherapy better without an ileostomy […] so I did go in for reversal in April but wasn't successful they perforated my bowel, so I had to sort of stick with the ileostomy, which I had got sort of throughout the chemo"

Participant 18

Family history and life events

Some participants reported that there were personal life events that were occurring during the time they were diagnosed that may have had an emotional impact on their ability to confront their diagnosis and consider their therapy options. Life events that were mentioned included a recent death of a relative (Participant 11) or having to care for elderly parents (Participant 13). One participant's account was a very good example of the kinds of thoughts that could pre-occupy patients.

"…my husband has had heart condition and I didn't want him all stressed and I thought with my son there that would make him feel better and also we had this agonizing decision because I thought I didn't want my son to see me in the hospital with a bag of wee at the bottom of the bed, that's what I thought about, I just didn't want that, but then I thought well I do want him here because I want to look after my husband and my cats are not allowed out and I'm worried in case my husband when he's uptight might leave the door open or something like that"

Participant 5

"…I think it was over the next few days I was thinking okay what a m I going to do workwise what am I going to do income wise, so you start thinking"

Participant 11

Some participants may also have concerns regarding how their diagnosis could affect members of their family

"…my son was absolutely devastated like I can hear in his voice and to this day I wish I hadn't said anything to him at this stage I wish I

had more information to reassure him even though he was 40 years old, so he is not like a baby"

Participant 5

Several participants mentioned that they had history of cancer in their family. This seemed to have different effects. For one participant, it heightened fear of cancer, while for another recall of her family history indicated that she may have avoided confirming her diagnosis. For a third participant, however, knowing she had a history of cancer meant that her diagnosis was not "*so much of a shock*" (participant 7), although she also reported that she had no prior knowledge of cancer except for "*the fact that my dad had died of it*", which could also indicate fear.

"My father actually died the day before and he had died of colon cancer. So, I was very aware that I already lost one person in my family who I was very close to, and I was just very petrified"

Participant 1

"…I noticed that there was blood in my poo, so I kept it to myself for a couple of days, because my mother died with bowel cancer"

Participant 18

Another participant compared her experience to other relatives who survived without the need for adjuvant chemotherapy and seemed to take that as an indication that she will be able to overcome her disease as well.

"I have a cousin who has the same as me but when they took part of the bowel out, she didn't need chemotherapy and my grandmother also at my age when she was just about 70 had part of her bowel removed but didn't need chemotherapy […] so we felt that if we could get over this bit [adjuvant chemotherapy] I had a very good chance of carrying on and being perfectly well"

Participant 3

The treatment decision

Treatment options

There are a few options regarding adjuvant chemotherapy that require a decision. First, whether to receive adjuvant chemotherapy after surgery to remove the tumour. Second, whether to receive single therapy (fluoropyrimidine) or combination therapy

(fluoropyrimidine + oxaliplatin). Third, whether to reduce or cease treatment with oxaliplatin when symptoms of acute neuropathy begin to increase in severity. Finally, there are also two types of fluoropyrimidines that could be administered: capecitabine, which is given in tablet form, and 5-FU, which is given through an intravenous infusion.

Accepting or declining adjuvant chemotherapy after surgery

All participants, except for three, perceived having a choice on whether to accept or decline adjuvant chemotherapy after surgery. For three participants, this choice was not discussed and instead chemotherapy was assumed or decided as the next step by the clinician.

> *"…I didn't have really a choice to say yes or no, it was just this is what we're going to do to you, this is it, that was my option […] I didn't know I had an option to refuse at the time, I know now I can, but at that time I knew nothing"*
>
> *Participant 1*

> *"…it's actually my surgeon who said you're going to be having chemotherapy. So, he actually said that to me in the hospital when I was first diagnosed, we're going to take this out, and then you're going to have chemotherapy and I was like, okay, that's what is going to happen […] once my surgeon said to me you were going to have chemo, I didn't even question it. He wrote a letter to Dr.X [the oncologist] saying that [patient] was really keen to have chemo and that was it. I was never asked whether I want it or not, ever."*
>
> *Participant 2*

> *"…I was told this is what would be happening and for how long. So, a hundred percent there was no discussion of do you want to do it or do you not want to do it type of thing."*
>
> *Participant 9*

Choice between single or combination therapy

Three participants perceived having a choice and deciding on the type of adjuvant chemotherapy they would receive. All remaining participants were unaware of the option between single and combination therapy. Those who received combination therapy were not aware that treatment with single therapy is possible, and similarly, those who received single therapy were not aware that the addition of oxaliplatin is a treatment option for stage III colon cancer.

"…only in passing from reading on the beating bowel cancel forum that other people were having it [oxaliplatin] but I didn't know what it was for, and it never crossed my mind query it"

Participant 7

"…and I never even thought about oxyplatin [mis-pronounced], I can never pronounce that properly, I wasn't even aware existence of the drug until maybe last year"

Participant 11

"…since then, I found that some people don't have the Oxaliplatin they only have the Capecitabine, but at the time I just went along with what was offered."

Participant 3

"Q: You didn't know what the drugs that you were going to take in your regimen were? Participant: No, I had no idea"

Participant 5

"…I do find it shocking when people say they even had a choice, I mean, to hear people say they had a choice, you know, they come on the forum and they say I've been told I could have this and I could have that, and I think, wow, you know, I didn't have that, so that's quite surprising"

Participant 2

Type of single therapy (capecitabine or 5-FU)

Regardless of the type of therapy that was received (a fluoropyrimidine with or without oxaliplatin), only four participants were aware of the two types of fluoropyrimidine available (capecitabine tablets or 5-FU intravenous infusion).

"…the treatment offered was the combination of medications and the forms were only really given in terms of oxaliplatin as infusion and capecitabine as tablets"

Participant 19

None of the four participants who were aware of the two types, however, perceived making an informed choice about which type to receive, rather, this was decided by the clinician. For most, capecitabine (tablets) was the one that was recommended.

However, one participant recalled that the 5-FU infusion was recommended as first line with an option to change to tablet if the infusion was not tolerated but was not clear on why this plan was suggested, i.e., why IV infusion was recommended as first line instead of tablets (Participant 16).

> *"…well, I will say that it wasn't a joint conversation […] I remember that there were two routes one I could have weekly injections that might take three or four hours, or I could do tablets, and the selling point really was, you know, you will find that much more convenient and the possibility that you would be able to return to work, some patients do. So, for me it was a bit of a no-brainer really setup that way, you would go for the tablets wouldn't you. But I don't recall a more rounded discussion about the pluses and minuses of both approaches really."*
>
> *Participant 11*

As the quote above indicates, there may be an assumption among clinicians that tablets would offer high convenience and would be preferred over an IV infusion. However, the participant found it more reassuring to be receiving the IV infusion form of the fluoropyrimidine component (5-FU) than taking tablets at home.

> *"…and then for some reason I think my emotional status improved and I really don't know why possibly because it's the placebo effect of going to the hospital on a more regular basis I was going in weekly and that is quite reassuring to a patient, you don't want to go to the hospital you are sick of the place but actually it is the place where they will look after you and that's quite reassuring"*
>
> *Participant 11*

Some participants reported that they did not perceive having a choice to change from one form to another when concerns were expressed, or side effects were experienced. One participant who received capecitabine and had an ileostomy was concerned that the tablets may not be absorbed due to the ileostomy and asked for an alternative but was not offered any. Another participant who started therapy with Capecitabine reported that 5-FU was not offered as an alternative even after he experienced serious side effects related to capecitabine.

> *"…I researched it so I knew there were two options [FOLFOX and CAPOX] and so when I went to the oncologist I was told that I would be having the three months regime [CAPOX] and it wasn't really, the*

other regime wasn't mentioned and I did ask what the options would be if I couldn't tolerate capecitabine because I was concerned that my ileostomy was quite difficult to control and so I was concerned that the tablets might not be absorbed so I was told that that would be kept an eye on but that there was not an alternative"

Participant 10

"…I sat in this meeting for about 45 or 50 minutes with my wife and I was not happy about taking those tablets again and we had various chats about what else we could take, is there any other options and we were told categorically that there is nothing else that would be suitable, which I know is a complete lie"

Participant 9

Choice to reduce or discontinue oxaliplatin

As symptoms of neuropathy begin to increase in severity with cumulative doses of oxaliplatin, a decision is needed on whether to reduce or discontinue oxaliplatin. Several participants required this change in their treatment. For some, the decision was made by the oncologist without a discussion, while others recalled that they agreed with the oncologist's recommendation after a discussion took place. Several participants reported feeling anxiety about reducing or ending treatment with oxaliplatin as they perceived this to compromise the maximum benefit that could be gained.

"…when they said to me that we're going to start reducing Oxaliplatin that was a bit concerning to me because I was thinking well if they don't give me the full whack of this then I'm not, it's not going to get rid of the cancer, so I kept saying to them no don't, I'll be fine, but they were like no we have to reduce it and then they reduced it and reduced it, but then obviously I went in on the last time and they said, I think I had session 8, went back for the blood on session 9, told her about the side effects and she said ok that's it now we're going to stop the oxy"

Participant 2

"…when the consultant had said that he wanted to reduce the chemo I was really quite worried about reducing it because if I was going to

go through chemo, I want to make sure that there is no, no cancer left"

Participant 4

"I saw the oncologist and he explained, he said that if I wanted to continue to the 12 cycles because there was some research done that eight would be sufficient and the other 4 probably were not totally necessary, so I jumped at it and said no, so that day it was the day before my birthday and it was then my last chemo and I had my pipes, you know the PICC line removed a bit later and I just thought wonderful I just felt free"

Participant 5

"…he said there had been various studies one was the SCOT trial and that indicated that going through eight cycles of chemotherapy was probably more damaging to the body and less effective against the cancer in the later sorts of cycles than for, so I ended up having only four cycles of chemotherapy"

Participant 13

"…she [oncologist] did explain it really well and I came out of that feeling much better about the decision that had been made, so it was at that point, and I just accepted that there was not going to be any more oxaliplatin and we continued with capecitabine only from then onwards"

Participant 17

Information

Benefits of treatment

Two participants reported being aware of the survival benefits associated with combination compared to single therapy (Participants 6 and 17). For one participant, this knowledge was largely due to initial consultations that took place in the private setting, and the participant's own research and questioning of the differences between the two options, while the other received this information from the oncologist spontaneously.

"…I had basically the first half of last year devoted to research, which was mainly American journals and journals in the UK on the effectiveness, marginal effectiveness of oxaliplatin"

Participant 6

There was a difference in recall between those two participants; the first (Participant 6) recalled exact and accurate figures, while the second did not. There was strong indication that this was due to the ways in which this information was subsequently used. Participant 6 was gathering information because he wanted to make a trade-off between the risks and benefits of treatment and decide on which to receive. By contrast, the other participant pre-decided that she was going to accept any treatment that was offered to her, regardless of the associated risks or benefits.

"I chose to avoid the Oxaliplatin because looking at the statistics which I could gather from my own research with no surgery the five-year life expectancy was zero, with surgery it's 56%, with surgery and Capecitabine it was 66%, and with Oxaliplatin as well it added a 3% increase in a five-year expectancy which I didn't think was sufficient margin to justify the high chance of peripheral neuropathy"

Participant 6

"…I think it went something like there's a 50 percent chance that coming back within five years and that was reduced by twenty five percent if I had adjuvant, but it was something like 10 percent less if I had the capecitabine only […] I was prepared to have the maximum that was available to me, which ultimately was my decision based on statistics or not […] I think I probably thought this actually before I even had the conversation with her [the oncologist] was that whatever was available, that's what I was going to have"

Participant 17

A third participant was aware of single or combination therapy but was not aware that they differed in survival benefit. She was told that the oncologist "would not recommend a regimen that changed the benefit" (Participant 20) and so she perceived the two options to only differ in duration, i.e., single therapy would be administered for six months, while combination therapy could be administered for three. Therefore, after choosing combination therapy based on a shorter duration, she experienced severe acute symptoms of peripheral neuropathy and made the decision to switch to single therapy.

The remaining participants were unaware that there was an option of single or combination therapy, and consequently, unaware that there may be different survival benefits associated with each.

> *"…they didn't tell me what percentage chance I had of it not coming back or the benefit, so we never talked about that. I didn't, they didn't tell me that having just the 5-FU gave you just this much chance and having the Oxaliplatin had this much chance, so it wasn't really, it wasn't even discussed"*
>
> *Participant 2*

In terms of the survival benefit that would be expected from receiving adjuvant chemotherapy (regardless of type), compared to surgery alone, only one participant received written information on this, and seemed to be the only participant to recall an exact figure. By contrast, the others reported having only a verbal discussion with the clinician, and in all cases, they were either unable to recall the figures that they were told or recalled rough and varying figures.

> *"…she did show us a printout of a computer program she had which she had put in all of my details and what my situation was and say what my chances were, are, of surviving 5 years and it was improved by about 6.9% if I had the chemotherapy and then she sent us away to think about it"*
>
> *Participant 3*

> *"…he gave a statistic, but my brain doesn't retain this information but, it, he did say how much having mop up chemo how much it would improve the chance of recurrence, and it wasn't a huge amount"*
>
> *Participant 4*

> *"…the oncologist explained that they can only cure 50% of the patients they see by surgery and if they have chemo it only increases it by 1% […] he explained that you know they cast 50-50 chance of being cured totally with the surgery but by adding the chemotherapy it increased to a 60% chance and he did warn me that I wouldn't know for a year whether I was in the 60% or the 40%"*
>
> *Participant 7*

> *"…he explained that there was a 75% chance of me living five years without cancer reoccurrence and that chemotherapy could possibly*

increase that to 80% and so therefore an appointment was made for chemotherapy"

Participant 11

Two participants reported incorrect information about therapy. One recalled being told that FOLFOX, a combination of 5-FU and oxaliplatin, has been used as adjuvant chemotherapy for 40 years and that it is uncertain which component is more effective. However, oxaliplatin's use in the adjuvant setting was only approved in 2004, and information on the effectiveness of each component is known and available. Similarly, a second participant recalled being told that the two components of combination therapy could be used interchangeably, while they are complementary i.e., more of one does not replace the effect of the other.

"…he said to me the FOLFOX has been around for around 40 years, it is tried and tested we know that it works, and we don't actually know which one is more effective the oxali[platin] or the 5-FU, yeah, he said we don't actually know which one does the job"

Participant 2

"…she said they were concerned the fact that I had such […] an extreme reaction so quickly […] that the, the IV [oxaliplatin] was only a quarter of the drugs, sort of counted as quarter of the drugs which is why they could just, they could up my, the pills [capecitabine] to cover it, and that's what we did"

Participant 14

By contrast, some participants did not have any information on survival benefit, and explicitly recalled that it was not provided or discussed.

"…when I asked about survival rates and things like that I was told that all the statistics that are available are out of date and that it wasn't helpful to look at those […] a few times I asked about things like what was the size of the tumour and what was the chance of it

coming back and I think I did ask about survival rates and things like that and each time I didn't get an answer"

Participant 10

"Question: Were you told about the chance of reducing the cancer coming back from surgery alone compared to chemotherapy compared to the regimen that you are taking?

Participant: No, no, that I didn't know"

Participant 14

"Question: Were there any statistics involved in terms of the chance of the disease coming back?

Participant: No, no, I don't think so"

Participant 16

Side-effects of treatment

All but two participants reported receiving information sheets, booklets, or leaflets, sourced from organisations such as the Macmillan Cancer Support or Bowel Cancer UK, on the side-effects associated with chemotherapy. The two that did not receive written material were diagnosed in 2010 and 2011, and it is possible none were available then. In addition to receiving written information material, all participants also discussed side effects with a healthcare professional, either an oncologist or a clinical nurse specialist. Those who perceived the amount of information they received to be sufficient reported feeling prepared and unsurprised by the treatment or the side-effects they experienced.

"…we had all of those leaflets and the nurse did spend a lot of time going through it so I was prepared for the side effects, and they weren't as bad as I, as they could be"

Participant 3

"I came out with a bag full of drugs you know preventative things so then I knew what was going to happen and I felt quite confident from

then on that I was doing the right thing, but I was very uneasy you know before then that first time"

Participant 5

However, despite receiving written information and/or having face to face discussions with a healthcare professional, for some participants, awareness of certain side-effects or their severity prior to starting treatment seemed to be lacking. As such, these participants reported that they became aware of some of the side-effects only during therapy, as they experienced them first hand. This lack of information resulted in underestimation of and under preparation for the associated negative effects of therapy, adding difficulty to an already difficult experience.

"…I wasn't really given a lot of detail about side effects, I will admit that, you know there are side effects that I am aware of now from Oxaliplatin, but I wasn't really, the only side effect they seem to worry about with me were pins and needles in my hands and my feet and I didn't really have that in great detail and that was the only thing ever mentioned to me"

Participant 1

"I think it made a huge difference and prepared myself mentally I'm going to have a stoma and knew what I have to do exercise wise to recover, while as for chemotherapy it was just such a huge shock the extent of the side effects and it just floored me, and I wasn't prepared for that"

Participant 10

"…talking about the side effects I think he just quickly ran through the form frankly, and I said the form that I've got in front of me and he said yes, […] he ticked a lot of boxes and I wasn't too concerned about what was ticked, I don't recall any comments about nervous system or cardiovascular system which I see they ticked here on the form, but nevertheless, he did talk I think about the possibility of kidney problems and I think that was pretty much it really, I certainly

don't remember any conversation about allergic reactions to chemotherapy"

Participant 11

"…some of the things [side effects] that you know I have since become aware of I can definitely hand on my heart say I was not made aware of at the time."

Participant 13

Peripheral neuropathy

Only one participant had a clear idea on the symptoms of peripheral neuropathy, the risk of permanent side effects, and the impact that it may have on lifestyle. He noted, however, that this information was not presented to him spontaneously, rather, it was due to his persistent inquiry.

"The reason I was able to get the information was because I did the research and I tested them over some length […] and I took it upon myself to ask particular questions such that I could make an informed decision, but I had to ask the question before I would be given that information."

Participant 6

For the remaining participants, information that patients received about the character, severity, persistence and the prevention or treatment of peripheral neuropathy symptoms seemed to be lacking. In addition, some reported that the only source of information on peripheral neuropathy was written information booklets or leaflets, and no discussion took place.

"I can recall that peripheral neuropathy was mentioned in a sort of question-and-answer kind of booklet, what are the side effects I could get, and chemo might give you pins and needles in your arms or fingers and toes sort of thing, but that doesn't explain as to why it

could be caused or how it could be avoided even so I think it was a very airbrushed sets of advice"

Participant 6

"…it [written information] didn't really go into much detail it was more about having pins and needles in the hands, I think they kind of skimmed over it quite a lot.

Participant 8

One participant mentioned that she was not aware which of the chemotherapy agents that she was receiving contributed to the condition.

"Question: were you told which drug was contributing to that side effect specifically?
Participant: No. So, I wouldn't know whether that it was the intravenous or tablets, no"

Participant 18

Character or severity of symptoms

Almost all participants reported that they were unprepared for the character or severity of the symptoms that they experienced. Some reported that not all symptoms were described or that they were described in simplistic terms. Some also perceived that a verbal description of the condition no matter how detailed "doesn't quite encapsulate" the true experience of symptoms (Participant 19).

"…I believed that peripheral neuropathy was just pains and just shooting up in your arms and legs and that was peripheral neuropathy I didn't realise that it was just tingling and numbness"

Participant 4

"…I'm starting to get, it's almost like arthritis in my hand, but I spoke to the nurse last time and she said she hadn't heard that, but I have seen people mention it on the forum […] when I mentioned sort of the arthritis type feeling to the nurse she had to go and ask someone"

Participant 8

"I was told about those side effects [tingling and sensitivity to cold] but what I wasn't told about was the spasming of the muscles, the cramping, that wasn't mentioned at all, and it was, it was kind of implied that it would be a little bit of inconvenience but not painful or

not particularly troublesome whereas it was a huge problem […] yes I was told about the side effects but I wasn't told about the extent of how debilitating they could be"

Participant 10

"…they tell you it's like pins and needles, but it's not really like pins and needles at all, that's not very accurate"

Participant 17

Persistence of symptoms

The risk of permanent symptoms is another important aspect of peripheral neuropathy that many of the participants seemed unaware of. For many, awareness of this possibility was gained only after they began to experience symptoms.

"…he didn't tell me that [PN can be permanent] right at the beginning, I wasn't, I don't think I was told that until about eight, about the eighth infusion, I know there was a lady who used to come in […] and she had a real problem she was probably about four or five ahead of me and it was then I realised that this could actually cause a problem […] where I had thought as soon as you stopped it would be all right [..] but it wasn't explained"

Participant 5

Experiencing persistent symptoms

"…my expectation would be that once you finish, it [peripheral neuropathy] disappears and doesn't come back. But from what I've seen online and looked on the Internet it looks like it could be a permanent thing"

Question: It was not discussed that there was a potential for it to be permanent?

Participant: No. That was not discussed at all"

Participant 9; Experiencing acute symptoms; Undergoing therapy at time of interview

"…it was only as we sort of went into things and I started reading more about other people's experiences with neuropathy that it sort of

became apparent that in certain cases this can be a very much a long-term thing"

Participant 13; Experiencing persistent symptoms

"Participant: Once I was found out what it was yes, I was told it could be permanent

Question: So, you became aware of the possibility after you had experienced it?

Participant: Yes"

Participant 14; Oxaliplatin stopped due to acute symptoms; No persistent symptoms

"…I thought it would perhaps just last while I was on the chemotherapy. I didn't think it would last, you know, um, after and I'm still sort of left my feet are always cold and my hands are always cold […] I don't think I remember being warned"

Participant 18; Acute symptoms during therapy only; No persistent symptoms

One participant, who previously worked as a dance and fitness instructor, despite being aware that symptoms may persist long-term and possibly permanently still decided to receive therapy regardless of the consequences. However, when asked how this decision was made considering her career, she reported that this was not something that was discussed or that she had considered.

"…I remember being told that potentially it [nerve damage] can be irreparable, but I think I don't think I really thought about that myself in line with my career"

Participant 17; Experiencing persistent symptoms

Treatment or prevention

One participant noted that she did not know whether certain supplements could be helpful in treating or reducing the symptoms, further demonstrating that certain

important information about the nerve damage that results from treatment with oxaliplatin was not discussed.

> *"I would like to know whether there's anything you could do like whether taking something like a high dose of vitamin B or anything like that might help but I'm just worried about taking something that might interfere with how the drugs are working"*
>
> *Participant 10*

Intravenous infusion of oxaliplatin

One participant described having a peripherally inserted central catheter (PICC) fitted, which is an invasive procedure that includes establishing access to a vein in the arm under local anaesthetic, without prior discussion explaining the purpose of the procedure.

> *"…I just sat having a PICC line in my arm not really knowing why I was there."*
>
> *Participant 5*

Another participant also recalled that the two different channels that could be used for the intravenous infusion of oxaliplatin (i.e., peripheral cannula or peripherally inserted central catheter (PICC)) only took place after the patient inquired, and the response she received indicates that she may have been given inaccurate information on the likelihood that a PICC line would be required.

> *"In the information she gave me there was information on PICC lines and central lines as well. And this wasn't actually something she mentioned […] we did ask her about PICC lines and central lines, and she said it's unlikely, but we have to tell you in case it's something that happens, and actually ended up being something that did happen, because on my first day of chemo […] it took five members of staff an hour and a quarter to get a cannula in, and after they've done that, they just said, that's it, we're going to book you in to have a PICC line put in"*
>
> *Participant 17*

Another participant's account also indicated that she may not have received sufficient information about the PICC line.

"…I would like to have the opportunity to talk to a chemo nurse in more detail about what is it, how they do it, and be shown that this is the chemo, this is what happens and find out a bit more about the ins and outs of having this PICC line put in"

Participant 1

The nature of chemotherapy

Leading up to the first cycle of chemotherapy, the unknown situational reality of undergoing chemotherapy or experiencing side-effects may act as a source of tension and unease. For example, one participant wondered about how quickly side-effects appeared after the first infusion, while another participant was fearful of what "having chemotherapy" entailed.

"…even during the chemo, I had no idea how quickly the side effects would start, I didn't know if it was during the infusion or if it was going to be on the way home, you know in the car and the journey home which is going to be an hour's drive. I wasn't sure if it would, if we would manage to get home before, and then how long it had to be"

Participant 4

"…that was a very frightening time the very first time, going in and having it and then dealing with, there weren't after-effects for me fortunately, but dealing with it and then finding out actually, that actually, there's nothing to worry about and then just managing to get on, so it was the thought that for the very first time how it's going to happen and what was going to happen and then just after that living with it and getting on with life"

Participant 1

One participant who described feeling uneasy about her first chemotherapy cycle, and not knowing what to expect, that perhaps being oriented to the chemotherapy ward and the procedures surrounding it would have eased some of her tension.

"…so I went to have a the chemo I get to the chemo ward and it was absolutely fantastic, you don't know what to expect but they obviously do that job day in and day out […] I could just imagine sitting there crying in the ward, and will I have privacy, and you know, it was all

those kind of things I was worried about, they made that so normal that that part was actually ok"

Participant 4

This is also reflected in the contrasting experience of those who did visit the chemotherapy ward prior to the first cycle and becoming oriented to what to expect.

"…they took me upstairs, the cancer nurse brought me upstairs, because it was, I was in the hospital where I had the chemotherapy, so she took me up to the chemotherapy suite and we had a little look around and she said look everybody is fine in here and they, you know, everyone is having treatment and it's ok"

Participant 2

"…I remember being shown around the chemo suite just before I started chemo, just so I knew where it was and what happened, but it is another world, it's like a little club, and I think I would have liked to have understood that a little bit more before I'd gone"

Participant 17

"…I had already been on, so I knew what to expect because my sister-in-law had breast cancer and I had gone with her, so I knew, you know, it wasn't a sort of, the environment wasn't a shock."

Participant 18

Feelings about the information provided

The perception of the quality and quantity of information acquired, whether through discussions or from information material, varied among participants. Some reported having gained a satisfactory amount of knowledge, while others reported and demonstrated gaps in their knowledge.

"…I did feel that I wasn't treated always like an intelligent person, sometimes I was just treated like someone they were just treating, and I didn't need to know, but I felt I did."

Participant 3

Several participants expressed unfavourable thoughts on the written material they received. Some felt they received a large amount of written information that they found overwhelming to read or understand, especially while also having to cope with the

shock of diagnosis, or complications of surgery. Others felt that they were superficial and generic, not relating to their specific case or circumstances.

> *"…during the whole thing there were so many pieces of paper and booklets to read about various things and when you're not so well, and you can't concentrate, a lot of these things never got read, or got scanned over very quickly"*
>
> *Participant 4*

> *"…if that [peripheral neuropathy] was explained at the time, it was lost in the, the overwhelming amount of information that was given the point of the initial consultations about the chemotherapy"*
>
> *Participant 19*

> *"…the side effect sheet could have been more detailed and there were a few that appeared that weren't really on the side effect sheet"*
>
> *Participant 8*

> *"…the leaflets were fine as far as the leaflet goes […] but I think it would've been nice if people sat down and talked through those leaflets with you as opposed to giving you stuff to take home and read by yourself, because you can read it, but you don't understand it"*
>
> *Participant 9*

> *"…it is called a Macmillan organiser […] a fairly thick thing has got to be about a centimetre or a centimetre and 1/2 thick never really read it thoroughly because it was so generic, you know, you want to know about you not the general public."*
>
> *Participant 11*

Participants felt that information, and being informed, was important to them, regardless of whether this would have influenced their treatment decision.

> *"If I had a little bit more information, I don't think it would have changed my mind, you know, I was fairly convinced I was going to go*

through and have the chemo, but it might have given me some more, I might have had some concerns"

Participant 1

Two participants recorded their meetings with the oncologist and emphasised the importance of ensuring that they capture and understand all the information that is provided to them.

"…one of the things that I was told by a very good friend who is a professor was to record the sessions and she said the thing is you don't remember the nuances and you don't remember all the facts […] to me that was the best of information I was given because as I said I have been able to go back and listen and remember exactly what was said"

Participant 7

"…my oncology nurse wrote down all the notes from the meeting on top of what I was recording as well […] so I did have it all written, written down by him through notes, through the meeting, so that I could refer to it and make sure I understood it all"

Participant 17

Healthcare professional-level factors

Recommendation for adjuvant chemotherapy

All participants recalled that oncologists recommended chemotherapy on the basis that one (or several) lymph nodes were found to have cancer cells during surgery, making it a necessary precaution to clear microscopic cancer cells that may have travelled to distant sites.

"…I saw my oncologist, who then went through what they had found during the surgery and the fact that it had gone into some of my lymph nodes, I would therefore require chemotherapy"

Participant 1

"…he explained to me about the fact that he would suggest that I did have chemotherapy as a mopping up operation specially since the tumour had gone through the bowel wall"

Participant 7

Treatment with oxaliplatin was described as the "gold standard" in two different accounts (Participants 6 and 9), while one participant who received single therapy was also told that he was receiving the "standard" treatment (Participant 11).

One factor that may have resulted in a strong recommendation for treatment may have been age, as was explicitly described by one participant.

"…there wasn't a lot of discussion around the chemotherapy, it was just you are having chemotherapy, you're too young, and if I didn't have it the cancer will just come back."

Participant 2

Communication during consultations

Several participants described their meetings as rushed and implied that there was no relationship established with the oncologist. This was mostly attributed to lack of time and a busy healthcare system.

"…the oncologist wasn't the best at the human interaction […] I don't think he was particularly encouraging of questions […] he was very matter of fact and you felt processed as just another case of cancer rather than looking at the patients and their needs. I can't say I warmed to the guy particularly so there is no real rapport building, it was rushed, and you know, did the business, and then left sort of thing"

Participant 11

"…they were fairly blunt, fairly to the point and matter of fact. I think it is difficult when you see somebody for a fairly short period of time as you do in these appointments to sort of develop a kind of working relationship with them […] sometimes it is not possible to develop

that warm and cosy relationship with the patient that you know perhaps somebody might be expecting […] he was doing his job but there wasn't an element, we didn't cross that line if you like where he needed to exhibit a more compassionate side"

Participant 13

"…the doctors don't have a lot of time to find out who you are and what exactly you want, and you know they have to go with their best knowledge, so it's difficult for both sides I think"

Participant 14

One participant had a distressing interaction during the first meeting with the oncologist where treatment with chemotherapy was discussed for the first time. She first described waiting a long time before being moved to what she described as a "cubicle" that she found uncomfortably small, and finally meeting the oncologist who seemed busy, provided little information about therapy and was abrupt in the discussion.

"…this lady I don't know she was very, very, uptight and very, very, busy came along and she, she didn't actually explain terribly well, I wasn't terribly happy in retrospect about it because you know she just said well, you're just going to have a PICC line put in and you'll have this, and you'll have that"

Participant 5

Several participants expressed dissatisfaction with their oncology consultations through comparisons to interactions with other specialists. One participant said that he was used to "more rounded discussions" with his GP (Participant 11) than what he experienced with the oncologist.

"…the surgeon when I first saw her, she discussed everything and told us everything, she's quite different."

Participant 3

"…I mean surgery was fine they explained what was happening […] yeah they sort of covered all bases you knew hundred percent what

was happening and what could happen throughout the whole process"

Participant 9

Two participants remarked on the value of being known to the treating physician before entering the meeting room. This point was illustrated by one participant's positive experience, where the oncologist had familiarized herself with the case notes before the meeting, and another participant's negative experience, where the oncologist was reading the notes after the meeting started.

"…the one time that I didn't see my regular oncologist she had obviously read my notes before she had come into the room which I quite liked the fact that she had done that as opposed to sitting there reading through them in front of me, you know she prepared she came in asking questions as opposed to you know relevant to my experience if that makes sense"

Participant 14

"…but knowing that it was the very first introduction to chemo and whether or not I was going to have it or not and I would be feeling very vulnerable, maybe in retrospect it would've been nice if she knew my name at least"

Participant 5

By contrast, some participants reflected positively on their interactions with their oncologists. Some of the features that were highlighted included "answered everything", "was very clear" (Participant 17); "fantastic person to speak to with regards to concerns, how to deal with sort of severity of side effects", "good source of information and advice throughout the process" (Participant 19); "very, very thorough", "spent a lot of time with me and my husband and every patient really" (Participant 20).

Another participant described the oncologist as someone who is "always fairly positive", and that he "jokes he wants to get me [the patient] till I'm about 84". The dynamic between the patient and the oncologist in this setting was different compared to other accounts. Of interest here is the patient's response to this, which was: "…and I tell him well, I don't want to live till I'm 84". This suggests that while the oncologist intended on lending hope, the patient perhaps wanted to remain realistic.

In general, the quality of the communication that takes place between a patient and a health care professional can leave a lasting impression on a patient, as demonstrated by the following account.

> *"…the next morning this lovely guy called X telephoned me from the endoscopy department where I had the colonoscopy […] I remember that very, very, distinctly as being, him ringing me lovely X that morning as being quite a reassuring high spot in the diagnosis"*
>
> *Participant 5*

Attitude towards patient involvement

Five of the interviewed participants explicitly stated that "no discussion" took place with the oncologist over chemotherapy.

> *"…I did ask him did I have to have chemotherapy, and he just said yes, you do. So, there wasn't really much discussion as such other than it was necessary for me to survive."*
>
> *Participant 1*

> *"…there wasn't really a discussion as to whether I would have it or not it was just, it was just what we recommend you have."*
>
> *Participant 8*

> *"…a hundred percent there was no discussion of do you want to do it or do not want to do it type of thing."*
>
> *Participant 9*

Only three participants reported that the oncologist was engaged in a discussion, encouraging of their involvement, and allowed them time to think about their options.

> *"…it was very clear it was entirely my decision, and when we talked about it and she explained what everything meant and she then gave us the time I was with my husband and she said, you know, go away for a week, think about it, I'll give you your consent forms, you don't have to sign them, but it's entirely your decision"*
>
> *Participant 17*

> *"…I think she was quite good at stepping back and giving me options of what I could or couldn't do, and very much leaving it to me […] the*

doctor was very thorough […] she spent a lot of time with me and my husband and every patient really."

