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What is already known on this topic?

The COVID-19 pandemic led to a significant reduction in the provision of endoscopy.

FIT and symptoms predict risk of colorectal cancer, but prioritisation strategies for endoscopy haven't been defined.

What this study adds?

The majority of 2 week wait referrals diagnosed with CRC have predictable high risk features.

A 2-stage triage pathway which utilised patient symptoms, FIT and CT results, effectively prioritised patients for LGI endoscopy.

How might it impact on clinical practice in the foreseeable future?

During periods of limited endoscopy provision, effective triage allows appropriate prioritisation of resources.

This 2-stage pathway both identified those at highest risk of CRC for further investigation with interim CT and prioritised the majority of CRC to undergo urgent endoscopic examination.

Abstract

Objective

The two-week-wait referral (2ww) pathway is used in England to fast-track patients with suspected colorectal cancer (CRC). A two-stage triage pathway was used to prioritise LGI endoscopy for suspected CRC during the COVID-19 pandemic.

Method

All patients referred for a lower gastrointestinal (LGI) endoscopy via a 2ww pathway between March-July 2020 were assessed. The first stage triaged patients to high, standard or low risk of CRC based on symptoms and FIT, and offered CT scans to those at high risk. The second stage, endoscopy prioritisation (EP), incorporated the CT results, FIT and symptoms to triage into four groups, EP1-EP4; with EP1 being the most urgent and EP4 the least. The primary outcome measure was CRC detection.

Results

514 patients were included. The risk of CRC was triaged as high in 190/514 (37%), standard in 274/514 (53%) and low in 50/514 (10%) patients. 422/514 (82%) patients underwent endoscopy with triage to EP1 in 52/422 (12%), EP2 in 105/422 (25%), EP3 in 210/422 (50%) and EP4 in 55/422 (13%). CRC was detected in 23 (5.4%) patients. CRC was significantly more frequent in the EP1 (23.1%, relative risk (RR) = 16.2) and EP2 (6.7%,RR = 4.7) group compared to EP3 (1.4%). All CRC lesions were identified by CT imaging when performed prior to LGI endoscopy.

Conclusion

This triage pathway designated 83% of patients with CRC to either EP1 or EP2. During a period of limited endoscopy provision, this pathway effectively prioritises endoscopy for those at greatest risk of CRC.

Introduction

The two week-wait (2ww) referral pathway is used in England to fast-track patients with suspected colorectal cancer (CRC). This pathway aims to improve early detection of CRC and increase survival, with lower gastrointestinal (LGI) endoscopy considered the gold standard diagnostic test. The COVID-19 pandemic significantly impacted the 2ww pathway. At the start of the pandemic national guidance advised pausing all but emergency endoscopic procedures (1).

The optimal approach to minimise diagnostic delays was uncertain. The British Society of Gastroenterology issued guidance in March 2020 suggesting alternative investigations to LGI endoscopy, such as CT scans and utilisation of Faecal Immunochemical Testing (FIT) (2). Pathways of care were developed regionally according to services available and the local impact of COVID-19.

Several predictors for CRC are recognised including clinical symptoms, iron deficiency anaemia (IDA) and FIT results (3-5). Studies report a higher risk of CRC when some symptoms present in combination rather than in isolation, in particular, rectal bleeding or IDA with other symptoms (6, 7). These predictors of CRC were used in a two-stage triage pathway to expedite investigations in those at greatest CRC risk. The first stage used FIT results and symptoms to identify those at a higher risk of CRC, who were then considered for a CT scan. The second stage utilised these results to prioritise endoscopy urgency when services resumed.

Methods

Patient cohort

The Sheffield Teaching Hospitals (STH) two-stage pathway was prospectively applied to patients who were awaiting a 2ww LGI endoscopy at the time endoscopy services were paused in March 2020 and those referred until July 2020 when delays in endoscopy were reduced. Investigations performed up until November 2020 were included in the analysis.

