Title page

Title: Perceived diagnostic delay and cancer-related distress: a cross sectional study of patients with colorectal cancer.

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Key words: cancer; oncology; colorectal; delayed diagnosis; psychological; stress disorders.

Abstract

Objective: This study aimed to examine the effect of perceived diagnostic delay on cancer-related distress, and determine whether fear of cancer-recurrence and quality of life mediate this relationship.

Methods: Cross-sectional study in which 311 colorectal cancer (CRC) survivors in Scotland completed a survey which included questions on cancer-related distress (IES-R), perceived diagnostic delay, quality of life (trial outcome index of the FACT-C: FACT-C TOI) and fear of cancer recurrence. 15 patients withheld consent to data matching with medical records, leaving a sample size of 296. Participants were an average of 69 years old (range 56 to 81) and between 3.5 to 12 years post-diagnosis. Multiple regressions were used to test predictors of distress, and regression and bootstrapping to test for mediation.

Results: Perceived diagnostic delay was correlated with higher cancer-related distress, while objective markers of diagnostic delay (disease stage at diagnosis and treatment received) were not. Some of the relationship between perceived diagnostic delay and cancer-related distress was mediated by quality of life, but not by fear of cancer recurrence.

Conclusions: Perceived diagnostic delay was associated with higher cancer-related distress among CRC survivors. While poorer quality of life partly explained such associations, fear of cancer recurrence, stage at diagnosis and treatment did not. The exact features of diagnostic delay that are associated with cancer-related distress remain unclear. Future research should examine the experiences patients go through prior to diagnosis that may increase distress, in an effort to improve our understanding of the factors affecting emotional wellbeing among CRC survivors.

Background

Earlier stage at diagnosis is strongly associated with improvements in cancer survival [1]. Consequently a number of initiatives have been introduced to try and reduce diagnostic delay among both patients [2] and health-care providers [3], with the emphasis on improving prognosis. However, little research has examined the psychological benefits of reducing diagnostic delay. A cancer diagnosis is always distressing, but the impact may be even worse if patients believe the route to diagnosis has been inefficient.

There are a number of reasons to expect adverse psychological effects as a result of diagnostic delay. Qualitative research into the experience of having colorectal cancer (CRC) diagnosed at screening found many people described the diagnosis as relatively untraumatic, due to the absence of a period of symptoms and associated worry about a potential cancer diagnosis, and simpler treatment which often involved surgery alone [4]. While receiving the actual diagnosis has been identified as the most stressful aspect, periods of waiting are also high on the list [5], and research in lung cancer patients found that a more rapid diagnosis was associated with less distress [6].

The need to identify and manage distress among cancer survivors is increasingly recognised, with calls to integrate psychological assessment into routine care [7]. Psychological difficulties following a cancer diagnosis include depression, anxiety, and stress-related responses including post-traumatic stress disorder (PTSD). Such difficulties are often comorbid among cancer survivors [8;9]. While symptoms of full-PTSD are typically less frequent than those of depression and anxiety, they are found in a significant minority of cancer survivors (e.g. [10-12]), with much higher rates of sub-threshold symptoms (e.g. 33% [5; 12]. Consequently, there have been specific calls for more research into factors that can increase vulnerability to cancer-related distress [10]. Symptoms of trauma comprise avoidance, intrusive thoughts, and hyper-arousal, and reflect subjective distress in

relation to a traumatic event. The presence of a specific cluster of symptoms or symptom intensity (indexed by cut-off scores) can be used to identify PTSD. While a number of demographic and clinical correlates of cancer-related distress have been identified, with higher cancer-related distress among younger people [13; 14], a more recent diagnosis [15], and patients with more advanced disease [10], the effect of diagnostic delay has received little attention. One exception is a study which found higher distress among people with longer objective markers of delay in diagnosis and treatment [16].

There are a number of ways in which perceived delay could affect the patient. Patients may be concerned that any delay in diagnosis has resulted in more advanced disease and necessitated more toxic or invasive treatments, both of which are associated with higher distress [10;17]. In addition, the belief that there has been a delay in diagnosis could also increase fears of cancer recurrence, and raise concerns that the cancer and its treatment have had an unnecessarily adverse effect on the individual's quality of life.