Participant 20

Variability in information and care

Some participants reported that they met with several oncology consultants during their therapy, which resulted in varying quality in the information and care that they received. Others also reported receiving conflicting information from surgeons and oncologists, which caused them confusion.

"…there's no consistency with the oncology team because I have not seen one person who is dealing with me, you've got to bear in mind I've only had two cycles and I have seen three maybe four different oncologists and they are all with different ideas and different opinions […] the oncologist that we saw last week was talking about different drugs different tablets and all sorts of stuff, we can try this and we can do this and we can do that. And that was completely contradictory to what I was told by the other person three times before who told me there was nothing else, so we are very confused at the moment."

Participant 9

"…and then at the end, I'm not quite sure what happened but I saw a different doctor, different chemotherapy doctor for the last couple of times and he was more open and told me a lot more so probably just the personality of the doctor I had before"

Participant 3

"…the consultant oncologist towards the end of my chemo I saw him all the time, but the first few times I saw different people. There was one particular Irish guy who was fantastic, he talked me through all the things"

Participant 5

As discussed earlier, often surgeons were first to recommend adjuvant chemotherapy and provide information about its importance. However, at times the information provided by the surgeon contradicted what was subsequently provided by the oncologist.

"…when she [surgeon] told me that I would need to have chemotherapy she said to me that I would probably have six months treatment […] and she said I'm sure you would be asked to have six months of treatment but when I saw the oncologist, I was just told that it would be three months"

Participant 10

"…I've had a shock since because the consultant, the surgeon said it was oh 60 or 70% chance of being cured and we were sure at the beginning when we saw the surgeon before the oncologist, he had given us higher figures than that so that's been a bit of a shock."

Participant 12

A clue as to how patients may perceive meeting with different clinicians throughout the course of their therapy may be found in one participant's description as not being "messed around":

"…it was not always [the same oncologist], but the person, if it wasn't the oncologist, it was a member of his team, so I wasn't messed around."

Participant 14

Patient-level factors

Patient's frame of mind

Several participants made a connection between factors of the pre-treatment context (discussed earlier), such as feelings of shock and fear about their diagnosis or the need to cope with surgery or with personal life events, and how that may have influenced their ability to consider adjuvant chemotherapy. Some participants felt that they assumed a more passive role in their interaction with the oncologist, which led them to accept and agree to treatment suggestions without a thorough discussion. One participant said that she did not "want to know about chemotherapy" and did not engage with the information that was provided to her because she had "enough to deal with" (Participant 4).

"…I was just so petrified, and scared, I was feeling very worried about what the future would bring because I had a stoma put in after the operation, and I was coping with the stoma as well as worrying about chemotherapy, and everything in my life had changed so

dramatically, I just accepted everything, you know, if he told me two and two were five, I would have accepted it, which is very, very much unlike me now, but at that time, that's all I could, you know, I believed everything I was told"

Participant 1

"…I think I spent the first probably, well, even through my therapy, even through my chemotherapy I was stunned […] I think actually shock hindered my ability to ask more questions or question it more"

Participant 2

"…I certainly learned a lot about, sort of cancer, and everything surrounding it since going through it myself, but as a layperson without too much understanding previously, certainly being told that you had stage III cancer when stage IV is the highest it goes up to is quite a, quite a scary thing, so we got told that the recommendation was eight three-week courses of chemotherapy."

Participant 19

In addition to pre-treatment factors, some participants also noted that being told about chemotherapy and realising that the extent of the cancer was advanced enough to require chemotherapy was also a shock in addition to the diagnosis. Some participants felt that they were unable to ask the oncologist any question or probe into what their treatment entailed due to this shock factor, while for others it was due to lack of prior knowledge of cancer or chemotherapy, which meant that they did not know what to ask about in the first place.

"…I think when you get hit with the first word chemo, I didn't really think of asking, I didn't have the information in my mind at that time […] I knew nothing, I never come across anyone, I didn't know anyone who had chemotherapy and I wasn't aware that I could turn around and say no I don't want it"

Participant 1

"…you start to realize that I don't know what treatment we're talking about, so you start to ask questions about that, but it's one of those where it's really hard to formulate questions and it's even harder to understand and process the answers because of the shock factor,

and it's not the language that is used but it's just because you're just suffering with shock, and you can't process the information"

Participant 11

Trust in clinician

The recommendation to receive chemotherapy was not often questioned by participants due to the perception that "experts" know what is best and trusting that the treatment they offered was the best available. This trust or faith in the treating physician is reinforced by the knowledge that their case is discussed in multidisciplinary teams. Therefore, patients seem to trust in what they perceive as a collective opinion.

"…from the very first appointment I put my complete faith in the consultants who had years of training and experience, and I know they had their multidisciplinary meetings, and I thought I'm sure it has been discussed and they decided that this is the best treatment for me or else it wouldn't have been offered to me"

Participant 2

"…I know they had their multidisciplinary meetings, and I thought I'm sure it has been discussed and they decided that this is the best treatment for me or else it wouldn't have been offered to me, I just had complete faith, you know, lasting side effects and things like that hadn't really entered my mind

Participant 4

"…you put an enormous amount of faith in the people that you see, and at the time you kind of just go with the flow"

Participant 10

Only one participant interrogated the oncologist's recommendation for combination therapy. Unlike the other participants, he expressed that he did not trust the recommendation made by clinicians, as he believed they recommend what they believe is the most effective therapy, without regard to the patient's lifestyle.

"…there was a presumption that I was a patient with no technical knowledge, and indeed I had no technical knowledge, and there was a presumption that I would simply follow the recommendation of the surgeon and the oncologist because that was the gold standard […] nobody in my opinion took an overall view as a physician would and

balanced the risks and rewards of the different processes with the patient's lifestyle."

Participant 6

Perception of chemotherapy

This emerging theme illustrates the ways in which participants viewed chemotherapy and rationalised its use.

Although all participants were aware that receiving adjuvant chemotherapy reduces, but does not eliminate, the probability of cancer recurrence, the language used by some participants indicated that they perceived it to be vital for their survival, which was "the most important thing" (Participant 3).

Some described chemotherapy as "necessary to survive" (Participant 1), that it will "make sure there is no cancer left" (Participant 4) or "stop the clock ticking about any residual cancer growing" (Participant 11). One participant reported that this perception was due to the clinician's own expression.

"…my surgeon had said if I didn't have the chemo, it would just come back, and those were his very words"

Participant 2

Some participants also used language such as "zap it once and for all" (Participant 13) and "hit [the cancer] on the head" (Participant 14) to describe how they pictured its effect. Other participants perceived chemotherapy as something that will give them "the best chance" (Participant 12). Chemotherapy and its associated side-effects were also viewed as a temporary phase that needed to be overcome after which they can get back to normal life. One participant perceived chemotherapy as part of a whole, which is cancer treatment in general, whereby having gone through surgery she viewed receiving chemotherapy as a continuation.

"…I felt that if there was any chance of you know getting clear completely or as completely as we could possibly hope then it was worth the sort of four months of inconvenience to go through it"

Participant 13

"…why go halfway down the road"

Participant 14

Almost all participants struggled to pronounce the names of the agents (capecitabine and oxaliplatin). One commented on the complexity of the names and noted that this

gives the impression that therapy itself is complex. This was also implied by two others who thought chemotherapy a form of therapy in itself, but later discovered that it consists of complex and varying regimens.

> *"…they talk about the different drugs, they've got all these great long names and that's hard enough to take in, I mean I know this combination of drugs has a specific couple of names that it could be referred to, I mean as I said I've got a bit of a medical understanding so for people who have no knowledge of medical things then the long names put you off apart from anything else so you know if they can work out a short form for some of these drugs and what they could do it probably would help "*
>
> *Participant 14*

> *"…I didn't really comprehend the different chemotherapy I had just thought chemotherapy is chemotherapy possibly with different names within it, but I haven't, I just thought, I didn't realise that different drugs have different effects."*
>
> *Participant 4*

> *"…I think I was quite naive about chemotherapy beforehand. It never crossed my mind, for instance, that different cancers have different chemotherapies […] you just assume cancer is the same if you don't know anything any better, and therefore the therapy is all the same, and of course, it's not, but I didn't know that, and it had never occurred to me"*
>
> *Participant 17*

Concerns about side effects and peripheral neuropathy

In general, for most participants the side-effects that were associated with chemotherapy had no bearing on the decision to receive therapy, including peripheral neuropathy. As discussed earlier, they perceived treatment to be necessary for survival and therefore willing to undergo therapy regardless of the side effects.

"…I wasn't really caring about the future, and you know what the lasting side effects would be because at that point it was still better than the other option of you know, maybe not surviving it"

Participant 4

"…it [peripheral neuropathy] was annoying, but my approach was if I wanted to, you know, survive. I've just got to put up with it […] I never felt the need to say you know, can we stop because of it, or can you do something because of it, it's just got to be done"

Participant 18

The most mentioned concern was an allergic reaction that would result in discontinuation of treatment, or potentially be life threatening. Others included hair loss, nausea and vomiting, and weight gain resulting from steroids (which were used to prevent some of the side effects).

Three expressed concerns about receiving capecitabine. One who had a colostomy was concerned that the tablets would not be absorbed, while another two were concerned about chest pain and other cardiac effects associated with capecitabine.

"…I am absolutely fine with this oxaliplatin […] the side effects are annoying but they're cope-able with […] but within half an hour putting the tablets in my mouth I feel absolutely awful, and I feel really, really bad […] the chest pains and other side effects that I'm getting from those tablets is enough to make me not want to take them"

Participant 9

The potential for permanent symptoms of peripheral neuropathy was of concern to only one participant and largely influenced his decision to receive treatment. He worried that this could interfere with daily life, and his priority was to avoid that outcome. He also rationalized that experiencing symptoms of peripheral neuropathy during treatment could result in a reduction or discontinuation of therapy, and thus, unrealizing the benefits yet risking permanent symptoms.

"…my concern about peripheral neuropathy was on the farm, and I just didn't want to be debilitated or irritated by having pins and needles in my fingers and toes"

Participant 6

Another participant mentioned tingling and numbness as a concern, mainly because he suffered from Raynaud's disease[4] and was worried that the chemotherapy could make these symptoms worse but was still willing to tolerate the effect and receive treatment (Participant 9).

For the remaining participants, peripheral neuropathy seemed to be of little concern, and this seems to be due to several factors. As discussed earlier, many lacked information on the difference between treatment with or without oxaliplatin and were therefore willing to tolerate any side effects from treatment that they perceived to be necessary for survival. Many also had incomplete information on the nature, severity, and risk of persisting symptoms. At the same time, regardless of when or how peripheral neuropathy became known to the participants, there was a degree of awareness that developing long-lasting symptoms is a possibility rather than a certainty, and so, many were willing to take the gamble in hopes that they would not be unfortunate. In addition, many patients expressed that neuropathy is a "strange" feeling that is "very difficult to describe". Therefore, symptoms of peripheral neuropathy and their effect on life may be a difficult to conceive, compared to other side effects that are immediate, potentially life-threatening, and more easily understood, such as an allergic reaction, hair loss, or nausea and vomiting.

"…I had really bad neuropathy and the skin on my hands was burning and peeling and so yeah I did talk to other people about it, but I just knew I had to do it, so it didn't really matter, you know, what people's bad experiences were I just knew I had to do it"

Participant 2

"…the oncologist, as I said, had told me about this and it sort of kind of described what it was like, and I read the information that they'd given me about neuropathy, but until you have it, it's, you can't really

[4] Raynaud's disease: a condition that affects circulation in fingers or toes and results in change in colour of skin (turning from normal pink to blue), pain, numbness, pins and needles, or difficulty in movement on exposure to cold.

imagine what it's like, and it isn't really like they describe it to you, and it can change as well"

Participant 17

"…they can't tell you it, you might not get it, or you might get it for six months after, or you might, it might never go away."

Participant 20

The wider context

There are several considerations related to the wider context surrounding the primary decision-making context where the interaction between patient and clinician takes place and information is exchanged, that could have an influence on how treatment is determined in direct or indirect ways.

Specialist nurses

One factor that was important to many participants during their care was having a clinical specialist nurse, who they thought played a crucial role in providing information and support. Most reported having long discussions with them about the diagnosis or side effects and felt able to contact them over the phone. Others thought that they were a channel through which they could ask questions or voice concerns. For one participant, the oncologist nurse made written notes of the first consultation that took place, which provided the participant with the information she needed to understand and contemplate the therapy that she was going to receive outside of the consultation.

"…we had all of those leaflets and the nurse did spend a lot of time going through it, so I was prepared for the side effects"

Participant 3

"…the nurse who explained all about the chemo when I went in to first collect the tablets was, I mean she took nearly an hour to go through everything with me and gave me the various drugs, the ointments, the special cards to the hospital"

Participant 7

"…you got the nurse you can ask the nurse as well if you've got any questions so that was absolutely fantastic support […] there's a phone number that if I need I can ring up the colorectal nurse and

they can answer questions and if they don't know the answer they will get you the answers, so not only can you ask questions when you were in an appointment there was that line of support there as well"

Participant 12

"…my oncology nurse wrote down all the notes from the meeting […] so he wrote the options that she was giving me so that I would have them to look back on when I got home, so that I understood the terminology and understood exactly what she was telling me and wasn't going to forget it by the time I got home"

Participant 17

One participant highlighted the importance of a clinical specialist role by describing it as "having a line of communication open", which would allow patients to ask questions if they arise at a later time. Another participant highlighted the same point; however, she believed that keeping the communication open requires an active effort on the nurses' part to make frequent calls and start the conversation, rather than leave the onus on the patient.

"…I think the important thing is having lines of communication open so that when you don't, when you do get a question later on in the day there is access"

Participant 14

"…I would have preferred if they [oncologist specialist nurses] phoned you on more regular basis […] just to have a general chat and listen to you, and during that conversation there might be questions that crop up, and you know, if we had a long conversation like I'm having with you today about peripheral neuropathy and the side effects and the percentages I might well have said during that conversation well what are the percentages? […] they would always say if you got any questions just give us a call, but nobody likes to make that call just for a chat you know"

Participant 4

However, experiences seemed to vary depending on specialty. On one occasion a comparison was made between the colorectal and oncology nurse specialists, where the interaction with the former was reported more favourably. Although not making a direct comparison, another participant explicitly praised his experience with the

colorectal nurse specialist, describing her as "*excellent […] the human face of the treatment*" *(Participant 11)* while his description of the oncology nurses was neutral, and indicated that it was only practical. Another participant thought that the oncology nurses were unsupportive and felt that they did not address her concerns adequately while prioritising their own.

> *" she [colorectal specialist nurse] spent probably an hour on the phone with me just explaining the situation making sure that I understood what was going on […] it's actually really reassuring to have somebody who contacts you or I could contact her if I felt I needed support […] she was hugely supportive and because she was so supportive I really felt that I was coping with the diagnosis […] although I had the oncology specialist nurse, I didn't ever feel well supported with them at all"*
>
> *Participant 4*

> *"…twice I was asked to stop the tablets, but I didn't, and they got annoyed about it, but I just thought well if I feel that I can tolerate the tablets I want to keep taking them […] I wasn't really sure why she would get upset […] so I carried on taking them and I just thought well surely that is my choice […] the nurses would phone me every other day they were more concerned about that [stomatitis], which is fine, but it wasn't really my main concern, my main concern was the nausea"*
>
> *Participant 10*

The presence of a clinical specialist nurse also seemed to vary. Some participants did not have a clinical specialist nurse that was involved in their care, some interacted with only one nurse throughout their diagnosis and treatment, while others interacted with several.

"Question: has there been any nurses involved in this process?

Participant: there is usually a nurse that sits in with him [oncologist] but that's all.

Question: okay, so you haven't had any conversations with the specialist nurse?

Participant: I've had one because I've had a blood clot with the PICC line"

Participant 16

"…I discussed the same things really with the colorectal nurses and there were three of them in my team"

Participant 9

"…if you had this nurse on the first day, they try to keep you with that nurse the whole time which I thought was a very good idea because they would get to know you"

Participant 14

Carers or family members

One of the factors that seemed important to participants was having a companion, primarily their spouse, when they were informed of the diagnosis, or when they met with the oncologist to discuss chemotherapy. In addition to providing reassurance and support, participants reported that their spouse played a role in gathering and understanding information. Some reported that the presence of a spouse at the consultations allowed for further discussions at home, while others reported that the spouse took notes and asked the questions that perhaps they would not have thought of. Although most participants referred to their spouse when they reported the presence of a relative during consultations, one participant reported that both her and her husband were accompanied by their daughter as she worked as a nurse and could aid in the discussion with the oncologist, further highlighting the importance of gaining and understanding the information provided.

"…I kind of walked away from that [first oncology consultation] not feeling too much, knowing that that was the initial meeting and that there would be another meeting which would be with my oncologist

and also one of the colorectal nurses, and in that meeting my husband came in with me."

Participant 2

"…my first meeting with the surgeon my wife was not able to attend […] and I was not expecting a cancer diagnosis so I went on my own which I think they were a bit surprised by that but you know no clues were given that I was needing to have somebody with me and that probably wasn't too helpful, but you know there we go it was what it was"

Participant 11

"…my wife was with me I think on that occasion so she was able to hear which was a good thing, particularly a good thing that a relative should be present because obviously the enormity of the whole thing you don't take it all in and anyhow, she was there and that was a reassuring thing"

Participant 13

"…we've gone in to see the oncologist and even took the daughter on because she's a nurse and she can ask relevant questions while the two of us sit there and can't think of anything"

Participant 12

In two accounts, participants reported that their spouse had an influence on their decision to receive treatment not only

"…my husband said anything that you are offered that could help, you know, continue to live, take it"

Participant 5

"…at one stage I almost stayed on the oxaliplatin, so I think that's what he [husband] wanted me to do because he could, he could see I was suffering, but he wanted to get it over with, so if anything it was between me and my husband the decision where I felt a bit, I wouldn't say I was pushed into it, but he obviously saw me suffering

and he just wanted me to get it over with and at one stage I was 50/50 whether or not to carry on with the oxaliplatin actually"

Participant 20

Almost all participants spoke in the plural form about their experience using the word 'we' instead of 'I' to describe events. Therefore, although some may have not explicitly mentioned the role that their spouse had played, the use of this language indicates their perception of a joint experience.

"…so we felt that if we could get over this bit […] we wanted to take all the chances we could."

Participant 3

"…we had the call to go see the colorectal surgeon […] after that we got the results of those biopsies"

Participant 9

This, however, is not necessarily true for everyone. One participant said that she preferred attending her appointments alone, because she did not want to concern her family. In addition, the emotional reactions of others, even if out of concern for her wellbeing, may become a burden and a distraction at a time when she needs to remain focused on the discussion taking place and the information provided.

"…I saw my oncologist myself, I didn't have anyone with me, I never take people in with me when I see anybody so it [the decision] is based on my feelings of the person who's talking to me what they are telling me and how much I feel that I can trust them to make the right decision. […] I wanted to deal with all this and take the worrying and concern away from everybody else […] I don't want them in what is quite a serious conversation with someone i.e., my oncologist and I don't want to have to deal with them getting upset when I need to be calm, cool, understand the facts and then make the right decision"

Participant 1

In addition, it is important not to overlook the distress that the companion may also be likely to experience, which can have a negative influence on the patient and their interaction with the healthcare system.

"…my husband had a little moan because of the length of wait in that little room and that probably didn't start very well, but I just felt I sat

there and felt what about me look this is you know this is my life and you two are talking amongst yourselves and so it was just a bad start really, that's probably because my husband can be a little bit, he wants things done properly and he felt that we were given short shrift because she was, she was looking through her notes and you know he said you don't even know anything about her"

Participant 5

Online forums and support groups

Several participants mentioned that they found online forums useful to gain insight into other patients' experiences with chemotherapy, which made them feel more prepared about undergoing chemotherapy and what to expect from this treatment. For one patient in particular, his exposure to online forums increased his awareness of side effects that could result from treatment, which led to further inquiry into the treatment he was receiving and eventually refusal to receive oxaliplatin.

"…I joined [online forum] as soon as I, on virtually on day one […] I noticed that a lot of people on there, I don't know 100 or 200 people I don't know, I must have looked at many articles and many comments and threads on that forum, and I deduced that so many people were suffering peripheral neuropathy or suffering anterior resection syndrome and I just thought what is, why are so many struggling and what does it mean, and how can I ensure that I don't get what they got"

Participant 6

For other participants, online forums provided reassurance about what constitutes 'typical' side-effects compared to what could be problematic for which they should seek help, while for others they were a source for emotional support.

"…on the forum you can vent your feelings, you can be angry you can be upset and ask for help you can ask any questions whatsoever and somebody will come back with an answer because they've been there as well.

Participant 7

"…there was very little support in my immediate area after my surgery, you know, I couldn't drive; the closest Maggie's Centre was

12 miles away there is nothing in the immediate area and it was the online forum that gave me the most support"

Participant 12

"…the main side effects were covered in the discussions but you know it was those niggling little things that sort of crop up sort of you know sort of 6 o'clock on a Saturday night when you suddenly feel oh, is this right and how to find solutions around them, you know what I mean? you know the reaction to cold, inability to pick up sort of cold things, well yes that was covered as a side effect but the ways around it came from sorts of other people [bowel cancer forum] who had been through that path before"

Participant 13

"…last week they [online forum] actually put up the different chemotherapy drugs that were available and I didn't realize that there were so many options"

Participant 8

A few participants also described the benefit they gained from engaging with support groups, as they met and engaged with others who were going through the same experiences and were alerted to ways in which they can cope better. The value that some patients may find from support groups is also reflected in the account of one participant who did not have one available but found value in the more personal connection that she established with just one other person who was having a similar experience.

"…they [nurses] also advised me to join a group called X which is for people with cancer in the local area and they meet once a month and again I found that quite beneficial because they have very good speakers coming and they also all been through what you're going through"

Participant 7

"…I mean, the online forum was good, through the forum I met a man who lives about half an hour's drive away and we supported each other on a daily basis sending messages to each other and talking because we were both diagnosed at the same time, we were both

going through the same surgery and the same chemotherapy, so we were just there to support each other"

Participant 12

As discussed earlier, the distress that a partner may be undergoing is also important to consider and engaging with support groups may be of value for them as well.

"…I did go to a charity [..] and we went on a couple of courses about living well with cancer and living well with chemotherapy then and they were very supportive, and they looked after me and my husband"

Participant 3

The importance of such means of support is especially evident for those who may not have a partner, family, or friends they can rely on. One participant described his experience and how he felt about the attitudes of people around him when they were made aware of his diagnosis, and the comfort he found by engaging with a charity.

"…friends wise it's a bit of a different story because I think once you mentioned the C word a lot of people think oh I don't understand that I don't know what it is all about I better keep my distance, and I think that that is a very common thing I think because people don't know how to react around it, they tend to shut people out because it's not something they're either comfortable with or they feel like they can sort of help with, yes I've had offers of help but you know it's like come and see me if you want anything or let me know if I can help, but then you know nine months down the line you've still got you know they have not phoned up to say how you're doing, it's that kind of isolation to some degree that I think people can suffer from but generally on the whole I feel that you know if I'm going to make anything of this then I need to make the lead and make the inroads myself, which is why volunteering for the charity has actually given me some kind of focus"

Participant 13

On the other hand, however, not all patients may immediately appreciate the value of these means of support and may underestimate the impact that their diagnosis and

course of therapy are having on their emotional wellbeing and the benefit that could be gained from engaging with support channels.

> *"…you are still trying to process information and work out what really are the important bits that you need to prioritise so it's hard and I think at that stage I would say if I had to say anything, that is probably where you needed the additional support and whilst Macmillan was mentioned I thought I'm a reasonably smart well-adjusted bloke I probably don't need them and in retrospect that was possibly one of the mistakes I made because I was completely ignoring the emotional impact really, trying to pretend there was no emotional impact when clearly there was"*
>
> *Participant 11*

One participant reported that she was advised not to join the online forums as they may contain negative information and experiences. However, although it is true that some people's experiences will be unfortunate, these unfortunate experiences nonetheless may occur with everyone, which patients should be prepared for. In addition, the forums may provide support, as seen in the earlier accounts, which patients find valuable.

> *"…I knew about forums to go on and the Macmillan forums but I was sort of told not to go on those because I was told most people that go on them post negative information or people that have had bad experiences rather than good so I didn't really read anything, I did afterwards when I had the side effects I went online to see if anybody else had the same side effects that I have found that yeah there were some people that had but a lot of people haven't so I think at the time I didn't feel too concerned I felt I got all the information that I needed but it was only afterwards and hindsight I thought actually I wish I had been given more information"*
>
> *Participant 10*

One participant highlighted the importance of early engagement with online forums. She indicated from her account that she was unaware of the existence of such channels in the earlier stages of her diagnosis and treatment, which she perceived would have been the most useful timing. She also suggested that she found the online forums through her own effort rather than through recommendation from healthcare professionals. This is an important finding because patients should be encouraged to

join online communities that are regulated by known charities, otherwise there is risk for misinformation from unregulated sources.

> *"…I think you tend to go down that route [online forums] more after, after everything kicks off, and I think you need to be pointed to that before it all starts. I think that would be more useful. Because what tends to happen, for example, on the Bowel Cancer Forum is some people will go on and say, I'm newly diagnosed and this is what the doctors told me, you know, what can I expect? But the majority of people are ones who are already going through chemo or just finished and have got things to talk about. So, I think there's a bit of a gap missing at the very, very early stages. I mean, possibly even as soon as you know that there's a possibility that you're going to have chemo or even maybe before surgery is probably even better when you can just talk to somebody who has, who has been through it […] I don't think you sort of think about looking for those online options, for instance, at that point, I think that comes later when you start to get a bit more inquisitive about things and then you think, oh, I wonder if this is a forum or something I can look for, and actually, when you find it, you think I could have done with this six months ago or three months ago or two months ago, and you've kind of missed out a little bit on the beginning stages.*
>
> *Participant 17*

Possible advantages to higher socioeconomic status

There were three accounts from two participants that indicate certain ways in which socioeconomic status can play a role in providing advantages that others may not experience.

One participant's surgical consultations and surgical care took place in the private healthcare setting. He reported spending a large amount of time with the surgeon, having several discussions, sometimes lasting an hour long, during which he discussed his surgical treatment options and was also made aware of his chemotherapy treatment options. In addition, he spent a large amount of time reading scientific journal articles to gain further knowledge. He approached chemotherapy from an informed standpoint, with awareness of the options available to him and the ability to engage in discussions, ask questions, and voice concerns.

"…when I went private, I had a very good surgeon, or I consider him very good, he was very frank with me and we had several discussions, he certainly spent sufficient time with me to explain everything. And I, anyway I have undertaken my own research and we had an hour-long telephone conference when I was keen to understand both surgery, which is when I opted specifically for a permanent stoma and also, we discussed the possibility of peripheral neuropathy. I further had another discussion with my oncologist, to press him on the chances of PN and he confirmed that it was probable"

Participant 6

For another participant, two different accounts contributed to this theme. First, the participant's profession seemed to have played a role and influenced the clinician's communication at the time of the diagnosis. Second, his status and network allowed him to gain more information about his condition and may have also resulted in receiving treatment from a more senior specialist.

"…he [surgeon] then said well, you're a solicitor aren't you and you are used to telling people what's what and the truth and so on and so I have to tell you that you are suffering from bowel cancer which was located between the rectum and the next section"

"One of my golfing friends used to be the chief surgeon in this department at the same hospital, and he retired about shall we say five years before, and as soon as he heard that I had this diagnosis he rang me up […] ended up giving me a fair amount of information […] I have no proof whatsoever and I never asked him, but I think he may well have requested that I would be put down on the list of one of the surgeons that he was particularly impressed with […] It's rather funny actually because this doctor […] saved the life of another golfer who was quite up in the club and actually that golfer was so pleased

with what he had done that he invited him to join the club you see, so this is how these things work isn't it, friendships and links and so on."

Participant 15

Wider experiences with healthcare services and information provision

Some participants described negative experiences with the healthcare system in general, relating to other elements of care. Although not directly related to adjuvant chemotherapy, events experienced during treatment can alter a patient's general emotional state or cause distress, and possibly influence or distract from the ability to re-evaluate their treatment decisions. This is especially important when patients start to experience side-effects because of treatment and may need to re-evaluate their choices.

"…so there was a series of things like that which on top of the chemotherapy it started to just get too much and I was just wondering you know by late September do I want to continue with this because it was really making me feel quite ill and if I have a pulmonary embolism again there is a balance to be struck here between benefit and risk, I am gaining 5% increased chance of living five years but at what risk to my body"

Participant 11

One participant who relied on district nurses to make a home visit to remove the 5-FU pump, described her experience with that aspect negatively, as she would make the appointment for the home visit, and the nurses would fail to attend.

One patient spoke about the difficulty of finding parking at the hospital, particularly because he was suffering from a large painful blister in his foot that formed as a side-effect from chemotherapy, making walking painful and difficult.

Several participants described hospitals to be very busy, which resulted in long waiting times to meet with the oncologist.

"…there were times when we had to hang around for a while before they got going but they were very busy, the nurses didn't have much time to talk to you, they did what they needed to do, and they would talk to you then but then they were off and after that it was difficult to

catch them because they were rushing here and there and everywhere"

Participant 3

Two participants described negative experiences relating to their interactions with the helpline when they experienced side effects due to treatment.

"…I think probably the worst thing was the blood clot in my hand which I got within days of having the PICC line fitted and I did ring the help line which you get, you know you got a 24hr on call helpline and they told me it was normal, but that was on the Sunday and so by the Tuesday when I went to the hospital for my routine visit the blood clot was very large"

Participant 16

"...they have the helpline you could phone and a couple of times I did need help because I had lots of trouble with my mouth, and they didn't always phone me back I had to leave a message with someone or leave an answer phone message and there was one time when I had to phone twice before I got anyone to phone me back"

Participant 3

Two participants described their experience with prescriptions, and the difficulty of obtaining the anti-sickness medication that they needed. Prescriptions for accompanying medications had to be obtained from the GP rather than the hospital, which may cause delays and add several layers of action for an unwell patient to carry out.

"…the reality of obtaining a different prescription while you're feeling very, very sick and feeling sick all the time is actually very difficult because the first time I phoned the oncology ward they said oh no you've got to phone your GP and I phoned the GP receptionist she had to get the GP to call me back, and then they had to fax the prescription to the chemist but then I had to find somebody to go to the chemist and pick it up and then bring it to the house for me to take and it just takes forever"

Participant 4

Two participants also mentioned an expectation of follow-up and care from the GP practice. This point was illustrated with two accounts, one positive, where follow-up

from the GP practice was appreciated, and the other where lack thereof was perceived negatively.

> *"…a bit later within a couple of hours [of diagnosis] my GP or the head of practice rang me, and I was so, what's the word, touched I suppose, I was thrilled the fact that you know they cared enough to ring me"*
>
> *Participant 5*

> *"…I had my surgery, I came out of hospital and I heard absolutely nothing from my GP, I would have expected for them to just you know checking up on me but it wasn't, the hospital phoned and they were phoning every couple of days to make sure I was okay and to be honest I would have expected more of that from my GP but I didn't get it"*
>
> *Participant 12*

Some participants also recalled being uninformed about other aspects related to their treatment and care. Although these elements are not directly related to the decision on adjuvant chemotherapy, these accounts indicate that there may be an issue with sub-optimal provision of information on healthcare services more widely.

One participant reported being unaware of the purpose of the medications that were prescribed to mitigate the side effects of chemotherapy, such as steroids, which led to nonadherence and consequent complications, while another was not aware that steroids could lead to weight gain.

> *"…in one session I didn't take the steroids because I thought they're keeping me awake I don't need them, and actually, for that whole cycle of chemotherapy I was really poorly, and it wasn't until I went back and told the nurse that I didn't take the steroids she said that they were actually supporting my body to get better after the session of chemotherapy. So maybe if they had explained what are the drugs I would be taking and why I was taking them that would have been helpful and they would have avoided you know 2 weeks of feeling really, really poorly which I did […] they told me I had to take them but they didn't say why they just said you need to take them, they*

give you a bag at the end of the session and say right, you take this and when you take it and then you take that"

Participant 2

"…I was putting on weight I was just eating for England. Now I know it was the steroids"

Participant 5

Colon cancer patients are tested for a tumour marker called the carcinoembryonic antigen (CEA) during their treatment. Those who spoke about the CEA reported struggling to be informed of the results.

"…I did feel that I had to keep on asking to get any information she would say your bloods were fine and I would say "well tell me what the numbers were, could you give me a printout?" and she wouldn't give me a printout […] and then one time she did tell me that my CEA which is a tumour marker had been raised for 3 months but she hasn't told me about that before and that I would have to have a scan because it still was. I was very distressed that day I cried all the way home thinking, you know, something is wrong, and they have not told me"

Participant 3

"…I was told that the CEA blood test, if that's what it's called, that I would have that blood test taken each time to see if the cells if there were any cells circulating, if that's what that was for, but when I went last time, they said the results hadn't come through. So, I do actually want to ask about that and I want to ask about what my pre-surgery levels were because I don't know what that was"

Participant 10

Time: a 'double edged sword'

Time had a role to play throughout diagnosis and treatment, both in the pre-treatment as well as the treatment decision contexts. The pace at which patients moved from diagnosis to surgery and then onto chemotherapy was both reassuring on the one hand, but also overwhelming.

Reassuring rapid course of management

Participants expressed relief at the speed at which the tumour was resected following diagnosis, and chemotherapy initiated following surgery. They perceived time to be against them, whereby delays in treatment would lead to worse prognosis.

