Colorectal cancer screening characteristics of patients presenting with symptoms of colorectal cancer and effect on clinical outcomes

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ABSTRACT

INTRODUCTION National colorectal cancer screening, utilising a faecal occult blood test (FOBT), is now well established in the UK. The aim of this study was to define the screening characteristics of patients presenting to secondary care with symptoms of colorectal cancer and to assess the effect of screening outcome on subsequent symptomatic presentation.

METHODS This was a retrospective analysis of all patients of screening age presenting within one calendar year in a tertiary trust via a two-week wait (2WW) pathway owing to suspicion of colorectal cancer. Colorectal cancer related outcomes were compared between patients in the cohort who had previously accepted bowel cancer screening and patients who had previously declined bowel cancer screening. The primary endpoint was overall incidence of colorectal neoplasia. Secondary endpoints included incidence of colorectal malignancy, cancer related mortality, cancer related outcomes and polyp related outcomes.

RESULTS Overall, 2,227 patients presented via the 2WW pathway; 955 were aged 60–75 years. Among the latter, 411 (43%) had been screened previously and had a negative FOBT, and 544 (57%) had declined screening. Incidence of colorectal neoplasia did not differ between the two groups (113 [27%] vs 143 [26%], $p=0.7$). Of those with a negative FOBT and subsequent symptomatic presentation, 16 (3.9%) were diagnosed with a colorectal malignancy compared with 36 (6.6%) of those who declined screening and had subsequent symptomatic presentation (relative risk: 1.7, 95% confidence interval: 0.96–3.02, $p=0.08$). There were no differences between the two groups with regard to TNM (tumour, lymph nodes, metastasis) stage, Dukes' stage, metastases, number of polyps or cancer related mortality (median follow-up duration: 20 months).

CONCLUSIONS The incidence of colorectal neoplasia was similar among patients who previously had a negative FOBT and those who declined screening. There was a higher incidence of colorectal cancer detected among those who declined screening but it did not reach statistical significance. All other cancer and polyp outcomes were similar between the groups.

KEYWORDS

Cancer – Screening – Colorectal

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The National Health Service bowel cancer screening programme for patients aged 60–74 years is now well established in the UK and was rolled out formally following three rounds of pilot screening performed in two strategic health authorities in the UK. Screening currently utilises guaiac-based faecal occult blood tests (FOBTs) followed by colonoscopy in patients who return a positive result.^{1,2} It is expected that bowel cancer screening will lower mortality by earlier detection of cancer and removal of adenomas. Three large trials of bowel cancer screening utilising FOBTs have shown a reduction in colorectal cancer specific mortality of 15%.^{3–7}

However, it has not been established whether screen detected cancers have a favourable outcome compared with non-screened cancers.^{8,9} FOBT represents risk reduction at

best and in case-controlled studies, the sensitivity of FOBT for the detection of bowel cancer lies between 25% and 46%.¹⁰ Recent studies have shown additionally that in screened populations, significant rates of residual cancers are detected, and the majority are Dukes' B and C cancers.^{11–15} In fact, the majority of people participating in bowel cancer screening will have a negative FOBT.

Improvements in access to secondary care for patients with colorectal symptoms has also increased significantly since the inception of colorectal cancer screening in the UK. A well defined two-week referral pathway was introduced by the Department of Health in 2000, becoming National Institute for Health and Care Excellence guidance in 2005.¹⁴ The number of patients referred on this pathway is increasing each year and has recently been influenced

by the recent UK health campaigns.^{15,16} The stated aim of this pathway is to detect 90% of all colorectal cancers. Screening characteristics of patients presenting on symptomatic pathways including impact of screening on clinical outcomes have not been described.

It is possible that accepting colorectal cancer screening and returning a negative FOBT falsely reassures the individual and therefore delays presentation when symptoms have occurred, after the negative FOBT. This may impact on survival or worsen outcome, owing to a delay in presentation and a more advanced state of malignancy, compared with patients who have not been screened. This risk has to be balanced against the number of cancer cases that may have been detected in patients who declined screening and subsequently presented symptomatically. The aim of this study was therefore to define the screening characteristics of patients presenting with symptoms of colorectal cancer and to examine the effect of previously accepting or declining bowel cancer screening in this group.