The cognitive model of persistent PTSD forwarded by Ehlers and Clark [18] proposes that persistent PTSD occurs only if "individuals process the trauma in a way that leads to a sense of serious, current threat", and that this can come from "excessively negative appraisals of the trauma and/or its sequelae." Fear of cancer recurrence (FCR) refers to fear that cancer could come back, or progress, in either the same place or in another part of the body, and researchers have argued that FCR provides a sense of current serious threat and can hence lead to post-traumatic symptomatology [19]. Consistent with this view, previous research has documented strong associations between FCR and cancer-related distress [19; 20]. It can also be argued that excessively negative appraisals of the sequelae of cancer can be indexed by patients' assessment of their quality of life. Quality of life is a multidimensional construct, comprising self-reported physical, functional, social/family, and

emotional wellbeing [21]. Previous research has shown PTSD responses are associated with both poor social functioning and reduced physical functioning [11; 22-24]. Hence according to this model, and previous research findings, both FCR and quality of life could mediate associations between diagnostic delay and distress.

The present study aimed to examine the predictors of cancer-related distress among patients with CRC and test mediational pathways between perceived delay and cancer-related distress. We hypothesized that:

1) Cancer-related distress would be higher among CRC patients who perceived there had been delay in their diagnosis.
2) Fear of recurrence and quality of life would contribute to explaining associations between perceived diagnostic delay and cancer-related distress, over and above any contribution of stage at diagnosis and treatment received.

Ethical approval

Ethical approval was obtained from Riverside Research Ethics Committee (reference number: 09/H0706/41). Approval for identifying potential participants via database linkage was granted by the NHS National Services Scotland Privacy Advisory Committee and the NHS Scotland Community Health Index Advisory Group.

Materials and Methods

Design and setting:

Cross-sectional study, examining people diagnosed with CRC in Scotland between 2000-2008.

Participants and recruitment:

Potential participants were identified by linking the Scottish Cancer Registry and Scottish Colorectal Cancer Screening Pilot databases by their Community Health Index (CHI) number. The CHI database was used to identify patients and GP details. The CHI is a unique identifier for individuals registered at general practices in Scotland, and contains information on date of birth and gender. Practitioner Services Division at NHS National Services Scotland (NSS) co-ordinated patient contact via their GPs. Patients identified as deceased, or as having moved from the area, were excluded. Practitioner Services Division were given template letters for GPs and patients; they added GP and patient details, and forwarded the letters to the GPs to pass on to eligible patients. This process was approved by the Riverside Research Ethics Committee, NHS NSS Privacy Advisory Committee, and the NHS NSS Community Health Index Advisory Committee. GPs were asked to confirm the diagnosis of CRC, and exclude patients who were deceased or terminally ill, unable to speak or read English, or lacked the capacity to take some or all decisions for themselves because of mental disorder or inability to communicate. The first survey was sent to GP practices in June 2012, and the reminder survey for non-responders in September 2012. Patients had their CRC diagnosed at FOBt screening or outside of screening (either following a negative screening result or because they lived outside the areas of the Scottish Pilot). Differences in psychological outcomes in relation to diagnostic pathway have been reported elsewhere [25].

Measures

Age, gender, Scottish Index of Multiple Deprivation (SIMD) [26], Dukes' stage at diagnosis,

treatment received (surgery, radiotherapy, chemotherapy) and time since diagnosis (in years) were supplied by NHS NSS with patient consent. All other variables were measured in the questionnaire. Employment status was assessed**,** and ethnicity was measured using questions from the Scottish Census 2011 with the addition of a 'Prefer not to say' response option. Co-morbidities were self-reported (heart or vascular disease, diabetes, epilepsy, stroke, arthritis, asthma, mental or emotional disorder, cancer (other than bowel cancer), any other illness (open-ended)), and combined into a single variable 'comorbidity' (Yes/No). Cancer recurrence was assessed with the item: "Has the cancer come back (recurred) since your first treatment?", response options: "Yes", "no", "I don't know / can't remember". "If yes, in what part of the body? (open-ended)."