> *"…I remember getting a letter when we were on holiday to go for sort of like for a pre-assessment and I missed the date, and I was really upset because I was thinking I need to have this chemotherapy quickly I don't want to be waiting another week and they managed to bring my date forward to start it"*
>
> *Participant 2*

> *"…I can't fault the system because I'm fully aware of how quick everything moved for myself you know from diagnosis to surgery to treatment you know it's all been really relatively quick"*
>
> *Participant 9*

> *"…and then you get up to the point of the preoperative assessment and I think at that point things are happening so you're much more comfortable and you can see a process happening and you are reassured that it is the process as described to you at the outset is now kicking in and they haven't forgotten you and you are on your way, so that's the reassuring piece really […] you're aware the clock is ticking all the time of course"*
>
> *Participant 11*

> *"…I also understood that delaying and hanging around is not necessarily the best of things so I can understand why they moved things quickly, because obviously when your body's healing from the surgery then any cancer can tend to be more active because everything that helps you heal actually helps your cancer grow and I was aware of that"*
>
> *Participant 14*

Lack of time to process information and prepare

The rapid movement through the course of management, although provides a sense of reassurance, as described above, may also be a disadvantage. Time may be needed

to cope with the diagnosis, process the information provided, engage with clinicians in discussions, and formulate thoughts and questions.

> *"…I didn't really have a lot of time to ask people, because my admission to A&E and then the subsequent surgery and chemotherapy just happened very, very quickly […] when I was diagnosed it was a shock diagnosis, but I think if I did, if it had been different if I had gone for routine colonoscopy because I have been referred by my GP and everything happened a lot more slower I think I would have wanted more involvement and more help and support but I didn't, I just sort of sat there for 3 or 4 months just stunned so shocked, that played a huge part"*
>
> *Participant 2*

This is highlighted further in the contrasting account from one participant who spent a large amount of time discussing and understanding his options in the private healthcare setting, reading scientific journal articles, and questioned the oncologists on multiple occasions (Participant 6).

Some participants reported that information about therapy, whether as written material or through a discussion, was typically provided during the first oncology consultation, with chemotherapy starting soon after. Two participants explicitly expressed that they would have benefitted from an interval during which they could process information and prepare questions, followed by a second meeting that allowed a more thorough discussion. One of the participants described this as a "layered approach" (Participant 11). They believed that if they had time to discuss at length, they would have been able to raise questions and concerns.

> *"…I think what the problem is and should have been and should happen is that you have the first meeting with your oncologist and this is your option and this is what we suggest you do to keep yourself alive and then give you all the information and then you go back and see them at a later date, but that didn't happen it was all done in one session […] I would have liked to spoken to him at a later time just to go back through everything"*
>
> *Participant 1*
>
> *"…I hadn't had time to absorb what the oncologist had said, and I hadn't had time to go home and read the leaflets and although on the*

face of it I was always going to take chemo if that was what was recommended, I just felt that I wasn't prepared"

Participant 4

"…what you are given you come out with a bunch of papers with the point of the meeting where you are in no position to process those you don't even want to process them and what would be far more beneficial would be to take sort of a more layered approach with a subsequent follow-up meeting where you can go through these things at a little bit less pace where you do have the opportunity to understand the context of why you're being given this what it means and what you need to do about it"

Participant 11

"…when we talked about it and she explained what everything meant and she then gave us the time I was with my husband and she said, you know, go away for a week, think about it. I'll give you your consent forms. You don't have to sign them […] I want you to go away and think about it and read and read the information I've given you"

Participant 17

Another participant's contrasting account highlights this point further. She described passively receiving information during the first meeting, and "walk[ing] away from that not feeling too much" (Participant 2), knowing that a second meeting where she could engage more actively would take place. Additionally, she attended the first consultation alone, therefore the second consultation allowed for her husband to be present, who provided support and aided in the discussion. This is especially important when patients have not had time to resolve the emotions that may influence the ability to process information, as highlighted by the following participant's account. For this participant, the result of the pathology report, which details the extent of the cancer, was discussed during the first meeting with the oncologist, causing the participant and his wife to become inattentive to the discussion that followed about chemotherapy.

"…that initial first meeting me nor my wife can really recall that conversation particularly well because we had the pathology results, then was straight away into what was, what it was what it meant what was happening next. I've got to be honest both me and my wife didn't really listen that well in that first meeting […] If I'm honest it wasn't

until later meetings where we had done our own research and had batches of questions to ask that things became more clear"

Participant 9

Some participants also met with an oncologist before each treatment cycle, which allowed a discussion of side-effects and concerns, while several participants reported seeing an oncologist only a few times during therapy, which they perceived as insufficient.

"…I saw the oncologist before chemo, I then saw him when I had the emergency admission and then I saw him at the end when he discharged me"

Participant 4

"…I saw him [the oncologist] twice throughout the entire six months"

Participant 11

"…I had no problems taking the medication apart from usual sort of side effects associated with that, but we discussed all those sort of, as I went through the appointment because I had an appointment with him before each cycle started"

Participant 13

Post-treatment

Feelings about treatment decision

Although all participants who received oxaliplatin considered a reduction in the risk of recurrence more important than any side effects, it is difficult to know whether reduction in risk of recurrence would still be preferable if they knew upfront oxaliplatin's margin of benefit compared to single therapy, and the risk of permanent peripheral neuropathy.

When asked whether knowledge of this would have changed the decision to take oxaliplatin, the answers varied. Most participants said that they would still choose to receive any treatment to increase their chance of survival regardless of side effects or how small the benefits are. This seemed the case regardless of age or experience of symptoms.

"…in hindsight I don't think I would ever change that decision I think I probably would have still stuck with it knowing what I know now"

Participant 1, experiencing peripheral neuropathy

"…it [neuropathy] has definitely affected my quality of life, but I wouldn't, I still would have had it even if I'd known that I was going to end up like this I still would have had it"

Participant 2, experiencing peripheral neuropathy

"…I would make the same decision yes, because I feel that it's giving me the best chance, you know, I could possibly have"

Participant 3, experiencing peripheral neuropathy

"…I didn't want that uncertainty and that's why even knowing about the peripheral neuropathy now I would still opt for chemotherapy, it's not an easy option but I would make that same decision"

Participant 4, experiencing peripheral neuropathy

By contrast, some participants said that they may have avoided oxaliplatin if they knew that the added benefit were only a few percentages, or that the side effects would be as severe as they had experienced.

"…I would not have had it, I would have avoided it, I think really more or less what I know now it's a horrible, horrible drug and I felt really that may be it wasn't 100% necessary if you've got, if it spread you have to have chemo that's different but if it's not 100% necessary and it was there just in case, I would not have had Oxaliplatin if I had been told that it [neuropathy] could be permanent."

Participant 5, experiencing peripheral neuropathy

"...if it was only a couple of percentages then I probably would just have the tablets [without oxaliplatin]"

Participant 10, experiencing peripheral neuropathy

"…if I'd known that if somebody give me a brief glimpse of all three regimes [combination therapy, single therapy with capecitabine tablets, single therapy with IV 5-FU] and what the side effects would be before I took the, actually, before I chose the treatment, I would

have gone straight for the bolus [IV 5-FU], absolutely no question, the other two were bad"

Participant 20, experienced acute peripheral neuropathy only

A few participants were not conclusive one way or another but said that they would have preferred if they were provided with more information at the time and involved in making the decision based on being more informed.

"…I think I would want to be involved in the decision, I mean it does increase it by a few percent but not by much and I mean if I hadn't had the neuropathy I would have gone through the whole cycle without an issue"

Participant 14

"…more explanation about, from the pathology results side of things what that entails to you as an individual moving forward with chemotherapy treatment or without it and you know what decisions you could make with the team to best suit you as an individual really"

Participant 9

"…if they said well, would you rather not have had this, not take the chemotherapy I suppose I would have said I would rather not have taken it but on the other hand if you are getting an extra chance to survive, I suppose you do, so you have to set one against the other"

Participant 15

Persistent peripheral neuropathy

Sixteen participants had completed therapy at the time of interview, ranging from eight years to a few months before, and eight described having persistent symptoms. Of the remaining participants, four did not receive oxaliplatin, two discontinued oxaliplatin due to acute symptoms, and two participants only experienced acute peripheral neuropathy during therapy but did not have persisting symptoms at the time of the interview. I report here how participants described their experience with peripheral neuropathy symptoms in terms of their influence on daily tasks and quality of life.

Influence on daily tasks

The most reported symptoms were numbness, tingling, and shooting pain in the hands, exacerbated by cold, or on touching cold objects, such as a metal door handle, shopping trolley handles, or objects retrieved from the fridge or freezer. Three

participants reported that due to loss of sensation in the fingertips or pain in the fingers, they were unable to type on a keyboard, which for one limited her ability to go back to her previous job (Participant 4, one-year post-therapy), and for another limited the options available for her as she sought employment (Participant 2, one-year post-therapy). Another participant also reported that loss of sensation in the fingertips limited his ability to perform actions that required fine manipulation, such as "picking up single screws" (Participant 13, 18 months post-therapy).

> *"…I do want to essentially go back to work but it is limiting as to what I can do so, obviously I have to avoid jobs where I am having to type because I can't type"*
>
> *Participant 2, one-year post-therapy*

Another reported manifestation of neuropathy affecting the hands was weakness in gripping objects such as the steering wheel, a pen, a knife, door handles, etc., limiting the ability to undertake basic activities such as driving, writing, cooking, or opening doors. Other examples of activities that were limited included doing and undoing buttons of a shirt, putting on earrings, twisting open bottle caps, pushing tablets out of their containers. A few participants described continuously dropping held objects. One participant described that she was "break[ing] crockery all the time" (Participant 5), or "breaking so many cups […] and the liquid goes everywhere" (Participant 19).

> *"…I picked up a pen and I thought I can't even tell if I'm holding the pen, I can't even tell how hard I'm gripping it, and then when I tried to write the first line that I wrote would be okay but then I couldn't control it to write anything it was totally out of my control, that was really upsetting that I couldn't write at all"*
>
> *Participant 4*

Participants also described similar unpleasant experiences of numbness, tingling, shooting pain, and cramping felt in the legs, which is also exacerbated by the cold. Some reported that symptoms experienced in the legs has limited their ability to go for walks during the winter months, go for a run, or sleep continuously at night. One participant whose job required her to be outdoors in different types of weather found going back to her job difficult.

> *"…with the neuropathy I am really concerned as the winter comes, previously I would be out walking in all-weather, cold, frost, snow, and I just know that my neuropathy will start playing up once the*

weather turns really cold, so that stopped me from going back to what I used to do"

Participant 2

"…I still can't stand on tile floors or laminate floors anything but carpet without slippers or socks on"

Participant 19

"…the feet, it's a nuisance in some ways if I get cold then the tingling gets much worse sometimes in the middle of the night, they wake me up I have to wear bed socks"

Participant 3

"…I used to do quite a lot of running, I definitely couldn't run at the moment, that would be too uncomfortable, so walking is kind of my limit at the moment"

Participant 19

One participant described a mix of experiences regarding her feet. At times she experienced prickling, which she described as "walking on a bed of nails", while in other times she described her feet as feeling extremely cold like "the beginning of a frostbite", and for that she used a hot water bottle even in the summer when the weather was "really hot, 30 or 35 degrees". She also described complete loss of pain, which she found concerning due to the possibility that she could injure herself without realising.

"…just last week I walked into something. I ripped one of my little toenails, I ripped half of it off my toe and I didn't even feel it […] the fact that it is clear ripped half my toenail off […] and I just didn't feel it at all, and that was quite concerning because it made me really aware of having to be so, so careful about what I'm doing"

Participant 17

Influence on quality of life

All participants reported that their symptoms improved over time. In addition, they have learned to adapt to the remaining limitations. For example, wearing gloves when going out in the cold, or taking a hot water bottle to bed to ease symptoms in the legs.

“I'm still managing to carry out day-to-day tasks washing, showering, obviously when I'm washing my hair when you, when you're running your fingers through your hair, my fingers are still sensitive and I'm quite slow and methodical doing that”

Participant 2

“…it doesn't stop me doing anything, we still go on long walks, we still climb mountains and things, so I can't really complain that it's very bad, but it's just there”

Participant 3

“…sometimes it's hard to remember how things were before an event to compare, and I know that sounds stupid, so you know if I feel that way it can’t be a problem, so really, it's not a problem.”

Participant 5

“…I still have that feeling now even sort of sitting here I can feel the tips of my fingers tingling and it's just sort of one of those things that I've learned to sort of deal with”

Participant 13

One participant in particular spoke about her experience of neuropathy at length and raised three difficulties, which although not expressed by others, are nonetheless important considerations. First, she expressed that although the symptoms were manageable, she did appreciate that her ability to carry out simple tasks independently is at times limited, which sometimes caused her frustration. Second, she found neuropathy a difficult concept to convey to and be understood by others, which she felt added to the emotional burden of what she was experiencing. Finally, she also found that not knowing what to expect in terms of the duration and severity of symptoms made planning for certain aspects of life difficult.

“…it’s so frustrating when you've got to find someone to help you to do that and, you know, if there is no one around you got to try and find a way to persevere. Yeah, I just find it frustrating and demoralising […] you come to end your chemotherapy and the cancer treatment and everyone's like oh congratulations well done and celebrating but it’s the last thing you feel like doing and then on top of that, I had the frustration that I couldn’t feel my hands and things, and everybody's like ooh you'll be back at work in a few

months or a few weeks and I'm thinking well, no, because I can't hold a pen, you know, and so, in some ways that was worse because you didn't have the understanding."

Participant 4

Although all participants reported coping with or adapting to the symptoms, there were three participants who mentioned work explicitly as something that has been affected.

"…I've got my work calling saying how are you getting on, and you know they're being very understanding but I find it very difficult because I don't know, you know, when I'd be back at work and I can't even hold a pen at the moment, I can't control a pen, I can't type."

Participant 4

"…my job is dancing and fitness, so my feet are really important, and the fact that they are most affected makes my potential for working again, very questionable. That was sort of difficult for me to reconcile with because it was, you know, potentially career ending for me."

Participant 17

"…with the neuropathy I am really concerned as the winter comes, previously I would be out walking in all weather, cold, frost, snow, and I just know that my neuropathy will start playing up once the weather turns really cold, so that stopped me from going back to what I used to do"

Participant 2

Discussion

This study was carried out using in-depth narrative interviews and aimed to investigate the decision-making process that determines the use of adjuvant chemotherapy for the treatment of stage III colon cancer, and in particular, the use of oxaliplatin.

Lack of shared decision-making

Most participants did not perceive having a choice of which treatment to receive. Except for three participants, those who received single therapy were not aware of oxaliplatin as an option, and those who received combination therapy with oxaliplatin were not aware that they could receive single therapy with a fluoropyrimidine without oxaliplatin. There were also indications that patients were not involved in discussions about other aspects of their treatment, such as the choice between two types of single therapy, duration of therapy, or when treatment should cease or be adjusted considering side effects. Given the strong emphasis that has been placed in recent years on shared decision-making, we should expect that doctors would work with their patients to select the most suitable course of treatment based on providing adequate information, engaging in an analysis of risks and benefits of all available options, and signalling to patients that a treatment decision needs to be made. However, this was not evident in this study. Instead, treatment was mainly evaluated by clinicians' judgment and experience. Decisions made by clinicians in the medical encounter could be described according to their temporal order as those made in the past (preformed), present, or future (conditional) (Ofstad et al., 2014). The findings of this qualitative study indicates that in most cases, the decision of providing treatment with oxaliplatin may have been pre-formed, that is, the decision to treat is made by the clinician before the medical encounter, and patients were informed, rather than consulted about this during the first meeting.

There has been little research on shared decision-making practices for colon cancer treatment or for other contexts, in the UK (Covvey et al., 2019). However, the findings here are in line with a few studies that were identified from elsewhere. In one study conducted in the US, Sanoff et al. (2010) asked 35 colon cancer patients with stage II or III disease if they discussed information or perceived elements of informed decision-making with clinicians during adjuvant chemotherapy consultations. Patients reported discussing on average approximately 15 of the 28 information items that they were asked about, with variation based on the type of items discussed as well as patient age, and reported that on average, 5 of 7 informed decision-making items took place.

Cancer stage, prognosis, and treatment were discussed more than short- and long-term side effects of treatment. Patients older than 70 years of age reported discussing fewer information items than those who are younger. Thirty-four percent of the patients reported not being asked about their preference for chemotherapy, while 23% reported that their doctor did not check whether they understood the discussion (Hanna K Sanoff et al., 2010). In one study conducted in one cancer centre in the US, patients with advanced gastrointestinal or hematologic cancer and their caregivers did not feel like a true decision existed and disagreed with their oncologist about how many treatment options had been presented (LeBlanc et al., 2018). In other research, oncologists were shown to rarely convey that a treatment decision needs to be made in the context of preference-sensitive neoadjuvant therapy decisions for rectal and breast cancer (Kunneman et al., 2016), and only half of surveyed patients thought that they were offered choices for their cancer treatment (Stacey et al., 2010). In another study conducted in a single Australian cancer centre, a coding system that consisted of 18 items was used to assess whether shared decision-making was taking place in oncology consultations regarding adjuvant therapy for breast, testicular, prostate, and lung cancers. It found that oncologists generally exhibited only half of the behaviours that were considered important in shared decision-making (Singh et al., 2010). Gregory and colleagues (2011) studied communications between doctors and patients about choices concerning the use of prescription medications in the US in the primary care setting. They collected data from doctors about how they communicate with patients when discussing the benefits and risks of prescription medications, and from patients discussed their concerns and the extent to which they found doctors to be responsive, which led to recommendations by the authors based on the PrOACT model (discussed in detail in the introduction to this chapter) (Gregory et al., 2011). Most clinicians in their study did not encourage a shared decision-making process. They believed they had training and experience, as well as trust and familiarity that were built through a long-term relationship with patients, that gave them a right and a responsibility to simplify treatment options and trade-offs and make a choice on the medical treatment most suitable to their patients (Gregory et al., 2011). While some patients perceived this to be the norm, many were disappointed and desired more information about their treatment options. In terms of identifying treatment alternatives, clinicians were found to prescribe a small number of medications already known to them, and there seemed to be mistrust of the information received from pharmaceutical companies on the benefits of new medications. This created frustration among patients for what they perceived to be clinicians refusing to offer or discuss alternatives. The study also found that clinicians may lack guidance on how to describe treatment consequences to patients,

i.e., the language to use or how to present this information. In addition, the multiple dimensions of consequences to observe or report, and in certain cases difficulty in observing or reporting certain consequences that may be more insidious, makes the information that clinicians need to collect from patients less accessible, and simultaneously, feedback from patients more emotionally or cognitively onerous. The study also found that clinicians may carry out an analysis of trade-offs, or the weighing of benefits and consequences, implicitly without explicit consideration of patients' objectives. This indicates that they may base this on their own experience and preferences. It also appears that the extent and content of trade-off discussions could be dependent on the nature and severity of the illness under treatment. For example, a discussion of trade-offs regarding the side effects of a certain treatment might be more likely with a patient who appears to be stable and has a better health status than with a patient who is suffering from an acute condition that requires immediate relief.

Factors influencing shared decision-making

Deferring to the clinician

There are several reasons that could explain why treatment with oxaliplatin is not presented as a decision that needs to be made. It may be that oncologists do not consider this a preference-sensitive treatment decision in the first place, as adjuvant chemotherapy with oxaliplatin is commonly described and recommended as the "standard therapy" in the literature. It is also possible that patients automatically assume a more passive role during the clinical consultation, giving the impression that they do not want to be involved in the decision. In this study, many participants expressed having trust in the "experts" who know what is best, and particularly those who knew that the recommended treatment resulted from a review by a multidisciplinary team, which is part of the standard of care for establishing cancer patients' treatment plan in England (Borras et al., 2014; Wood et al., 2008). Jorgensen et al. (2013) found that trust in physician was an important factor when considering whether to have adjuvant chemotherapy following surgery among both younger and older patients (Jorgensen et al., 2013). Salkeld et al. (2004) also found that patients placed trust in the surgeon as the most important factor when considering treatment options, and that trust was built on both a perception that the surgeon was concerned about the patient's well-being, as well as a perception of their expertise (Salkeld et al., 2004). However, evidence suggests that oncologists may base treatment decisions on their own preferences and factors that are not supported by evidence or clear guidance (El Shayeb et al., 2012; Keating et al., 2008). Treatment decisions made by

multidisciplinary teams also do not incorporate patient preferences, and it is not clear whether decisions made in this way are better than those made by individual clinicians (Hamilton et al., 2016). This is not to say that clinicians should not provide treatment recommendations. Providing a treatment recommendation is important to cancer patients and is part of shared decision-making (Bomhof-Roordink, Fischer, et al., 2019). In this study, oncologists were quick to offer their treatment recommendation, and often described treatment with oxaliplatin as the standard therapy. However, it may be important for clinicians to delay offering a recommendation to allow patients time to develop their preferences without influencing that process (Scherr et al., 2017).

Deferring the decision to clinicians could also be due to reasons other than trust. Patients may do so because they feel compelled to conform to socially sanctioned roles, feel that physicians are authoritarian or fear coming across as difficult, and this is true even for relatively affluent and well-educated patients (Frosch et al., 2012). In this study, many participants reported that they were informed of the treatment they received in a definitive way, leaving no room for discussion. This indicates that open communication was lacking and a discussion to clarify expectations and agree on a management plan did not occur from the outset. The importance of effective communication in increasing patient participation in health care decisions is well established (Sowden et al., 2001). A study conducted in Norway found that even when patients actively participate during the consultation by asking questions and expressing emotional cues, clinicians still showed low shared decision-making behaviour (Amundsen et al., 2018). Thus, clinicians shared decision-making behaviour may not be associated with patients' behaviour, and to truly achieve shared decision-making in clinical practice, the responsibility falls on clinicians to foster this approach. Furthermore, a few participants described their interactions with the oncologist as matter of fact, and others reported negative experiences or that their expressed concerns were ignored. Assessments of the quality of shared decision-making, and consequently, the practice of shared decision-making, often focuses on the techniques used during the clinical consultation, and do not consider the 'humanistic' aspects of the communication between patients and clinicians such as respect, compassion, and empathy (Kunneman et al., 2019). Lack of focus on these elements may reduce the patient-centeredness of shared decision-making and undermine its contribution to patient care

Inadequate information exchange

Some participants reported that if the oncologist provided more information about treatment options, they may have wanted to be involved in making decisions. This is supported by findings from a quantitative study of 375 colorectal cancer patients, where nearly 80% indicated that if the doctor told them everything, they would be more likely to want to make decisions (Beaver et al., 2009). In this study, most participants reported feeling inadequately informed about both the survival benefits, as well as side effects. All were aware that receiving adjuvant chemotherapy reduces, but does not eliminate, the probability of cancer recurrence. However, there was a perception among some that cancer recurrence is certain without it. This is inaccurate because although there is a considerably higher probability of cancer recurrence without adjuvant chemotherapy, it is not a certainty. Additionally, none reported discussing how therapy might influence their lives, or what could be important for them to consider. Clinicians making treatment decisions should do so after assessing and considering how a treatment may impact a patient's daily life (Geessink et al., 2017). In one study, shared decision-making practices, particularly communicating potential harms and benefits, and discussing what matters to patients, occurred in usual care was investigated using a sample of oncology patients, radiologists, and oncologists (Pilote et al., 2019). They found that clinicians presented a median of 8 potential harms using quantitative estimates only 17% of the time. They also found that clinicians initiated 63% of discussions of harms and benefits while patients and families initiated 69% of discussions about values and preferences. Only 56% of patients reported their clinician asked what mattered to them.

In addition to being a barrier for involvement in the decision-making process, patients who do not receive adequate information may turn to the internet to find answers to their questions. However, this may have adverse effects, as patients may use basic search engines to find information, leading to websites that contain inaccurate information and result in confusion (Sajid et al., 2011).

Several factors may contribute to inadequate exchange of information between patient and clinician. Several patient-level factors that can influence information exchange, reflected in this study's theme on pre-treatment context. A cancer diagnosis is known to cause a shock reaction among patients. High anxiety after a cancer diagnosis influences how much information patients can remember and may motivate patients to choose aggressive treatment, regardless of the probabilities for benefits or harms, or influence the clinical interaction as well as patients' understanding of their prognosis (Derry et al., 2019; Nguyen et al., 2019; Orom et al., 2017). All participants reported

that emotional distress may have precluded their ability to process information or engage in productive conversations with the clinician. Although emotional support has not been found to be an important element of care to cancer patients in several studies (Booij et al., 2013; Narbutas et al., 2017), addressing and managing the emotional distress brought about by the diagnosis and the course of treatment may improve patients' ability to remember information, as well communication between patients and clinicians. Furthermore, Elkin and colleagues (2007) found that patients had overestimated expectations regarding the curative nature of chemotherapy and researchers believed that this finding could be attributed to patients' selective memory during their clinical encounter. Several factors can influence a cancer patient's information seeking and avoidance behaviour. For example, patients may be less likely to seek information or ask questions because of their trust in the medical expertise, or due to fear of a distressing answer (Chae, 2016; Miles et al., 2008). However, the need to regain sense of control may be an important motivator for seeking information. Therefore, patients' information-seeking behaviours have been shown to change over the course of their experience with the disease and cancer patient's information needs should be frequently re-assessed. Patients may focus initially on being cancer free and getting through surgery rather than longer term implications (Park et al., 2014). However, as was shown in this study, some participants were willing to reduce or discontinue treatment upon experiencing some of its side effects, while others questioned whether they would make the same decision had they been adequately informed.

Most participants in this current study reported that survival was what mattered most to them. Therefore, it is possible that this was clear during consultations and the reason why clinicians may have not engaged in a conversation about harms, benefits, or patients' preferences. However, even if patients wished to receive therapy regardless of what the risks or benefits are, being informed and involved in the decision-making process may be more important than the decision itself. It has been shown that perceptions of the amount of information received about medical options, including information to prepare patients of potential side effects, are more important in increasing patients' satisfaction and reducing their anxiety than actual involvement in the decision (Wroe et al., 2013). It has also been shown that satisfaction with the treatment decision is dependent on the extent to which patients felt informed (Martinez et al., 2009). This is supported by findings from this study, in which most participants expressed dissatisfaction with the quality and quantity of information they received and did not feel strongly about who made the decision.

It is also possible that clinicians may provide information that they think is important to disclose but is not what patients what to know. In a study conducted in the Netherlands, surgeons' opinions on what pre-operative information should be provided to colorectal cancer patients undergoing surgery was compared to what is actually provided in practice (Snijders et al., 2014). Additionally, clinicians may assume a smaller role in terms of information exchange due to the availability of other resources. More than a decade ago, the primary source of information about treatment with adjuvant therapy for colorectal cancer was verbal instructions by surgeons and oncologists (Jefford et al., 2005). Today, written information is available for patients to refer to. Beaver and colleagues (2009) found that patients had a greater understanding of written information as opposed to verbal information given to them by healthcare professionals. However, participants in this study reported feeling overwhelmed by the amount of written information they received and unsatisfied by its generic and non-personalised nature.

Clinicians may also rely on nurses to assess patients' information needs, fill the gaps in knowledge and understanding, establish a relationship with patients, and ensure that their values and preferences are conveyed. Indeed, most participants reported that they relied on nurses to gain and understand information on side effects. This supports the study by Beaver and colleagues (Beaver et al., 2009), which found that 83.5% of patients indicated that talking to nursing staff helped them make sense of the information given by their doctor. In one study, better recall of information among patients was associated with discussing potential harms with a nurse after seeing the physician (Pilote et al., 2019). A systematic review exploring the roles of the nurse during cancer treatment decision making found that nurses play a crucial role as a trusted source of information (Tariman & Szubski, 2015). In the UK, the clinical nurse specialist role was introduced in 1995 to provide care for patients with cancer in a holistic way, serving as a conduit of information between clinicians and patients and ensuring that patients are guided, and their needs addressed through diagnosis, treatment, follow-up, and end of life care if needed (Royal College of Nurses Policy Unit, 2009) (Leary, 2021). There are, however, variations in access to nurse specialists across the UK (Palmer, 2018); as shown by this study, participants' experiences with nurses seemed to vary. Some noted the presence of a colorectal nurse specialist who was present throughout the course of their diagnosis and treatment, while others only mentioned surgical and oncology nurses during their surgery and chemotherapy phases of treatment, respectively. When participants made comparisons, interactions that took place with surgical nurses were consistently favoured compared to those with

oncology nurses. This could be due to differences in communication skills, or differences in the nature of the procedures and information required for each type of treatment. Additionally, participants often reported confusion about the information they received from varying people involved in their care, which may further highlight the importance of a specialist nurse guiding the process and providing a reliable source of information.

Factors outside the interaction between patient and clinician could also have an influence on information exchange. For example, time outside of the clinical consultation is an important part of information exchange and the decision-making process (Bomhof-Roordink, Fischer, et al., 2019; van Veenendaal et al., 2018), as patients may deliberate about their treatment choices within their daily lives and return to a second consultation with a better understanding for and ability to express what is important to them. Even when the course of treatment is not presented as a decision that needs to be made, and as such patients are not deliberating about choice of treatment, time outside of the consultation allows for patients and their carers to return to a second meeting with questions to ask or concerns to express. Therefore, the number of clinical consultations is an important determinant of how much information is exchanged, how it is received and processed, as well as to the nature of the relationship that is established between patient and clinician. Having only one meeting during which the course of treatment is discussed and decided does not allow for adequate deliberation about treatment choices or information exchange to occur, and at least two consultations have been recommended for making important decisions (Bomhof-Roordink, Fischer, et al., 2019).

Shared decision-making models recognise that the decision-making process often involves multiple people, such as multiple specialists and family members, and is not limited to the patient and clinician. Therefore, whether a patient is accompanied during a clinical consultation could also have an influence. Having a companion during the meeting provides support and aids the patient in taking notes, asking questions, and retaining information (Dove et al., 2017; Hirpara et al., 2016). However, although some patients may prefer to be accompanied, others may not. For example, in one study older adults reported significantly lower influence of support on decision-making than younger adults (Krok-Schoen et al., 2017).

It is also possible that engaging with online resources and forums could influence the type and quantity of the information that is exchanged between patient and clinician. In the current study, those who engaged with online forums found them beneficial because it alerted them to issues that led to further inquiry during the consultation or

provided them with experiential and practical knowledge of side effects and what to expect from treatment. This is in line with research that has shown the importance of experiential knowledge sharing among patients (Kaiser et al., 2021). The study explored information needs among 41 colorectal cancer patients in Germany and found that patients need practical information from other people living with the disease and who shared their experiences.

Knowledge and understanding of Peripheral neuropathy

Participants' understanding of peripheral neuropathy seemed to be lacking on several fronts. Some reported being unaware of the side effect until symptoms began to appear. Others who were aware of the condition reported lack of awareness of its potential to be long lasting. This is in line with other research that reported lack of patient understanding of chemotherapy-induced peripheral neuropathy (CIPN) (Padman et al., 2015; Tanay & Armes, 2019). Some participants in this study suggested that discussions about peripheral neuropathy either did not take place, or the severity and extent were not emphasised, which is in line with research documenting that CIPN was discussed and recorded by clinicians in less than half of the cases (Knoerl et al., 2019). Therefore, it appears that the clinical consultation focused on providing information on immediate or potentially severe or life-threatening side effects, such as nausea and vomiting or allergic reactions. The severity and extent of acute neurotoxicity (which occurs during treatment) was also communicated, but the potential for less-severe neuropathic symptoms to persist were often left unexplained. This finding is aligned with a review of 27 studies, which found that although serious adverse events and acute complications were mentioned, long-term and mild-to-moderate side-effects that affect daily life were usually lacking in publications (Narbutas et al., 2017). This finding is in line with another study that noted how chronic low-grade toxicities are mostly ignored in current value frameworks (Basch, 2016). However, initiatives to assign more importance to such mild-to moderate and daily life-affecting adverse events are on the horizon. The American Society of Clinical Oncology updated their framework to also include mild-to moderate adverse events due to the high volume of comments received after its publication (Schnipper et al., 2015).

Strengths and limitations

One limitation of this study is that given the length of the transcripts and the limited resources it was not possible to double code the data and assess inter-coder agreement. To overcome this, every effort was made to increase the rigor and

trustworthiness of the analysis by tracking the analysis using a detailed and comprehensive audit trail, as well making use of memos throughout the analysis. Another limitation is that the study only captured the views of those who had a positive outcome (i.e., no recurrence) from treatment. It is possible that a negative outcome may have resulted in different feelings about the treatment received and the decision-making process that led to it. Furthermore, some participants were reluctant to be critical of the NHS, as they felt gratitude for the healthcare that they received and owed their survival to. This may have resulted in some curtailing the narrative on their negative experiences or perhaps subconsciously avoiding recall of negative experiences. A second limitation is that only one participant provided perspective on the decision-making process that led to refusing treatment with oxaliplatin. More narratives on this regard would have provided insight into the personal, social, economic, or other factors that might be important to patients who refuse therapy. Another limitation is that all participants were of White British ethnicity and so the views and experiences of ethnic minorities were not captured. It may be that ethnic minorities do not engage in the online forums through which recruitment occurred, or that they are less likely to volunteer for research. Accounting for these limitations relating to the composition of the sample would have required more targeted recruitment through access to hospital records to identify those patients.

On the other hand, one of the study's strengths in terms of representation is that participants varied in other characteristics such as age, capturing perspectives of both younger and older adults; income-level, with the participation of those who self-identified with low, mid, and high-income levels; and education status, which ranged from no qualifications to higher education. Another strength of this study is that the interviews were narrative in nature, meaning that participants were told to tell their story. This allowed them to relay their experiences in the way that they remembered them, to focus on the issues that were important to them.

This study also captured experiences within a wide time frame, which presents both a strength and a limitation. Although experiences of those diagnosed nearly ten years ago might not reflect more recent practices in the NHS, these accounts provided insight as to how little the healthcare system seems to have changed over time, and how long the emotional impact of their experiences could last. Carrying out the interviews over the telephone also poses both a strength and a limitation. The strength of this approach is that it allowed flexibility to recruit participants from different parts of the UK, increasing the representativeness of the sample. However, the drawback is that some

important non-verbal cues that hold meaning and could provide the opportunity for more in-depth understanding may have been missed.

Conclusions and recommendations

It is known that in the UK, shared decision-making is often not implemented in practice (Coulter et al., 2017), and this study has shown that this may apply even in a context where the treatment decision can have a long-lasting influence on quality of life, such as in this case with adjuvant chemotherapy for stage III colon cancer.