Methods

A retrospective cohort study was performed. All patients aged 60–75 years (colorectal cancer screening age in the UK) presenting via the two-week wait (2WW) pathway to a single tertiary referral centre for colorectal cancer (at University Hospitals Coventry and Warwickshire NHS Trust) during a 12-month period (1 January – 31 December 2012) were included in the analysis. This age group was chosen to encompass all of those patients who were screened in the previous two years (a single screening round).

An electronic database of all patients referred via the 2WW specialist pathway is kept in the trust and maintained prospectively. This was interrogated to identify the aforementioned population. Patients fulfilling those criteria were cross-matched with the Coventry and Warwickshire colorectal cancer screening database to identify two groups of patients: those who had accepted screening in the preceding screening round (1 January 2010 – 31 December 2011) and had returned a valid negative FOBT, and those who had declined screening in the preceding screening round.

Clinical and pathological outcomes for the two populations were compared to assess the primary and secondary endpoints. Figure 1 provides a flowchart that summarises the populations and study design while Figure 2 summarises the 2WW colorectal cancer referral criteria used in the trust.

Definitions

Screening characteristics were defined as outcome of invitation to screening, and outcomes of screening test and subsequent investigations. Patients were defined as accepting screening if they returned a FOBT sample and defined as declining screening if they did not return a FOBT during the screening round.

Colonic neoplasia was defined as primary adenocarcinoma or adenomatous polyp(s) with histological confirmation, detected in the colon or rectum. Patients with a diagnosis of colonic carcinoma on computed tomography (CT) who did not have histological confirmation were also included in the analysis. Metaplastic polyps were excluded. All pathological outcomes were reported according to Royal College of Pathologists guidelines for colorectal cancer histopathology reports.¹⁷

Endpoints

The primary endpoint of the study was overall incidence of colorectal neoplasia (primary adenocarcinoma or adenomatous polyp(s)). Both cancer and polyps were considered in the endpoint given the morbidity that can be associated with the detection of a polyp and the subsequent possible progression. The secondary endpoints were incidence of colorectal malignancy, incidence of colonic polyps, cancer related mortality during the follow-up period and stage of colorectal neoplasia detected (TNM [tumour, lymph nodes, metastasis] stage).

Statistical analysis

Normality of distribution was assessed using skewness and kurtosis as well as by producing Q-Q plots. Fisher’s exact test was used for comparisons between groups for categorical variables and Student’s t-test for continuous variables. Data were analysed using SPSS® version 21.0 (IBM, New York, US). A *p*-value of <0.05 was considered statistically significant.

Results

A total of 2,227 patients (980 women, 44%; overall mean age: 66 years, standard deviation [SD]: 9 years) were seen in 2WW colorectal clinics over a period of 12 months

following a referral from their general practitioner for relevant symptomatology (Fig 1). Of these, 955 (403 women, 42%) were aged between 60 and 75 years (mean age: 62 years, SD: 5 years) and were analysed to identify those who did/did not participate in screening during the preceding round; 411 (43%) had accepted colorectal cancer screening and returned a sample with a definitive negative result while 544 (57%) had declined colorectal screening during the preceding round.

Of the 955 patients aged 60–75 years, 890 (93%) underwent endoscopic imaging of the colon (872 colonoscopies and 18 flexible sigmoidoscopies), 32 (3%) underwent CT colonography, 8 (1%) had CT of the abdomen and pelvis with no bowel preparation, and 25 (3%) declined any investigation. None of the latter were diagnosed subsequently with cancer or died during the follow-up period (median: 20 months, range: 14–26 months). Table 1 summarises the demographics for the study groups.

Primary study endpoint

The overall incidence of colorectal neoplasia (primary adenocarcinoma or adenomatous polyp(s)) did not differ between patients who accepted screening and returned a negative FOBT (113 neoplasias, 27%) and those who had declined screening (145 neoplasias, 26%) (*p*=0.7).

Table 1 Demographics for the different study groups				
Group	<i>n</i>	Mean age	Female patients	Colorectal malignancy
Patients screened between 2010 and 2012	58,493	66 yrs (SD: 4 yrs)	31,001 (53%)	318 (0.5%)
Negative FOBT between 2010 and 2012	56,125	66 yrs (SD: 3 yrs)	26,322 (47%)	Not available
All 2WW patients seen in 2012	2,227	66 yrs (SD: 9 yrs)	980 (44%)	116 (5.2%)
2WW patients aged 60–75 yrs seen in 2012	955	62 yrs (SD: 5 yrs)	403 (42%)	51 (5.3%)
2WW = two-week wait; SD = standard deviation; FOBT = faecal occult blood test				

