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Addressing the variation in adjuvant chemotherapy treatment for colorectal cancer: Can a regional intervention promote national change?

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Abstract

Analysis of routine population-based data has previously shown that patterns of surgical treatment for colorectal cancer can vary widely, but there is limited evidence available to determine if such variation is also seen in the use of chemotherapy. This study quantified variation in adjuvant chemotherapy across both England using cancer registry data and in more detail across the representative Yorkshire and Humber regions. Individuals with Stages II and III colorectal cancer who underwent major resection from 2014 to 2015 were identified. Rates of chemotherapy were calculated from the Systemic Anticancer Treatment database using multilevel logistic regression. Additionally, questionnaires addressing different clinical scenarios were sent to regional oncologists to investigate the treatment preferences of clinicians. The national adjusted chemotherapy treatment rate ranged from 2% to 46% (Stage II cancers), 19% to 81% (Stage III cancers), 24% to 75% (patients aged <70 years) and 5% to 46% (patients aged ≥70 years). Regionally, the rates of treatment and the proportions of treated patients receiving combination chemotherapy varied by stage (Stage II 4%-26% and 0%-55%, Stage III 48%-71% and 40%-84%) and by age (<70 years 35%-68% and 49%-91%; ≥70 years 15%-39% and 6%-75%). Questionnaire responses showed significant variations in opinions for high-risk Stage II patients with both deficient and proficient mismatch repair tumours and Stage IIIB patients aged

Abbreviations: 5FU, fluorouracil; ACCENT, Adjuvant Colon Cancer End Points; ASCO, American Society of Clinical Oncology; CAPOX, oxaliplatin and capecitabine; CORECT-R, COloRECTal Repository; dMMR, deficient mismatch repair; DPD, dihydropyrimidine dehydrogenase; ESMO, European Society for Medical Oncology; FOLFOX, oxaliplatin and 5FU; MDT, multidisciplinary team; NCCN, National Comprehensive Cancer Network; NICE, National Institute for Health and Care Excellence; pMMR, proficient mismatch repair; QUASAR, QUick And Simple And Reliable; SACT, Systematic Anticancer Therapy (SACT); YCR BCIP, Yorkshire Cancer Research Bowel Cancer Improvement Programme.

≥70 years. Following a review of the evidence, open discussion in our region has enabled a consensus agreement on an algorithm for colorectal cancer that is intended to reduce variation in practice.

KEYWORDS

adjuvant chemotherapy, colorectal cancer, multidisciplinary team, population-based, treatment guidelines

1 | INTRODUCTION

The Food and Drug Administration approved the use of adjuvant fluorouracil (5FU) chemotherapy for Stage III colon cancer in 1990; the initial recommended duration of 1 year was revised down to 6 months by the end of the decade.[1,2] Since 2000, the uses of capecitabine and oxaliplatin have been established, the former being shown to be at least equivalent to 5FU and the latter further improving survival.[3-6] In 2011, the National Institute for Health and Care Excellence (NICE) released permissive guidance for the use of adjuvant chemotherapy for high-risk Stage II disease. This was subsequently echoed in American Society of Clinical Oncology (ASCO) guidance and then incorporated into both National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidance.[7-9] More recently the duration of treatment has been further shortened to 3 months; the evidence strongest when using oxaliplatin and capecitabine (CAPOX) but the shorter course can still be considered for single agent capecitabine or oxaliplatin and 5FU (FOLFOX).[10,11] Again, ASCO and NCCN guidelines quickly adopted these changes as a new standard of care for all except patients with high-risk Stage III disease where 6 months is still recommended. More recently NICE have recommended 3 months for all patients when using CAPOX.[12]

Beyond stage, benefits of adjuvant chemotherapy may differ by molecular phenotype, patient age and site of disease. Microsatelite instability is present in 15% of colorectal cancers and is a result of deficient mismatch repair (dMMR) caused by a germline mutation in an MMR gene or epigenetic inactivation of the *MLH1* gene.[13] Although dMMR is a good prognostic factor, especially in Stage II disease, data on whether it is predictive treatment efficacy are mixed.[14,15]

In terms of increasing age, data are mixed for single-agent fluoropyrimidine; the QUASAR trial suggested diminishing benefit whereas a pooled analysis of the ACCENT database showed benefit was preserved in patients over 70 years.[16,17] Data on oxaliplatin are more consistent with no benefit found for patients over 70 years.[18,19] Age-related variance in benefit may relate to both an ability to tolerate chemotherapy and differences in biology of disease with increasing age.[20]

The evidence for a benefit of adjuvant chemotherapy for rectal cancer patients is inconclusive. Following a review of the evidence, ESMO concluded that the benefit of adjuvant 5FU following surgery alone was smaller than for colon cancer. Randomized trials have not shown benefit for adjuvant 5FU for patients who have received neoadjuvant radiotherapy and no consistent survival benefit has been shown for the addition of oxaliplatin to 5FU either during chemoradiotherapy and/or in the adjuvant setting.[21-25] Two studies exploring total neoadjuvant treatment recently reported improved 3-year disease-free survival or disease-related treatment failure, but data are too early to assess impact on survival.[26,27]