Efforts should be aimed at preparing patients for the consultation with the oncologist. This could include using a questions prompt list, for example, that encourages them to ask more questions, and plan questions before the consultation. It can provide guidance on the types of questions they could ask, such as on the options that are available for their condition, or how treatment could influence their daily lives (Licqurish et al., 2019). Evidence suggests that audio recording consultations offers limited benefit in improving communication or information exchange between patients and their physicians (Licqurish et al., 2019). However, this may not be true for all patients; some may find this beneficial and therefore should have the opportunity to do so if they wished. This may be especially important for the first consultation when they may be learning about the extent of their disease or the intensity of the treatment that is being offered. In these cases, patients may be unable to process the information they are receiving as other thoughts may take precedence, such as realising the disease is more serious than they originally hoped or worrying about side effects of chemotherapy especially for those who hold negative pre-conceptions. However, further research is required to establish whether the use of a recorder would be acceptable to clinicians and move towards implementation by addressing potential barriers. It may also be important to ensure that patients understand the purpose of the clinical meetings and their preference for being accompanied before the meeting take place. The presence of a companion during consultations provides support, as well as aids in gaining and understanding information.

Although patients do receive information on the side effects that they should expect, accounts from this study revealed that practical knowledge may be lacking. Patients should be encouraged to engage in appropriate online forums that are moderated by established charities at an early stage in their diagnosis. This will increase their understanding of the changes that they will go through and may also alert them to bring questions on what they do not understand to the clinical consultation. In addition, written information provided to patients about treatment side effects should include

evidence from qualitative scientific studies that describe patients' perspectives and experiences and stories on how they may influence daily life. Descriptions from patients in this study suggests that this may not be routinely provided. To my knowledge, information provided to patients are not standardised across the country, that is, different NHS Trusts may provide information produced by different sources. Within NHS England, "The Information Standard" to judge the quality of information produced by organisations. Any organisation that meets this quality standard can apply to be certified for producing information. The principles of The Information Standard require that an organisation has a process in place to produce information based on evidence, produced by people with expertise and involving end users, considers the health literacy or accessibility needs of its end users. However, these are broad guidelines that apply to all conditions. They are not specific to cancer, or to type or stage of cancer. Therefore, the information that a cancer patient receives may vary depending on where they are treated, and the source of information used. Further research could explore whether information provided to patients appropriately cover the topics they are intended for and meet patients' knowledge needs.

Events that occur in patients' daily lives can influence patients' emotions, in addition to the daunting experience of a cancer diagnosis and treatment. Therefore, support for cancer patients at home from primary care practitioners, social workers, the clinical nurse specialist, and pharmacists is important to aid in the mitigation of the effect that negative emotion can have on the processing of treatment information and the decision-making process. This support is also important in the early phase of treatment, when patients are still adjusting to their treatment schedules and side effects, and re-evaluating their choices (Arber et al., 2017).

Programmes are needed to improve clinicians' communication skills and improve their understanding that the importance of shared decision-making lies more with encouraging patients' participation in the decision-making process rather than with who makes the final decision. Patients may lack the clinical knowledge that is required to determine the appropriate treatment for a given condition, however, the importance of patients' participation is to ensure that they are informed about, prepared for, and have fully considered how treatment decisions may affect their bodies and their lives. Therefore, it is important that they are informed of not only what the treatment is but why it was the most suitable.

It is also important that clinicians not only encourage open communication and engage patients in discussion, but also allow for a relationship to develop that is based on respect and compassion. Perhaps it is rational to take on board the suggestion that

decision-making should be adapted from being shared to being guided (Gieseler, 2018). Gieseler argues that despite efforts to clarify the advantages and disadvantages of therapeutic options, the asymmetry in knowledge between doctors and patients could never truly be balanced. He also argues that for the affected patient such decisions are unique and life altering, while for the clinician, attending to patients in difficult situations constitutes their daily practice. Therefore, a clinician may not want to share in these situations, but rather, guide patients through them with empathy. In fact, one of the challenges faced by NICE in the development of their guidelines for shared decision-making was disagreement among stakeholders on the term that should be used, many preferring “understanding and supporting informed patient choice” instead of shared decision-making (Wohlgemuth et al., 2019).

Chapter 7: Level of information about, and involvement in, the decision-making process of adjuvant chemotherapy among stage III colon cancer patients

Introduction

For many health care situations, when available treatment options are associated with uncertainty in their benefits and harms, shared decision-making has become the recommended model for how treatment decisions should be made in clinical practice. Shared-decision making is the process by which the clinician and the patient agree on a management plan together based on the patient's informed preferences (Charles et al., 1997). Shared decision-making is important because preferences between individuals may vary, and choice of therapy can influence patients' survival and health-related quality of life during and after treatment.

Treatment for colorectal cancer is one such situation where choices require weighing of pros and cons. Evidence suggests that toxicity due to adjuvant treatment for colorectal cancer has an impact on patients' health-related quality of life, causing distress and discomfort (Dunn et al., 2003). Therefore, some patients may prefer to undergo aggressive therapy for a small benefit, while others may choose less aggressive options or to decline treatment to avoid side effects (Couture et al., 2005; Pieterse et al., 2007). Considering patient preferences during oncology treatment is regarded as an indicator of good quality healthcare (Oliver & Greenberg, 2009). Patients should be provided with adequate information on their clinical diagnosis and the available therapeutic options and their attributes and are assisted in clarifying what is important to them (Charles et al., 1997).

While some patients may have preferences and want to make decisions regarding their treatment, others may not. Nevertheless, studies have found that even when patients preferred a more passive role, they still wanted to be informed and take part in the decision-making process (Cranley et al., 2017). This may vary on certain characteristics, for example, people with higher educational level, younger age and female sex were expressed more desire to participate in decision-making. Active decision-making was more common in patients with certain cancers, such as breast,

than others, such as prostate (Gaston & Mitchell, 2005). Beaver et al. (2005) conducted semi-structured interviews with 41 colorectal cancer patients to identify patients' views on participation in the decision-making process. The study found that it was more important to patients to feel informed and involved rather than who makes the final decision, and that lack of information and medical knowledge reduced patients' desire for participation (Beaver et al., 2005). In fact, van Vliet et al. (2019) showed that those who feel completely informed about the benefits and risks of their treatment options perceived receiving patient-centred care more than those who felt incompletely informed (van Vliet et al., 2019). This indicates that receiving adequate information is important to patients and may lead to increased patient satisfaction and participation in the decision-making process. This is reflected in three studies conducted in the UK, which showed that one of the top five needs that were identified among cancer patients was the need for health information (Morrison et al., 2012), and that the majority of patients wanted all possible information about their diagnosis and treatment, whether it was good or bad (Cox et al., 2006; Jenkins et al., 2001). In a scoping review conducted by Van Mossel et al. (2012), 239 articles were analysed to examine which information needs, sources of information, and timing of providing information, were captured by studies that investigated these topics among colorectal cancer patients (Van Mossel et al., 2012). Of 26% studies that mentioned information needs, the majority were treatment related. Among those, information on treatment side effects and treatment options were the most and second most frequently mentioned. Of studies that mentioned timing of information, the review found that most did not address any specific stage in the cancer care continuum. This indicated that more attention may be required for the information needs of patients at varying stages throughout their diagnosis and management.

Evidence suggests that cancer patients' involvement in treatment decision making is associated with higher satisfaction with treatment decisions, reduced decisional conflict, and better well-being (Brown et al., 2012; Gattellari et al., 2001; Keating et al., 2002). Others have shown that patient-clinician information engagement leads to better adherence to follow-up or monitoring after treatment (Tan et al., 2012). The association between patient-clinician information engagement and higher patient treatment satisfaction has been shown to be mediated by patients' feelings of being informed (Martinez et al., 2009).

Given the modest additional benefit in survival from oxaliplatin compared to single therapy, and the trade-off with the potential for permanent side effects, we should expect to see strong indications that those who receive oxaliplatin are informed about

its future side effects, their treatment options, and are involved in the decision-making process that determined which treatment they received. The National Cancer Patient Experience Survey (NCPES) presents an opportunity to explore this among stage III colon cancer patients in the UK. The NCPES is an annual national survey that has been conducted since 2010. It was designed to understand patients' experiences throughout the full continuum of their cancer care in the National Health Service (NHS) in England. The survey asks questions on patients' perceptions of the information they received, their involvement in care decision, and their interactions with healthcare professionals, and their involvement in the care they. Since its launch in 2010, data from NCPES has been used in several studies to explore inequalities in cancer patients' experiences of cancer care by different characteristics such as age, gender, ethnicity, deprivation group, and type of cancer. One study used the 2011-2012 survey to explore variations in the overall experience with cancer care by sociodemographic, clinical, and National Health Service (NHS) Trust-level factors (Bone et al., 2014), and another used the NCPES 2012-2013 to describe variations of information provision and communication by ethnic sub-category (Trenchard et al., 2016). The 2012-2013 survey was also used to explore overall patient satisfaction and patients' experiences of interacting with clinical nurse specialists, hospital doctors and ward nurses among those from minority ethnic backgrounds (Pinder et al., 2016), while the 2015 survey was used to explore determinants of overall patient satisfaction with cancer care, specifically, which aspects of care were most associated with overall satisfaction (Gomez-Cano et al., 2020). However, the analysis in these studies included all NCPES respondents in the corresponding surveys, without differentiation by cancer type. By contrast, El Turabi et al. (2013) used the 2010 survey to explore variations in the question on patients' involvement in the treatment decisions by different sociodemographic and tumour characteristics, and for each type of cancer. They found that most colon cancer patients reported the most positive experience of involvement in treatment decisions compared to other types of cancer (El Turabi et al., 2013). However, they only examined the question pertaining to involvement and did not look at any other questions in the survey. Saunders et al. used the 2011-2012 survey to explore sociodemographic variations across all questions of the survey (64 questions) and reported on the likelihood of reporting positive or negative responses for each type of cancer, compared to rectal cancer (Saunders et al., 2015). They found that colon cancer patients were less likely to report positive experiences for questions on information and involvement in the decision-making process than rectal cancer patients. However, the study did not provide a breakdown for each of the responses of these questions. For example, the most positive response "yes, definitely" and the less

positive response “yes, to some extent” were both combined and considered a positive response without differentiation. Additionally, the studies that have provided analysis by cancer type provided insight on experiences for each cancer diagnosis as a whole and did explore stage-specific experiences. Within each cancer diagnosis, experiences of cancer care and treatment may vary for different stages of the disease. Furthermore, to my knowledge, none of the studies that used NCPES explored difference in experiences by type of treatment.

In this study, I used the NCPES data for stage III colon cancer patients diagnosed between 2012 to 2017 in England. The aim was to explore the extent to which perceived being informed about side effects of chemotherapy, long-term side-effects, and treatment options, and of being involved in the treatment decision, comparing those who received single therapy to those who received combination therapy.

Methods

National Cancer Patient Experience Survey (NCPES)

Patient experience surveys were conducted in a small number of NHS Trusts in the years 2000 and 2004. The 2004 questionnaire was then revised by the Department of Health to produce the first version of the 2010 National Cancer Patient Experience Survey (NCPES). The Department of Health reports that an advisory group was set up for the NCPES with the National Cancer Director, professionals, voluntary sector representatives, academics, and patient survey experts (Department of Health, 2010). The 2010 questionnaire underwent many revisions based on discussions amongst the advisory group as well and four rounds of cognitive testing. Survey questions should be designed to be interpreted and understood consistently by all participants to ensure that the data collected to be reliable and unbiased. Cognitive testing is one of the techniques used to identify issues in the interpretation or comprehension of survey questions by participants (Collins, 2003). The Macmillan Cancer Support recruited 25 patient volunteers who had different types of cancer to participate in cognitive interviewing about the questionnaire and the accompanying covering letter. The NCPES that were conducted in subsequent years mostly replicated the 2010 questionnaire, with occasional amendments made to some questions and response options made by an expert panel.

The NCPES data provides information on patients' perceptions of several elements of the care they received. The NCPES includes questions on patients' perceptions of the interactions with and level of care from general practitioners, hospital doctors, ward nurses, and clinical specialist nurses. It also includes questions on their experiences in the hospital and as outpatients including the level of support that was available to them. The NCPES also includes questions on patients' perception of the information they received on their diagnosis, diagnostic tests, operations, treatment, as well as their level of involvement in treatment decisions. The survey was conducted for the first time in 2010, and the most recent survey was in 2018. The NCPES is sent to all adult (aged 16 and over) NHS patients (identified from the Hospital Episode Statistics database), with a confirmed primary diagnosis of cancer, discharged from an NHS Trust after an inpatient episode or day case attendance for cancer related treatment. The time periods that each survey covers are shown in Table 37.

Table 37 – Calendar year of conducting NCPES surveys and calendar period each survey covers

Year survey conducted	Time period surveyed patients discharged from hospital
Round 1: 2010	1st January to 31st March 2010
Round 2: 2011/12	1st September to 30th November 2011
Round 3: 2013	1st September to 30th September 2012
Round 4: 2014	1st September to 30th November 2013
Round 5: 2015	1st April to 30th June 2015
Round 6: 2016	1st April to 30th June 2016
Round 7: 2017	1st April to 30th June 2017
Round 8: 2018	1st April to 30th June 2018

There were eight cancer patient experience surveys conducted from 2010 to 2018. After 2014 amendments were made to the survey resulting in some questions that were not common to all versions.

There were three questions relevant to this study that were common to all NCPES rounds. The questions were of multiple-choice format, consisting of four to five choices and asked whether patients had side effects explained to them in a way they understood; whether they were told about future side effects; and whether they were involved as much as they would have liked in the treatment decision (Table 38).

Table 38 – Questions included in NCPES that were common to all NCPES rounds

Were the possible side effects of treatment(s) explained in a way you could understand?
Yes, definitely
Yes, to some extent
No, side effects were not explained
I did not need an explanation
Not sure / can't remember
Before you started your treatment(s), were you also told about any side effects of the treatment that could affect you in the future rather than straight away?
Yes, definitely
Yes, to some extent
No, future side effects were not explained
I did not need an explanation
Not sure / can't remember
Were you involved as much as you wanted to be in decisions about your care and treatment?
Yes, definitely
Yes, to some extent
No, but I would like to have been more involved
Don't know / can't remember

Five further questions that were used in the NCPES were also found to be relevant to this study but were not common to all NCPES rounds (Table 39). Those questions were analysed separately within the NCPES rounds that they corresponded to. The questions were of multiple-choice format, consisting of four to five choices. One question asked whether a patient was provided with written information about side effects, another asked whether a patient was given a choice of different types of treatment, a third asked whether a patient thinks their views were taken into account while making the treatment decisions, the fourth asked whether a patient received all the information they needed on chemotherapy, and finally a fifth question asked whether their treatment options were explained to them.

Table 39 – NCPES questions not common to all NCPES rounds and analysed separately

Questions common to rounds 3 and 4 (2012-2013)
Before you started your treatment, were you given written information about the side effects of treatment(s)?
Yes, and it was easy to understand Yes, but it was difficult to understand No, I was not given written information about side effects Don't know / can't remember
Before your cancer treatment started, were you given a choice of different types of treatment?
Yes I was given a choice because only one type of treatment was suitable for me No, but I would have liked a choice Not sure / can't remember
Do you think your views were taken into account when the team of doctors and nurses caring for you were discussing which treatment you should have?
Yes, definitely Yes, to some extent No, my views were not taken into account I didn't know my treatment was being discussed by a team of doctors / nurses Not sure / can't remember
Questions common to rounds 5, 6, and 7
Beforehand, did you have all of the information you needed about your chemotherapy treatment?
Yes, completely Yes, to some extent No I did not need any information
Before your cancer treatment started, were your treatment options explained to you?
Yes, completely Yes, to some extent There was only one type of treatment that was suitable for me No Don’t know/ can’t remember

Statistical analysis

Data from the NCPES was linked to the cancer registry and the Systemic Anti-Cancer Therapy (SACT) data (described in Chapter 5) based on patient and tumour unique identifiers to allow for the identification of responses received from those with stage III colon cancer.

The characteristics of the population of stage III colon cancer patients in the cancer registry was compared to those who responded to NCPES. Frequency tables were used to examine the overall distribution each group by age, sex, deprivation group, ethnicity, year of diagnosis, size of tumour (T), number of lymph nodes involved (N), and type of chemotherapy. Logistic regression was used to obtain crude and odds ratios mutually adjusted for each of the demographic and clinical characteristics.

Responses to the eight questions obtained from NCPES (as described above) were compared between those who received monotherapy and those who received combination therapy among stage III colon cancer patients, adjusting for demographic and clinical characteristics.

Frequency tables were used to examine the overall distribution of the responses, as well as by the type of therapy received. Answers to the NCPES questions were treated as the dependent variable, and the type of therapy received was treated as the independent variable; I compared the probability – or the odds – of different responses to each of the questions by treatment status. Multinomial logistic regression using the 'nnet' package (Ripley, 2002) in R (R Core Team, 2020) was used to obtain crude and adjusted odds ratios (ORs) for the association between answers to each of the NCPES questions and the type of therapy received. Adjustment was made for age, sex, ethnicity, deprivation group, year of diagnosis, size of the tumour, and number of lymph nodes involved. The strength of the association between the categories of the exposures with the categories of the outcomes was assessed with the Wald test.

Results

Five Cancer Patient Experience Surveys (rounds 3, 4, 5, 6, and 7) representing patients who were discharged from an NHS Trust after receiving a cancer related treatment, between 2012 to 2017, were linked with the Cancer Registry, the Index of Multiple Deprivation (IMD) and the Systemic Anti-Cancer Treatment databases (these databases were described in detail in Chapter 5).

Of 8,750 stage III colon cancer patients who underwent adjuvant chemotherapy with either single or combination therapy (identified in a separate analysis as described in Chapter 5; thereafter 'the cancer registry population'), there were 3,010 (34.4%) who responded to the NCPES. The distribution of the number of patients by round is shown in Table 40.

Table 40 – The number of patients who responded to each round of the NCPES

Year survey conducted	Time period surveyed patients discharged from hospital	NCPES respondents Count (%)
Round 3: 2013	1st September to 30th September 2012	370 (12.3%)
Round 4: 2014	1st September to 30th November 2013	532 (17.7%)
Round 5: 2015	1st April to 30th June 2015	768 (25.5%)
Round 6: 2016	1st April to 30th June 2016	663 (22.0%)
Round 7: 2017	1st April to 30th June 2017	677 (22.5%)
Total		**3010 (100%)**

Characteristics of NCPES respondents

The sampling frame that would have allowed for a direct comparison of respondents to non-respondents was not available at the time of this analysis. Therefore, NCPES respondents were compared to the population of stage III colon cancer patients in the cancer registry (Table 41).

There was a difference between NCPES respondents and the cancer registry population in terms of all the characteristics that were explored, except for sex and number of lymph nodes involved. The distribution of males and females was similar for NCPES respondents and the cancer registry population, with males making up 53.2% and 54.4%, and females making up 46.8% and 45.6%, respectively. The distribution of patients with less than three lymph nodes (N1) and more than three lymph nodes (N2) was also similar for both groups (Table 41).

In terms of age, there was a statistically significant lower proportion of patients less than 60 years of age as well as between 75 to 80 years among NCPES respondents compared to the cancer registry population, but an approximately equal distribution of patients who were 60 to 70 years among the two groups (Table 41).

There was also a statistically significant higher proportion of patients who were in the least deprived group among NCPES respondents (25.7%) compared to the cancer registry population (21.9%), and a lower proportion of patients from the most deprived group among NCPES respondents (12.8%) compared to the cancer registry population (16.2%). Due to the small number of patients above 80 years (4.6%), those respondents were grouped with those who were 75-80 (10.6%) for the remainder of the analysis, making up 15.2% (Table 41).

The NCPES contains a question on self-identified ethnicity. This question was given priority over the ethnicity data that is assigned in the cancer registry to determine the ethnicity of respondents, where an answer was given. Of the 3,010 patients who responded to NCPES, there was agreement between the two data sources for 90% (2703) of patients, while only 1.8% self-identified differently to what was assigned in the cancer registry, and 3.7% (110) of patients did not provide an answer to ethnicity in NCPES and as such, the ethnicity assigned in the cancer registry was used instead. The NCPES respondents had a higher proportion of patients of White ethnicity (92.8%) and of patients from ethnic minority groups (6.9%) compared to the cancer registry population with 89.4% and 5.7%, respectively. By contrast, there was a lower proportion of patients with missing information on ethnicity (0.3%) compared to 4.8% among the cancer registry population (Table 41).

As mentioned in the methods section, respondents to NCPES are those who received a cancer-related treatment in the three-month period before receiving the survey, therefore, patients could be diagnosed in prior years, but receiving treatment in the NCPES survey year. The distribution of the year of diagnosis and the year NCPES was undertaken was explored, and results are shown in (Table 42). Many respondents were diagnosed in the same year as the NCPES survey, and another large proportion were diagnosed in the year before. Most patients were diagnosed in the previous or same year to the NCPES survey. A very small proportion of patients (2.86%) were diagnosed two or more years before participating in the survey.

As for tumour size, there was no difference between the two groups in the proportion of patients with T1 or T2, and in T3 tumours (Table 41). However, those who responded

to NCPES had a lower proportion of T4 tumours (38.1%) compared to the cancer registry population (40.5%).

Finally, there was a significantly higher proportion of patients who received combination therapy among NCPES respondents compared to the cancer registry population, with 78.3% and 70.3%, respectively (Table 41).

Table 41 - Characteristics of NCPES respondents with stage III colon cancer compared to the cancer registry population with the same diagnosis

	Cancer registry population (n=5740)		NCPES Respondents (n=3010)		Crude OR	Adjusted OR*	Adjusted p-value
	Count	**%**	**Count**	**%**			
Age							**< 0.001***
< 50 years	718	12.5%	249	8.3%	0.55 (0.53,0.57)	0.56 (0.54,0.58)	< 0.001
50-60	1086	18.9%	555	18.4%	0.80 (0.78,0.82)	0.81 (0.78,0.83)	< 0.001
60-65	897	15.6%	568	18.9%	1.05 (1.02,1.08)	1.02 (0.99,1.05)	0.188
65-70	1018	17.7%	643	21.4%	*1 (reference group)*		
70-75	1038	18.1%	540	17.9%	0.98 (0.95,1.01)	1.05 (1.02,1.08)	0.002
75-80	699	12.2%	316	10.5%	0.86 (0.83,0.90)	0.89 (0.86,0.93)	< 0.001
>80	284	4.9%	139	4.6%	0.94 (0.90,0.99)	0.96 (0.91,1.01)	0.10
Deprivation							**< 0.001***
Least deprived	1259	21.9%	775	25.7%	*1 (reference group)*		
2	1288	22.4%	747	24.8%	0.94 (0.92,0.97)	0.97 (0.94,1.00)	0.031
3	1140	19.9%	583	19.4%	0.72 (0.70,0.74)	0.74 (0.72,0.76)	< 0.001
4	1123	19.6%	520	17.3%	0.68 (0.66,0.70)	0.70 (0.68,0.72)	< 0.001
Most deprived	930	16.2%	385	12.8%	0.62 (0.61,0.64)	0.60 (0.58,0.62)	< 0.001
Sex							**0.272***
Male	3053	53.2%	1637	54.4%	*1 (reference group)*		
Female	2687	46.8%	1373	45.6%	0.97 (0.95,0.98)	0.99 (0.97,1.01)	0.272

Ethnicity							**<0.001***
White	5132	89.4%	2793	92.8%	*1 (reference group)*		
Minority ethnic groups	330	5.7%	209	6.9%	1.20 (1.15,1.24)	1.51 (1.45,1.57)	< 0.001
Missing	278	4.8%	8	0.3%	0.06 (0.05,0.06)	0.06 (0.05,0.07)	< 0.001
Year of diagnosis							**< 0.001***
2012	397	6.9%	403	13.4%	1.24 (1.20,1.29)	1.23 (1.19,1.28)	< 0.001
2013	619	10.8%	534	17.7%	1.30 (1.26,1.34)	1.28 (1.24,1.32)	< 0.001
2014	1091	19.0%	334	11.1%	0.48 (0.46,0.49)	0.46 (0.45,0.48)	< 0.001
2015	954	16.6%	688	22.9%	*1 (reference group)*		
2016	1179	20.5%	623	20.7%	0.77 (0.74,0.79)	0.77 (0.75,0.79)	< 0.001
2017	1500	26.1%	428	14.2%	0.44 (0.43,0.46)	0.44 (0.43,0.45)	< 0.001
Size of tumour							**< 0.001***
T1 or T2	477	8.3%	271	9.0%	*1 (reference group)*		
T3	2935	51.1%	1590	52.8%	0.96 (0.92,0.99)	0.99 (0.96,1.03)	0.82
T4	2326	40.5%	1148	38.1%	0.88 (0.84,0.91)	0.91 (0.88,0.95)	< 0.001
Number of lymph nodes							**0.6***
N1	3651	63.6%	1878	62.4%	*1 (reference group)*		
N2	1997	34.8%	1065	35.4%	0.98 (0.97,1.00)	1.01 (0.99,1.03)	0.6
Type of therapy							**< 0.001***
Single therapy	1706	29.7%	653	21.7%	*1 (reference group)*		
Combination therapy	4034	70.3%	2357	78.3%	1.08 (1.05,1.11)	1.15 (1.12,1.18)	< 0.001

*Odds Ratio adjusted for age, sex, deprivation, ethnicity, year of diagnosis, size of tumour, number of lymph nodes, and type of therapy

Table 42 - The distribution of patients across year of diagnosis and the NCPES survey year

	Year of survey						
Year of diagnosis	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**Total**
2012	370	18	No round of NCPES in 2014	11	3	1	86 (2.9%)
2013		514		12	6	2	
2014				296	22	16	
2015				449	226	13	
2016					406	217	2924 (97.1%)
2017						428	
Total	370	532		768	663	677	3010 (100%)

	Number of patients diagnosed two or more years prior to the NCPES survey year
	Number of patients diagnosed in the previous or same year of the NCPES survey year

NCPES 2012-2017 (rounds 3 to 7)

Three questions were common to all five NCPES rounds: whether side effects were explained in a way that patients could understand; whether patients were told about side effects that could affect them in the future; and whether patients were involved as much as they wanted to be in the treatment decision. The distribution of responses is shown in Table 43.

For the first question on side effects, three-quarters of patients (75.4%) answered “yes, definitely”, 21.1% answered “yes, to some extent”, and small numbers giving other answers (Table 43). For the second question on whether they were told about future side effects, however, a smaller proportion (52.3%) gave a definitive response (yes, definitely), while a larger proportion (27.1%) gave a less certain response (yes, to some extent). A total of 16.2% gave a negative response, that they were either were not told about future side effects (14.4%), or that future side effects were not explained to them (1.8%). And a further total of 4.7% said that they did not need an explanation of future side effects (1.6%) or were not sure or could not remember (3.1%) (Table 43).

For the question on whether patients were as involved as they would have liked to be in the treatment decision, the majority (77.6%) answered “yes, definitely” and 16.9% answered “yes to some extent”, while 2.4% said that they were not involved, although they would have liked to be, and a total of 3.1% were not sure or did not give an answer (Table 43).

For the question on whether side effects were explained in a way that patients could understand, a higher proportion of those who received single therapy answered “yes, definitely” compared to those who received combination therapy, with 79.9% and 74.2%, respectively. By contrast, a lower proportion of those who received single therapy answered “yes, to some extent”, which indicates a less certain response, compared to those who received combination therapy, with 16.2% and 22.4%, respectively. The adjusted logistic regression analysis showed a statistically significant association between the response to this question and the type of therapy received. Those who received combination therapy had 1.40 the odds of answering “yes, to some extent” than “yes, definitely” compared to those who received single therapy (OR: 1.40; CI: 1.09,1.79; p=0.008) (Table 43).

For the second question on future side effects, a similar pattern of answers is seen in the comparison between the treatment types. A higher proportion of those who received single therapy answered “yes, definitely” (56.8%) than those who received combination therapy (51%), and a lower proportion answered “yes to some extent”

among the single therapy group, compared to the combination therapy group, with 20.1% and 29%, respectively. Among both single and combination therapy groups, there was approximately equal proportion of 13.9% and 14.6% of patients who reported that future side effects were not explained to them. The adjusted logistic regression analysis showed a statistically significant association between the response to this question and the type of therapy received. Those who received combination therapy had 1.48 the odds of answering “yes, to some extent” than “yes, definitely” compared to those who received single therapy (OR: 1.48; CI: 1.17,1.88; p=0.001) (Table 43).

For the third question on whether a patient was involved as much as they wanted to be in the treatment decision, a similar pattern to the first two questions is seen, where a higher percentage answered “yes, definitely” among those who received single therapy (81.2%) compared to those who received combination therapy (77.6%), and the reverse for “yes, to some extent”, with 13.6% and 17.8%, respectively. A higher proportion of patients among those who received combination therapy answered “no, but I would have liked to be more involved” (2.4%) compared to 1.1% among those who received single therapy. However, there was no evidence to reject the null of no association between the responses to this question and type of therapy received (p=0.311) (Table 43).

Table 43 – Comparison of the responses to three NCPES questions between those who received single therapy and combination therapy. NB: the explanatory variable (type of therapy) is presented in columns and each of the outcomes (NCPES questions) are presented in rows.

	Single therapy		Combination therapy		Total		Crude OR	Adjusted OR*	Adjusted p-value
	Count	**%**	**Count**	**%**	**Count**	**%**			
Were the possible side effects of treatment(s) explained in a way you could understand?									0.038
Yes, definitely	522	79.9%	1749	74.2%	2271	75.4%	*1 (reference category)*		
Yes, to some extent	106	16.2%	529	22.4%	635	21.1%	1.49 (1.18 ,1.87)	1.47 (1.15 ,1.88)	0.002
No, side effects were not explained to me	9	1.4%	44	1.9%	53	1.8%	1.46 (0.71 ,3.02)	1.98 (0.91 ,4.29)	0.08
I did not need an explanation	4	0.6%	15	0.6%	19	0.6%	1.12 (0.37 ,3.39)	1.49 (0.45 ,4.91)	0.51
Not sure/ Can't remember	5	0.8%	5	0.2%	10	0.3%	0.30 (0.09 ,1.03)	0.38 (0.09 ,1.58)	0.18
Missing	7	1.1%	15	0.6%	22	0.7%	0.64 (0.26 ,1.57)	0.75 (0.28 ,2.04)	0.57
Total	**653**	**100%**	**2357**	**100%**	**3010**	**100%**			
Before you started your treatment(s), were you also told about any side effects of the treatment that could affect you in the future rather than straight away?									0.027
Yes, definitely	371	56.8%	1202	51.0%	1573	52.3%	*1 (reference category)*		
Yes, to some extent	131	20.1%	684	29.0%	815	27.1%	1.61 (1.29 ,2.01)	1.51 (1.20 ,1.92)	<0.001

No, side effects were not explained to me	91	13.9%	343	14.6%	434	14.4%	1.16 (0.90 ,1.51)	1.25 (0.95 ,1.66)	0.12
I did not need an explanation	18	2.80%	29	1.2%	47	1.6%	0.50 (0.27 ,0.91)	0.78 (0.40 ,1.51)	0.46
Not sure/ Can't remember	27	4.10%	66	2.8%	93	3.1%	0.75 (0.48 ,1.20)	0.91 (0.54 ,1.52)	0.71
Missing	15	2.30%	33	1.4%	48	1.6%	0.68 (0.36 ,1.26)	1.27 (0.63 ,2.56)	0.51
Total	**653**	**100%**	**2357**	**100%**	**3010**	**100%**			
Were you involved as much as you wanted to be in decisions about your care and treatment?									0.311
Yes, definitely	530	81.2%	1806	76.6%	2336	77.6%	*1 (reference category)*		
Yes, to some extent	89	13.6%	420	17.8%	509	16.9%	1.38 (1.08 ,1.77)	1.22 (0.94 ,1.59)	0.14
No, but I would like to have been more involved	7	1.1%	64	2.7%	71	2.4%	2.68 (1.22 ,5.89)	2.10 (0.92 ,4.76)	0.08
Not sure/ Can't remember	10	1.5%	18	0.8%	28	0.9%	0.53 (0.24 ,1.15)	0.52 (0.22 ,1.23)	0.13
Missing	17	2.6%	49	2.1%	66	2.2%	0.85 (0.48 ,1.48)	0.92 (0.50 ,1.71)	0.80
Total	**653**	**100%**	**2357**	**100%**	**3010**	**100%**			

*Adjusted for age, sex, ethnicity, deprivation group, year of diagnosis, size of the tumour, and number of lymph nodes

NCPES 2013-2014 (rounds 3 and 4)

There was a total of 902 patients who responded to NCPES rounds 3 (2012) and 4 (2013), and three questions that are common to these rounds. One question asked whether patients were provided with written information about side effects, another asked whether patients were given a choice of different types of treatment, and the third asked whether patients thought their views were taken into account while making treatment decisions. For all three questions the adjusted logistic regression analysis showed no difference between the two groups for any of the responses (Table 44). It is possible that this is due to the smaller sample of patients who received single therapy compared to those who received combination therapy, and thus small samples to compare for each of the responses. Although no statistical association was found, I report the results descriptively.

Among the total sample of patients regardless of type of therapy, 88.2% said that they were given written information about side effects. A lower percentage of those who received single therapy thought the information was easy to understand (78.6%) than those who received combination therapy (85.3%) (Table 44). A total of 14.8% among those who received single therapy gave negative responses, that the information was difficult to understand or that they were not given any information about side effects, compared to those who received combination therapy (9.6%).

For the question on whether patients were given a choice of different types of treatment, more patients who received single therapy thought they had a choice in treatment (34.2%) compared to those who received combination therapy (30.5%), while an approximately equal number thought that they did not have a choice (4.6% and 4.3%, respectively) (Table 44). Most patients from both groups thought that only one treatment option was suitable for them, with 59.2% among those who received single and 60.8% among those who received combination therapy.

For the final question on whether patients thought that their views were taken into account when treatment was discussed by their attending team of doctors and nurses, the majority from both groups gave a positive response with either “yes, definitely” or “yes to some extent”, with a total of 84.2% and 83.5% for those who received single or combination therapy, respectively (Table 44). An approximately equal percentage of patients from both groups were also not aware that their treatment was being discussed by a team of doctors or nurses (5.6% and 5.0%, respectively).