Table 2 Colorectal malignancy outcomes for patients aged 60–75 years seen in a 2-week wait clinic over 12 months

	Did not participate in screening	Negative screening	p-value
	544 (57%)	411 (43%)	–
<i>Colorectal malignancy</i>			
Yes	36 (6.62%)	16 (3.89%)	0.08
No	508 (93.38%)	395 (96.11%)	
<i>Dukes' stage</i>			
A	2 (0.37%)	2 (0.49%)	0.4
B	11 (2.02%)	7 (1.70%)	
C1	12 (2.21%)	4 (0.97%)	
C2	3 (0.55%)	0 (0%)	
<i>T stage</i>			
1	0 (0%)	1 (0.24%)	0.6
2	2 (0.37%)	1 (0.24%)	
3	20 (3.68%)	9 (2.19%)	
4	6 (1.10%)	3 (0.73%)	
<i>Nodes</i>			
Yes	16 (2.94%)	7 (1.70%)	0.9
No	20 (3.68%)	9 (2.19%)	
<i>Metastases</i>			
Yes	6 (1.10%)	4 (0.97%)	0.5
No	30 (5.51%)	12 (2.92%)	
<i>Underwent treatment with curative intent</i>			
Yes	30 (5.51%)	13 (3.16%)	0.9
No	6 (1.10%)	3 (0.73%)	
<i>Dead at follow-up</i>			
Yes	4 (0.74%)	5 (1.22%)	0.08
No	32 (5.88%)	11 (2.68%)	

Cancer related outcomes

Among the 955 patients aged 60–75 years seen in 2WW clinics in 2012, 55 malignancies were diagnosed (5.6%), 51 of which were colorectal malignancies (5.3%).

Of the 411 patients who had accepted screening and returned a negative FOBT, 18 (4.4%) were diagnosed with a malignancy (16 colorectal malignancies [3.9%] and 2 with an inoperable cholangiocarcinoma), compared with 37 malignancies (6.8%) (36 colorectal malignancies [6.6%] and 1 inoperable hepatocellular adenocarcinoma) in those who declined screening (relative risk: 1.7, 95% confidence interval: 0.96–3.2, $p=0.08$). There were no differences between the two groups with regard to TNM stage, Dukes' stage, sites of metastases or mortality during the follow-up period (median: 20 months, range: 14–26 months) (Table 2).

Overall, 125 colorectal malignancies (5.5%) were diagnosed in all patients presenting to a 2WW clinic in 2012 and 24 screening detected colorectal malignancies were treated in the trust in that year. The incidence of colorectal malignancy in the positive FOBT cohort among those who were screened was 8% and the incidence of adenomatous polyps was 40%.

Polyp related outcomes

A total of 97 patients (20%) were diagnosed with at least one colonic polyp (9 patients with multiple polyps) among those who were seen at a 2WW clinic and had accepted screening in the preceding round. Among patients who declined screening, 107 (20%) were diagnosed to have at least one polyp (14 with multiple polyps). The incidence of dysplasia did not differ either ($p=0.98$).

Discussion

This study is the first in the UK to describe outcomes and screening characteristics in patients presenting with symptoms of bowel cancer. The main findings of this study are:

- > The proportion of neoplasias detected (mostly adenomas) was lower in patients presenting with symptoms of bowel cancer than in those with a positive FOBT as part of the national bowel cancer screening programme.
- > The proportion of colonic cancer cases among patients presenting with symptoms of bowel cancer was higher in those who had previously declined screening than in those who had previously accepted screening although the incidence of adenomas was comparable.
- > In patients presenting with symptoms of bowel cancer, a higher proportion than expected had declined colorectal cancer screening.

A 2013 retrospective study from Sweden has suggested that FOBT use in primary care delays time to diagnosis in patients with colorectal cancer and concern remains about false reassurance from negative FOBTs as part of screening.¹⁸ It should also be remembered that the majority of patients who accept screening have a negative test and a large number of individuals need to be screened to detect a single cancer. With the sensitivity and specificity of FOBTs ranging from 25% to 46%, interval cancers in screened patients are expected to occur.¹⁰

Secondary care is also now easier to access since the large trials of colorectal cancer screening took place. The 2WW referral system has been introduced for symptomatic patients and attendance to services has increased. Additionally, the government has recently launched public awareness studies that have increased symptomatic presentation significantly, with a smaller effect on screening rates. The increase in new diagnoses during the awareness campaign was made up totally of symptomatic patients in our locality.^{15,16} It is already known that a high proportion of patients who have had a positive FOBT have a high rate of significant colonic symptoms.^{19,20} The screening characteristics of patients presenting symptomatically have not been examined.