International bodies have provided guidance in these areas. The NCCN and ESMO guidelines support testing and recommend observation alone for dMMR high-risk pT3 stage II disease.[8] NICE and ASCO do not include guidance based on MMR status. In terms of rectal cancer, ESMO recommends that decision making should be shared with the patient while balancing the risk of relapse and predicted toxicity. NCCN, NICE and ASCO are more definite and support the use of adjuvant chemotherapy for both patients with higher risk disease irrespective of pre-op treatment. Only NICE mentions patient age as a factor to be considered in addition to performance status, comorbidity and personal preferences.

Given the degree of variance in published guidelines, and lack of a definitive evidence base for certain patient populations, there is potential for variation in adjuvant chemotherapy decision making. Colorectal cancer multidisciplinary Teams (MDTs) are responsible for the treatment and management of patients in the English National Health Service; ensuring every patient is discussed by a team of specialists including a clinical nurse specialist, surgeon, radiologist, oncologist, pathologist and gastroenterologist making sure all treatment

What's new?

Population-based data have shown that surgery practice for colorectal cancer varies widely among different regions. Here, the authors delved into the population data to quantify the variation in adjuvant chemotherapy across England. They found a surprisingly high variation in chemotherapy rates for high-risk stage II patients, and they suggest this difference results in part from clinicians' differing opinions about the effectiveness of chemotherapy for these patients. By highlighting the amount of regional variation in treatment practice, they achieved a consensus agreement on an algorithm they developed to provide standardized guidance for the use of chemotherapy.

options are considered. This study aimed to quantify any variation in adjuvant chemotherapy treatment across England and to explore this variation in greater detail using the large representative region of Yorkshire. This evidence was then used to help develop a consensus guideline for implementation across the region's 16 MDTs in an effort to minimize variation and improve colorectal cancer outcomes.

2 | MATERIALS AND METHODS

2.1 | Study design

The study was designed as part of the Yorkshire Cancer Research Bowel Cancer Improvement Programme (YCR BCIP); a regional intervention-based programme that is aiming to significantly improve colorectal cancer outcomes across a large representative region (Yorkshire and the Humber). It aims to do this by quantifying variation in practice and engaging with regional MDTs to understand this and develop educational interventions. A number of specialty groups (surgery, clinical oncology, medical oncology, radiology, pathology, clinical nurse specialists and anaesthetics) have been established to provide clinical direction, review the data and to develop appropriate initiatives. The YCR BCIP region accounts for approximately 10% of the colorectal cancer population of England[28] and hosts 16 of the 146 nationwide colorectal MDTs.

The study employed an iterative design, involving the region's oncologists on a number of occasions (Supplementary Figure S1). Variation in the use of adjuvant chemotherapy was investigated at a national level, using population-based data across all colorectal cancer MDTs treating patients in England. A more detailed account of the variation was then undertaken at a regional level, covering the MDTs participating in the YCR BCIP. Simultaneously in a separate qualitative study, the first of two rounds of questionnaires addressing the use of adjuvant chemotherapy for CRC were sent to regional oncologists.

A series of face-to-face and teleconference meetings for all oncologists from the YCR BCIP region were held to discuss the variance both in prescribing practice seen in regional and national data and the approaches taken by different MDTs seen from the questionnaire responses. Subsequently a further round of questionnaires was sent to assess if differences persisted and a further meeting to agree a final treatment algorithm, for use across the 16 MDTs in the region, with the aim to reduce treatment variation.

2.2 | Population-based data

Individuals aged ≥18 years, diagnosed with a first primary Stage II or III colorectal cancer (International Classification of Diseases 10th revision: C18-C20) in England from 1 January 2014 to 31 December 2015, were provided by the National Cancer Registry and Analysis Service. Through its data repository COloRECTal Repository (CORECT-R), the UK Colorectal Cancer Intelligence Hub provides linkage of these cancer registry data to a number of additional routine data sets across the English National Health Service, including hospital admission data and the systematic anticancer therapy (SACT) data set.[29] Submission of SACT data via electronic prescribing is mandatory for all NHS-funded providers in England and includes all cancer patients receiving systemic anticancer treatment. All patients who underwent a major resection and had not received neoadjuvant radiotherapy treatment were identified using previously described algorithms.[30,31] Patients were assigned a managing colorectal MDT using the hospital admission procedure closest to the patient's diagnosis date. If no procedure was found, the closest inpatient or outpatient appointment to the diagnosis date at a hospital with a colorectal MDT was used. The <1% of patients that could not be assigned an MDT were excluded from the study. In addition, 3% of all patients in the cancer registry data had an unknown stage of disease so it was not possible to ascertain if any of these were Stage II or III cancer and will have been excluded from these analyses. Two MDTs, including one within the YCR BCIP region, were found to have not submitted SACT data in the adjuvant setting at the time of data collection so were excluded from the analysis.