Table 44 - Comparison of the responses to three NCPES questions (from rounds 3 and 4 (2012-2013)) between those who received single therapy and combination therapy. NB: the explanatory variable (type of therapy) is presented in columns and each of the outcomes (NCPES questions) are presented in rows.

	Single therapy		Combination therapy		Total		Crude OR	Adjusted OR*	P-value
	Count	**%**	**Count**	**%**	**Count**	**%**			
Before you started your treatment, were you given written information about the side effects of treatment(s)?									**0.68**
Yes, and it was easy to understand	154	78.6%	602	85.3%	756	83.8%	*1 (reference category)*		
Yes, but it was difficult to understand	11	5.6%	29	4.1%	40	4.4%	0.67 (0.33, 1.38)	0.68 (0.31, 1.46)	0.32
No, I was not given written information about side effects	18	9.2%	39	5.5%	57	6.3%	0.55 (0.31, 0.99)	0.87 (0.45, 1.67)	0.67
Don't know / can't remember	8	4.1%	21	3.0%	29	3.2%	0.67 (0.29, 1.54)	0.90 (0.36, 2.24)	0.82
Missing	5	2.6%	15	2.1%	20	2.2%	0.77 (0.27, 2.14)	0.85 (0.28, 2.61)	0.78
Total	**196**	**100%**	**706**	**100%**	**902**	**100%**			
Before your cancer treatment started, were you given a choice of different types of treatment?									**0.52**
Yes	67	34.2%	215	30.5%	282	31.3%	*1 (reference category)*		
No, but I would have liked a choice	9	4.6%	30	4.3%	39	4.3%	1.03 (0.47, 2.29)	1.20 (0.51, 2.85)	0.68

I was given a choice because only one type of treatment was suitable for me	116	59.2%	432	61.2%	548	60.8%	1.16 (0.82, 1.63)	1.14 (0.79, 1.65)	0.49
Not sure / can't remember	3	1.5%	20	2.8%	23	2.5%	2.07 (0.60, 7.17)	1.90 (0.51, 7.03)	0.34
Missing	1	0.5%	9	1.3%	10	1.1%	2.79 (0.35, 22.4)	3.56 (0.41, 31.2)	0.25
Total	**196**	**100%**	**706**	**100%**	**902**	**100%**			
Do you think your views were taken into account when the team of doctors and nurses caring for you were discussing which treatment you should have?									**0.56**
Yes, definitely	133	67.9%	452	64.0%	585	64.9%	*1 (reference category)*		
Yes, to some extent	32	16.3%	138	19.5%	170	18.8%	1.27 (0.82, 1.95)	1.23 (0.78, 1.95)	0.38
No, my views were not taken into account	4	2.0%	29	4.1%	33	3.7%	2.13 (0.74, 6.16)	2.16 (0.71, 6.58)	0.18
I didn't know my treatment was being discussed by a team of doctors / nurses	11	5.6%	35	5.0%	46	5.1%	0.93 (0.46, 1.89)	1.07 (0.50, 2.28)	0.87
Not sure / can't remember	13	6.6%	35	5.0%	48	5.3%	0.79 (0.41, 1.54)	0.76 (0.37, 1.57)	0.46
Missing	3	1.5%	17	2.4%	20	2.2%	1.66 (0.48, 5.76)	2.46 (0.65, 9.34)	0.19
Total	196	100%	706	100%	902	100%			

*Adjusted for age, sex, ethnicity, deprivation group, year of diagnosis, size of the tumour, and number of lymph nodes

NCPES 2015-2017 (rounds 5, 6, and 7)

There was a total of 2,108 patients who responded to NCPES rounds 5 (2015), 6 (2016) and 7 (2017), and two questions that are common to these rounds. The first asked whether patients had all the information they needed about chemotherapy before starting treatment, and the second asked whether their treatment options were explained to them (Table 45).

Most patients from both the single and the combination therapy groups answered “yes, definitely” to the first question with an approximately equal distribution of 78.6% and 76.7%, respectively. There was, however, an unequal distribution for the remainder of the responses. Of those who received combination therapy, 15% answered “yes, to some extent” compared to 7.4% of those who received single therapy, with almost twice the odds of giving this answer as shown by the adjusted logistic regression analysis (OR: 1.93; CI: 1.30,2.88; p=0.001). Of those who received combination therapy, 6.7% did not provide an answer to this question compared to 13.1% of single therapy group, having almost half the odds of not giving an answer to this question (OR:0.48; CI:0.33,0.70; p<0.001). None of the 2,081 who responded to the survey said that they did not need this information (Table 45).

For the second question that asked whether treatment options were explained before treatment started, a similar percentage of patients who received single therapy answered “yes, definitely” (78.8%) compared to those who received combination (76%), and “yes, to some extent” with 9% and 10.1%, respectively. Among those who received combination therapy 12% thought that there was only one type of treatment that was suitable for them, compared to 8.5% among those who received single therapy. Although there is no overall association between this question and the type of therapy received (LRT p=0.154), those who received combination therapy had 1.51 (CI: 1.02,2.23; p=0.04) the odds of answering that there was only one type of therapy suitable for them compared to those who received single therapy (Table 45).

Table 45 - Comparison of the responses to two NCPES questions (from rounds 5, 6, and 7) between those who received single therapy and combination therapy. NB: the explanatory variable (type of therapy) is presented in columns and each of the outcomes (NCPES questions) are presented in rows.

	Single therapy		Combination therapy		Total		Crude OR	Adjusted OR*	Adjusted p-value
	Count	%	Count	%	Count	%			
Beforehand, did you have all of the information you needed about your chemotherapy treatment?									**< 0.001**
Yes, completely	359	78.6%	1267	76.7%	1626	77.1%	*1 (reference category)*		
Yes, to some extent	34	7.4%	247	15.0%	281	13.3%	2.06 (1.41 ,3.00)	1.93 (1.30 ,2.88)	0.001
No	4	0.9%	27	1.6%	31	1.5%	1.91 (0.66 ,5.50)	1.88 (0.61 ,5.77)	0.27
I did not need any information	0	0.0%	0	0.0%	0	0.0%	----------	----------	------
No answer	60	13.1%	110	6.7%	170	8.1%	0.52 (0.37 ,0.73)	0.48 (0.33 ,0.70)	<0.001
Total	457	100%	1651	100%	2108	100%			
Before your cancer treatment started, were your treatment options explained to you?									**0.154**
Yes, completely	360	78.8%	1254	76.0%	1614	76.6%	*1 (reference category)*		
Yes, to some extent	41	9.0%	166	10.1%	207	9.8%	1.16 (0.81 ,1.67)	1.03 (0.69 ,1.52)	0.89
No	3	0.7%	14	0.9%	17	0.8%	1.34 (0.38 ,4.69)	0.87 (0.22 ,3.40)	0.84
There was only one type of treatment that was suitable for me	39	8.5%	198	12.0%	237	11.2%	1.46 (1.01 ,2.09)	1.51 (1.02 ,2.23)	0.04
Don't know / can't remember	1	0.2%	5	0.3%	6	0.3%	1.44 (0.17 ,12.32)	1.54 (0.13 ,17.93)	0.73
No answer	13	2.8%	14	0.9%	27	1.3%	0.31 (0.14 ,0.66)	0.54 (0.23 ,1.30)	0.17
Total	457	100%	1651	100%	2108	100%			

*Adjusted for age, sex, ethnicity, deprivation group, year of diagnosis, size of the tumour, and number of lymph nodes

Discussion

For this study, data from the National Cancer Patient Experience Survey conducted between 2012-2017, linked to the cancer registry and the SACT datasets was used to compare how patients who received single, or combination, adjuvant chemotherapy perceived the information they received about chemotherapy. This included information on side effects; having a choice on treatment options; their involvement in the treatment decision; and the extent to which their views were taken into account when the medical team discussed their treatment.

Summary and interpretation of findings

The study has shown that the perceived level of information varies with the type of adjuvant chemotherapy received. For the full sample of patients who responded to NCPES between 2012-2017, the odds of answering “yes, to some extent” (as opposed to “yes, definitely”) was higher among those who received combination therapy compared to those who received single therapy for questions on whether they understood the information they received about side effects in general, as well as whether they received information on future side effects. A similar pattern was seen for the smaller sample of those who responded to NCPES rounds 5, 6, and 7 (2015-2017) (n=2,108) on the question of whether they received all the information they needed before starting chemotherapy. The results from these three questions on information indicate that those who received combination therapy may have been less certain about their knowledge of treatment side effects compared to those who received single therapy. This could be because those who received combination therapy may have perceived their treatment to be more complicated, and consequently the information that they received as also more complicated, harder to understand, or overwhelming. The main difference between single and combination therapy is the addition of oxaliplatin, and so it is possible that this difference in the perception of information between the two groups is related to the information received on oxaliplatin more specifically. The response to the question on future side effects, in particular, provides some indication that this could be the case. To my knowledge, in the treatment of stage III colon cancer, oxaliplatin is the only agent that could result in future side effects (peripheral neuropathy), and those who received combination therapy provided a less certain answer compared to those who received single therapy on whether they were told about future side effects of their treatment. Another important finding from this analysis is that none of the patients (n=0) from either group said that they “did not need

any information" when asked whether they received all the information they needed before starting chemotherapy in the NCPES 2015-2017. This suggests that patients do have a need for knowledge and information about treatment, regardless of the type of therapy they receive.

To my knowledge, no other study has explored these questions from NCPES for colon or any other type of cancer to compare these results to. However, some studies have looked at information needs of cancer patients using other tools. In a Choice Consultation Survey conducted by the Department of Health in the UK almost 90% of respondents stated that they required more information to make treatment and care choices (Lawrence, 2004). In a recent study that aimed to assess how information needs among individuals with colorectal cancer are met across all stages of cancer care, the authors conducted an international survey which included 1,041 respondents from Canada (55%), the United States (33%), the UK (10%), and other countries (2%) (Dau et al., 2020). Most participants had colon cancer (59%), of those 40% were diagnosed with stage III disease. Among participants who were undergoing treatment at the time of the survey (25%) and those who completed treatment (75%), several topics of general information were found to have been unmet, including on long-term side effects and the types of chemotherapy available. By contrast, topics on how treatment works, short-term side effects, how to deal with side effects, and what to expect from chemotherapy were largely met. In another study, 35 patients with stage II and III colon cancer were asked whether a discussion of certain information items and elements of an informed decision-making process took place with the oncologist during the initial adjuvant chemotherapy consultations (H. K. Sanoff et al., 2010). The study found that information about cancer stage, prognosis, and treatment were discussed more commonly than information about short-term and long-term effects of therapy. The findings from these studies are in line with the results found from this NCPES analysis. That is, among the total sample of stage III colon cancer patients who received adjuvant chemotherapy (regardless of type), approximately 52% gave the most positive answer "yes, definitely" to the question on "future" side effects, compared to a higher proportion of approximately 75% who gave this answer to the question on side effects. This suggests a difference in perception for two types of information provided, with the latter perceived more favourably than the former.

Regarding whether patients felt as involved as they wanted to be in the treatment decision, the majority gave a definitive answer and there was no difference between the two treatment groups with regards to any of the responses that were provided. However, there was still approximately a total of 20% of respondents who thought they

were involved only “to some extent”, were not involved at all, or could not remember. A similar pattern is seen with a similar question that was examined among the smaller sample of those who responded to NCPES rounds 3 and 4 (2012-2013) on whether they thought their views were taken into account by the clinical team involved in their treatment, where approximately 19% of patients thought their views were taken into account “to some extent”, and a further total of 14% said that their views were not taken into account, they did not know their treatment was being discussed, or couldn’t remember. These two questions indicate that although a large proportion of patients feel their preference for how involved they wanted to be was met, or that their views considered, there is still a considerable proportion of patients who feel otherwise, regardless of the type of therapy received.

These findings on involvement in the decision is in line with a study that explored experiences of involvement among those who responded to the 2010 NCPES survey, whereby 72% of all cancer patients reported the most positive experience of involvement in treatment decision making (yes, definitely), 22% reported “yes, to some extent” and 6% reported a negative experience. For colon cancer specifically, about 76% of patients reported the most positive experience (El Turabi et al., 2013).

Involvement in the decision-making process has been shown to be associated with patient satisfaction. The 2015 NCPES was used in a study to determine the elements of cancer patients’ care experience that are the key drivers of overall satisfaction with cancer care (Gomez-Cano et al., 2020). Ten elements that were common experiences to all cancer patients and a further 16 experiences that apply to a specific subset of patients or care pathways were examined. The question on whether patients felt involved in decisions about care and treatment was the third strongest predictor of overall satisfaction with cancer care after care administration (for example, receiving letters at the right time, doctors having the right notes/tests results, etc.) and care coordination (defined as different people involved in a patient’s care, such as GPs, hospital doctors or nurses, working well together to provide care). This was the case within the elements that applied to all patients as well as those that only applied to a subset of patients or care pathways. A question on shared decision-making was also found to be associated with higher overall satisfaction in another study in Denmark (Heerdegen et al., 2017).

However, although most patients in the current study indicated that their preference for how involved they wanted to be was met, one limitation of this question is that it does not give insight as to the role patients took in the decision-making process, i.e., whether they actively participated or assumed a more passive role. Another potential

limitation of this question is that unlike the option to express preference for more involvement, there is no option to express preference for less involvement (El Turabi et al., 2013).

Furthermore, although most patients perceived being involved in the treatment decision, it is possible that this is driven by involvement in the decision to receive or not receive adjuvant chemotherapy after surgery, without awareness that there is *another* decision that determines the *type* of treatment given. This suspicion is partly supported by findings from two questions that asked about treatment options. The first from NCPES rounds 3 and 4 (2012-2013) asked whether patients were given a choice about different types of treatment, the majority (60%) from both groups believed that there was only one treatment option that was suitable for them. The second question from NCPES rounds 5, 6, and 7 (2015-2017) asked whether treatment options were explained to them. For this question, although a much lower proportion from both treatment groups gave that answer (8-12%), there was evidence that those who received combination treatment were more likely to believe that there was only one treatment option that was suitable for them. This indicates that there is a considerable proportion of patients who may not have been aware of the treatment options that are available to them and may not have been involved in the decision on which treatment to receive. It is possible that this contrast between the two questions in the percentage of patients who gave this response is due to a change in practice occurring in the more recent years that correspond to the second question from NCPES rounds 5, 6, and 7 (2015-2017), which meant that treatment options were more likely to be explained and patients more likely to be aware of them. However, one limitation here is that although the questions may appear similar, and have similar responses, there is a difference in the way they were worded, which limits the interpretations that could be made. The first question asks whether patients were *'given a choice'*, while the second asks whether treatment options were *'explained'*. The former is more explicitly a question about whether there was a choice in treatment options. The latter leaves room for patients to focus more on answering whether options were 'explained', even if there was only one option of treatment, rather than on answering whether they had more than one option in the first place. To my knowledge, amendments to the survey questions, which created the need to analyse the two cohorts of NCPES (2012-2013 and 2015-2017) separately (as discussed in the methods section) were largely guided by members of the NCPES advisory group, with no further cognitive testing carried out beyond what had been undertaken for the 2010 survey (Department of Health, 2010, 2012). Therefore, it is possible that some of the new questions that have been added or

amended since the 2010 questionnaire lack validity, making it difficult to ascertain how patients may have interpreted or understood the questions and the response options.

Strengths and limitations

One limitation of this analysis is that it was not possible to determine the sampling frame that would have allowed for a direct comparison of respondents to non-respondents. As discussed in the methods section, NCPES is sent to all non-deceased, adult cancer patients discharged from an NHS Trust after a cancer related treatment in a specific time-period. The Hospital Episode Statistics dataset, from which the list of discharged cancer patients would be obtained, was not available during the time the analysis was carried out. Instead, the demographic and tumour characteristics of those who responded to NCPES were compared to the cancer registry population of stage III colon cancer patients who did not have a NCPES record. There was no difference between the two groups by sex and number of lymph nodes involved. However, there was a lower proportion of patients less than 60 years of age, and of those from more deprived groups, with larger tumours (T4). The lower proportion of patients less than 60 years of age, and of those from more deprived groups could be due to non-response by these groups. A study by Abel et al. (2016), who had access to the sampling frame enabling a comparison of respondents to non-respondents among patients who received the survey, found that response to NCPES was more likely to be lower among younger patients and those from deprived areas (Abel et al., 2016). The lower proportion of those with larger tumours (T4) could be explained by morbidity or survival, as those patients may be more likely to be unwell or deceased at the time of the survey, therefore, either less likely to respond or less likely to be included in the sampling frame. By contrast, there was a higher proportion of patients who received combination therapy than in the cancer registry population. It is possible that a higher proportion of those who received combination therapy among NCPES respondents reflects more complicated or longer duration of treatment that required more frequent hospital visits, which makes those patients more likely to be included in the sampling frame.

The current analysis has also shown that there was a higher proportion of patients diagnosed in 2012 or 2013, and a lower proportion diagnosed in 2014, 2016 and 2017 compared to the year 2015 among NCPES respondents than in the cancer registry population. Additionally, there was also a higher proportion of those from minority ethnic groups among NCPES respondents than the cancer registry population. These findings are harder to explain. It is possible that the survey was conducted differently in

more recent years that resulted in reduced participation. It is also possible that the management of patients with stage III disease has changed in more recent years, resulting in a reduced frequency or duration of inpatient or outpatient hospital visits, and thereby less likely to be included in the sampling frame.

The representativeness of the sample can be influenced by the sampling process, post-sampling mortality, and survey non-response, thereby limiting the generalisability of the findings to all stage III colon cancer patients. In one study, data from the sampling frame of the 2010 NCPES was used to assess the predictors of post-sampling mortality and survey nonresponse (Abel et al., 2016). The study found that after inclusion in the sampling frame, men, older patients, those from deprived areas and with poorer prognosis were more likely to be excluded from the survey due to post-sampling mortality in the two-to-three-month period following treatment, during which the survey is mailed out. The same study reports that only 4.6% of 6,874 colon cancer patients were excluded due to post-sampling mortality, which consists of all colon cancer patients, including those of more advanced disease. To my knowledge, there is no similar reporting on post-sampling mortality for the NCPES years included in this analysis, however, it is unlikely that it would differ widely from the proportion reported for 2010. With potentially more advanced treatment and healthcare services since 2010, post-sampling mortality could be potentially smaller. In addition to post-sampling mortality and non-response, evidence suggests that mood can also influence survey responses, which can in turn be influenced by the health status of the respondent at the time of the survey (Cohen et al., 1988). Therefore, it is possible that those who received combination therapy had more advanced disease or experienced peripheral neuropathy which resulted in less favourable or less certain responses compared to those who received single therapy, due to the influence of their affect on their responses.

Another limitation of this analysis is that changes to the survey from year to year, with the addition, removal, or modification of some of the questions or response options, limited the ability to combine the samples from all NCPES rounds and necessitated separate analyses with smaller samples. In particular, among NCPES respondents, there was a larger sample of patients who received combination therapy than those who received single therapy. This may have resulted in some imprecise estimates with wide confidence intervals. However, this analysis still provided evidence for differences between these two groups in terms of their perception of treatment information and involvement in decision-making, particularly when these findings are combined with

findings of other complementary studies (as will be discussed in the Chapter 8, in view of the qualitative study that was undertaken as part of this thesis).

A major strength of this study is that it was possible to link data on personal characteristics from the cancer registry and data on the type of therapy from the SACT dataset to the respondents of the survey. This allowed the identification of stage III colon cancer patients who underwent post-surgical adjuvant chemotherapy, and an insight into those patients' experiences with the decision-making process. To my knowledge, this is the only study that aimed to explore experience for a specific stage of disease and make comparisons based on treatment type. Another strength of this study is that 34% of all stage III colon cancer patients diagnosed between 2012-2017 responded to at least one of five NCPES surveys. This resulted in a notable sample of 3010 patients, which allowed comparisons between all response options of the included questions and between the two treatment groups. This is a higher response rate compared to approximately 25% of stage III colorectal cancer patients diagnosed between 2007 to 2013 who responded to at least one survey during 2010-2014 (Alessy et al., 2019). However, 34% is low response rate compared to the total response rate of the NCPES, which has been between 60-68% since its launch. Therefore, it would be important to understand reasons underlying low response among some groups compared to others.

Finally, in this study, most patients were diagnosed in the previous or same year to the NCPES survey, with only a small proportion of approximately 3% were diagnosed two or more years before participating in the survey. This increases confidence in that the responses captured in these surveys were of recent experiences, reducing the likelihood of recall bias.

Conclusions and recommendations

The findings of this study indicate that stage III colon cancer patients may be receiving insufficient information about treatment side effects and are unaware of the full range of treatment options that may be available to them. One of cornerstones of shared decision-making is to be informed of treatment options and their attributes, including side effects. Therefore, although patients may perceive being involved in the decision-making process, lack of information about side effects precludes the ability to make decisions based on informed preferences that weighs the advantages and disadvantages of treatment in view of patients' values. Some research suggests that in the clinical setting, clinicians may underestimate how much information patients would like to receive (Fröjd & von Essen, 2006; Jefford & Tattersall, 2002). In addition, the

perceptions of patients and clinicians may differ in terms of the quality of care and the type and amount of information they receive and provide, respectively. In one study conducted in Denmark among colorectal cancer patients who received surgery, answers on information and communication showed disagreement in perception between the two groups. Clinicians were more likely than patients to report that information was provided on postoperative pain, risk of complications, and future bowel function. Clinicians were also more likely to report a higher perception than patients of the quality of the information provided and the time spent to answer questions (Mathiesen et al., 2007). Therefore, efforts should include training to increase healthcare workers' awareness of patients' information needs and how to assess patients' requirement for information at multiple points throughout diagnosis and treatment. It should also include training on how to assess whether information provided was retained, understood, and have answered patients' questions. Efforts should also include increasing patients' ability to ask questions on treatment options and side effects. This could include encouraging patients to consider questions they might have before arriving at consultations and allowing more time within a consultation or with healthcare professionals such as a clinical nurse specialist who are able to answer questions.

Chapter 8: Discussion

For colon cancer patients diagnosed at stage III of the disease, surgery to remove the tumour is often insufficient as the disease at that stage has spread to the surrounding lymph nodes. Therefore, surgery is followed by adjuvant chemotherapy needed to eradicate microscopic cancer cells that cannot be removed by surgery. Six months with a fluoropyrimidine agent has been the mainstay of post-operative adjuvant chemotherapy since the 1990s (Rodriguez-Bigas MA, 2003; Wolmark et al., 1999). Oxaliplatin was found to offer an additional survival benefit when combined with a fluoropyrimidine and was approved for use in 2004 by the FDA (André et al., 2004). Since then, clinical guidelines have recommended that stage III colon cancer patients should be offered either a fluoropyrimidine agent alone (single therapy) or with oxaliplatin (combination therapy) (Bromham et al., 2020). However, treatment with oxaliplatin, could also result in peripheral nerve damage (peripheral neuropathy), which occurs during therapy in up to 90% of patients, and could persist for years after treatment completion (Beijers et al., 2014).

Summary and interpretation of findings

In this thesis, I conducted four studies that aimed to establish the prevalence of persistent peripheral neuropathy; the predictors of uptake of combination chemotherapy; the decision-making process that leads to the uptake of adjuvant chemotherapy; and patients' satisfaction with the information they received and their involvement in the decision-making process.

Peripheral neuropathy

The systematic review that was undertaken aimed to synthesise all available evidence on the prevalence of peripheral neuropathy among people who received oxaliplatin-containing adjuvant chemotherapy for stage III colon cancer. The purpose was to determine the duration and extent to which symptoms persist after treatment completion.

It was possible to conclude from the synthesis of the CTCAE tool that symptoms of any severity are likely to persist among 40% of patients at six months, and between 25-30% at twelve months. The results also showed that the prevalence of symptoms may not diminish greatly beyond twelve months, with an indication that it remains at 25% at 18 months. Symptoms of grade-II (interfere with function but not activities of daily

living) severity are likely to be at 4% by twelve months, and the results indicate that it may persist beyond twelve months. Grade-III symptoms (interfere with daily living) were found to be at 5% by six months, and the confidence intervals crossed zero at twelve months and long-term follow-up. Synthesis from the CIPN-20 patient reported outcome measure complemented these findings and provided insight into the nature of the symptoms that may persist. It showed that tingling and numbness in the limbs persisted "quite a bit" or "very much" at long-term follow up in 21-28%, with additional symptoms such as shooting or burning pain, weakness, and cramps persisting in 4-14% of patients. Therefore, although the CTCAE tool shows that symptoms of grade III, which are considered to "interfere with daily living" may be unlikely to persist beyond six months, but from patients' perspective, symptoms that are experienced "quite a bit" and "very much" persist into the long term for a considerable proportion of patients. Findings from the qualitative study that was undertaken for this thesis showed that some participants who had peripheral neuropathy at the time of the interview learned to live with the symptoms that persisted. However, the detailed accounts of symptoms experienced and the how they limited daily activity suggests that this may be due to adaptation to the outcome, rather than an improvement in the severity or frequency of symptoms, which has been shown to occur over time in other studies (Stein et al., 2014; Zanville et al., 2016). These findings suggest that peripheral neuropathy can persist in a considerable proportion of people and can also limit a wide range of activities. However, despite this, findings from the qualitative study also showed that participants' understanding of peripheral neuropathy seemed to be lacking on multiple levels. Some were unaware of the side effect until symptoms began to appear, indicating that this was not discussed as a possibility, or perhaps was not emphasised enough and therefore not retained. For others, although acute neurotoxicity that occurs during treatment was explained, the severity and character of the symptoms that could be experienced, and the possibility that they may persist, were often left unexplained. This was supported by findings from the NCPES analysis. The results from this quantitative analysis showed that those who received combination chemotherapy were more likely to give a less certain answer (i.e., "yes, to some extent) when asked whether they knew about side effects and future side effects of treatment, compared to those who received single therapy, who answered "yes, definitely". These questions in NCPES were specifically related to chemotherapy and given that the population included in the NCPES analysis was restricted to stage III colon cancer patients, it is likely that patients who received combination therapy were referring to peripheral neuropathy when answering the question on 'future' side effects. The NCPES analysis study also found that a large proportion of patients who received combination therapy

believed that only one treatment option was suitable for them, which also supports patients' accounts in the qualitative study. All participants who received oxaliplatin in the qualitative study considered a reduction in the risk of recurrence more important than any side effects. However, it is difficult to ascertain whether reduction in risk of recurrence would still be preferable if oxaliplatin's margin of benefit compared to single therapy, as well as the extent to which neurotoxicity can occur and limit activities, were known to patients before starting therapy. When asked whether knowledge of this would have changed the decision to take oxaliplatin, participants' answers varied, with some reporting that they may have considered it more carefully or avoided combination therapy. This is in line with a study by Sanoff et al. (2015), who surveyed 116 survivors of rectal cancer to assess how certain side effects of their therapy, including peripheral neuropathy affect their daily activities and whether knowing about these symptoms beforehand would have changed their treatment decisions. Of these participants, 24% reported that their lives were affected "a lot" by peripheral neuropathy symptoms, half of which said that they would change the treatment decision if they knew about these symptoms prior to treatment (Sanoff et al., 2015).

Variation in treatment at the group level

In this thesis I also explored the variations in the receipt of chemotherapy and the type of chemotherapy through the analysis of the cancer registry linked to the Systemic Anti-Cancer Therapy (SACT) data. The study found that receiving treatment and the type of treatment that was received both varied by sociodemographic characteristics. Those of older age, of non-White ethnicity, and of lower socioeconomic status were less likely to receive combination therapy than those who were of younger age, White ethnicity, or higher socioeconomic status. Differences in treatment between groups indicate that patient, provide, or healthcare system characteristics or factors are acting or interacting on a systemic, rather than individual, level. As McLaren & Hawe (2005) stated, individuals are nested in increasingly broader systems that work together to influence health (McLaren & Hawe, 2005).

Patient-related factors that may result in the observed variations could include the presence or lack of certain abilities, commonly held perceptions or beliefs, or characteristics of the wider social network that are innate within certain groups. Patients' social network could also play a role in treatment differences between groups (Richard et al., 2011). Evidence suggests that people with more social links are more likely to seek health information from family, friends, or other sources, and that the education level of individuals in a patient's social network also plays a role, where a

higher education level average in a social network is associated with a higher frequency of a patient consulting healthcare professionals (Shim, 2010; Song & Chang, 2012). Physician characteristics such as race, sex, specialty, and degree of experience have been shown to be predictors of variations in clinical care and treatment (McKinlay et al., 2002; Shackelton-Piccolo et al., 2011). In addition, professionals of any organisation, including medical care, apply their own values, cultural experiences, and cognitive shortcuts in their practice. Therefore, clinicians may show explicit (conscious) or implicit (unconscious) biases in how they process and perceive certain patient characteristics, and consequently, how they may tend treat or communicate with patients. Explicit bias could manifest when, for example, characteristics such as age, sex, race, or socioeconomic status result in an evaluation of a patient's social worth or function (Spencer & Grace, 2016). This means that certain patient characteristics are used as indicators of a patient's cognitive and behavioural inclinations, which subsequently either led to their current or could predict their future health status. Such perceptions about a patient could influence whether they are thought to be 'worthy' of medical attention or treatment, or whether they are thought to have high regard or function in society. In one study, doctors were found to engage in "pattern recognition", that is, using clues from a patients' health status to link them to one of a small set of familiar medication options (Gregory et al., 2011).

Consistent with findings of the quantitative study, whereby older patients were less likely to receive adjuvant chemotherapy or combination therapy, evidence suggests that older patients may be more likely to prefer treatment that preserve their memory and cognitive ability over those that prolong life (Dhakal et al., 2021). It is possible that clinicians may be less likely to discuss treatment or spend less time with older than younger patients (Ajaj et al., 2001; Radecki et al., 1988). A study that used the National Cancer Patient Experience Survey found that older patients were less likely to report receiving written information that was easy to understand about their test, less likely to receive information about side effects, and less likely to receive the name of the clinical nurse specialist (Saunders et al., 2015). The qualitative study undertaken in this thesis provided a few examples of the ways in which age may have played a role. Two participants in the study who were 35 and 33 years old described that their age was a strong determinant for receiving combination therapy. In one account, age was explicitly mentioned as the reason for why she should receive chemotherapy, and the decision was perceived to be made by the clinician without discussion and without an option to refuse therapy.

Evidence suggests that those from low socioeconomic groups perceived that their socioeconomic status affected their health care, which may influence how they interact with healthcare professionals or the extent to which they engage with healthcare (Arpey et al., 2017). A systematic review of the literature showed that those of lower socioeconomic status have lower social links and that this was associated to socioeconomic inequalities in healthcare (Uphoff et al., 2013). The qualitative study provided a few examples of the ways in which patients of higher socioeconomic status navigate the healthcare system, which provides them with advantages that are less likely to be experienced by those of lower socioeconomic status. One participant reported consultations that took place in private care, which allowed for more time and a thorough discussion with a clinician. The participant also seemed to be less willing to trust the clinicians' recommendations for treatment and was more inquisitive compared to others. Another participant reported informally gaining information on his condition from a medical specialist within his social network and believed that this also provided him with access to a more experienced specialist in the hospital. It is important to emphasise that single experiences cannot be generalised to a wider group. However, these accounts do bring into attention the various mechanisms that can alter patient-clinician interactions and communication and contribute to differences and inequalities between groups, which warrants efforts to uncover and correct through reliable and valid research.

The decision-making process at the individual level

It is well established in statistics that inferences should not be made directly from group-level data to what occurs for any given individual (Fisher et al., 2018). That is, the mechanisms responsible for the variations observed between groups as discussed above, may not necessarily translate to what each individual patient might experience. As such, the main purpose of the qualitative study was to understand the decision-making process that takes place at the individual level. That is, how the type of chemotherapy used to treat stage III colon cancer was determined. I was interested in patients' accounts of this process, including their interactions with physicians and other healthcare workers, the feelings they experienced, what was important for them to consider, and the factors that determined or influenced how the course of treatment was decided and by whom.

The study found that most participants lacked awareness of the available treatment options, whether this pertained to the choice between single or combination therapy, the type of single therapy that is available (oral capecitabine or intravenous 5-FU), or

the duration of therapy. Those who received combination therapy did not realise that single therapy was an option, and vice versa. This was partly supported by findings of the NCPES study, which showed that patients from single and combination therapy groups believed there was only one treatment option that was suitable for them in answer to the question on whether they were given a choice about different types of treatment. This indicates that patients from both groups may not have been aware of the treatment options that were available to them and may not have been involved in the decision on which treatment to receive. In the qualitative study, most participants reported that the treatment decision was made by the clinician, whether it was for single or combination therapy, and patients were informed rather than consulted about this during the first meeting. However, despite these findings from both studies, most patients answered the NCPES question on involvement positively, indicating that they were involved as much as they wanted to be, and participants in the qualitative study also did not express dissatisfaction about their role in the decision-making process. The findings from these two studies strongly support the notion that the importance of shared decision-making does not lie in who makes the ultimate decision about which treatment to receive. Instead, being informed and consulted seems to be what matters most. It is possible, however, that this perception was driven by their involvement in the decision to receive or not receive adjuvant chemotherapy after surgery, without awareness that there is another decision that determines the type of treatment given. This is supported by participants' accounts in the qualitative study, where almost all participants knew they had a choice to refuse or accept therapy, and at the same time did not realise that there were treatment options (i.e., single or combination, type of single therapy, or routes of administration). Additionally, although the NCPES analysis showed a mainly positive response regarding involvement, there was still approximately a total of 20% of respondents who thought they were involved only "to some extent", were not involved at all, or could not remember. A similar pattern is seen with a similar question that was examined among the smaller sample of those who responded to NCPES rounds 3 and 4 (2012-2013) on whether they thought their views were taken into account by the clinical team involved in their treatment, where approximately 19% of patients thought their views were taken into account "to some extent", and a further total of 14% said that their views were not taken into account, they did not know their treatment was being discussed, or couldn't remember. These two questions indicate that although a large proportion of patients feel their preference for how involved they wanted to be was met or that their views considered, there is still a considerable proportion of patients who feel otherwise, regardless of the type of therapy received.