The first stage of the pathway involved a case notes and laboratory data review by consultant gastroenterologists. Patients were categorised as having either a high, standard or low risk of CRC based on their FIT result and clinical symptoms. FIT results >60µgHb/g were considered to indicate a high risk, 10-60 µgHb/g a standard risk and <10 µgHb/g a low risk of CRC. These thresholds were chosen based on FIT data describing the risk of CRC in patients with high risk symptoms; these indicated that a FIT <10µgHb/g had a <1% risk of CRC, a FIT 10-59 µgHb/g had a 2.6% risk of CRC whereas a FIT 60-100 µgHb/g was associated with a 7.3% risk of CRC and patients with a FIT >100µgHb/g had a 20.7% risk of CRC (8). Referrers were asked to provide a FIT result for 2ww referrals, apart from those with rectal bleeding or a palpable mass, although it wasn't mandated. In patients without a FIT result, clinical symptoms were reviewed and categorised as high, standard or low risk for CRC (see table 1). Patients with symptoms that did not fulfil NICE Guidance 12 (NG-12) criteria and those who had undergone a colonoscopy in the last 3 years, were categorised as low risk of CRC.

Risk of CRC	Symptoms
High risk	**FIT ≥60 µgHb/g** Where FIT not available IDA with Hb <10g *Rectal bleeding with*; CIBH, IDA, Weight loss or Abdominal pain *IDA with* Weight loss, abdominal pain or CIBH
Standard risk	**FIT 10-59.9 µgHb/g unless palpable mass** Isolated IDA with Hb ≥10g Isolated symptoms
Low risk	**FIT <10µgHb/g unless palpable mass** Colonoscopy in last 3 years Symptoms not fulfilling NICE guideline 12 criteria

Table 1 Risk of CRC based on FIT, Hb and symptoms

Case notes were also reviewed to identify risk factors for COVID-19 complications including comorbidities and age, with a threshold of >70 years. Patients judged to be at high risk of colorectal cancer, without risk factors for COVID-19 complications, were offered a CT scan while awaiting resumption of endoscopy services. Patients were informed that CT was a more accessible intervention during the pandemic, but was not as accurate at diagnosing CRC as LGI endoscopy (9-11).

CT examination

Oral contrast was utilised to prepare patients for CT imaging. 5ml Omnipaque 350 was dissolved in 100ml of water three times a day for three days, with a further dose on the morning of the scan. This preparation technique was previously offered to frail patients at this trust as a less invasive and time-consuming alternative to CT (virtual) colonoscopy (CTC), which was not available during the

early phases of the pandemic over concerns regarding COVID-19 transmission (12). The CT findings were categorised as high risk where there were features highly suggestive of a cancer, medium risk when non-specific findings such as bowel wall thickening were found and low risk when the scan was reported as normal. Colonic mass lesions on CT were considered highly predictive of CRC and beneficial in endoscopy prioritisation, allowing earlier diagnosis and treatment.

Prioritisation of patients

The second stage of the triage pathway prioritised the urgency of LGI endoscopy based on the FIT test result, CT findings, clinical symptoms and whether they had undergone a colonoscopy in the last 3 years. A higher priority was also applied to those who had a prolonged delay in investigation, as delays in CRC diagnosis are associated with worse outcomes (13). This composite score was used to assign a level of endoscopy prioritisation (EP) as either EP1, EP2, EP3 or EP4 with EP 1 having the greatest priority and EP4 having the lowest priority (table 2). The composition of groups was chosen based on the perceived cancer risk in each group and the endoscopy capacity.