Patients receiving chemotherapy treatment were identified in the SACT data set if their first regimen after resection was within 6 months and the primary treatment diagnosis within SACT was confirmed as C18-C20. Those receiving the combination regimens of CAPOX or FOLFOX and the single agent regimens of capecitabine or 5FU were classified as receiving adjuvant treatment. Patients receiving a regimen usually used for metastatic disease were assumed to have progressed to an advanced disease stage and excluded (3% of those receiving chemotherapy). Patients receiving nonstandard regimens, commonly used for treatment of different cancers, were assumed to have been coded incorrectly and excluded (<1% of those receiving chemotherapy).

Multilevel logistic regression models were used to assess factors associated with adjuvant chemotherapy treatment, treating MDT as a random effect. The binary-dependent variable was set as whether the patient received adjuvant chemotherapy or not. Analyses were stratified by age and tumour stage, with the following covariates considered: age (when not stratified by), sex, socioeconomic status (income domain of the Index of Multiple Deprivation 2010), Charlson comorbidity score[32] and tumour stage (when not stratified by).

Funnel plots[33] were used to compare the rates of adjuvant treatment across MDTs within England. Each individual's probability of adjuvant treatment was derived from the logistic model and used to calculate MDT-specific treatment ratios. These were then multiplied by the average national adjuvant treatment rate (indicated by the horizontal line on the funnel plot) to calculate MDT-specific treatment rates. These rates were then plotted against the MDT workload (number of major resections performed). The funnelcompar command in Stata Version 15 was used to calculate and add 95% and 99.8% control limits around the average national rates, which is indicated by the inner and outer dashed lines, respectively. Those MDTs falling outside the range of limits are considered to be significantly different from the national average at the $P < .05$ and $P < .002$ levels. Example of Stata code for calculating and plotting MDT-specific treatment rates is given in Supplementary Information.

TABLE 1 Number of colorectal cancer patients, adjusted ORs and 95% CI for receiving adjuvant chemotherapy in England, diagnosed from 1 January 2014 to 31 December 2015

	Total cases	No adjuvant treatment		Single-agent treatment		Combination treatment		Total adjuvant treatment			
	N	N	%	N	%	N	%	N	%	OR (95% CI)	*P* value
Total	23 402	15 150	64.7	3175	13.6	5077	21.7	8252	35.3		
Age group											
<50	1242	437	35.2	158	12.7	647	52.1	805	64.8	4.25 (3.66, 4.93)	<.001
50 to 59	2643	1129	42.7	388	14.7	1126	42.6	1514	57.3	3.22 (2.89, 3.59)	<.001
60 to 69	6002	3020	50.3	890	14.8	2092	34.9	2982	49.7	2.31 (2.13, 2.51)	<.001
70 to 79	7902	5374	68.0	1371	17.4	1157	14.6	2528	32.0	Reference	
80+	5613	5190	92.5	368	6.6	55	1.0	423	7.5	0.14 (0.12, 0.16)	<.001
Sex											
Male	12 801	8263	64.5	1725	13.5	2813	22.0	4538	35.5	Reference	
Female	10 601	6887	65.0	1450	13.7	2264	21.4	3714	35.0	1.07 (1.00, 1.14)	.057
Site of tumour											
Colon	19 895	13 000	65.3	2700	13.6	4195	21.1	6895	34.7	Reference	
Rectal	3507	2150	61.3	475	13.5	882	25.1	1357	38.7	0.79 (0.72, 0.87)	<.001
Stage											
Stage II	12 073	10 201	84.5	1301	10.8	571	4.7	1872	15.5	Reference	
Stage III	11 329	4949	43.7	1874	16.5	4506	39.8	6380	56.3	9.42 (8.77, 10.13)	<.001
Charlson comorbidity level											
0	16 398	9939	60.6	2348	14.3	4111	25.1	6459	39.4	Reference	
1	4403	3055	69.4	579	13.2	769	17.5	1348	30.6	0.78 (0.71, 0.85)	<.001
2	1537	1225	79.7	167	10.9	145	9.4	312	20.3	0.53 (0.45, 0.61)	<.001
3	1064	931	87.5	81	7.6	52	4.9	133	12.5	0.29 (0.24, 0.36)	<.001
Index of multiple deprivation											
1	5284	3331	63.0	740	14.0	1213	23	1953	37.0	Reference	
2	5644	3554	63.0	760	13.5	1330	23.6	2090	37.0	0.99 (0.90, 1.09)	.83
3	4853	3219	66.3	596	12.3	1038	21.4	1634	33.7	0.84 (0.76, 0.93)	.0013
4	4188	2759	65.9	591	14.1	838	20	1429	34.1	0.87 (0.78, 0.98)	.016
5	3433	2287	66.6	488	14.2	658	19.2	1146	33.4	0.75 (0.75, 0.85)	<.001
YCR BCIP multidisciplinary team											
No	21 027	13 621	64.8	2788	13.3	4618	22.0	7406	35.2	Reference	
Yes	2375	1529	64.4	387	16.3	459	19.3	846	35.6	1.14 (0.86, 1.51)	.37

Abbreviations: CI, confidence interval; OR, odds ratio; YCR BCIP, Yorkshire Cancer Research Bowel Cancer Improvement Programme.