In contrast to involvement, results from NCPES also showed that those who received combination therapy were less likely to answer with certainty on the questions regarding side effects as well as future side effects, and less likely to be certain that they received all the information they needed about chemotherapy prior to starting treatment. Participants in the qualitative study reported dissatisfaction with the information they received and gave insight to some of the underlying reasons for their dissatisfaction. Many noted that they received generic information which they did not consider to be personalised to them. Therefore, even if the material they received did contain all the necessary information on benefits and harms of the treatment, it is possible that participants may not have reviewed them with high attention, as people are more likely to focus on the content of a message when it is conveying personalised information (Petty & Cacioppo, 1986). Furthermore, it was evident that participants interacted with and received information about the benefits and risks of treatment from many healthcare professionals. This included surgeons, several members of an oncology team, information leaflets, nurses, and online support forums, with many indicating that information received from different sources conflicted at times. In addition, inconsistent information, in addition to the uncertainty inherent to much of medical treatment, may influence risk perceptions and the choices people make (Han et al., 2006). The qualitative study showed that most patients were aware that adjuvant chemotherapy reduces the risk of cancer recurrence but does not eliminate it, and those who were aware of peripheral neuropathy knew that it is a possibility rather than a certainty. Very few participants knew probabilities associated with either outcome. Ambiguous or inconsistent information may influence how people process information and make decisions and can cause people to form pessimistic or optimistic biases of risk (Han et al., 2006; Innes & Payne, 2009). For example, uncertainty in the probabilities of the benefits or harms of a treatment option may cause someone to form a pessimistic bias of risk, whereby they perceive having a higher risk of developing a negative outcome (i.e., not achieving the survival benefit, or sustaining the harmful side effects). On the other hand, it may lead to an optimistic bias of risk, whereby they are hopeful that they will realise treatment benefits or will not experience the adverse effects.

These findings around sub-optimal receipt of information indicates that the role of the Clinical Nurse Specialist in cancer care (CNS) is therefore crucial. The Clinical Nurse Specialist coordinates services and personalises the cancer care pathway to support patients and their carers (National Cancer Action Team, 2010). The benefit of CNS for cancer patient outcomes has already been recognised, as well as potential detrimental

effect of gaps in access (Griffiths et al., 2013; Tod et al., 2015). This was supported by some accounts from the qualitative study, where several participants indicated not having a dedicated CNS, while others reported varying experiences and levels of support received from specialist nurses, indicating inconsistencies in this healthcare service.

Emotion has been shown to influence perception of risk and drive decision-making and could have both positive as well as negative influences (Lerner et al., 2015). Integral emotions are defined as the feelings that arise from the matter at hand, triggered by its potential outcomes (Lerner et al., 2015). Increased anxiety or worry about the outcome (e.g., cancer recurrence or treatment side effects) could lead to increased perceived risk of experiencing that outcome, and choices or behaviours that aim to reduce these negative feelings. High anxiety after a cancer diagnosis has been shown to result in patients choosing aggressive treatment regardless of the probabilities for benefits or harms (Orom et al., 2017). The qualitative study highlighted the role of emotion as an important factor that influenced their interaction with clinicians and drove their desire for chemotherapy. Participants expressed fear and anxiety about cancer recurrence, and therefore were willing to tolerate therapy regardless of any negative side effects it might have. On the other hand, if the worry is about side effects from a particular treatment, that might lead an individual to avoid that treatment, as was seen by one participant who refused combination therapy in the qualitative study. Anxiety after a cancer diagnosis can also influence how much information patients can remember (Nguyen et al., 2019). Therefore, the dissatisfaction with the information that patients received could be partly attributable to their emotional state. However, a similar emotional state would be expected among all patients, regardless of the type of therapy they received. Therefore, the differences seen in the answers to the NCPES questions on information between those who received single, or combination therapy indicate that provision of information may be flawed on a health system-level.

Individuals also show a tendency to avoid actions that could lead to regret or perform actions to avoid regret. People have been shown to engage in a thinking process where they weigh the risks associated with a decision against the risk of regretting that decision (Miller & Taylor, 2014). The way that information is presented could play a role in people's perception of whether a given action (or lack of) could cause regret. For example, options that represent an "act of commission" may be more likely to result in regret than "acts of omission". As such, default options represent an act of omission because they do not require a deliberate change of an existing condition, while acts of commission require that individuals deliberately take, or commit, a certain action.

Therefore, individuals may be more likely to choose an option that is presented as the default option (Halpern et al., 2013). The qualitative study has shown that oncologists were quick to offer a treatment recommendation. Those who received or were offered combination therapy, reported that it was often described as standard therapy. Therefore, an oncologist's recommendation may represent the default option that a patient is automatically opted-into, and therefore, less likely to cause regret. By contrast, refusing therapy that is recommended by an oncologist could represent an act of commission, perceived as actively opting out of the default option. The analysis from NCPES, which showed that most patients perceived that only one option was suitable for them, provides some support that the treatment option that was presented to patients, regardless of the type (single or combination), was the default option that patients were aware of and opted for. In contrast avoiding actions that could lead to regret, evidence suggests that people could also be driven to act if they perceive that failing to act could result in poor outcomes and regret. For example, in one study, loss-framed messages about screening, where people were presented with the negative outcomes of failure to screen, were more effective in increasing participants' intentions to screen than gain-framed messages (Ferrer et al., 2012). This is because loss-framed messages trigger anticipated regret that drive people to attend screening to avoid these negative emotions. Interventions that aim to trigger anticipated regret from failure to screen have been shown to be effective in increasing screening uptake (O'Carroll et al., 2015). As discussed earlier, some participants in the qualitative study reported that they may have avoided combination therapy or considered the decision to receive it more carefully if they knew the marginal benefit of oxaliplatin or had a better understanding of its long-term adverse effects.

The conceptual framework

As discussed in chapter 3, a literature review for theoretical frameworks that describe determinants of cancer chemotherapy suggested that an all-encompassing model is not available. Instead, a conceptual framework that guided this work was developed from concepts in other theoretical models describing treatment choice in general, or other treatment modalities (e.g., radiotherapy) within the cancer context.

Four studies were conducted for this thesis, guided by the conceptual framework that was developed and described in Chapter 3. The first study aimed to illuminate and provide information on the prevalence of peripheral neuropathy, an important attribute that could influence the choice of treatment. Until now, the prevalence of peripheral

neuropathy and the nature of symptoms that could be expected after treatment with oxaliplatin for stage III colon cancer was unclear. The study conducted here provides information that should contribute to the discussion of treatment options that takes place between patient and clinician. The study also underscores why such discussions and considerations of side effects are important. The qualitative study conducted for this thesis showed that peripheral neuropathy may not be emphasised as a potentially serious side effect in discussions about stage III cancer treatment. This could be because an accurate estimate of prevalence was unclear, and as such, the potential for this side effect to occur because of treatment was underestimated, with a focus on side effects that were more serious, i.e., life-threatening, or more common. However, discussing uncertainty and ensuring that patients understand uncertainty is an important aspect of shared decision-making. Ultimately, in this case, peripheral neuropathy could persist in 25-30% of people, at a level that can influence daily tasks, and as such, it was important that patients were aware, and prepared, for this possibility. Failing to discuss uncertainty may lead patients to be inadequately informed. Analysis of NCPES provided support to this finding, showing that patients who received combination therapy were less certain about the adequacy of the information they received, particularly on side effects, than those who received single therapy.

The qualitative study also shed light on multiple aspects relating to the conceptual framework, including, the nature of the communication that takes place between patient and clinician; patients' perceptions of cancer and chemotherapy, and the psychosocial factors that may act as barriers to being involved in the decision-making process. To some extent, the study also shed light on the mechanisms that underlie how patient characteristics, particularly age and socioeconomic status, can shape the patient clinician interaction and can influence treatment choices. In addition, it also provided insight on how family, referrers, as well as local practice patterns and multidisciplinary teams could play a role to influence patients and their perception, and thus, influence the decision-making process.

Exploring variations in treatment using the cancer registry linked to the SACT data provided statistical evidence of the patient characteristics that influence treatment decisions, indicating flaws in the opportunity and equity for therapy on a systemic level (whether relating to patient, provider, or health system related factors). This provides support to the notion that treatment decisions are often not reached on an individual, or case by case, basis, as discussed earlier in the summary section of this chapter.

Similarly, in addition to differences in therapy between groups, information provision was perceived as less adequate among those who received combination therapy compared to those who received single therapy. This was another indication of flaws occurring on a systemic level, whereby the type or quantity of information provided is not determined by individual level factors but rather varies by the type of treatment received, and thus, not used by each individual patient when a treatment decision is being considered.

The conceptual framework that was discussed in Chapter 3 is shown in Figure 26. It has been slightly adapted to include the explicit elements of the discussion that should occur between patient and clinician in a shared decision-making context, as described by Bomhof-Roordink, Fischer, et al. (2019) (discussed in the introduction of Chapter 6) and as has been shown in the results of the qualitative study. The figure here is colour coded to indicate how it relates to each of the chapters in this thesis.

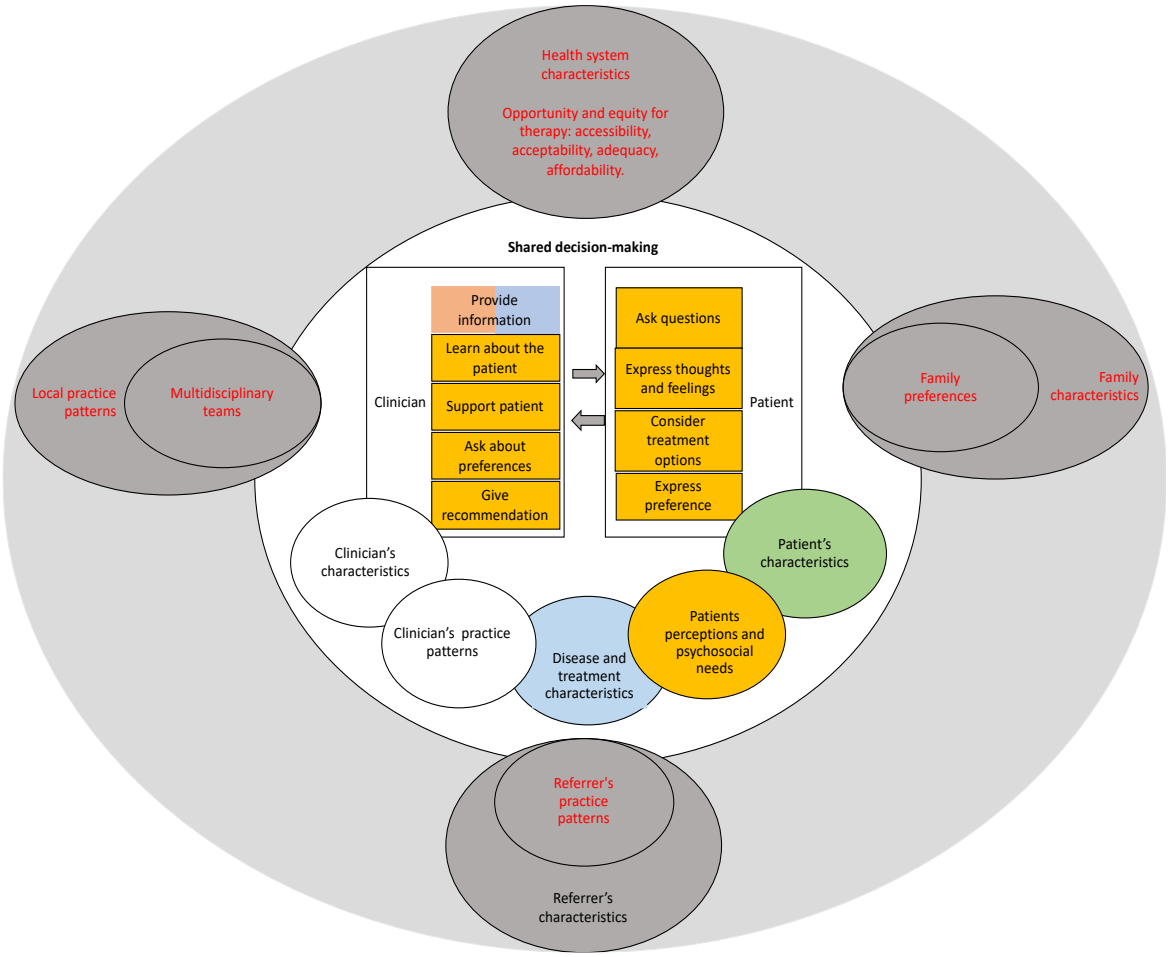


Figure 26 - Conceptual framework adapted to include more elements derived from the research undertaken

	Both the literature review (Chapter 2) and the Systematic review (Chapter 4) contribute to this element
	Quantitative analysis of the cancer registry and SACT (Chapter 5) contributes to this element
	Qualitative study exploring patients' perception of the decision-making process (Chapter 6) contributes to these elements
	Quantitative analysis of NCPES (Chapter 7) contributes to this element
Red font	Thesis contributed to some understanding of how these elements could influence the shared decision-making process, although not as primary areas under study

Strengths and limitations

One of the main strengths of this thesis is the use of multiple methods to answer different research questions, which aimed to explore determinants of adjuvant chemotherapy receipt among stage III colon cancer patients at different levels and adds to the literature in several ways. The systematic review was undertaken to provide useful information on peripheral neuropathy that could be considered by both patients and clinicians when making a treatment decision. The remaining studies

allowed for an in-depth understanding of interpersonal and wider contextual factors that influence the treatment decision on individual level and uncovered systemic-level factors that could cause variations in treatment between groups. These findings could be used to inform changes to healthcare services that could improve patients' experiences with cancer treatment.

The focus on a particular subgroup of cancer patients is another strength. The mainstay for therapy is surgical removal of the tumour, followed by adjuvant chemotherapy with either single or combination therapy. There is no additional radiotherapy, chemotherapeutic regimens, neo-adjuvant chemotherapy, or immunotherapy options to consider in this setting. For example, palliative treatment for metastatic disease (stage IV) requires a fair amount of clinical judgement guided by the rate of progression of the disease. Similarly, rectal cancer patients may require radiotherapy, or chemotherapy before surgery, resulting in a less straightforward and more complex decision-making process. Therefore, decision-making process in the context of stage III colon cancer could be thought of as relatively simpler in comparison to other more complicated therapy that may be required for other cancers or more advanced stages. As such, this context allows for a clearer understanding of what takes place between and around the patient-clinician interaction, without the confounding effects of the considerations for other modes of treatment or trade-offs. In addition, due to the uncertainties in the benefits and risks of oxaliplatin, a thorough discussion with patients may carry more weight than clinical judgment. However, despite this relative simplicity, patients' involvement in the decision-making process and awareness of options and side effects were limited, and there was evidence of inequalities in the receipt of treatment. Therefore, these issues are likely to also apply in the context of other cancer sites, or where more complicated treatment, and are not specific to this context only. As such, the findings of this study can be used to improve practice more widely.

The samples used in the quantitative and qualitative studies of this thesis present both a strength and a limitation. Several factors indicate that the results reported in this thesis are representative of a wide range of stage III colon cancer patients in the UK. The qualitative study was advertised on multiple widely reaching cancer forums, and interviews were conducted on the phone, which allowed patients from all over the country to participate. There was a wide variation in the age of those who participated, ranging from 35 years to 75. Those who were between 60-75 years of age or diagnosed in 2013 and 2014 were more likely to respond to the NCPES compared other age groups or later years of diagnosis. Therefore, the interviews captured the

views of younger patients, as well as those diagnosed in more recent years, who were less represented in the NCPES. The interviews also captured the views of those who self-identified at middle- or low-level income, in contrast to NCPES where the least deprived were the most represented. Additionally, while the interviews only captured the perspective of White British patients, those of minority ethnic groups were more represented in NCPES. However, ethnic minorities may have strong religious faith could have a different understanding of illness and therefore a different way of approaching treatment. Therefore, the perspectives of these groups should be explored qualitatively to inform how health care professionals interact with patients from different cultural backgrounds to their own (Koffman et al., 2008). Additionally, the use of online platforms for recruitment to the qualitative study also posed a limitation. This form of recruitment meant that groups who had limited availability or accessibility to online platforms, such as those from very deprived backgrounds or of lower technological literacy, or anyone who does not engage with online forums or support groups, for any reason, may have been missed. The views and experiences of those who were recruited for the qualitative study may be very different from those who were not captured by these methods. Since NCPES is a voluntary survey, a similar consideration also applies for the NCPES sample. Patients who responded to NCPES may be very different in characteristics compared to those who did not respond. By contrast, however, the analysis of the variations in the type of chemotherapy provided a large representative cohort of patients with stage III colon cancer who receive care from the National Health Service in England, and high quality, routinely collected data.

As this thesis is focused on patients' perspectives, one obvious limitation is that it lacked healthcare professionals' perspectives. Investigating healthcare professionals' perspectives on how they perceive their communication with patients could reveal areas where they are aware of gaps in their communication skills and those where awareness may be lacking. It may also provide explanations and insight into their beliefs about therapy, and where their priorities lie. It is possible that healthcare professionals prioritise survival above all else, especially for young patients. Another limitation of the study was the timing of the qualitative and quantitative studies. Due to issues with data access leading to time constraints, it was not possible to undertake these studies iteratively and mixing of the methods at the data collection and analysis stages. For example, results from the analysis of NCPES could have informed questions to ask in the qualitative study, and themes from the qualitative analysis could have informed additional analysis of CPES. Therefore, mixing of the two studies was limited to the interpretation of findings, which was undertaken in this current chapter.

Conclusions and recommendations

It is widely accepted now that treatment decisions, regardless of the clinical situation, should be based on shared decision-making and patients' preferences. However, in practice, we might find that certain clinical conditions where the advantages of treatment outweigh the disadvantages to such a large extent that physicians' recommendations and patients' preferences are likely to be strongly aligned, and treatment is presumed and agreed without an explicitly apparent shared decision-making process. It is possible that this is the case for single-agent adjuvant chemotherapy of stage III colon cancer. There is strong evidence for a large survival benefit that is obtained in addition to surgical removal of the tumour, which may mean its use in the treatment of stage III colon cancer has become unquestionable. However, additional treatment with oxaliplatin has lower margins of benefit and may cause permanent nerve damage. With patients now living longer after a cancer diagnosis, attention needs to be paid to those who may experience pain or other symptoms that could result in reduced function because of cancer treatment. Therefore, if a treatment option is known to increase the risk of such symptoms, such as in the case of treatment with oxaliplatin, this should be adequately explained and considered. Management of such symptoms among cancer survivors requires a holistic approach, which in addition to the psychological forms of coping and self-management that are used, should also include education and empowerment of patients to understand and prepare for the risks and the influences of treatment on their quality of life before they receive it. Patients undergoing treatment for cancer, whether in this setting or more generally, may differ in how they weigh the risks and benefits of their treatment options and make choices, especially given the uncertainties around the occurrence or the nature of side effects or effectiveness of treatment. Therefore, a shared decision-making model that aims to increase patients' participation in the decision on the treatments they receive has become a standard of care. Adopting this approach with all patients also potentially reduces inequalities that result from healthcare professional and system biases, as it shifts the power dynamics and empowers patients to take control of what happens to them. In 2011, a Department of Health report set out the government's strategy to improve patients' experience and reduce inequalities in health care outcomes by putting patients at the heart of cancer health services (Department of Health, 2011).

Recent publications that have more precisely defined the use of combination chemotherapy in terms of its absolute survival gains, the clinical characteristics it is most useful for, and the duration of therapy should be noted (André et al., 2020).

Guidelines suggest that those with a larger tumour size or a greater number of lymph nodes involved should be offered six months of therapy, while those with a smaller tumour or lower number of lymph nodes can be offered three months of therapy. Therefore, patients will benefit now from more tailored regimens and durations based on clinical characteristics. However, the treatment decision should not be based solely on clinical characteristics as benefits may be marginal even for more advanced disease, and patients may decline chemotherapy due to concerns about toxicity even if it offers benefits (El Shayeb et al., 2012). It is important to remember that guidelines on duration of therapy that are based on the extent of disease and low or high margins of benefit do not reflect the margin of risk that each individual patient may be willing to tolerate or forgo. As such, the even with these new guidelines, the American Society of Clinical Oncology still recommends a shared decision-making approach, considering patient characteristics, values and preferences, and a discussion of the potential for benefit and risks of harm associated with treatment duration for all patients, regardless of extent of disease (Lieu et al., 2019).

Evaluation of shared decision-making has been challenging due to the variety of instruments and outcomes that have been used (Scholl et al., 2018). However, although there is no conclusive evidence for the effectiveness of shared decision-making, results from systematic reviews are suggestive of beneficial effects on affective-cognitive outcomes and quality of life. In addition, evidence suggests that shared decision-making may result in improved outcomes particularly among disadvantaged groups. Despite its importance in healthcare delivery, shared decision-making is often not implemented in clinical practice, and this could be due to many reasons related to patients, healthcare professional, or the healthcare system. Limited time and resources are an important barrier to the implementation of shared decision-making. To tackle this, organisational leadership is needed. Shared decision-making should be elevated from being an initiative that is expected of individual clinicians to an organisational priority and a shared responsibility, whereby appropriate training is provided to all healthcare providers, and the time and personnel necessary are made available to support them. Evidence from the UK suggests that some clinicians believe they already practice shared decision making when they involve patients in making the final decision about their care, while others believe that for shared decision-making to be possible decision aids are necessary (Joseph-Williams et al., 2017). Both these views highlight the importance of efforts to increase clinicians' awareness and understanding of what constitutes shared decision-making.

It is true that decision aids could be useful tools that provide information on treatment options and their benefits and harms. Some may also include values clarification components, with the aim to clarify patients' personal values about what is important to them (Witteman et al., 2016). Indeed, a recent update on the Cochrane review of decision aids for people facing treatment or screening decisions concluded that people exposed to decision aids are better informed about their options, clearer about their values, more involved in the decision-making process, and more satisfied with their decision and the decision-making process compared to usual care (Stacey et al., 2017). This was true for a wide range of contexts. However, decision aids are not available for every scenario in medical practice, nor is it practical to aim for such a goal. The development of decision aids is often resource intensive, and with continuous improvements to medical treatments, decision aids can become outdated if not continuously updated. In addition, research suggests that the design and evaluation of a vast majority of decision-aids and value clarification methods are not theoretically based, and evidence on the effectiveness of values clarification methods is mixed (Durand et al., 2008; Witteman et al., 2016). As such, decision aids that are developed could potentially be of low quality, and if not evaluated rigorously, their effect on relevant outcomes may not be known. Several systematic reviews have shown that the decision aids currently available for breast, prostate, and colorectal cancers are characterised by low quality of communication, as assessed using two quality instruments (the International Patient Decision Aid Standards (IPDAS) and Communicative Aspects (CA) checklist) (Hommes et al., 2021; R. Vromans et al., 2019; R. D. Vromans et al., 2019). For colorectal cancer,18 decision aids that were both academically tested as well those freely available online were included. The study concluded that they lacked personalisation of treatment information, and that the information presented was biased towards a specific treatment, lengthy, and not written in plain language. However, although the decision aids were assessed against communication quality criteria, their effectiveness in terms of outcomes was not assessed (Hommes et al., 2021). In another systematic review, which included only three decision aids for colorectal cancer due to narrower inclusion criteria, found that these were associated with increased patient knowledge, satisfaction, and preparation for making a decision, although two out of three scored low on quality (Goldwag et al., 2019). Therefore, decision aids, as the name suggests, are ultimately tools that could aid in the process but should not be a substitute for the process itself. Furthermore, successful shared decision-making constitutes more than just information provision or asking patients to make a choice about their care. The motivation to advocate for shared decision-making was initially ethical, aimed to protect patients' autonomy. In

recent years, however, there have been debates in the literature about the concept of autonomy, with criticisms of its current interpretation as too “individualistic”, and a move towards a “relational” understanding of autonomy instead (Gomez-Virseda et al., 2019). This means that individuals are connected to and interdependent on others and are not separate from their social and cultural contexts, whereby society and culture have a role in the development of patients’ values. It also suggests that family members and healthcare professionals have a role in the development of patients’ ability to make decisions, for example, by providing new perspectives or emotional support. Therefore, clinicians have a responsibility to facilitate patients’ relation to family and to themselves and other healthcare professionals in decision-making. This includes encouraging patients to deliberate with clinicians and family members when they are considering treatment. This emphasises the importance of increasing clinicians’ understanding of what constitutes shared decision-making, which goes beyond safeguarding autonomy. That is, that shared decision-making is not only concerned with who makes the final decision, but more importantly, the process of making the decision. Elwyn and colleagues argue that a good decision is characterised by both the process of arriving at the decision, or *deliberation*, and the decision itself, or the *determination* of a decision. The process involves gaining the relevant information and knowledge about the condition and its treatment options, appraising the adequacy of this information, imagining counterfactuals, forecasting affective responses to the counterfactuals, and constructing preferences. Arriving at a decision involves integrating all components of this process to make a choice. If the process is conducted in this manner described, then the decision made will inherently be one that is based on patients’ involvement and preferences, regardless of who makes the final decision. As such, good communication between patients and clinicians is imperative. In a study conducted in 2005, Thorne and colleagues stated that ‘poor communication in cancer care seems unfortunately prevalent’ (Thorne et al., 2005)(pg.875), and this thesis shows that little may have changed in patient-clinician communication over the past two decades. Therefore, it is important to improve clinicians’ relational communication skills, defined as communication that focuses on the expression and interpretation of messages within close relationships (Step et al., 2009). In one study, patients perceived good relational communication from simple actions, such as interacting with the physician outside of the consultation room and being invited to express their concerns during consultation. Only invited expressions of concern were associated with a higher rating of the communication, not concerns that were expressed without invitation (Shay et al., 2012). As such, it is important that clinicians have the skills to encourage patients to participate in a discussion, ask questions, and express their worries and concerns.

Interestingly, Shay et al. (2012) also found that the amount of time patients spent waiting to be seen by a physician or spent with a physician did not contribute to a higher rating of the communication. This highlights that any training provided to clinicians should be done after understanding patients' perspectives of what constitutes good communication.

Good communication also includes that clinicians ensure patients' understanding of the information they receive and inquire about their preferences for information at various stages throughout diagnosis and treatment. The experience of a cancer diagnosis and treatment is a daunting one for patients, most of whom likely cannot anticipate what information they will need or find useful, nor when they might need it. Therefore, it is possible that some may not require or desire information at the start, but it should not be assumed that this will be the case throughout. People's information needs may change as they go through the different phases of diagnosis and treatment (der Molen, 1999), and patients may also want to be given information continuously over time, not just once (Van Mossel et al., 2014).

It may be important to explore whether clinicians face difficulties in communicating health information to patients, particularly risk information, and aim to develop standards for health risk communication, such as, what information should be provided to patients and in which format. In addition, increasing clinicians' awareness of how their framing and presentation of treatment options or risks and benefits could influence patients' perceptions and choices. Furthermore, practical guidance may be needed on how to provide explicit comparisons of available alternatives. Particularly, that any of the medication included in a chemotherapy regimen are evaluated relative to each other, in addition to their evaluation relative to no treatment. Finally, guidance on how to aid patients in considering their expectations, concerns, and which aspects of a choice are most important to them may also be useful. This is important not only to allow for a choice based on patient preferences, but also it may help clinicians understand how to frame and communicate with patients in terms that they understand (National Research Council 1989). If the benefits or the risks of a certain treatment option, for example, are articulated in ways that resonate with patients, that is, capture their attention in terms of what they value most and what is important to them, then patients' may have a better ability to make the correct trade-offs regarding their treatment. The best treatment alternative for any given individual is the one that is most likely to meet (or avoid) the most concerns. Trade-offs should also be made in the context of how patients respond to treatment. In the case of treatment with oxaliplatin, for example, patients may experience severe and acute side-effects such as peripheral

neuropathy after multiple cycles of treatment, which would necessitate a trade-off analysis on whether to continue or stop treatment that is separate from the one that was discussed before treatment started. For example, should treatment be stopped as soon as a patient experiences symptoms or allow a few more cycles? At what point do the risks outweigh the benefits? How is the judgment made that “enough” oxaliplatin was provided to realise its benefits while also preserving function?

As for patients, it is important to encourage them to think clearly about their own objectives, communicate this to their treating clinicians, and hold their clinicians accountable by ensuring that their concerns are addressed by the doctor. It is also important to increase patients’ awareness of what chemotherapy is; that it consists of one or more medications, each with their own sets of risks and benefits, rather than perceive “chemotherapy” to be the treatment. This is a perception that was shown to be held by several participants in the qualitative study.

Although NCPES includes questions on whether patients felt informed about side effects or future side effects, further insight would be provided from a question that asked whether they felt they were as informed as they wanted to be (similar to the one that already exists on whether patients were “involved as much as they wanted to be”), a question on whether they were informed of the benefits of treatment, and one on whether they were aware of the medications that constituted their chemotherapy regimen. As shown in the qualitative study, many participants reported that they were not aware of the survival benefits of single compared to combination therapy, or what constituted their chemotherapy regimen in the first place. It may also be beneficial to compare self-reported measures of information, such as the questions in the NCPES against objective measures of information, to identify whether the gaps in information provision are perceived or true. In the former case, research could focus on identifying what influences perceptions of information among patients, while in the latter case, efforts would be directed at improving the availability or presentation of information. A future study, for example, could include content analysis of the information leaflets or booklets that patients receive regarding side effects of treatment, and long-term side effects such as peripheral neuropathy, to determine the adequacy of such information in preparing patients for these outcomes or in increasing patients’ knowledge as a means of facilitating their participation in the decision-making process, and their ability to raise issues and ask questions. Another future study could also be conducted to explore whether patients receive inconsistent or conflicting information from different healthcare workers involved in their care, explore reasons for this, and ways by which

information can be moderated and delivered more consistently across the healthcare system.

Future research could also aim to understand the mechanisms behind the observed variations in treatment, and the extent to which this may be due to patients' perceptions or lack of abilities that are inherent within certain groups, healthcare professionals' explicit or implicit biases, or an interaction between the two. For example, clinicians' biases that result in a judgement of social worth or function could feedback into patients' lack of confidence or lack of desire to engage with the healthcare system. Similarly, low numeracy evidenced from patients of certain characteristics could feedback into re-enforcing clinicians' biases. Uncovering these mechanisms can lead to constructive programmes that could aim to correct such patient perceptions or clinician biases.

Randomised controlled trials provide robust evidence for differences between groups and allow for causal inferences to be made, unlike observational studies that support inferences on association but not causation. For this reason, the randomised controlled trials that were undertaken to evaluate the effectiveness of oxaliplatin, such as in MOSAIC, NSABP-C07, or XELOXA had unique opportunities to evaluate the effect of treatment with oxaliplatin on the development of peripheral neuropathy, and perhaps could have also investigated its impact on quality of life. However, the trials did not support such longer-term studies. The longest follow-up of patients was for 18 months after therapy, and the effect of symptoms on quality of life was not investigated. Additionally, patient-reported outcome measures which would have given an indication on experiences of patients were also not used, the trial used measures that relied on healthcare professional physical examination only, and the concern was on toxicities or side effects from a clinical point of view. These are missed opportunities of randomised controlled trials, which consume large amounts of funds and human resources to carry out. Therefore, in future research, the use of such RCTs should be extended to gain knowledge about other aspects that could benefit from long-term follow-up and comparisons between groups, by carrying out studies that could make use of the randomisation and the structures that are already put in place for drug efficacy outcomes. Furthermore, research into the effectiveness of treatment in the routine setting should also be emphasised and encouraged with robust methodology that minimises bias. Such studies would provide insight into the true effect of treatment on survival in uncontrolled conditions (i.e., real life, compared to randomised controlled trials).

Finally, as Lerner et al. note that “emotions exert causal effects on the quality of our relationships, sleep patterns, economic choices, political and policy choices, creativity, physical and mental health, and overall well-being”, and therefore, understanding emotion allowed for “understanding not only human decision making but also much of human behaviour as a whole” (Lerner et al., 2015); pg. 817. Therefore, we should strive to create societies that understand the role of emotion in decision-making and human behaviour and invest efforts and resources into prioritising and providing mental health, well-being, and support services that are accessible to everyone. This, however, is an idealistic ambition. In more realistic and perhaps tangible terms, efforts and resources aimed at provision of services that support cancer patients who are faced with treatment decision could be effective in increasing patients’ participation in making these decisions. This includes educating individuals in recognising their integral as well as incidental emotion, how these may influence their judgment, and equipping them with strategies to minimise the effect of negative emotion in decision-making. This is not only limited to specialised services, but also through increasing healthcare professionals’ awareness of these factors that influence decision-making. It is also important to recognise that emotion can influence clinicians’ ability to make treatment decisions. Evidence suggests that reliance on emotion in decision-making increases with stress, dealing with unpleasant tasks, such as delivering distressing news, or communicating complex information, such as the uncertainties associated with risks and benefits. These are all factors associated with medical practice, and as such, clinicians may be prone to negative emotion influencing their practice. Therefore, further research to understand how clinicians’ emotions influence the treatment recommendations that they make to patients and decision-making process is needed. In addition, interventions are also needed to reduce stress among clinicians, reducing the time pressures and constraints that are placed on their clinical consultations, and support their wider mental health and wellbeing.

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Appendices

Appendix 1

Peripheral Neuropathy Assessment Tools

CTCAE versions 1 to 4.03

Version	Grade-I	Grade-II	Grade-III	Grade-IV	Grade 5*
1	Mild paraesthesia, loss of deep tendon reflexes	Mild or moderate objective sensory loss; moderate paraesthesia	Severe objective sensory loss or paraesthesia that interfere with function	-	-
2	Loss of deep tendon reflexes or paraesthesia (including tingling) but not interfering with function	Objective sensory loss or paraesthesia (including tingling), interfering with function, but not interfering with activities of daily living	Sensory loss or paraesthesia interfering with activities of daily living	Permanent sensory loss that interferes with function	-
3	Asymptomatic; loss of deep tendon reflexes or paraesthesia (including tingling) but not interfering with function	Sensory alteration or paraesthesia (including tingling), interfering with function but not interfering with activities of daily living	Sensory alteration or paraesthesia interfering with activities of daily living	Disabling	Death
4/4.03	Asymptomatic; loss of deep tendon reflexes or paresthesia	Moderate symptoms; limiting instrumental activities of daily living	Severe symptoms; limiting self-care activities of daily living	Life-threatening consequences. Urgent intervention indicated	Death

*The CTCAE is a classification system for all types of adverse effects caused by therapy, some of which could result in death. Therefore, grade 5 exists for the purpose of other adverse events but does not occur with peripheral neuropathy.