Prioritisation of endoscopy	Criteria
EP1	Abnormal imaging/ rectal mass suspicious of cancer*
	FIT >60 µgHb/g
	Patients >10 week on pathway (excluding polyps and FIT <10)
EP2	Any risk and >8 weeks on pathway with no imaging
	High risk symptoms with no imaging
	High risk polyps
	Non-specific imaging abnormalities
EP3	High risk symptoms and normal imaging
	Standard risk symptoms
	FIT 11-59 µgHb/g
	Standard risk polyp
EP4	FIT <10 µgHb/g
	Low risk polyps
	Symptoms not fulfilling NICE guideline 12 criteria

Table 2 Prioritisation of colonoscopy when endoscopy services had resumed (* Patients found to have changes consistent with CRC on CT had an expedited LGI endoscopy performed by exception)

Ethical approval

This work commenced following ethical approval and registration with STH NHS FT (STH21506) and the Health Research Authority (HRA) and Health and Care Research Wales (HCRW) (reference number 20/HRA/4866).

Statistical analysis

The primary outcome measure was the detection of CRC in the four prioritisation groups. Statistical analysis was carried out using Graphpad software version 9, USA, with significance set at a p-value of <0.05. Categorical variables were summarized by descriptive statistics, including total numbers, percentages and relative risk with comparisons between groups performed using the chi-square test or Fisher exact test. Continuous variables were summarized by mean and standard deviation (SD).

Secondary outcome measures include alternative diagnoses such as inflammatory bowel disease, a non-colonic cancer and advanced polyps (defined as a polyp >1cm, with high grade dysplasia or villous histology). Univariate and multivariate binomial regression using backward elimination were used to demonstrate factors associated with a CRC.

Results

There were 514 patients referred for an LGI endoscopy during the study period (see figure 1). There was an equal gender representation with 257 (50%) males and a mean (SD) age of 64.5 (12.7) years. A FIT test was available in 194 (37.7%) patients with 40/194 (20.6%) having a result >100µgHb/g, 7/194 (3.6%) had a FIT 60-99µgHb/g, 79/194 (40.7%) had a FIT 10-59µgHb/g and 68/194 (35.1%) had a FIT <10 µgHb/g.

The most common reason for referral was a change in bowel habit (47%) with a smaller proportion of patients having abdominal pain (27%), rectal bleeding (25%), IDA (23%) and weight loss (15%), with 43% having a combination of symptoms.

The first stage of the triage pathway judged the risk of CRC to be high in 190/514 (37.0%), standard in 274/514 (53.3%) and low in 50/514 (9.7%) of patients.

CT findings

Radiological imaging with a CT was performed in 195/514 (37.9%) patients, of whom 158 subsequently had an LGI endoscopy. CT findings highly suspicious of cancer were reported in 15/195 (7.7%). Non-specific findings such as bowel wall thickening were reported in 18/195 (9.2%). Polyps were reported in two patients.

Prioritisation of colonoscopy

Following initial referral, 422/514 (82%) patients underwent a lower GI endoscopy (see supplemental information for reasons patients did not proceed to endoscopy). The second stage of the triage pathway allocated 52/422 (12.3%) to the EP1 group with 105/422 (24.9%), 210/422 (49.8%) and 55/422 (13.0%) allocated to the EP2, EP3 and EP4 group respectively.

Colorectal cancers detected

CRC was detected in 22/422 (5.2%) patients who underwent endoscopy, with one further CRC detected at CT and operated on without undergoing LGI endoscopy. The mean (SD) age of patients with CRC was 70 (8) years and 18/23 (78.3%) were male. Cancers were found in all parts of the colon with 9 (39.1%) being rectal, 6 (26.1%) right sided, 6 (26.1%) left sided, one patient had synchronous left and right-side cancers and one patient had an anal cancer. When CT findings highly suggestive of CRC were reported, 13/15 (86.7%) patients were subsequently found to have cancer. A cancer was also found in a patient in whom a polyp was reported after CT imaging. No CRC was found in any of the patients with a normal CT report or with non-specific thickening. In the 9 patients whose CRC

were initially detected during endoscopy without a prior CT, 6 were seen on the subsequent staging CT and the other 3 had polyp cancers, which had all been removed prior to CT.