2.3 | Questionnaires

Two rounds of online surveys considering questions on the management of adjuvant chemotherapy in the YCR BCIP region were sent to all 14 medical and 15 clinical oncologists at the 16 regional MDTs to complete. These were completed anonymously, but the oncologist's MDT membership was reported. Questions related to general management and a set of hypothetical patient scenarios relate to stage, MMR status and age. In Round 1 of the questionnaires, patient scenarios pertained to chemotherapy and radiotherapy naïve colorectal cancer patients with Stage II (with and without high-risk features; T4 stage, extramural vascular invasion, low nodal count, emergency surgery and poor differentiation in pMMR patients) and Stage III disease (with either IIIA or B stage). These were modified and repeated in Round 2 of the questionnaires, along with another questionnaire specifically relating to rectal cancer patients who had received neoadjuvant radiotherapy treatment. For each set of patient scenarios, the oncologist was asked to indicate their preferred treatment option. Recipients were given the option to specify a different treatment option not listed in the set treatment options. Question details and the treatment options available are given in Supplementary Information.

3 | RESULTS

3.1 | Assessment of national variation

A total of 23 402 resected colorectal patients from England were included in the analysis (52% Stage II and 45% Stage III). The number of patients receiving adjuvant chemotherapy was 1872 (16%) and 6380 (56%) for Stage II and Stage III disease, respectively. The odds of receiving treatment decreased with increasing age, comorbidity level and socioeconomic deprivation and for those with a rectal cancer. The choice of single agent or combination therapy varied greatly by age and stage of disease (Table 1).

Across 144 English MDTs, the adjusted adjuvant chemotherapy treatment rate ranged from 2% to 46% for Stage II patients (Figure 1A) and from 19% to 81% for Stage III patients (Figure 1B). When stratifying