CIPN20

Sensory symptoms and problems

1. Tingling fingers or hands
2. Tingling toes or feet
3. Numbness in fingers or hands
4. Numbness in toes or feet
5. Shooting or burning pain in finger or hands
6. Shooting or burning pain in toes or feet
7. Trouble standing or walking because of difficulty feeling the ground under your feet
8. Difficulty distinguishing hot and cold water
9. Difficulty hearing

Motor scale

10. Cramps in hands
11. Cramps in feet
12. Difficulty holding a pen making writing difficult
13. Difficulty handling small objects with fingers (e.g., buttoning a blouse)
14. Difficulty opening a jar or bottle due to weakness in hands
15. Difficulty walking because feet drop downwards
16. Difficulty walking stairs or standing up from a chair due to weakness in legs
17. Only for those driving: Difficulty driving due to use of pedals

Autonomic scale

18. Dizziness when standing up from a sitting or lying position
19. Blurry vision
20. Only for males: Difficulty getting or maintaining an erection

FACT GOG-NTX12

1. I have numbness or tingling in my hands

   No at all / a little bit / Somewhat / Quite a bit / Very much

2. I have numbness or tingling in my feet

   No at all / a little bit / Somewhat / Quite a bit / Very much

3. I feel discomfort in my hands

   No at all / a little bit / Somewhat / Quite a bit / Very much

4. I feel discomfort in my feet

   No at all / a little bit / Somewhat / Quite a bit / Very much

5. I have joint pain or muscle cramps

   No at all / a little bit / Somewhat / Quite a bit / Very much

6. I feel weak all over

   No at all / a little bit / Somewhat / Quite a bit / Very much

7. I have trouble hearing

   No at all / a little bit / Somewhat / Quite a bit / Very much

8. I get a ringing or buzzing in my ears

   No at all / a little bit / Somewhat / Quite a bit / Very much

9. I have trouble buttoning buttons

   No at all / a little bit / Somewhat / Quite a bit / Very much

10. I have trouble feeling the shape of small objects when they are in my hand

    No at all / a little bit / Somewhat / Quite a bit / Very much

11. I have trouble walking

    No at all / a little bit / Somewhat / Quite a bit / Very much

12. I have pain in my hands or feet when I am exposed to cold temperatures

    No at all / a little bit / Somewhat / Quite a bit / Very much

FACT GOG-NTX4

1- I have numbness or tingling in my hands

No at all / a little bit / Somewhat / Quite a bit / Very much

2- I have numbness or tingling in my feet

No at all / a little bit / Somewhat / Quite a bit / Very much

3- I feel discomfort in my hands

No at all / a little bit / Somewhat / Quite a bit / Very much

4- I feel discomfort in my feet

No at all / a little bit / Somewhat / Quite a bit / Very much

Neuropathy Symptom Score (NSS)

Score 1 point for presence of a symptom.

I. Muscle weakness

A. Bulbar

1. Extraocular
2. Facial
3. Tongue
4. Throat

B. Limbs

5. Shoulder girdle and upper arm
6. Hand
7. Glutei and thigh
8. Legs

II. Sensory disturbances

A. Negative symptoms

9. Difficulty identifying objects in mouth
10. Difficulty identifying objects in hands
11. Unsteadiness in walking

B. Positive Symptoms

12. Numbness, asleep feeling, like Novocain, pickling – at any site
13. Pain – burning, deep aching, tenderness – at any location

III. Autonomic symptoms

14. Postural fainting
15. Impotence in men
16. Loss of urinary control
17. Night diarrhea

Appendix 2

Search terms by database

Scopus

(TITLE-ABS-
KEY (colo* W/4 (cancer* OR neoplasm* OR malignan* OR carcinoma* OR tum or* OR tumour*))

AND TITLE-ABS-KEY (stage-iii* OR stage-3* OR "stage III*" OR "stage 3*" OR "duke* C" OR "stage three" OR "third stage" OR stage-three OR "local* invasi*" OR "local* advanc*" OR nonmetasta* OR "non-metasta*" OR "non metasta*" OR "not metasta*" OR "no metasta*" OR "without metasta*")

OR (oxaliplatin W/4 (treat* OR based OR administ*)) OR (adjuvant W/4 (setti ng OR treatment OR chemotherapy OR therapy OR patient*)))

AND TITLE-ABS-
KEY (adjuvant OR oxaliplatin* OR eloxatin* OR fluox* OR flox* OR folfox* OR xelox OR capox OR capeox)

AND TITLE-ABS-
KEY (neuropath* OR polyneuropath* OR neurotoxic* OR neurosensory OR neuro logic* OR neuralgi* OR (nerve* W/4 (damage* OR impair* OR injur* OR periph eral)))

AND PUBYEAR > 1993)

Medline

1. exp Colonic Neoplasms/ or exp Colorectal Neoplasms/ or exp Adenocarcinoma/
2. (colo* adj4 (cancer* or neoplasm* or malignan* or carcinoma* or tumo?r*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
3. 1 or 2
4. (stage-iii* or stage-3* or "stage III*" or "stage 3*" or "duke* C" or "stage three" or "third stage" or stage-three or third-stage).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
5. ("local* invasi*" or "local* advanc*" or "non-metasta*" or nonmetasta* or "without metasta*" or "no metasta*" or "not metasta*").mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
6. (oxaliplatin adj4 (treat* or based or administ*)).mp.
7. (adjuvant adj4 (setting or treatment or chemotherapy or therapy or patient*)).m

8. 4 or 5 or 6 or 7
9. adjuvant.mp. or exp Chemotherapy, Adjuvant/
10. exp Antineoplastic Agents/ or exp Oxaliplatin/ or exp Antineoplastic Combined Chemotherapy Protocols/ or oxaliplatin*.mp.
11. eloxatin*.mp.
12. (fluox* or flox* or folfox*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
13. (xelox or capox or capeox).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
14. 9 or 10 or 11 or 12 or 13
15. exp Neuropathology/ or neuropath*.mp.
16. exp Polyneuropathies/ or polyneuropath*.mp.
17. neurotoxic*.mp.
18. neurosensory.mp.
19. neurologic*.mp.
20. exp Neuralgia/ or neuralgi*.mp.
21. (nerve* adj4 (damag* or impair* or injur* or peripheral)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
22. exp Peripheral Nerves/ or exp Peripheral Nervous System Diseases/ or exp Peripheral Nervous System/
23. exp Peripheral Nerve Injuries/
24. 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25. 3 and 6 and 14 and 24
26. limit 25 to (english language and yr="1994 -Current")

Embase

1. (colo* adj4 (cancer* or neoplasm* or malignan* or carcinoma* or tumo?r*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

2. exp colon cancer/ or exp colorectal cancer/ or exp colon carcinoma/

3. 1 or 2

4. (stage-iii* or stage-3* or "stage III*" or "stage 3*" or "duke* C" or "stage three" or "third stage" or stage-three or third-stage).mp. [mp=title, abstract, heading word, drug

trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

5. ("local* invasi*" or "local* advanc*" or "non-metasta*" or "nonmetasta*" or "without metasta*" or "no metasta*" or "not metasta*").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

6. (oxaliplatin adj4 (treat* or based or administ*)).mp.

7. (adjuvant adj4 (setting or treatment or chemotherapy or therapy or patient*)).mp.

8. 4 or 5 or 6 or 7

9. exp oxaliplatin/ or oxaliplatin*.mp. or exp capecitabine plus oxaliplatin/

10. eloxatin*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

11. (fluox* or flox* or folfox*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

12. (xelox or capox or capeox).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

13. exp adjuvant/ or exp adjuvant chemotherapy/ or exp adjuvant therapy/ or adjuvant.mp. or exp cancer adjuvant therapy/

14. 9 or 10 or 11 or 12 or 13

15. exp neuropathology/ or neuropath*.mp.

16. exp polyneuropathy/ or polyneuropath*.mp.

17. neurotoxic*.mp. or exp neurotoxicity/

18. neurosensory.mp. or exp sensory dysfunction/

19. exp neuralgia/ or neuralgi*.mp.

20. (nerve* adj4 (damag* or impair* or injur* or peripheral)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

21. exp peripheral nerve injury/ or exp peripheral nerve/

22. exp peripheral neuropathy/ or exp chemotherapy-induced peripheral neuropathy/ or exp peripheral nervous system/ or exp nerve injury/

23. 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22

24. 3 and 8 and 14 and 23

25. limit 24 to (english language and yr="1994 -Current")

PsychINFO

1. (colo* adj4 (cancer* or neoplasm* or malignan* or carcinoma* or tumo?r*)).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh]

2. exp Neoplasms/ or exp Gastrointestinal System/ or exp Colon Disorders/

3. 1 or 2

4. (stage-iii* or stage-3* or "stage III*" or "stage 3*" or "duke* C" or "stage three" or "third stage" or stage-three or third-stage).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh]

5. ("local* invasi*" or "local* advanc*" or "non-metasta*" or "nonmetasta*" or "without metasta*" or "no metasta*" or "not metasta*").mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh]

6. (oxaliplatin adj4 (treat* or based or administ*)).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh]

7. (adjuvant adj4 (setting or treatment or chemotherapy or therapy or patient*)).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh]

8. 4 or 5 or 6 or 7

9. (fluox* or flox* or folfox*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh]

10. (xelox or capox or capeox).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh]

11. exp Drug Therapy/ or exp Chemotherapy/ or adjuvant.mp.

12. oxaliplatin*.mp.

13. eloxatin*.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh]

14. 9 or 10 or 11 or 12 or 13

15. exp Peripheral Neuropathy/ or exp Neuropathic Pain/ or exp Neuropathy/ or exp Neurotoxicity/

16. exp Neuropathy/ or exp Nervous System Disorders/ or exp Neuropathology/ or exp Neuropathic Pain/ or neuropath*.mp.

17. exp Neuropathy/ or polyneuropath*.mp.

18. exp Neurotoxicity/ or neurotoxic*.mp.

19. exp Sensory Neurons/ or exp Sensory System Disorders/ or neurosensory.mp.

20. exp Neurology/ or exp Sequelae/ or exp Nervous System Disorders/ or neurologic*.mp.

21. neuralgi*.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh]

22. exp Neuralgia/ or neuralgia.mp.

23. (nerve* adj4 (damag* or impair* or injur*)).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh]

24. exp Peripheral Nervous System/ or exp Peripheral Neuropathy/

25. 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24

26. 3 and 8 and 14 and 25

27. limit 26 to (english language and yr="1994 -Current")

Web of Science

11

670

#10 AND #9 AND #2 AND #1

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1994-2019

10

178,745

#8 OR #7 OR #6 OR #5

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1994-2019

9

445,666

#4 OR #3

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1994-2019

8

81,920

((ts=(adjuvant NEAR/4 (setting or treatment or chemotherapy or therapy or patient*)))) AND LANGUAGE: (English)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1994-2019

7

3,620

((ts=(oxaliplatin NEAR/4 (treat* or based or administ*)))) AND LANGUAGE: (English)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1994-2019

6

48,066

((((ts=("local* invasi*" or "local* advanc*" or non-metasta* or "non metasta*" or nonmetasta* or "without metasta*" or "no metasta*" or "not metasta*"))))) AND LANGUAGE: (English)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1994-2019

5

58,752

((((((ts=(stage-iii* OR stage-3* OR "stage III*" OR "stage 3*" OR "duke* C" OR "stage three" OR "third stage" OR stage-three OR third-stage)))))) AND LANGUAGE: (English)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1994-2019

4

65,380

((((ts=(nerve* NEAR/4 (damag* or injur* or impair* or peripheral)))))) AND LANGUAGE: (English)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1994-2019

3

401,448

(((((ts=(neuropath* or polyneuropath* or neurotoxic* or neurologic* or neuralgi* or neurosensory))))))) AND LANGUAGE: (English)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1994-2019

2

177,831

((((((ts=(adjuvant or oxaliplatin* or eloxatin* or fluox* or flox* or folfox* or xelox or capox or capeox)))))) AND LANGUAGE: (English)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1994-2019

1

249,118

((((ts=(colo* NEAR/4 (cancer* OR neoplasm* OR malignan* OR carcinoma* OR tumor* OR tumour*)))))) AND LANGUAGE: (English)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1994-2019

CINAHL

S22

S3 AND S8 AND S13 AND S21

Expanders - Apply equivalent subjects

Search modes - Boolean/Phrase

View Results (288) View Details Edit

S21

S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20

Expanders - Apply equivalent subjects

Search modes - Boolean/Phrase

View Results (124,052) View Details Edit

S20

nerve* N4 (damag* OR injur* OR impair* OR peripheral)

Expanders - Apply equivalent subjects

Search modes - Boolean/Phrase

View Results (13,666) View Details Edit

S19

(MM "Peripheral Nerves+")

Expanders - Apply equivalent subjects

Search modes - Boolean/Phrase

View Results (14,387) View Details Edit

S18

"neurosensory" OR neurologic*

Expanders - Apply equivalent subjects

Search modes - Boolean/Phrase

View Results (59,739) View Details Edit

S17

(MM "Neuralgia+") OR neuralgi*

Expanders - Apply equivalent subjects

Search modes - Boolean/Phrase

View Results (7,582) View Details Edit

S16

(MM "Neurotoxicity Syndromes+") OR neurotoxic*

Expanders - Apply equivalent subjects

Search modes - Boolean/Phrase

View Results (4,805) View Details Edit

S15

(MM "Polyneuropathies+") OR polyneuropath*

Expanders - Apply equivalent subjects

Search modes - Boolean/Phrase

View Results (6,862) View Details Edit

S14

(MM "Peripheral Nervous System Diseases+") OR neuropath*

Expanders - Apply equivalent subjects

Search modes - Boolean/Phrase

View Results (46,175) View Details Edit

S13

S9 OR S10 OR S11 OR S12

Expanders - Apply equivalent subjects

Search modes - Boolean/Phrase

View Results (32,265) View Details Edit

S12

Fluox* OR flox* OR folfox* OR xelox OR capox OR capeox

Expanders - Apply equivalent subjects

Search modes - Boolean/Phrase

View Results (3,315) View Details Edit

S11

"eloxatin"

Expanders - Apply equivalent subjects

Search modes - Boolean/Phrase

View Results (306) View Details Edit

S10

(MM "Oxaliplatin") OR "oxaliplatin*"

Expanders - Apply equivalent subjects

Search modes - Boolean/Phrase

View Results (2,670) View Details Edit

S9

(MM "Chemotherapy, Adjuvant+") OR "adjuvant"

Expanders - Apply equivalent subjects

Search modes - Boolean/Phrase

View Results (27,524) View Details Edit

S8

S4 OR S5 OR S6 OR S7

Expanders - Apply equivalent subjects

Search modes - Boolean/Phrase

View Results (2,727,872) View Details Edit

S7

adjuvant N4 (setting or treatment or chemotherapy or therapy or patient*

Expanders - Apply equivalent subjects

Search modes - Boolean/Phrase

View Results (2,688,969) View Details Edit

S6

(oxaliplatin N4 (treat* or based or administ*))

Expanders - Apply equivalent subjects

Search modes - Boolean/Phrase

View Results (962) View Details Edit

S5

"local* invasi*" OR "local* advanc*" OR non-metasta* OR "non metasta*" OR nonmetasta* OR "without metasta*" OR "no metasta*" OR "not metasta*"

Expanders - Apply equivalent subjects

Search modes - Boolean/Phrase

View Results (77,889) View Details Edit

S4

stage-iii* OR stage-3* OR "stage III*" OR "stage 3*" OR "duke* C" OR "stage three" OR "third stage" OR stage-three OR third-stage

Expanders - Apply equivalent subjects

Search modes - Boolean/Phrase

View Results (104,170) View Details Edit

S3

S1 OR S2

Expanders - Apply equivalent subjects

Search modes - Boolean/Phrase

View Results (40,037) View Details Edit

S2

(MM "Colonic Neoplasms+")

Expanders - Apply equivalent subjects

Search modes - Boolean/Phrase

View Results (6,362) View Details Edit

S1

colo* N4 (cancer* OR neoplasm* OR malignan* OR carcinoma* OR tumor* OR tumour)

Expanders - Apply equivalent subjects

Search modes - Boolean/Phrase

View Results (39,638)

Cochrane

colo* NEAR/4 (cancer* OR neoplasm* OR malignan* OR carcinoma* OR tumor* OR tumour*) in Title Abstract Keyword AND stage-III* OR stage-3* OR stage III* OR “stage 3*” OR “duke* C” OR “stage three” OR “third stage” OR stage-three OR third-stage OR "local* invasi*" OR "local* advanc*" OR nonmetasta* OR "non-metasta*" OR "non metasta*" OR "not metasta*" OR "no metasta*" OR "without metasta*" OR (oxaliplatin NEAR/4 (treat* OR based OR administ*)) OR (adjuvant NEAR/4 (setting OR treatment OR chemotherapy OR therapy OR patient*)) in Title Abstract Keyword AND adjuvant OR oxaliplatin* OR eloxatin* OR fluox* OR flox* OR folfox* OR xelox OR capox OR capeox in Title Abstract Keyword AND neuropath* OR polyneuropath* OR neurotoxic* OR neurosensory OR neurologic* OR neuralgi* OR (nerve* NEAR/4 (damage* OR impair* OR injur* OR peripheral)) in Title Abstract Keyword - with Cochrane Library publication date Between Jan 1994 and Dec 2019 (Word variations have been searched)

Appendix 3

NCI-CTCAE Raw data

At six months

Author, year	Sample	Any grade	Grade-I	Grade-II	Grade-III
Andre, 2004	1058	434	338	82	14
Land, 2007	1235	865	.	.	.
Lee, 2009	159	.	.	.	2
Storey, 2010	54	31	18	5	8
Park, 2015	1548	604	.	.	118
Kim, 2018	36	29	20	5	4
Number of studies contributing data		5	3	3	5

At twelve months

Author, year	Sample	Any	Grade-I	Grade-II	Grade-III
Andre, 2004	1018	300	240	49	11
Land, 2007	1013	295	242	48	5
Lee, 2009	159	.	.	.	0
Storey, 2010	63	22	3	2	5
Park, 2015	1548	381	.	.	45
Tanishima, 2017	47	22	.	.	.
Kim, 2018	36	23	18	1	4
Number of studies contributing data		6	4	4	6

At Long-term

Author, year	Sample	Any	Grade-I	Grade-II	Grade-III
Andre, 2004	967	229	191	33	5
Park, 2011	24	19	9	7	3
Vatandoust, 2014	27	17	5	9	3
Padman, 2015	18	9	5	1	3
Dault, 2016	10	7	4	2	1
Number of studies contributing data		5	5	5	5

Appendix 4

Decisions on how values of Nodes (N) found in the Cancer Registry data were treated

Values found in the data	Decision how to treat in the analysis	Notes
Missing	Missing	
+	1	+ assumed to mean positive lymph nodes
0	0	
"00"	0	
1	1	
1a	1	
1b	1	
1c	1	
1mi	1	
1P	1	Not possible to determine what letter stands for, therefore letter is ignored, only number taken into account
2	1	
2a	1	
2b	1	
2P	1	Not possible to determine what letter stands for, therefore letter is ignored, only number taken into account
3	1	
3a	1	
3P	1	
4	1	
9	Missing	9 is a commonly used number to denotes missing values
10	Missing	
11	Missing	

N0	0	Not possible to determine what letter stands for, therefore letter is ignored, only the number is considered
P0	0	
P1	1	
P2	1	
X	Missing	

Decisions on how values of Metastasis (M) found in the Cancer registry data were treated

Values found in the data	**Decision how to treat in the analysis**	**Notes**
Missing	Missing	
0	0	
1	1	
1a	1	
1b	1	
1c	1	
1e	1	
2	1	
3	1	
9	Missing	9 is a commonly used number to denote missing values
P	Missing	Not possible to determine what letter stands for
X	Missing	
Y	Missing	

Appendix 5

OPCS codes used to identify patients who underwent resectional surgery for colon cancer

H01.1	Emergency excision of abnormal appendix and drainage HFQ
H01.2	Emergency excision of abnormal appendix NEC
H01.3	Emergency excision of normal appendix
H01.8	Other specified emergency excision of appendix
H01.9	Unspecified emergency excision of appendix
H02.1	Interval appendicectomy
H02.2	Planned delayed appendicectomy NEC
H02.3	Prophylactic appendicectomy NEC
H02.4	Incidental appendicectomy
H02.8	Other specified other excision of appendix
H02.9	Unspecified other excision of appendix
H04.1	Panproctocolectomy and ileostomy
H04.2	Panproctocolectomy and anastomosis of ileum to anus and creation of pouch HFQ
H04.3	Panproctocolectomy and anastomosis of ileum to anus NEC
H04.8	Other specified total excision of colon and rectum
H04.9	Unspecified total excision of colon and rectum
H05.1	Total colectomy and anastomosis of ileum to rectum
H05.2	Total colectomy and ileostomy and creation of rectal fistula HFQ
H05.3	Total colectomy and ileostomy NEC
H05.8	Other specified total excision of colon
H05.9	Unspecified total excision of colon
H06.1	Extended right hemicolectomy and end to end anastomosis
H06.2	Extended right hemicolectomy and anastomosis of ileum to colon
H06.3	Extended right hemicolectomy and anastomosis NEC
H06.4	Extended right hemicolectomy and ileostomy HFQ
H06.5	Extended right hemicolectomy and end to side anastomosis
H06.8	Other specified extended excision of right hemicolon
H06.9	Unspecified extended excision of right hemicolon
H07.1	Right hemicolectomy and end to end anastomosis of ileum to colon
H07.2	Right hemicolectomy and side to side anastomosis of ileum to transverse colon
H07.3	Right hemicolectomy and anastomosis NEC
H07.4	Right hemicolectomy and ileostomy HFQ
H07.5	Right hemicolectomy and end to side anastomosis
H07.8	Other specified other excision of right hemicolon
H07.9	Unspecified other excision of right hemicolon
H08.1	Transverse colectomy and end to end anastomosis

H08.2	Transverse colectomy and anastomosis of ileum to colon
H08.3	Transverse colectomy and anastomosis NEC
H08.4	Transverse colectomy and ileostomy HFQ
H08.5	Transverse colectomy and exteriorisation of bowel NEC
H08.6	Transverse colectomy and end to side anastomosis
H08.8	Other specified excision of transverse colon
H08.9	Unspecified excision of transverse colon
H09.1	Left hemicolectomy and end to end anastomosis of colon to rectum
H09.2	Left hemicolectomy and end to end anastomosis of colon to colon
H09.3	Left hemicolectomy and anastomosis NEC
H09.4	Left hemicolectomy and ileostomy HFQ
H09.5	Left hemicolectomy and exteriorisation of bowel NEC
H09.6	Left hemicolectomy and end to side anastomosis
H09.8	Other specified excision of left hemicolon
H09.9	Unspecified excision of left hemicolon
H10.1	Sigmoid colectomy and end to end anastomosis of ileum to rectum
H10.2	Sigmoid colectomy and anastomosis of colon to rectum
H10.3	Sigmoid colectomy and anastomosis NEC
H10.4	Sigmoid colectomy and ileostomy HFQ
H10.5	Sigmoid colectomy and exteriorisation of bowel NEC
H10.6	Sigmoid colectomy and end to side anastomosis
H10.8	Other specified excision of sigmoid colon
H10.9	Unspecified excision of sigmoid colon
H11.1	Colectomy and end to end anastomosis of colon to colon NEC
H11.2	Colectomy and side to side anastomosis of ileum to colon NEC
H11.3	Colectomy and anastomosis NEC
H11.4	Colectomy and ileostomy NEC
H11.5	Colectomy and exteriorisation of bowel NEC
H11.6	Colectomy and end to side anastomosis NEC
H11.8	Other specified other excision of colon
H11.9	Unspecified other excision of colon
H29.1	Subtotal excision of colon and rectum and creation of colonic pouch and anastomosis of colon to anus
H29.2	Subtotal excision of colon and rectum and creation of colonic pouch NEC
H29.3	Subtotal excision of colon and creation of colonic pouch and anastomosis of colon to rectum
H29.4	Subtotal excision of colon and creation of colonic pouch NEC
H29.8	Other specified subtotal excision of colon
H29.9	Unspecified subtotal excision of colon
H33.1	Abdominoperineal excision of rectum and end colostomy
H33.2	Proctectomy and anastomosis of colon to anus
H33.3	Anterior resection of rectum and anastomosis of colon to rectum using staples
H33.4	Anterior resection of rectum and anastomosis NEC

H33.5	Rectosigmoidectomy and closure of rectal stump and exteriorisation of bowel
H33.6	Anterior resection of rectum and exteriorisation of bowel
H33.7	Perineal resection of rectum HFQ
H33.8	Other specified excision of rectum
H33.9	Unspecified excision of rectum
X14.1	Total exenteration of pelvis
X14.2	Anterior exenteration of pelvis
X14.3	Posterior exenteration of pelvis
X14.8	Other specified clearance of pelvis
X14.9	Unspecified clearance of pelvis

Appendix 6

A list of treatments received by stage III colon cancer patients in addition to single and combination adjuvant chemotherapy

Single therapy		Combination therapy	
Name of medication	**Number of patients that received this medication**	**Name of medication**	**Number of patients that received this medication**
ABIRATERONE	1	ABIRATERONE	4
AFLIBERCEPT	8	AFATINIB	3
BENDAMUSTINE	1	AFLIBERCEPT	12
BEVACIZUMAB	53	ANASTROZOLE	1
CABAZITAXEL	1	AXITINIB	1
CARBOPLATIN	7	BCG	3
CETUXIMAB	81	BENDAMUSTINE	1
CHLORAMBUCIL	1	BEVACIZUMAB	135
CISPLATIN	8	BICALUTAMIDE	2
CYCLOPHOSPHAMIDE	4	BORTEZOMIB	3
DENOSUMAB	2	BUSULFAN	1
DOCETAXEL	2	CABAZITAXEL	1
ENZALUTAMIDE	2	CABOZANTINIB	1
EPIRUBICIN	3	CARBOPLATIN	19
ETOPOSIDE	2	CETUXIMAB	169
FLUDARABINE	1	CHLORAMBUCIL	1
FOLINIC ACID	58	CISPLATIN	17
GEMCITABINE	2	CRIZOTINIB	1
HYDROXYCARBAMIDE	1	CYCLOPHOSPHAMIDE	19
IMATINIB	1	CYTARABINE	1
IPILIMUMAB	1	DENOSUMAB	2
IRINOTECAN	235	DEXAMETHASONE	33
MITOMYCIN	4	DOCETAXEL	13
NIVOLUMAB	1	DOXORUBICIN	8
PAMIDRONATE	1	ENZALUTAMIDE	5
PANITUMUMAB	10	EPIRUBICIN	8
PAZOPANIB	1	ERIBULIN	1
PEMBROLIZUMAB	1	ETOPOSIDE	10
PEMETREXED	2	EVEROLIMUS	1
PERTUZUMAB	1	FLUCONAZOLE	2
RALTITREXED	3	FOLINIC ACID	266
RITUXIMAB	3	FULVESTRANT	3
RUXOLITINIB	1	GEMCITABINE	6
STEROID	141	GOSERELIN	1
TRASTUZUMAB	4	HYDROCORTISONE	1
VINORELBINE	1	HYDROXYCARBAMIDE	1
ZOLEDRONIC ACID	3	IBRUTINIB	2
		IMATINIB	4
		INOTUZUMAB OZAGAMICIN	1
		IRINOTECAN	413
		LANREOTIDE	1
		LENALIDOMIDE	4
		MELPHALAN	1
		MESNA	3
		MITOMYCIN	14
		NAB-PACLITAXEL	1
		NIVOLUMAB	1
		PACLITAXEL	9

		PAMIDRONATE	2
		PANITUMUMAB	30
		PAZOPANIB	1
		PEMBROLIZUMAB	4
		PEMETREXED	2
		PERTUZUMAB	1
		RALTITREXED	25
		RITUXIMAB	15
		RITUXIMAB BIOSIMILAR (TRUXIMA)	1
		STEROID	2681
		THALIDOMIDE	2
		TRASTUZUMAB	9
		TRASTUZUMAB EMTANSINE	3
		TRIFLURIDINE–TIPIRACIL	1
		TRIFLURIDINE TIPIRACIL	11
		VINCRISTINE	10
		VINORELBINE	7
		ZOLEDRONIC ACID	5

Appendix 7

Recruitment Advertisement

You are invited to participate in a research study being done as part of a PhD degree conducted jointly at Birkbeck College and the London School of Hygiene and Tropical Medicine, University of London.

The aim of the study is to understand what factors stage III CRC patients feel are important for them to consider when deciding whether or not to accept treatment with chemotherapy, such as Oxaliplatin.

According to statistics from Cancer Research UK, about 40,000 people get diagnosed with bowel cancer in the UK every year, with about 22-25% of which diagnosed at stage III of the disease.

Treatment for colorectal cancer patients at stage III of the disease often consists of surgical resection of the tumour, followed by chemotherapy. There is no standard chemotherapy regimen. Patients often have to decide whether to take a single drug to reduce the chance of the disease coming back, or a combination of drugs that may include an agent called Oxaliplatin. Adding Oxaliplatin to the chemotherapy regimen further reduces the chance of the disease coming back but may cause long term consequences like neuropathy (weakness, numbness, or pain in the hands and feet).

You are invited to participate in this study if you have been diagnosed with stage III colorectal cancer and underwent surgery to remove the tumour. It does not matter whether or not you have received chemotherapy after surgery, and if you have, it does not matter what kind of chemotherapy you received. We would also like to hear from you if you are experiencing any complications caused by receiving chemotherapy.

All the information you provide will be completely anonymous, treated with the utmost confidence, and will not be used for purposes other than the current study.

This study has been given ethical approval by the Department of Psychological Sciences' Ethics Committee, Birkbeck University of London.

If you would like to participate or ask questions, please contact the investigator on the details provided below.

Dr Syreen Hassan

syreen.hassan@lshtm.ac.uk

Tel: 020 7079 0836

The study is supervised by Dr Anne Miles. If you wish to contact the supervisor, please find contact details below:

ae.miles@bbk.ac.uk

Department of Psychological Sciences, Birkbeck University of London, Malet St, London WC1E 7HX

Tel: 020 7631 6488

Appendix 8

Participant Information Sheet

Thank you for your willingness to participate in this study.

My name is Syreen Hassan. I am a medical doctor, and I am currently a PhD Student at Birkbeck College and The London School of Hygiene and Tropical Medicine in London.

As per the posted invitation that you are responding to, for this study we would like to hear from individuals who were diagnosed with colorectal cancer at **stage 3**, who underwent **surgery to remove the tumour**, and who were offered chemotherapy after surgery.

Before you decide to take part in this study, it is important for you to understand why the research is being done and what it will involve so you can make an informed choice about taking part.

Please ask questions if there is anything that is not clear or if you would like more information. You do not have to decide whether or not you wish to take part right away. Please take one to two days to think about it or discuss it with others and contact me when you have decided.

Background and purpose of the study:

Colorectal cancer (CRC) is very common among men and women in the UK, and a large proportion of people get diagnosed at stage III. The standard treatment for all stage III CRC patients is surgical resection of the tumour followed by chemotherapy, and this can be either by taking a single agent, or a combination that includes Oxaliplatin, each with advantages and disadvantages. The decision about whether or not to take chemotherapy, and if so, whether or not to take one drug or two, poses different difficulties for different people and will depend on how much someone knows about the disease, the different options, and the factors that are important to each person.

I would like to hear your personal story and experience with regards to how the decision was made on whether or not to receive chemotherapy, the type of chemotherapy to receive, the reasons why you decided one way or the other, how you feel about your decision now, and whether you feel there are areas you required additional support while making the decision.

If you developed neuropathy as a result of therapy, I would like to also know what it is like to be living with peripheral neuropathy, what is it that you find most difficult, and whether there were things that had you known in advance would have changed your decision.

The information I gather from you and others who will participate in this research will be used to inform future studies that will help other patients consider important physical, emotional, or social factors that may initially be difficult to contemplate or articulate at the time of the decision but which can ultimately influence the decision.

Explanation of what taking part involves: what will happen to me if I take part?

Taking part in this research means agreeing to an in-depth interview, which may last up to 60 minutes. The interview will be semi-structured. This means that there is no set of questions that I will be asking you to answer. Instead, I would like you to think of this as having a conversation. I am interested in hearing your story and your experience, however way you would like to tell it. I would like you to tell me about your experience of having to decide whether or not to receive chemotherapy after your surgery, starting from when your doctor told you this is what will be required after your surgery, to when you made the decision. What was the process that you went through to reach the decision, what did you think about, who did you talk to, and how did you feel?

I may ask you some questions from time to time to guide the conversation or ask you to clarify or expand on certain points.

If you feel that the nature of this interview will be difficult for you and may cause you to be upset, you are free to express that and decide not to take part.

What are the possible benefits from taking part?

Research done previously to understand how people who face different treatment options make their decisions showed that peoples' preferences for which option to choose are often formed as they develop a better understanding of what it means to undergo each of the options and become clearer about what is important to them.

Sharing your experience may help other patients who are facing this decision by bringing their attention to factors that would be important for them to think about. It will also help them better understand what is means to live with long term consequences such as neuropathy.

What are the possible disadvantages/risks from taking part?

During the interview, I may ask you to discuss something that you may find difficult or may cause you to feel upset. You will not have to discuss anything that you do not feel

comfortable with. You can refuse to answer any questions at any time. You can also stop the interview at any time without a reason.

If the discussion raises any concerns, whether emotional, social, or financial, or causes you to feel distressed, there are ways in which you can seek support.