Patients categorised as having a high risk of CRC based on FIT and clinical symptoms had an increased prevalence of CRC 18/190 (9.5%) than those defined as standard risk 5/274 (1.8%) (relative risk (RR) 5.2, 95% CI = 2.0 - 13.7, p <.001). There were no cancers in the low risk group.

The second stage of the triage pathway, endoscopy prioritisation, performed well with a significantly higher prevalence of cancer in the EP1 (12/52 (23.1%) patients, relative risk (RR) = 16.2, 95% CI 5.1 to 51.7, p <.001) and EP2 (7/105 (6.7%) patients, RR = 4.7, 95% CI 1.34 to 16.3, p = .018) groups compared to the EP3 priority group (3/210 (1.4%) patients) (see table 3).

Prioritisation group	Total cancer	Number LGI endoscopy performed	Percentage diagnosed with CRC	Relative risk (95% CI)
EP1	12	52	23.1	16.2 (5.1-51.7)
EP2	7	105	6.7	4.7 (1.3-16.3)
EP3	3	210	1.4	1
EP4	0	55	0	0 (0-4.7)

Table 3 Number of cancers per prioritisation group

Prior to recommencement of endoscopic services, 39 LGI endoscopies were performed by exception. Of these, CRC was diagnosed in 8 (20.5%), of which 7 had had a prior CT suggestive of cancer.

Non-CRC findings

Advanced polyps were found in 47/400 (11.8%) patients who didn't have CRC. Inflammatory bowel disease was diagnosed in 12/422 (2.8%) patients. Relevant extra colonic disease was found in 9/514 (1.8%) patients including 7 cancers (1 pleural, 2 renal cell, 1 cholangiocarcinoma, 1 hepatocellular, 1 pancreatic and 1 small intestinal neuroendocrine tumour) as well as 1 case of peritoneal tuberculosis and 1 of sarcoidosis.

Symptoms and FIT results

Most patients with CRC presented with a combination of symptoms (15/23 (65.2%)) rather than isolated symptoms (8/23 (34.8%)). The relationship between clinical symptoms and CRC is summarised in supplemental information. FIT testing had been performed in 11/23 (47.8%) patients diagnosed with CRC. The FIT result was ≥10 µgHb/g in 10/11 of these patients and was >60 µgHb/g in 6/11 patients. The single patient with a FIT <10µgHb/g had a palpable rectal cancer. The positive

predictive value for a FIT >60µgHb/g was 13% with a negative predictive value of 98.1% for a FIT <10µgHb/g.

Regression analysis

Factors associated with CRC diagnosis on univariate analysis were male sex, increasing age, a FIT >60µgHb/g and >100µgHb/g, increasing number of symptoms, rectal bleeding with abdominal pain and rectal bleeding with weight loss. Multivariate logistic regression analysis found that a FIT >100µgHb/g and rectal bleeding with weight loss remained independently associated with the presence of CRC.

Patients not undergoing lower GI endoscopy

LGI endoscopy was not performed in 92/514 (17.9%) patients. Of these, CT imaging had been performed in 37/92 (40.2%) patients and 28/92 (30.4%) had undergone FIT analysis. This was <10µgHb/g in 15/28 (53.6%), 10-60µgHb/g in 11/28 (44%) and >60µgHb/g in 2/28 (7.1%). The most common reason endoscopy wasn't performed was patient choice to defer due to concerns regarding transmission of COVID-19 (see supplemental information).

Discussion

The COVID-19 pandemic dramatically limited the provision of endoscopy services (14). Therefore, a prioritisation system was required to minimise delays in cancer diagnosis. We utilised the availability of CT imaging to assess for evidence of CRC in those at highest risk and minimise diagnostic delays. This pragmatic approach prioritised more than half of all CRC cases to the most urgent group which compromised only a tenth of the patients. Most of the remaining cancers were in the next highest priority group leaving only 13% of CRC patients in the third EP group.