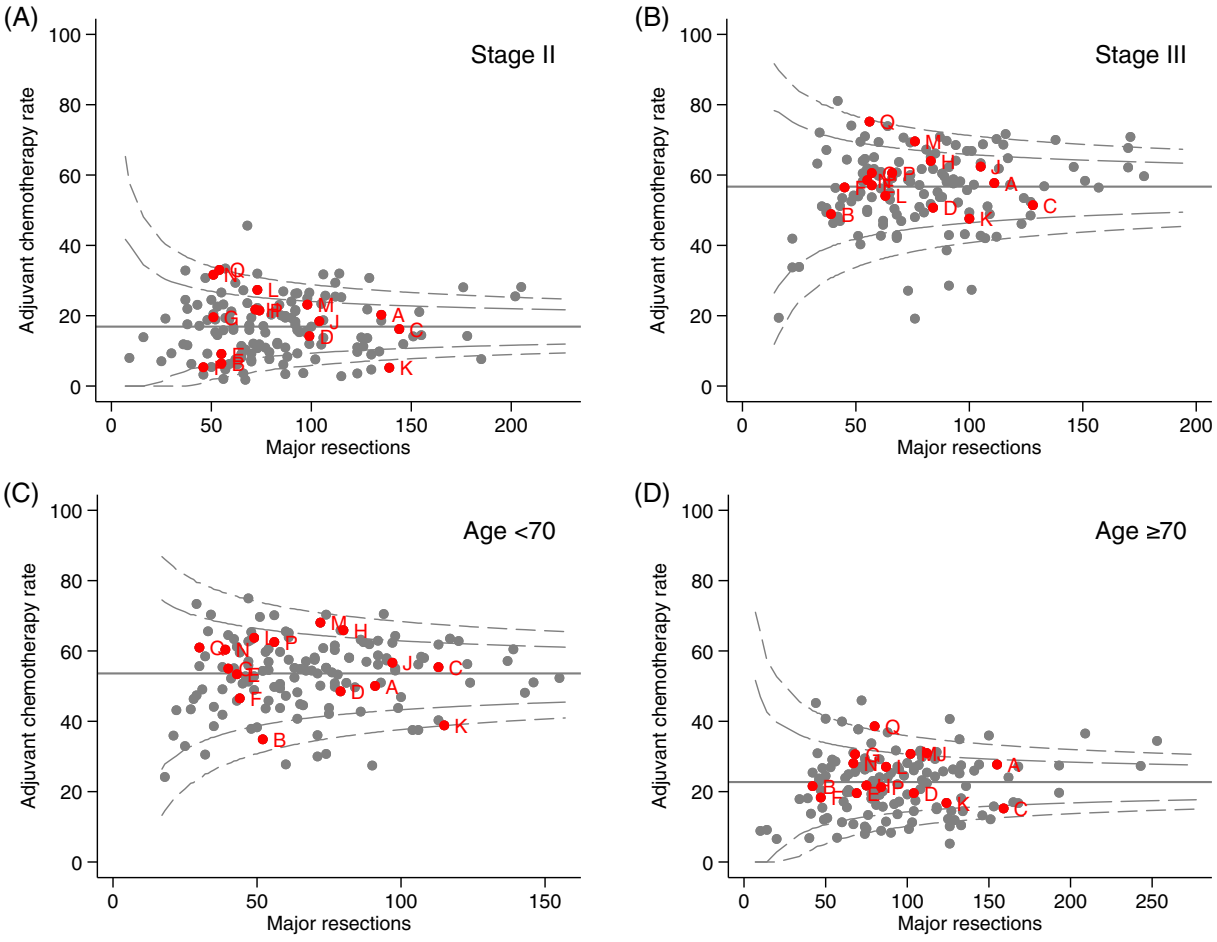

FIGURE 1 Funnel plots for risk-adjusted adjuvant chemotherapy rates for colorectal cancer patients with Stage II tumours (A), Stage III tumours (B), patients aged <70 years (C) and patients aged ≥70 years (D) by English MDTs for patients diagnosed from 1 January 2014 to 31 December 2015. Red points (A-Q) indicate MDTs covered by the Yorkshire Cancer Research Bowel Cancer Improvement Programme. The solid line represents the average national rate, and the inner and outer dashed lines are the 95% and 99.8% control limits [Color figure can be viewed at wileyonlinelibrary.com]

by age, the treatment rate ranged from 24% to 75% for patients aged <70 (Figure 1C) and from 5% to 46% for patients aged ≥70 (Figure 1D).

3.2 | Assessment of regional variation

The variation seen at national level was mirrored within the YCR BCIP region (n = 2375), with overall rates of adjuvant treatment similar to those outside the region (Supplementary Table S1).

Although a number of MDTs showed significantly outlying adjusted rates for both Stage II and III diseases, this was most prominent for Stage II (Figure 1). Variation was seen in the observed rates of patients receiving treatment (range: Stage II 4%-26%, Stage III 48%-71%). Combination therapy was mostly higher for Stage III patients (range: 40%-84%) but not for Stage II patients (range: 0%-55%) (Figure 2).

For patients aged <70 years, higher proportions of combination therapy were observed (treatment range: 29-69%, combination range: 49-91%). For patients aged ≥70 years, MDTs had an overall observed treatment rate of <40%, with a lower proportion of combination therapy in all but two MDTs (treatment range: 14-38%, combination range: 6-75%).

3.3 | Further investigation of regional variation

Responses to Round 1 (Stage II and III questionnaires) were received from oncologists at 15 of the 16 regional MDTs. Responses to Round 2 (Stage II, Stage III and rectal cancer after neoadjuvant radiotherapy questionnaires) were received from oncologists at 10, 10 and 13 of the 16 MDTs, respectively. All but one regional MDT partook in at least one of the questionnaires. MDT representation for each individual questionnaire can be found in Supplementary Table S2.

3.3.1 | MMR and DPD testing

All respondents cited informing adjuvant chemotherapy decision making for Stage II disease as a reason to request MMR testing; 12/15