The ***Macmillan Free Cancer Support*** includes a range of support services including information and counsellors that you can speak to. You can reach them on this free phone number: 0808 808 00 00 from 9am to 8pm Monday to Friday. You can also visit their website on www.macmillan.org.uk to see the range of services they offer.

You are also entitled to ***free mental health services through the NHS*** and can speak to the GP you are registered with for a referral. If you would like to seek any of these support services but preferred if this was arranged for you, please let me know and I can do so on your behalf if you wish.

I will work to keep any discomfort felt during the discussions to a minimum.

What happens if I don't want to take part in the interview, or want to withdraw from the study after taking part?

You are free to decide if you want to take part in the interview. If you decide not to take part, or if you wish to withdraw from the study after having taken part in the interview, this will not affect you in any way. It also does not stop you from receiving any services or benefits that you normally receive.

How will my information be kept confidential?

All efforts will be made to keep your personal information confidential.

If you decide to participate in this study, you will need to contact me again to inform me of your decision, provide me with your availability for an interview, and with the telephone number I can use to call you on the agreed interview date.

Your name and e-mail address or phone number will be kept in a spreadsheet that will only be accessible to me and my two supervisors. The spreadsheet itself will be password protected, and on a password protected, computer with an encrypted hard drive. This information will only be kept for the purpose of calling you for the interview on the agreed interview date. Once the interview is finished, I will immediately delete this information.

I will call you using the number your give me on the agreed interview date. This call will be recorded. First, you will be asked to state your name and give your consent to participate in the study. I will read several statements to you to which I would like you to

answer with a yes if you agree or a no if you disagree. We will start the interview after the consent. The recording will be stopped after the consent and will be started again for the interview. That way the consent recording, which will contain your full name, can be separated from the recording of the rest of the interview, during which we will only use your first name. This will allow me to store the two recordings separately, on different password protected computers, so that the information you provide in the interview cannot be linked to your name.

The interview recordings will then be transcribed to written documents. No personal information will be transferred to the written documents, including your first name. The written documents will be saved on a password protected computer along with the interview recordings, separate from the consent recordings, and therefore cannot be linked to your full name.

These recordings and the written documents will be kept for a maximum of ten years, for the full duration of my PhD study, and to allow time for publication.

What will happen to the results of the study?

The findings of this study may be used for publication, or in conferences. Results are normally presented in terms of groups of individuals. If any individual data are presented, the data will be anonymous, without any means of identifying the individuals involved.

You are able to withdraw your data up to the point of publication. Once the data has been published, you will no longer be able to withdraw.

Who is organising and funding this study?

The Bloomsbury Colleges PhD Studentships programme. The Bloomsbury Colleges group was set up in 2004 and currently consists of 5 Higher Education Institutions. They provide research opportunities for people who wish to pursue a PhD degree. I have been awarded a Bloomsbury Colleges PhD Studentship to conduct this research.

Ethical review of the study:

All research on human volunteers is reviewed by ethics committee. They protect the rights and welfare of the people taking part in the research. This research has received ethical approval from the Department of Psychological Sciences Research Ethics Committee of Birkbeck College, University of London. If you have questions or concerns about your rights as a research participant you may contact the Department of Psychological Sciences Research Ethics Committee of Birkbeck College. You can do this anonymously if you wish.

Appendix 9

Consent Form

Please state for the record your name and date today.

Please agree with a yes or disagree with a no after each statement

- You have read the Patient Information Sheet and willingly consent to take part. You had the opportunity to ask questions and are aware that you can ask questions at any time. The questions you asked have been answered to your satisfaction.
- You understand that you can withdraw your consent for the study at any time without giving a reason, you can decline to answer questions, and you can withdraw your data up to the point of publication.
- You understand that all the information you provide, the audio recordings and the transcripts of the interview, will be confidential, will not be used or made available for any purposes other than the research project, will only be accessible to myself and my two supervisors.
- You understand how your personal information, the audio recordings and the transcripts will be handled, stored, and for how long; and how the results of the study will be used.
- You understand that if this interview causes you any distress, you can find support through the McMillan support group, you can contact your GP for referral to mental health services, and I can contact support services on your behalf if you prefer.
- You confirm that you are over 16 years of age.

Appendix 10

Free codes

Code	Example Quotes
'Accepting what I was told'	“I was just really accepting what my oncologist was telling me that it would be alright, and everything will be fine. I never questioned that it may not be fine. I just accepted everything. I was just… my mindset was, if they say it's going to be fine, it's going to be fine. And I just went on and accepted it all” Participant 1
Perception of self when accepting without questioning	“…if he told me two and two were five, I would have accepted it, which is very, very much unlike me now” Participant 1
'Enough to deal with'	“I didn't research chemotherapy because I didn't really want to know I had enough to deal with the diagnosis and the surgery and the little that I did know about chemotherapy was enough I couldn't cope with more information about that...” Participant 4
'Getting on with life’	“…to make sure that I got over this and then I can put it behind me and get on with life.” Participant 3
'I had to do it'	“I did talk to other people about it but I just knew I had to do it so it didn't really matter, you know, what people's bad experiences were I just knew I had to do it” Participant 2
'No discussion' with oncologist	“So, there wasn't a lot of discussion around the chemotherapy, it was just you are having chemotherapy, you're too young, and if I didn't have it the cancer will just come back. So yeah, there wasn't really much discussion around chemotherapy” Participant 2
'They are the experts'	“we very much were of the same view that you know if they offered you chemotherapy, they are the experts, you know” Participant 4
'They' decided or 'they wanted'	“I thought I’m sure it has been discussed and they decided that this is the best treatment for me or else it wouldn’t have been offered to me” Participant 4
Concerns relating to chemotherapy or side effects	“I think, the fact that I was told some of the side effects might not go away because of the treatment that was one thing I was a bit concerned about” Participant 3
Feeling about the treatment decision after treatment	“ I would probably make the same decision again” Participant 1 “I don’t know if I really had time to reflect on it [participant pauses] and the impact on my hands, if my hands hadn't improved, if they had got worse through till January and then hadn't started to improve I think I would feel a very different story, but because my hands had improved [participant pauses], but it's just the fact that there are no guarantees and they can't tell you whether your hands will improve or how much will improve and it's the unknown is the hardest thing to get your head around” Participant 4
Dealing with family and other life events	“I was dealing with my father’s death. I was dealing with sorting out the estate for my mother because she couldn't cope with it and getting my husband to deal with it. My daughter was in her last year at uni, and she was in the middle of her dissertation when my father died, and then obviously I was diagnosed with cancer and I was dealing with sorting through making sure that she was coping […] I had plenty of other things to deal with rather than worry about chemo or length of time or anything like that”

	Participant 1
Coping with stoma or complications of surgery	“I didn't research chemotherapy because I didn't really want to know I had enough to deal with the diagnosis and the surgery and the little that I did know about chemotherapy was enough I couldn't cope with more information about that” Participant 4
Neuropathy	“I had grade, I think I had grade 2 neuropathy, as soon as I had my first session of FOLFOX, I walked down to the toilet afterwards to go to the loo on the way out and I remember running my hands under the tap and they started to tingle straight away” Participant 2
Different physicians involved in care	“I saw the oncologist first of all, but she wasn't my actual oncologist, she was like, what do you call it, she was like filling in, so the initial consultation where she told me what chemotherapy I would be having, and the second consultation was with my actual […] the oncologist, so the second oncologist that I saw was Dr. E and she was the one who said, told me exactly what was going to happen” Participant 2
Busy hospital	“Went to [the] Cancer Centre and I was really, got smacked when I walked in I mean that part of the hospital is just dedicated to cancer treatment and I was absolutely awed at the amount of people who were in there” Participant 2
First consultation with oncologist	“we had a little bit of conversation, she told me in that conversation that my tumour has burst, and that was another reason, and then I started to cry, and I said nobody has ever told me that, and then she looked at her computer and she was like oh I’m so sorry that was actually the last person the last patient that came in that wasn't you. So, I was more upset about that, that was a shock really. So, I kind of walked away from that not feeling too much, knowing that that was the initial meeting and that there would be another meeting which would be with my oncologist and also one of the colorectal nurses, and in that meeting my husband came in with me” Participant 2
Experience with the surgical specialty	“the surgeon when I first saw her, she discussed everything and told us everything, she's quite different” Participant 3
Fear of cancer	“I just wanted to, I just, I was just worried about not living I just didn't want to die. You know, I was so concerned about dying from this that I was very, very frightened into my mind” Participant 1
Feelings about diagnosis	“the colorectal specialist nurse gave me a call which was actually a great shock when she first called because I hadn't actually accepted that it was cancer at that point, I was so hopeful that it wasn't because I was, I didn't have any symptoms” Participant 4
Feelings about information	“I went to see the oncologist and he explained which chemotherapy I would be on and he explained some of the side effects and also gave me something like 6 sheets of paper with all the possible, or some of the possible side effects which was really quite daunting to get that and you couldn't help but look at the sheet and think am I going to get them all or, you wouldn't want to be hopeful that you would have none because that wasn't realistic but it was really difficult to find the balance with that” Participant 4
Having family history	“My father actually died the day before and he had died of colon cancer. So I was very aware that I already last one person in my family who I was very close to and I was just very petrified” Participant 1
How diagnosis was reached	“I was diagnosed after an A&E admission. So, I walked into A&E after being poorly. I was, first of all they did an X ray because they, I had a distended bowl, my tummy has blown up. So they did an X-Ray first of all and then they did a CT scan and then following a CT scan they said to me there is

	definitely a mass and then I had a colonoscopy, which confirmed that it was cancer, they didn't take any biopsies but they just knew. So, they said to me we are treating you for bowel cancer. I then had, so I was admitted to hospital because I actually had a blockage." Participant 2
Decision on reduction of treatment	"No, the doses were adjusted because the second treatment I had, I did have a bad reaction I got very distressed and I couldn't breathe and so they turned it right down and I think they made the Oxaliplatin about 75% so instead of a 2 hour treatment I went to a 4-hour treatment, but no apart from that I think the fact that I presented myself on a Wednesday morning I was carrying on, nobody ever said to me do you want to carry on, I didn't have to sign any other consents nobody ever said this is too bad you could consider stopping" Participant 3
How treatment decision was made	"I don't actually remember a huge amount about it you know he just explained that it was mop up chemo and that it was the XELOX combination that I was having he explained that it would be an IV" Participant 4
Written information	"she did give me a leaflet, it said what chemotherapy I was going to be having, what were some of the side effects were, there were some links to help lines and things like that" Participant 2
Information about diagnosis	"It was my husband actually who told me I had stage III bowel cancer. I came out of hospital with a letter and it said, what my staging was, and they didn't even discuss with me what any of it meant, I didn't know what the numbers or letters meant, I didn't know anything, it was actually my husband that sat down and said you know you've got stage 3 bowel cancer, and, I mean at that point we didn't know how many lymph nodes it was in" Participant 2
Information about neuropathy	"I knew it was one of the main ummm, side effect of that drug, ummm, but as I said I thought it was the shooting pain going up your legs, it was more your legs I had thought, because my husband is a diabetic so I had slight knowledge, he doesn't have peripheral neuropathy but I knew that that's a long term trouble of diabetics, I knew a little bit about it, but I had just thought it was a pain shooting up your legs I didn't realise it was numbness and tingling" Participant 4
Information about other elements of care	"I always see the doctor to discuss the blood tests that I had done the week before… before I went for the chemotherapy on the Wednesday, and I did feel that I had to keep on asking to get any information she would say your bloods were fine and I would say well tell me what the numbers were could you give me a print out and she wouldn't give me a printout she said she couldn't and I'm not quite sure why she couldn't because I'm sure she could have done" Participant 3
Information about side effects	"I didn't really know what the side effects are going to be. I'm not sure whether the, I'm not sure whether, I don't think the chemotherapy doctor told me anything much about the side effects" Participant 3
Information about treatment benefit	"She did show us a print out of a computer program she had which she had put in all of my details and what my situation was and say what my chances were, are, of surviving 5 years and it was improved by about 6.9% if I had the chemotherapy and then she sent us away to think about it" Participant 3
Need for more information	"it was only afterwards and hindsight I thought actually I wish I had been given more information." Participant 10
Need for repeat meetings with oncologist	"I kind of walked away from that not feeling too much, knowing that that was the initial meeting and that there would be another meeting which would be

	with my oncologist and also one of the colorectal nurses, and in that meeting my husband came in with me” Participant 2
Need for support	“Although I had the oncology specialist nurse, I didn't ever feel well supported with them at all […] it's more the support in general which may well involve percentages and the likelihood of things cropping up, but its more the general support I think is more important” Participant 4
Need to ask more questions	“the one thing I feel strong about is the oncologist specialist nurses I would have preferred if they phoned you more regular basis not to tell you what the next step of treatment is but just to have a general chat and listen to you, and during that conversation there might be questions that crop up, and you know, if we had a long conversation like I'm having with you today about peripheral neuropathy and the side effects and the percentages I might well have said during that conversation well what are the percentages?” Participant 4
No previous knowledge about cancer or chemotherapy	“…at that time, I knew nothing. I never come across anyone. I didn't know anyone who had chemotherapy and I wasn't aware that I could turn around and say no I don’t want it.” Participant 1
Not asking questions about treatment	“I just sort of became very matter of fact, and I believed everything that I was told I didn't question at that time anything” Participant 1
Not wanting to involve family	“I saw my oncologist myself, I didn't have anyone with me, I never take people in with me when I see anybody so it's… it's based on my feelings of the person who's talking to me what they are telling me and how much I feel that I can trust them to make the right decision… I trust my husband but he wasn't there he didn't have the discussion with the doctor maybe on hindsight he should come in but it was just me and me alone… I wanted to deal with all this and take the worrying and concern away from everybody else” Participant 1
Oncologists' explanation for recommending chemotherapy	“I don't actually remember a huge amount about it you know he [oncologist] just explained that it was mop up chemo” Participant 4
Other experiences with healthcare	“A couple of times they, they have the helpline they could phone and a couple of times I did need help because I had lots of trouble with my mouth, and they didn't always phone me back I had to leave a message with someone or leave an answer phone message and there was one time when I had to phone twice before I got anyone to phone me back” Participant 3
Perception of chemotherapy	“I didn’t really comprehend the different chemotherapy I had just thought chemotherapy is chemotherapy possibly with different names within it but I haven’t, I just thought, I didn’t realise that different drugs have different effects” Participant 4 “…[chemotherapy] will make sure there is no cancer left” (Participant 4)
Pre-cancer condition	“I hadn't actually accepted that it was cancer at that point I was so hopeful that it wasn't because I was, I didn't have any symptoms” Participant 4 “…so I sat there feeling really really healthy, surrounded by people that look really ill and it was it was quite upsetting” Participant 20
Reasons for taking chemotherapy	“we wanted to take every chance possible” Participant 3
Role of family	“He [husband] came to the appointments with me, for the oncologist, he came to all of the appointments with me, I don't know, we didn't discuss, I

	don't remember discussing much with him we obviously talked about my worries and concerns and his worries and concerns" Participant 2
Support groups, charities, online forums	"I did go to a charity Penny Brohn, and we went on a couple of courses about living well with cancer and living well with chemotherapy then and they were very supportive, and they looked after me and my husband." Participant 3
Surgeon recommending chemotherapy	"…it's actually my surgeon who said you're going to be having chemotherapy. So, he actually said that to me in the hospital when I was first diagnosed, we're going to take this out, and then you're going to have chemotherapy" Participant 2
The option for type of therapy	"we didn't have any choice about what chemotherapy it was going to be, she just told me what I would have if I had it and the fact that I would have 8 three week cycles" Participant 3
The option to refuse chemotherapy	"I didn't know I had an option to refuse [chemotherapy] at the time" Participant 1 "…so I went back and said yes, I would like the chemotherapy and, umm, it started in the middle of June" Participant 3
Time to gain or process information about chemotherapy	"I hadn't had time to absorb what the oncologist had said and I hadn't had time to go home and read the leaflets and although on the face of it I was always going to take chemo if that was what was recommended I just felt that I wasn't prepared" Participant 4
Time from diagnosis to treatment	" I remember getting a letter when we were on holiday to go for sort of like for a pre-assessment and I missed the date and I was really upset because I was thinking I need to have this chemotherapy quickly I don't want to be waiting another week and they managed to bring my date forward to start it" Participant 2
Trust or faith in doctors	"from the very first appointment I put my complete faith in the consultants who had years of training and experience" Participant 4
Visit to chemotherapy ward before start of treatment	"the cancer nurse brought me upstairs, because it was, I was in the hospital where I had the chemotherapy so she took me up to the chemotherapies suite and we had a little look around and she said look everybody is fine in here and they, they, you know, everyone is having treatment and is ok" Participant 2

Main themes (based on topic and events or timing of events)

At this stage, free codes were re-organised under main themes based on topic or events and timing of events: the treatment decision, family, feelings, information, leading up to chemotherapy, neuropathy, other experiences with healthcare, Support groups, charities, online forums, time.

Highlighted categories are those that emerged in addition to free codes shown above.

Arrows within a category represent merging and re-naming of categories.

The treatment decision
'Accepting what I was told'

Perception of self when accepting without questioning
Discussion with oncologist
'No discussion' with oncologist
'They' decided or 'they wanted'
Asking/not asking questions about treatment
Concerns relating to chemotherapy or side effects
First consultation with oncologist
Decision on duration of treatment
Decision on reduction of treatment
Oncologist recommendation for chemotherapy/framing of chemotherapy
Patients' reasons for receiving chemotherapy
Desire to receive chemotherapy not influenced by knowledge of side effects
Perceptions of chemotherapy
The option for type of chemotherapy
The option to refuse chemotherapy
Trust or faith in doctors
'They are the experts'
Different physicians involved in care
Different sources of information
Wanting to avoid neuropathy
How the treatment decision was made
'I had to do it'
No previous knowledge about cancer or chemotherapy
Need to ask more questions
Family
Family history of colon cancer
Not wanting to involve family
Role of family through diagnosis and treatment
Feelings
Feelings about diagnosis
Feelings about discussions with oncologists
Feelings about information
Feeling prepared and knowing what to expect
Feelings about interaction with doctors and nurses
Feelings about treatment decision after treatment
Information
Written information
Information about diagnosis
Information about neuropathy
Information about other elements of care
Information about side effects
Information about treatment benefit
Need for more information
Leading up to chemotherapy

Experience with the surgical specialty
Not thinking about chemotherapy
'Enough to deal with'
Coping with family and life events
Coping with stoma or complications of surgery
How diagnosis was reached
Pre-cancer condition
'Getting on with life' → Wanting to get back to normal life
Surgeon recommending chemotherapy
Neuropathy
Other experiences with healthcare
Need for support from specialist nurses → Specialist nurses
Busy hospital or clinic
Visit to chemotherapy ward before start of treatment
GPs
Helpline
Support groups, charities, online forums
Time
Time to gain and process information about chemotherapy
Need for repeat meetings with oncologist
Time from diagnosis to treatment

Main themes (based on events and timing of events)

At this stage, themes that were based on topic were re-organised under the events or timing of events they related to, resulting in five main themes: leading up to chemotherapy the treatment decision, the wider context, time, post-therapy.

Highlighted categories are those that emerged in addition to free codes shown above.

Arrows within a category represent merging and re-naming of categories.

(1) Leading up to chemotherapy

Feelings about diagnosis → Reaction to diagnosis
Experience with surgical specialty
'Enough to deal with'
Coping with family and life events
Coping with stoma or complications of surgery
How diagnosis was reached
Pre-cancer condition

Wanting to get back to normal life
Surgeon recommending chemotherapy
Information about diagnosis
Family history of colon cancer
Not wanting to involve family

(2) The treatment decision

'Accepting what I was told'
Perception of self when accepting without questioning
Discussion with oncologist → Attitude towards patient involvement
'No discussion' with oncologist → Attitude towards patient involvement
'They' decided or 'they wanted'
Asking/not asking questions about treatment → Patients' frame of mind
Concerns relating to chemotherapy and side effects
First consultation with oncologist
Decision on duration of treatment
Decision on reduction of treatment
Oncologist recommendation for chemotherapy/framing of chemotherapy
'I had to do it' → Patients' reasons for receiving chemotherapy
Desire to receive chemotherapy not influenced by knowledge of side effects
No previous knowledge about cancer or chemotherapy → Perceptions of chemotherapy
The option for type of therapy
The option to refuse chemotherapy
Trust or faith in doctors
'They are the experts'
Wanting to avoid neuropathy
How the treatment decision was made
Information about treatment benefit
Information about side effects
Information about peripheral neuropathy
Information about intravenous infusion of oxaliplatin
Information about the nature of chemotherapy
Visit to chemotherapy ward before start of treatment → Feeling prepared/knowing what to expect → Feelings about information provided
Variability in information and care
'Not thinking about chemotherapy → Patients' frame of mind
Feelings about interaction with doctors → Communication during consultations

(3) The wider context

Specialist nurses
Carers or family members
Possible advantages to higher SES
Busy hospital or clinic
GPs
Support groups, charities, online forums
Information about other elements of care
Helpline

(4) Time

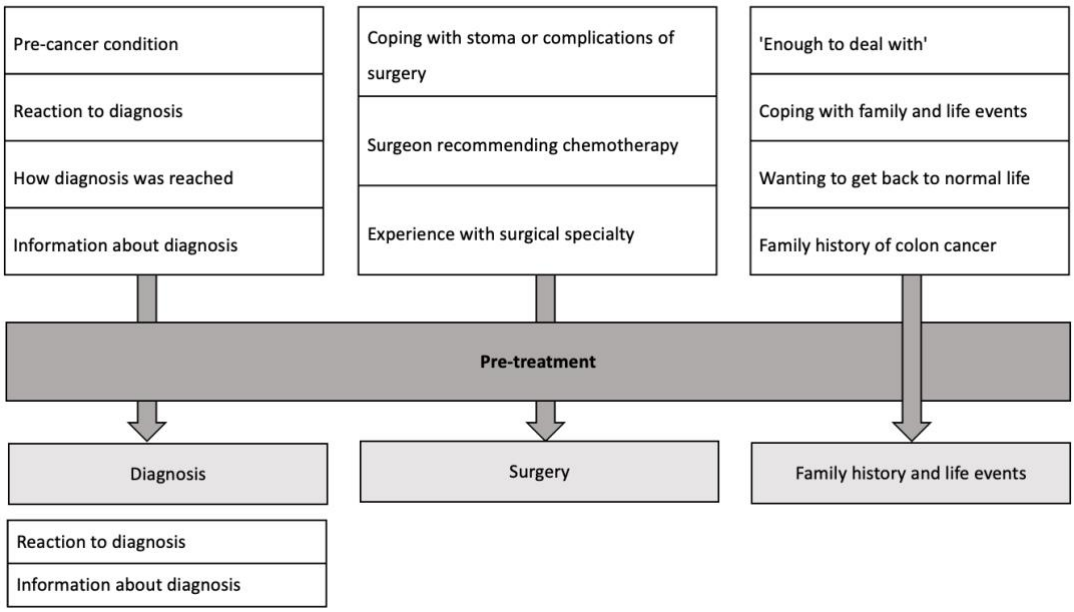
Time to gain and process information about chemotherapy
Time waiting from diagnosis to treatment
Need for repeat meetings with oncologist

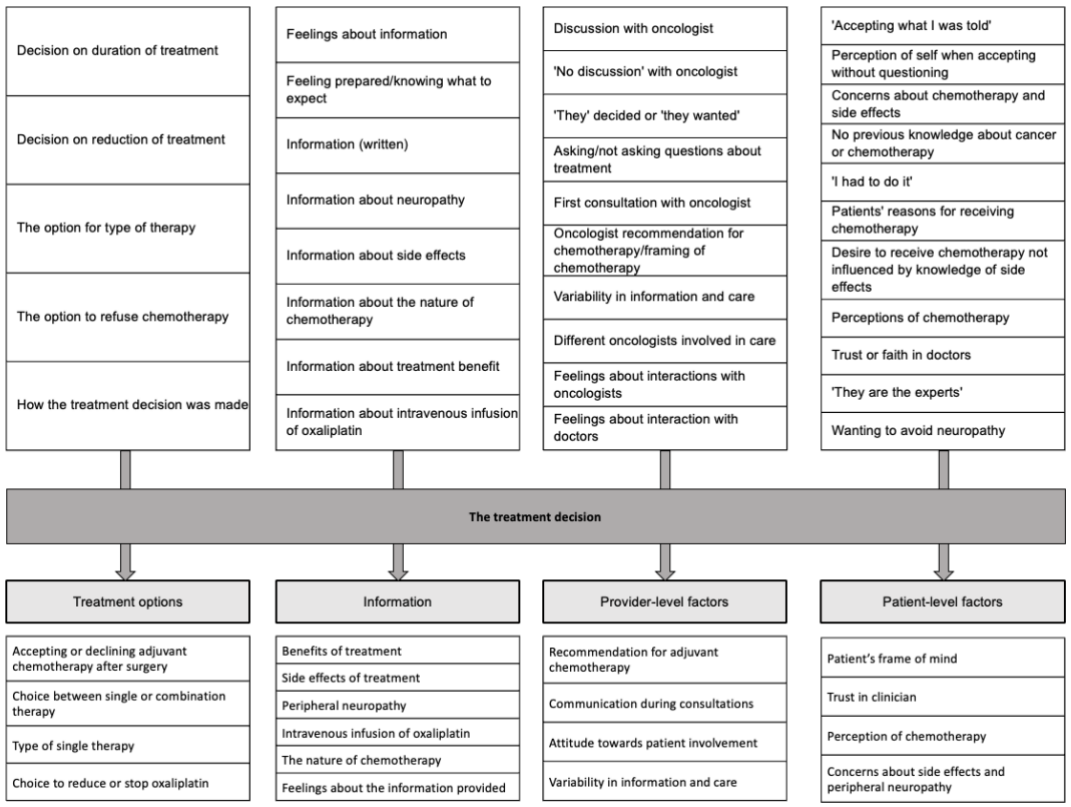
(5) Post-treatment

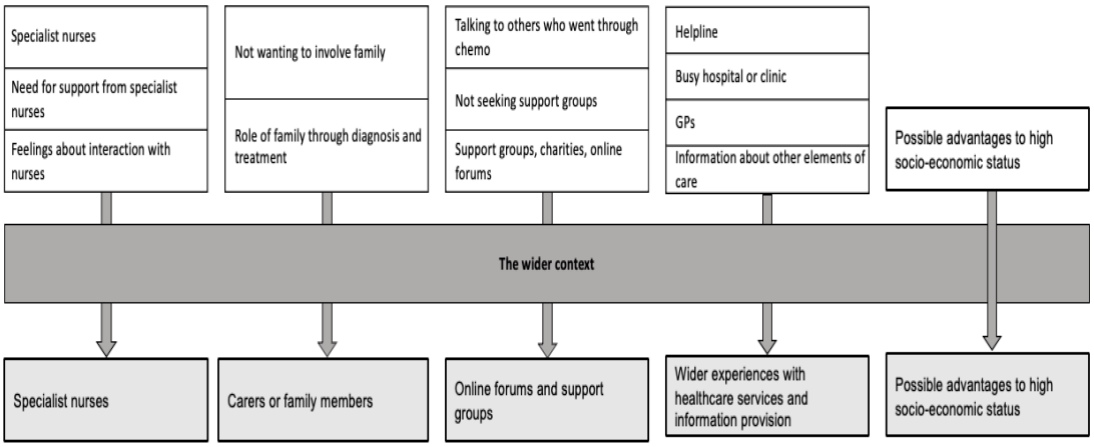
Feelings about treatment decision after treatment
Persistent peripheral neuropathy

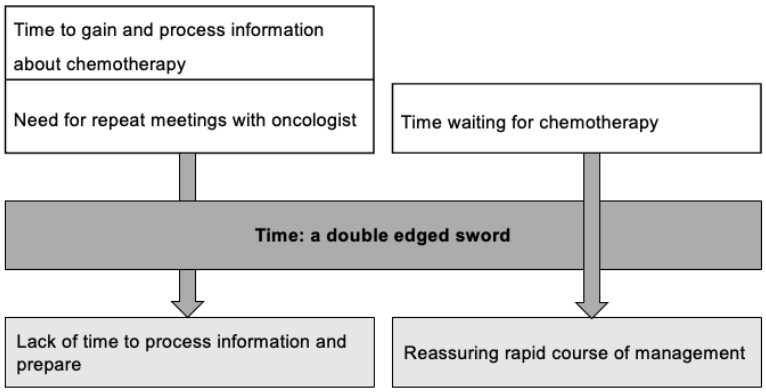
Final themes and sub-themes

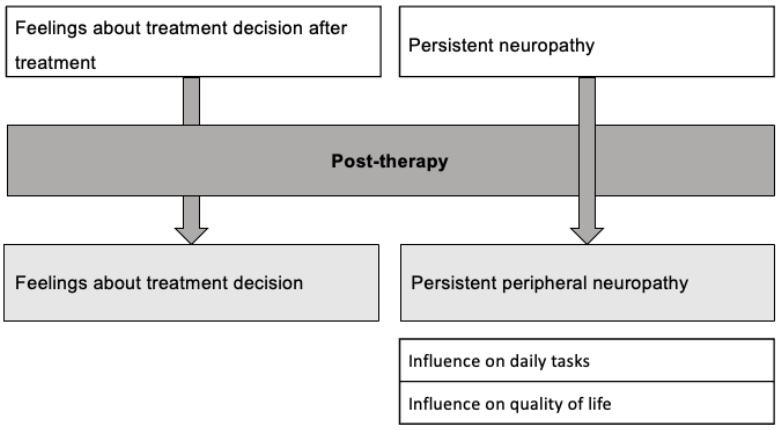
In the final stage of the analysis, one of the five main themes “the treatment decision” was divided into two main themes: “the treatment decision” and “the treatment decision context”. The former related to the decision itself, that is, how treatment options were presented and the decision on which treatment to receive was made. The latter consisted of the factors that related to the immediate context of the treatment decision, such as information, patient, and healthcare professional-level factors. Therefore, the final number of main themes that resulted from the analysis was six. Three related to the treatment decision, its immediate context, and it’s wider context. Two consisted of factors or events that took place before or after treatment (i.e., pre-treatment context, post-therapy), and the last theme on time was re-names as “Time: a double-edged sword”, to reflect both positive and negative influences of the passage of time before and during treatment. In addition, the categories under each of these main themes were re-organised into sub-themes as shown.


Pre-cancer condition
Reaction to diagnosis
How diagnosis was reached
Information about diagnosis
Coping with stoma or complications of surgery
Surgeon recommending chemotherapy
Experience with surgical specialty
'Enough to deal with'
Coping with family and life events
Wanting to get back to normal life
Family history of colon cancer
Pre-treatment
Diagnosis
Surgery
Family history and life events
Reaction to diagnosis
Information about diagnosis


Decision on duration of treatment
Decision on reduction of treatment
The option for type of therapy
The option to refuse chemotherapy
How the treatment decision was made
Feelings about information
Feeling prepared/knowing what to expect
Information (written)
Information about neuropathy
Information about side effects
Information about the nature of chemotherapy
Information about treatment benefit
Information about intravenous infusion of oxaliplatin
Discussion with oncologist
'No discussion' with oncologist
'They' decided or 'they wanted'
Asking/not asking questions about treatment
First consultation with oncologist
Oncologist recommendation for chemotherapy/framing of chemotherapy
Variability in information and care
Different oncologists involved in care
Feelings about interactions with oncologists
Feelings about interaction with doctors
'Accepting what I was told'
Perception of self when accepting without questioning
Concerns about chemotherapy and side effects
No previous knowledge about cancer or chemotherapy
'I had to do it'
Patients' reasons for receiving chemotherapy
Desire to receive chemotherapy not influenced by knowledge of side effects
Perceptions of chemotherapy
Trust or faith in doctors
'They are the experts'
Wanting to avoid neuropathy
The treatment decision
Treatment options
Information
Provider-level factors
Patient-level factors
Accepting or declining adjuvant chemotherapy after surgery
Choice between single or combination therapy
Type of single therapy
Choice to reduce or stop oxaliplatin
Benefits of treatment
Side effects of treatment
Peripheral neuropathy
Intravenous infusion of oxaliplatin
The nature of chemotherapy
Feelings about the information provided
Recommendation for adjuvant chemotherapy
Communication during consultations
Attitude towards patient involvement
Variability in information and care
Patient's frame of mind
Trust in clinician
Perception of chemotherapy
Concerns about side effects and peripheral neuropathy


Specialist nurses
Need for support from specialist nurses
Feelings about interaction with nurses
Not wanting to involve family
Role of family through diagnosis and treatment
Talking to others who went through chemo
Not seeking support groups
Support groups, charities, online forums
Helpline
Busy hospital or clinic
GPs
Information about other elements of care
Possible advantages to high socio-economic status
The wider context
Specialist nurses
Carers or family members
Online forums and support groups
Wider experiences with healthcare services and information provision
Possible advantages to high socio-economic status


Time to gain and process information about chemotherapy
Need for repeat meetings with oncologist
Time waiting for chemotherapy
Time: a double edged sword
Lack of time to process information and prepare
Reassuring rapid course of management


Feelings about treatment decision after treatment
Persistent neuropathy
Post-therapy
Feelings about treatment decision
Persistent peripheral neuropathy
Influence on daily tasks
Influence on quality of life

Example of notes made during analysis

When oncologists use the language of “mopping up any remaining cells”, it seems that this becomes internalised by patients. Patients express those reasons for wanting chemotherapy is to make sure "there is nothing left", or “zap it once and for all ".
Participant 6 was involved in the decisions that related to his care from the start. Private care (high socioeconomic status) provided advantages: time to read and think, frequent and thorough discussions with clinicians.
Some participants reach the oncology consultations already primed by the surgeon that they need chemotherapy and should receive it. Interaction with surgeon influences interaction with oncologist.
Immediately after expressing complete trust in what the doctor says, or the fact that they didn’t ask questions, or that they believed what they were told - some patients expressed their feelings about what that means to them now. Here, the participant described accepting without questioning as "stupid really". With other participants an expression of what they are "normally" like, indicates that they may think this is not a normal situation – therefore not asking questions is not how they usually are, but under these circumstances it was.