Three studies have examined interval colorectal cancers occurring after acceptance of screening in the UK.^{11–13} All have considered only colorectal cancers and worked backwards from point of diagnosis. We are not aware of a UK study that has also considered adenoma detection.

Steele *et al* compared pilot screen detected cancers, interval cancers and missed cancers with those of an unscreened population.¹³ This study confirmed that screened cancers are of an earlier stage and also found that interval cancers had a better outcome than cancers in the population not offered screening. It is important to note that cancers from individuals who were offered but declined screening were not included in this study. The age range considered (50–69 years) also does not reflect the current screened population. Interestingly, the proportion of interval cancers increased across the three pilot screening rounds (although absolute numbers did not change), possibly as prevalent cancers were removed by screening. It is therefore likely that adenoma detection becomes more important in mortality reduction as screening matures.

Gill *et al* examined data from the Northern Colorectal Cancer Audit Group and cross-matched with screening data.¹¹ Four groups were identified: patients diagnosed with cancer before they were offered screening (controls), interval cancers, non-uptake of screening and screen detected cancers. As expected, screen detected cancers were found to be of earlier stage and had better outcomes than other groups. Patients with interval and non-uptake cancers were comparable in terms of location, stage and short-term survival (mean follow-up duration: 29.3 months).

Finally, Hallifax *et al* examined data from the Gloucestershire pathology service and cross-referenced these with the local bowel cancer screening hub.¹² Patients diagnosed with cancer aged 60–69 years who had also been invited for screening were identified. Individuals with interval cancers had similar stage and location to those who had not accepted screening. This study found that interval cancers represented 24% of cancers detected in the population of screening age.

The cohort of patients in our study was made up of those who would have been offered screening in the previous screening round and presented with symptoms consistent with a new onset colorectal malignancy via the 2WW pathway. This cohort was chosen carefully so that the offer of screening (and the result in those who accepted) was within a period short enough to influence decision making of symptomatic presentation. In our trust in 2011, the screening uptake was approximately 58% but this figure varies nationally. Only 40% of referrals of screening age in our cohort had accepted screening, equating to a higher than expected number of patients who had not accepted screening presenting symptomatically.

A higher number and proportion of cancer cases were detected in the group who had declined screening, with a relative risk of 1.7. Although this approached significance, the confidence intervals were wide and the study was underpowered to detect this. Stage and outcome of colorectal cancers were also comparable across the study groups, and this confirms what has been found in pilot

screening and in the subsequent retrospective cohorts outlined above.

In our study, approximately 26% of patients in both groups had colorectal neoplasia. This is comparable with our whole 2WW population, regardless of age. It is important that symptomatic referral on suspicion of bowel cancer has a lower chance of detecting colorectal cancer than patients who are FOBT positive and approximately half the number of adenomas are detected in the symptomatic group when compared with our local FOBT positive patients. Despite improved access to secondary care, this emphasises the importance of screening, especially in adenoma detection, which may lead to long-term colorectal cancer prevention.

Study limitations

The data used for this study came from prospectively maintained databases but the data were retrieved and analysed retrospectively. The total number of patients considered was over 2,000, with nearly 1,000 of screening age. It is therefore reasonable to compare overall outcomes with those found in the local hub of the national bowel cancer screening programme. The proportion of neoplasia (approximately 25%) is also large enough to assume that there was no difference in this respect between the two subgroups compared. It is accepted, however, that the number of colorectal cancers detected means that analysis across the two groups is underpowered and there is a possibility of a type II error. Furthermore, it would be of much interest to assess outcomes including all patients who declined screening or who were simply not given the opportunity to be screened and then developed relevant symptoms.

In this study, only those who were referred to a 2WW clinic were captured for analysis. It would be difficult to assess the whole population of those who did not participate in screening and then developed symptoms without performing a laborious population analysis where all of these patients would be contacted separately. As access to secondary healthcare improves, further studies with prospective data are needed to fully establish the impact of screening on subsequent symptomatic presentation.

Conclusions

Overall, this study suggests that screening uptake needs to be improved to detect cancers and adenomas in patients who would usually decline screening. Accepting screening does not appear to worsen outcome of symptomatic presentation.

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