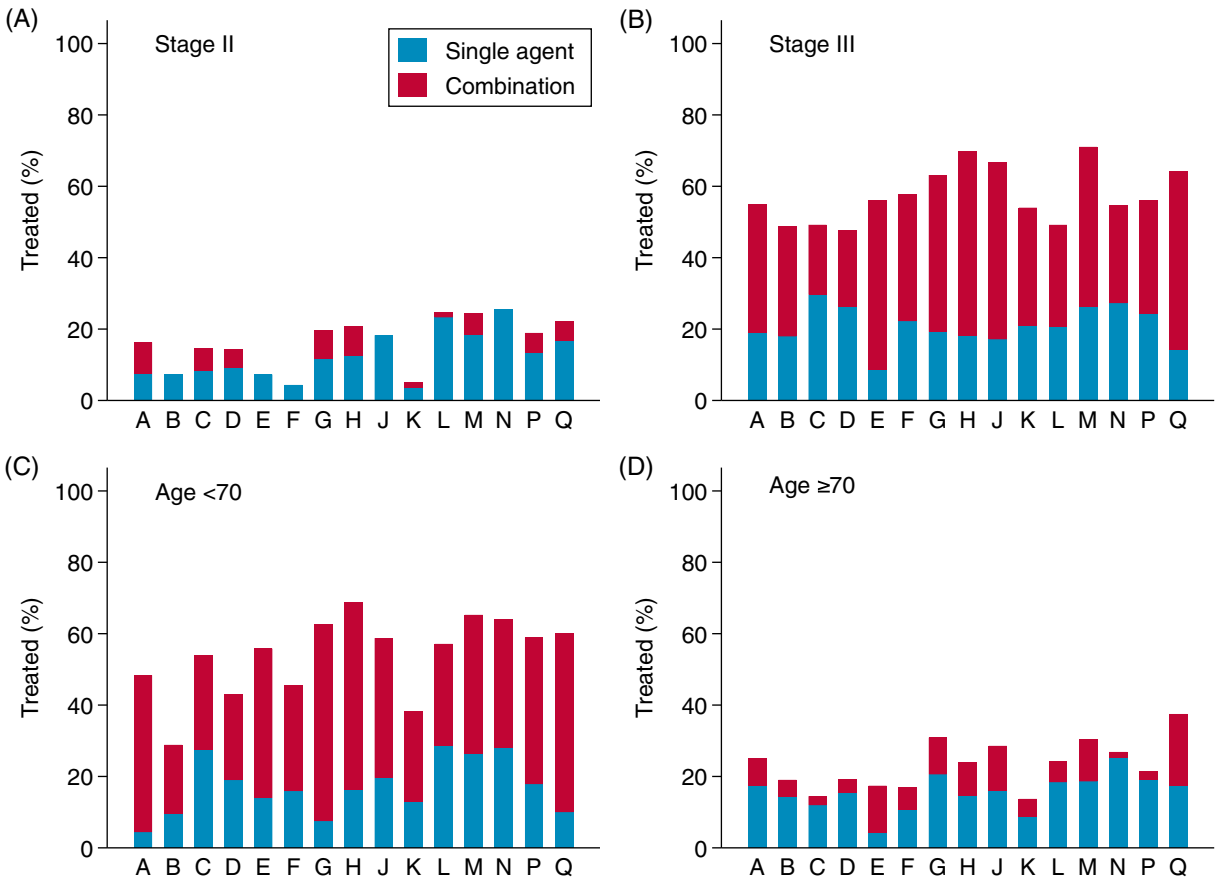

FIGURE 2 Use of and type of adjuvant chemotherapy by MDTs (A-Q) in the Yorkshire Cancer Research Bowel Cancer Improvement Programme for colorectal cancer patients with Stage II tumours (A), Stage III tumours (B), patients aged <70 years (C) and patients aged ≥70 years (D), diagnosed from 1 January 2014 to 31 December 2015 [Color figure can be viewed at wileyonlinelibrary.com]

sited screening for Lynch syndrome. In the second round of questionnaires, half of respondents reported that (dihydropyrimidine dehydrogenase) DPD testing was available.

3.3.2 | Stage II disease

In Round 1 of the questionnaire (Figure 3), for patients displaying low-risk features, the 15 oncologists were largely in agreement, with at least 11 (73%) selecting surveillance at the treatment option for all sets of patients <70 years. No oncologist reported chemotherapy as a treatment option for those low-risk feature patients aged ≥70.

There was less agreement for patients displaying high-risk features; for dMMR patients aged <70 years, clinicians were split between the use of combination chemotherapy and observation; for pMMR patients, clinicians were mostly split on whether they are single agent or combination. With increasing age, clinician's decision making became more conservative.

In Round 2 (Figure 3), T4 patient scenarios were separated out from the high-risk patient group and the 13 oncologists were split on single agent (n = 6, 46%) or combination (n = 6, 46%) for T4 pMMR patients aged <70 years. Nearly all oncologists now favoured single agent treatment for other high-risk pMMR patients in both those aged <70 (n = 12, 92%) and those aged ≥70 (n = 13, 100%).