This is the first study to describe the outcomes of an endoscopy prioritisation system that considered the results of CT imaging alongside clinical symptoms and FIT results. There were no CRCs detected in patients whose CT scans were reported as normal, however, 37 of these patients did not undergo endoscopy. Although this strategy may have missed patients with early or small cancers it suggests that in the setting of reduced endoscopy capacity, a CT examination in those at high risk of CRC based on FIT and clinical symptoms is a reasonable strategy to reduce time to diagnosis. This provides reassurances to both patients and relevant stakeholders regarding investigating safely and in a timely manner. The downside of this strategy is the additional burden on radiology departments and increased exposure to ionising radiation, as just over a third of patients had high risk features based on symptoms and FIT results. There are also additional resources associated with the risk prioritisation process, although this would be minimised by greater use of FIT testing.

Based on FIT alone, 10 of the 11 patients with CRC would have been detected at a level ≥10μgHb/g and the single patient with a FIT <10μgHb/g had a palpable rectal cancer. The limitation of FIT in patients with rectal lesions is well recognised and the findings at rectal examination should be considered alongside the FIT result (15). Our data is consistent with the findings of previous studies which have reported a sensitivity of 90.9-97% and a NPV of 99.8–98.9%, with a FIT of 10-150 mcg/g (5). This supports the use of a FIT level <10 μgHb/g in combination with a normal rectal examination as a safe method to exclude patients from a cancer pathway.

Despite communications to primary care clinicians and subsequent patient letters, disappointingly, a FIT result was available in only 38% of patients. Maclean et al demonstrated FIT results could be obtained in over 94% of referrals by sending the kit directly to patients and, using a 10 μgHb/g cut-off, half of patients were excluded from further investigations (16). If this were applied in our cohort, 35.7% of the patients with a FIT result would have been excluded. We believe FIT testing should be considered imperative for all 2ww referrals without a mass or rectal bleeding, and we

recognise this was recommended by a recent independent review of Diagnostic services for NHS England (17).

Almost a fifth of patients did not proceed to endoscopy following referral. Patient choice was the reason in over half of cases with 20.6% deferring due to the pandemic. Anxiety to undergo endoscopy during the pandemic has been described (18). This high rate of incomplete investigations is a further indication of this. However, this concern does not appear to be justified, with a UK multicentre study of 6208 patients, undertaken after the first lockdown, reporting no cases of COVID-19 transmission (19). The long-term outcomes associated with decisions to decline investigation is uncertain and worthy of further research.

Abnormalities were seen on the CT of all 13 patients who underwent CT before endoscopic confirmation of CRC.(12) However, 37 patients did not go on to have LGI endoscopy after their CT. Studies of CT examinations have reported a CRC miss rate between 0-30%, and this predominantly relates to the early CRC associated with the best prognosis (9-11). Therefore, if there were significant endoscopy restrictions again, we would advocate CT with oral contrast as an endoscopy prioritisation tool but not a definitive method of CRC exclusion.

This study was limited to a single centre and 23 patients with CRC. Planning a coordinated response with little notice during the height of a pandemic is challenging. Regardless, FIT and CT imaging are widely available and therefore the study outcome is applicable to many centres.

A major strength of this study is that it is a 'real world' prospective study with incomplete endoscopy investigations highlighting patient concern related to COVID during hospital attendance. Accepting these limitations this prioritisation strategy effectively allocated most patients with CRC to the highest endoscopy priority groups.

Conclusion

The COVID-19 pandemic has, and continues, to affect the delivery of endoscopy services. Utilisation of CT imaging in those at highest risk of CRC is an effective strategy to prioritise endoscopy during a period of limited endoscopy capacity.

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Figures and tables

figure 1 Study flow chart demonstrating proportion of patients deemed to be at high risk of CRC, CT scan provision and subsequent prioritisation of endoscopy

table 1 Risk of CRC based on FIT, Hb and symptoms

table 2 Prioritisation of LGI endoscopy when services had resumed (* Patients found to have changes consistent with CRC on CT had an expedited LGI endoscopy performed by exception)

table 3 Number of cancers per prioritisation group