The main outcome variable was current cancer-related distress, measured by the Revised Impact of Events Scale (IES-R) [27] which has three subscales: intrusion, avoidance, and hyperarousal, as well as a total score. The IES-R can be used to measure distress (range 0-88) or suspected presence of PTSD (scores of 33 or higher). The IES-R was chosen because it is one of the most commonly used measures of cancer-related distress [28], with scale items directly corresponding to 14 of the 17 symptoms of PTSD outlined in DSM-IV [29] (the DSM version in use at the time of the study). Participants were asked to indicate how they had been feeling during the past seven days with respect to their cancer.

The main predictor was perceived diagnostic delay: "Do you think your cancer could have been diagnosed sooner than it was" with response options: "yes", "not sure", and "no", and was entered into analyses as an ordinal variable. Quality of life and FCR were potential mediators. Quality of life at the time of study participation (i.e. over the preceding seven days) was assessed using the FACT-C [30]. This is a 34 item questionnaire that generates four wellbeing subscales: physical, functional, social/family, and emotional, which can be summed to form a general score (the FACT-G) allowing

comparisons to be made across cancer, and an additional CRC subscale which, along with the other subscales, forms a colorectal-cancer specific measure (the FACT-C). To reduce conceptual overlap with cancer-related distress, we used the Trial Outcome Index (FACT-C TOI), which sums the physical, functional and CRC subscales.

Fear of cancer recurrence at the time of the study was assessed using a four item scale [31] with the wording altered to ask about bowel cancer (the term commonly used for CRC in the UK) rather than breast: "How often have you worried about getting bowel cancer again" "How often have worries about getting bowel cancer again affected your mood", "How often have worries about getting bowel cancer again affected your ability to carry out your daily activities", and "How concerned were you about getting bowel cancer again" Response options were: "Not at all or rarely", "sometimes", "often", "a lot". Participants were asked to rate their concerns over the past month, and the scale showed good levels of internal reliability (Cronbach's alpha = 0.773).

Statistical analysis

Predictors of cancer-related distress were examined using linear and logistic regression. Potential mediators of the link between perceived diagnostic delay and cancer-related distress were assessed using the software Mplus 7.11, and the robust weighted least squares estimation technique [32].

Response rate

GPs were sent research invitation letters for 675 patients, of whom 142 were not contacted (either because the patient met one or more exclusion criteria (n=70), or the GP did not wish to participate in the research (n=72)); leaving 533 patients who were mailed a questionnaire (a response rate of 58.3%, N=311). Fifteen withheld consent for data-matching to NSS, leaving 296 as the sample for analysis; a response rate of 55.5%.

Missing data

Scores on the IES-R, FACT-C and FCR scales were only computed if patients had answered at least 50% of the items otherwise they were recorded as missing. Missing data were 5% or higher for Dukes' stage, receipt of radiotherapy, and the FACT-C TOI, but less than 5% for all the other variables (see Table 1). The mediation analysis was conducted both with completed data and with data imputed for missing values.

Results

Background variables

Descriptive and clinical characteristics of the whole sample are shown in Table 1. The average age was 69 years, ranging from 56 to 81; consistent with the age of invitation to the Scottish CRC Screening Pilot (50-69) and time since diagnosis. Time since diagnosis ranged from 3.5 to 12 years. Half **of** the sample (49%) were men, almost all described their ethnicity as white (99%) and the majority were retired from work (75%). Participants were less deprived than the general population of Scotland, with over 20% in each of the higher quintiles.

Predictor and outcome variables

Perceived diagnostic delay was significantly correlated with receiving chemotherapy ($r=0.204$; $p<0.001$) and radiotherapy ($r=0.122$; $p=0.044$). The correlation with Dukes' stage at diagnosis approached significance ($r=0.120$; $p=0.055$).

On the IES-R, 6% scored 33 or higher, indicating the likely presence of PTSD, consistent with other studies using symptom checklists where rates between 5-12% are reported [24]. Participants reported similar quality of life scores to other research on CRC patients [30], with levels equivalent to CRC survivors with no evidence of disease [33]. Cut-off scores for the FACT-G show 19% of the current sample reported poor quality of life [33] (see Table 1). Clinical cut-off scores for FCR have not been

developed [34], but average scores were low, with 13.1% of participants reporting an average score of 2 or more, and only 1.4% reporting an average score of 3 or more.