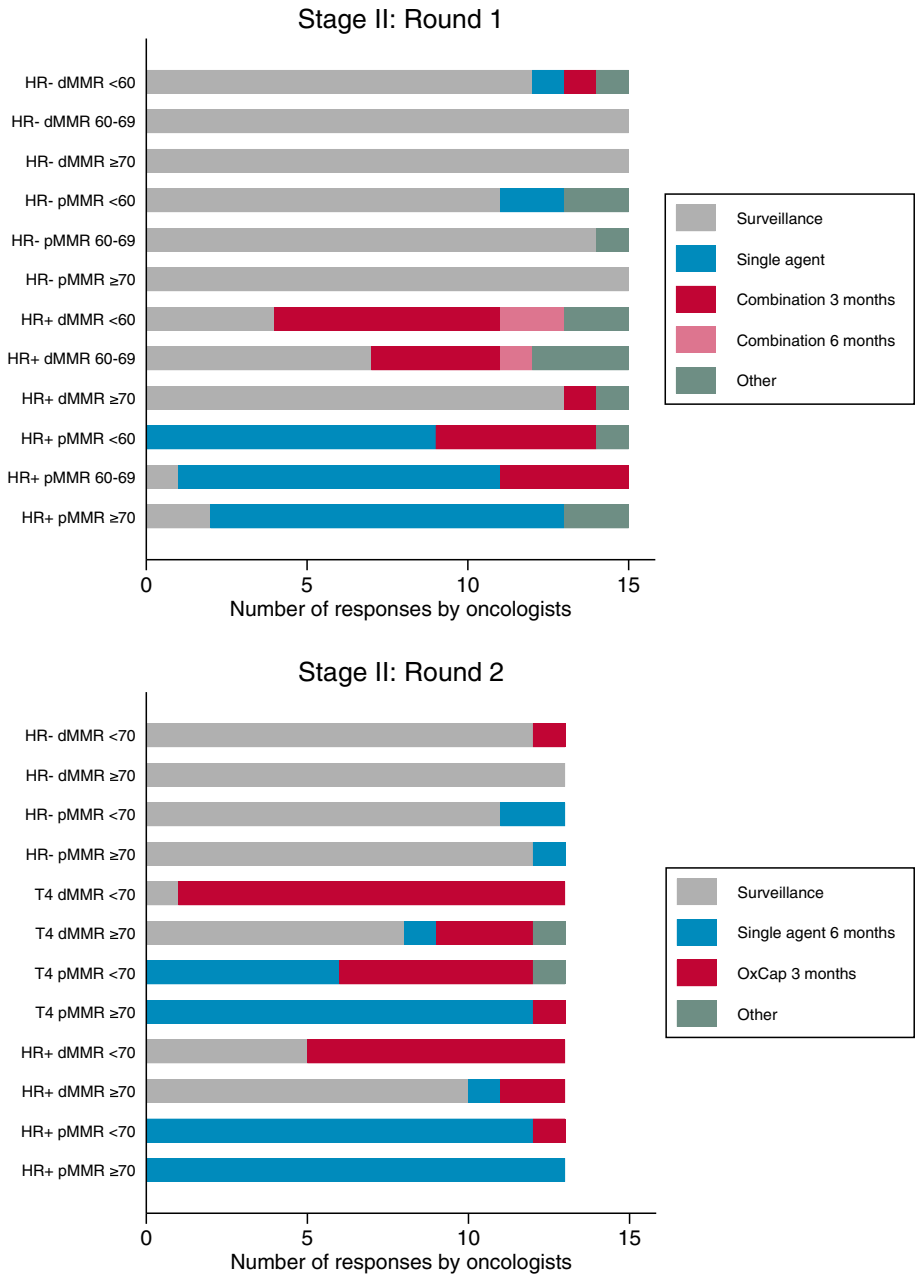

FIGURE 3 Number of treatment options selected by oncologists from MDTs in the Yorkshire Cancer Research Bowel Cancer Improvement Programme to the set of Stage II patient scenarios. HR − and HR+ indicate low- and high-risk features; in Round 2 T4 disease is separated from other high-risk features. dMMR, deficient mismatch repair; pMMR, proficient mismatch repair [Color figure can be viewed at wileyonlinelibrary.com]

3.3.3 | Stage III disease

In Round 1 of the questionnaire (Figure 4), for all Stage III patients aged <70 years there was uniformity among the 15 oncologists for recommending combination chemotherapy for pMMR patients, bar one who recommended single agent treatment for those aged 60 to 69 years.

For Stage IIIA patients ≥70 years, the majority of oncologists suggested single agent for pMMR patients (n = 9, 60%), but not for dMMR patients (n = 3, 20%). For Stage IIIB patients ≥70 years, oncologists were split on single agent (n = 6, 40%), combination (n = 5, 33%) and surveillance (n = 1, 7%) for pMMR patients; for dMMR patients, more clinicians suggested combination chemotherapy (n = 9, 60%).

In Round 2 (Figure 4), oncologists generally displayed more agreement but were still split on single agent (7/11, 64% in IIIA and 6/11, 55% in IIIB) or combination treatment (4/11, 36% in IIIA and 5/11, 45% in IIIB) for pMMR patients aged ≥70.