Predictors of cancer-related distress

Average level of distress by perceived diagnostic delay showed a linear trend across the three points of the scale (no: 8.31; not sure: 11.49; yes: 13.78]. When all variables that were significant in univariate analyses were entered into the model, only age, perceived diagnostic delay, FCR and FACT-C TOI scores remained significant predictors. Using suspected PTSD caseness as the outcome (yes/no), only perceived diagnostic delay and FACT-C TOI were significant predictors of cancer-related patient distress in multivariate analyses (see Table 2).

Mediation analysis

In order to test whether FCR or quality of life mediated the relationship between perceived diagnostic delay and cancer-related distress, variables that predicted cancer-related distress in multivariate analyses were entered into a model (see Figure 1). Correlations between these variables are shown in Table 3. The product of regression coefficients (used to calculate indirect effects) often violates the assumption of a normal distribution, potentially leading to biased results, so bias-corrected bootstrapping (N=5000) was used to generate confidence intervals around the mediation analyses [35]. The sample size was sufficient to detect medium effect-size associations in mediational analyses [36]. As shown in Figure 1, quality of life (FACT-C TOI) mediated some of the relationship between perceived diagnostic delay and cancer-related distress, but there was no pathway from perceived diagnostic delay to distress via FCR. The model accounted for 54% of the variance in cancer-related distress. The indirect effect from perceived diagnostic delay to cancer-related distress via FACT-C TOI was significant (0.052, CIs: 0.001 to 0.103, p=0.045), as were the indirect effects between age and distress via both FCR (-0.105, CIs: -0.050 to -0.160, p<0.001) and

FACT-C TOI (-0.057, CIs: -0.006 to -0.109, p=0.029). All indirect effects remained significant using imputed data. There was a strong correlation between FCR and FACT-C TOI.

Conclusions

In line with our predictions, we found that cancer-related distress was higher among cancer survivors who perceived diagnostic delay. However, neither disease stage at diagnosis nor treatment predicted distress, showing it was the subjective perception, rather than objective markers, of delay that was associated with adverse psychological outcomes. When examining predictors of likely presence or absence of PTSD, only perceived diagnostic delay and poorer quality of life were significant predictors in multivariate analyses, confirming the importance of exploring perceived delay in the context of cancer distress.

Mediation analysis showed that, in addition to a direct effect on cancer-related distress, perceived diagnostic delay also had an indirect effect via quality of life, but FCR, although a significant predictor of distress, was not significantly associated with perceived delay. However, the study was underpowered to detect small mediation effects. The majority of participants were diagnosed over five years prior to study participation, and concerns about the effect of diagnostic delay on recurrence may have reduced, with the realisation that any delay had not proved fatal.

Consistent with previous research, we found that younger age was associated with higher levels of cancer-related distress [11]. Part of this association was mediated by greater FCR and poorer self-reported physical, functional and colorectal quality of life. Green et al [5] have speculated that negative associations between age and distress may be due to the more unexpected nature of the diagnosis, and greater impact on both the patient's life and that of their family, due to work and care-giving commitments. An additional explanation is that older people may have developed greater

resilience to stress [37]. Causes are likely to be multiple, but the present study confirms the need to be vigilant to the multiple cancer-related concerns that may exist among younger adults, including FCR and on-going symptomatology and functional impairment.

A strong association was also observed between FCR and physical functional and colorectal quality of life. Lee-Jones et al [38] raise the possibility that FCR can lead to an increased focus on somatic symptoms. Similarly the presence of bodily symptoms could promote fears of a recurrence, and may explain the associations observed between these variables in the current study.

To our knowledge, this is the first study to compare the effect of perceived diagnostic delay on psychological outcomes in the context of CRC (see [39] for details of a study in progress).
The present study benefits from validated measures of cancer-related distress and quality of life specific to colorectal cancer; and objective data on demographic and clinical characteristics. Weaknesses include the use of the IES-R to measure PTSD, which does not align as closely with DSM criteria as other measures (e.g. the PCL-C), and cannot be used to diagnose full or sub-threshold PTSD. A further weakness is the retrospective assessment of perceived diagnostic delay. It could be argued that current levels of cancer-related distress or quality of life negatively influenced people's judgments about delay. Against this argument is the lack of association between FCR and perceived delay, so there does not appear to be a global tendency to infer delay based on current distress and concerns.

A further limitation is the cross-sectional assessment of variables, so no causal inferences can be made. Future research could help clarify the relationship by measuring delay closer to the time of diagnosis, and its relationship to the later development of cancer-related distress in a prospective design. Some limitations with the sample should also be noted: response rates were below 60%, the

sample was less deprived than the general population of Scotland, and responders were almost exclusively of white ethnicity, thereby limiting the generalizability of the results to other ethnic groups and people with lower levels of literacy.

Consistent with previous research we observed associations between higher cancer-related distress a shorter time since diagnosis [11; 15], poorer quality of life [22], and higher concerns about recurrence [19]; but unlike previous research, we found no links with objective disease outcomes, such as stage at diagnosis or treatment and distress [11]. The lack of association with stage of disease may be the result of small numbers of participants diagnosed with very late stage disease in this study. Gurevich et al [28] observed that only studies including patients with advanced disease showed an association between PTSD and stage at diagnosis, while in their meta-analysis Abbey et al [10] found higher rates of PTSD in studies that included patients with advanced stage disease. Reported rates of PTSD among cancer patients vary widely across studies, and method of assessment, with symptom checklists often resulting in higher rates than those determined by clinical interview. As noted in the results, the rate of PTSD in the current study is towards the lower end of that observed in previous research [24], most probably due to the sample skew towards earlier stage at diagnosis. This suggests that in practice, rates of PTSD are quite low among colorectal cancer survivors, at least several years post-diagnosis, but rates of both partial and full PTSD in patients shortly after diagnosis remain unknown.

When it comes to experiencing cancer as a traumatic stressor, new criteria for PTSD (in DSM-5) specify that "…a life-threatening… or debilitating medical condition is not necessarily considered a traumatic event. Medical incidents that qualify as traumatic events involve sudden, catastrophic events". The severity of cancer as a stressor has typically been indexed by diagnostic stage and intensity of treatment [11], however disease stage and treatment variables did not explain

associations between perceived delay and distress in the present study. Other factors associated with perceived diagnostic delay, such as intolerance of uncertainty or anxiety, may determine longer term psychological wellbeing rather than perceived diagnostic delay *per se*. Or it may be due to the experiences patients go through prior to diagnosis. A UK study of patients attending hospital appointments with specialists for prostate and bladder cancer diagnostic investigations reported that 31% of patients suffered clinical levels of anxiety – which were associated with their worry about their appointment and its outcomes (i.e. cancer diagnosis), their perceived social support and their personality [40]. Differences in distress observed in the present study could relate to feelings associated with the perception of diagnostic delay *per se* (e.g. the belief there has been a medical error), or the experiences people go through that may be correlated with perceived delay, such as discovering symptoms which may take time to be diagnosed, or situations requiring urgent medical attention (e.g. emergency admission to hospital).

This study took place prior to the introduction of nationwide screening programmes for colorectal cancer in the UK. Screen-detected disease is associated with lower perceived diagnostic delay [25], and as rates of screening uptake increase, perceived delay and any associated distress will reduce. However, groups less likely to accept the offer of screening, such as people with higher levels of deprivation and ethnic minorities [41], are more vulnerable to the development of cancer-related stress as a result of their diagnostic pathway.

Given the potential links between trauma and cancer progression [42] the need to understand and reduce factors that promote cancer-related distress in cancer survivors is a key area for future research and psychosocial intervention, and greater attention could be paid to the experiences patients go through prior to diagnosis that promote distress.

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Table 1: Demographic, clinical and psychological characteristics (N=296)

	% (n)
Age when completed study	
50-59	4.4 (13)
60-69	49.3 (146)
70-79	44.6 (132)
80+	1.7 (5)
Gender	
Male	49.3 (146)
Female	50.7 (150)
Scottish Index of Multiple Deprivation (fifths)	
1 (most deprived)	7.4 (22)
2	16.9 (50)
3	24.0 (71)
4	26.7 (79)
5 (least deprived)	24.0 (71)
Missing	1.0 (3)
Employment status	
Working (full-time, part-time, self-employed)	18.2 (54)
Retired	74.3 (220)
Other (home maker, students, unemployed, too ill to work/ disabled)	6.4 (19)
Missing	1.0 (3)
Ethnic group	
White	98.3 (291)
Non-white	1.0 (3)
Missing	0.7 (2)
Time since diagnosis (years)	
3 to 4.9	11.1 (33)
5 to 9.9	70.3 (208)
10+	18.6 (55)
Dukes' stage	
A	23.0 (68)
B	35.1 (104)
C	28.4 (84)
D	2.0 (6)
Missing	11.5 (34)
Surgery	
Yes	96.6 (286)
No	2.4 (7)
Missing	1.0 (3)
Radiotherapy	
Yes	12.5 (37)
No	80.4 (238)
Missing	7.1 (21)
Chemotherapy	
Yes	40.2 (119)
No	55.1 (163)
Missing	4.7 (14)

Comorbidities	
Yes	70 (208)
No	30 (88)
Reported cancer recurrence following first diagnosis (both related and unrelated to initial bowel cancer diagnosis)	
Yes	8.4 (25)
No	88.5 (262)
Don't know or can't remember	1.0 (3)
Missing	2.0 (6)
Perceived diagnostic delay	
Yes	26.7 (79)
Not sure	13.9 (41)
No	58.4 (173)
Missing	1.0 (3)
Fear of cancer recurrence (1-4) mean (sd)	1.50 (0.54) Range: 1-4 (n=291)
Quality of life	
Overall quality of life (FACT-C total), mean (sd)	111.94 (17.21) Range: 41.10-136.00 (n=266)
Overall quality of life (FACT-G total), mean (sd)	89.8 (14.3) Range: 32.1 to 108.00 (n=267)
Proportion reporting low quality of life (FACT-G scores less than 78.8)	19.1 (51) (n=267)
Physical, functional and colorectal subscales (FACT-C TOI) (0-84), mean (sd)	69.78 (12.72) Range: 14.17-84.00 (n=269)
Cancer-related distress (IES-R)	
Total score (0-88), mean (sd)	10.23 (13.19) Range: 0 - 80.20 (n=289)
Avoidance (0-32), mean (sd)	4.70 (5.76) (n=289)
Hyper-arousal (0-28), mean (sd)	2.20 (4.11) (n=289)
Intrusions (0-28), mean (sd)	3.34 (4.58) (n=289)
Suspected PTSD caseness (participants scoring 33 or higher)	6 (17)

Table 2: Multivariate predictors of cancer-related distress

	Cancer –related distress as a continuous variable (standardized Beta weights)	**Cancer-related distress as a dichotomous variable: suspected caseness yes/no (ORs and 95% CIs)**
	Adjusted [c]	Adjusted [c]
Age	-0.117 [a]	0.89 [0.76 to 1.06]
Fear of cancer recurrence	0.413 [b]	3.59 [0.64 to 20.17]
Quality of life (physical, functional and colorectal)	-0.351 [b]	0.87 [0.80 to 0.94] [b]
Perceived diagnostic delay	0.107 [a]	3.87 [1.20 to 12.44] [a]

a $p<0.05$
b $p<0.001$
c adjusted for variables significant in univariate analyses

Table 3: Correlations between variables entered into the mediation model (imputed values given in brackets)

	Age	Perceived diagnostic delay	Fear of cancer recurrence	Quality of life (physical, functional, colorectal)
Perceived diagnostic delay	0.030 (-0.005)	1.00		
Fear of cancer recurrence	-0.252 (-0.266)	0.083 (0.082)	1.00	
Quality of life (physical, functional, colorectal)	0.152 (0.168)	-0.136 (-0.136)	-0.507 (-0.530)	1.00
Cancer-related distress	-0.260 (-0.266)	0.198 (0.184)	0.635 (0.664)	-0.609 (-0.629)

Figure 1: Significant pathways between perceived diagnostic delay and cancer-related distress. Standardized coefficients (standardized coefficients from analysis using imputed data)