3.3.4 | Rectal cancer after neoadjuvant radiotherapy

All 12 respondents indicated that their postoperative management of patients treated with neoadjuvant radiotherapy differed from patients with colon cancer. Eight (67%) oncologists reported that they used both preoperative clinical and postoperative histological stage

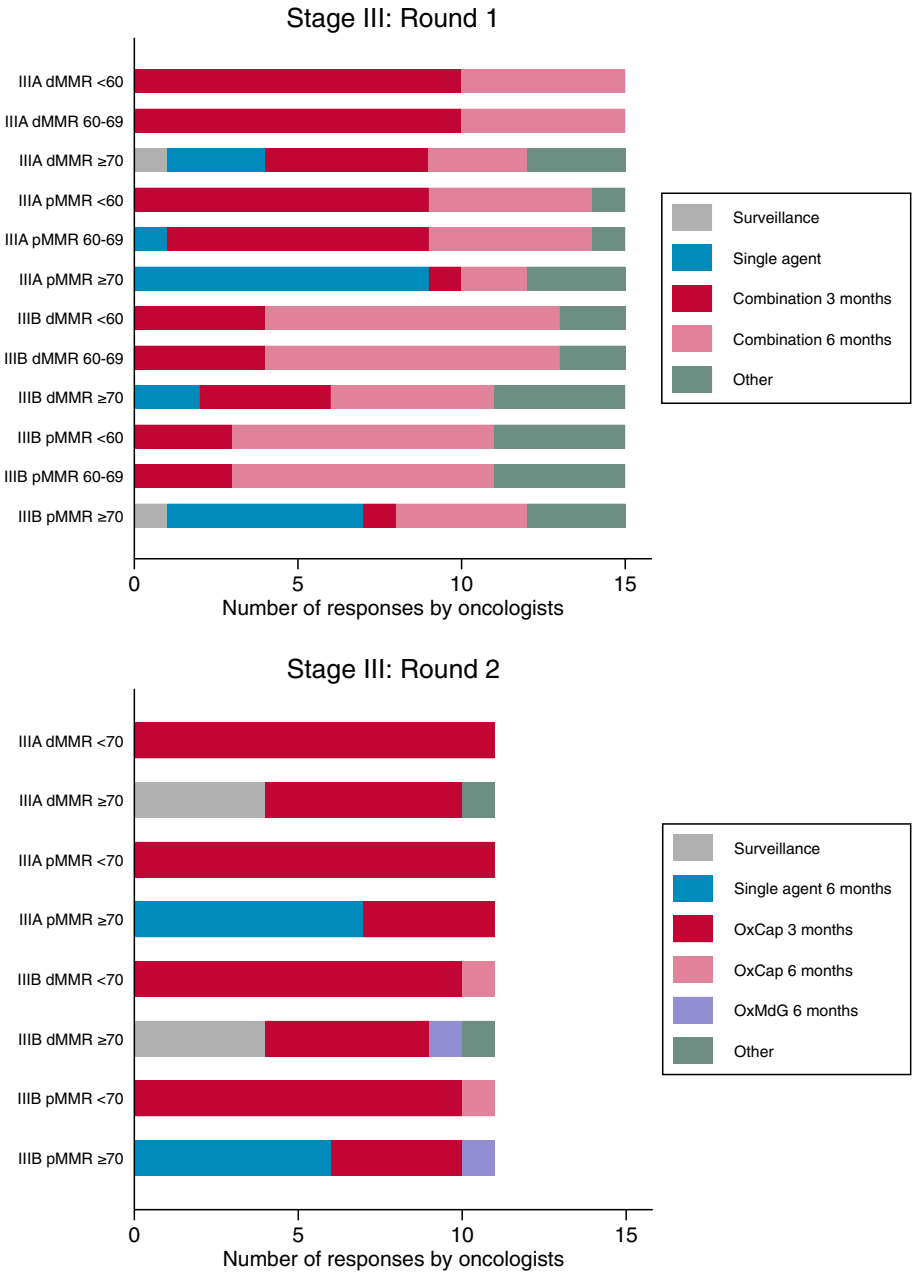

FIGURE 4 Number of treatment options selected by oncologists from MDTs in the Yorkshire Cancer Research Bowel Cancer Improvement Programme to the set of Stage III patient scenarios. dMMR, deficient mismatch repair; pMMR, proficient mismatch repair [Color figure can be viewed at wileyonlinelibrary.com]

information, three (25%) reported that they used just only preoperative cross-sectional imaging and one (8%) only postoperative histological stage. Six (50%) oncologists reported they had a higher threshold for using adjuvant chemotherapy for this group than for patients with colon cancer and six also reported they did not consider single-agent FU chemotherapy worthwhile for this patient group. Six (50%) oncologists reported they predominantly restrict adjuvant chemotherapy to those under age 70. For patients with pathological complete response, three (25%) reported that they would consider adjuvant chemotherapy based on clinical stage at diagnosis.

3.4 | Treatment guideline

After the discussion among the region's oncologists at the consultation meetings in which the regional variation and previous published evidence were discussed, a treatment algorithm for Stage II and III colorectal patients was constructed and proposed as a guideline for regional MDTs at various stages during the study, before the finalised version was agreed upon (Figure 5). Given the ubiquitous availability of MMR testing across the region, we included guidance for patients with either dMMR or pMMR testing in accordance with ESMO and

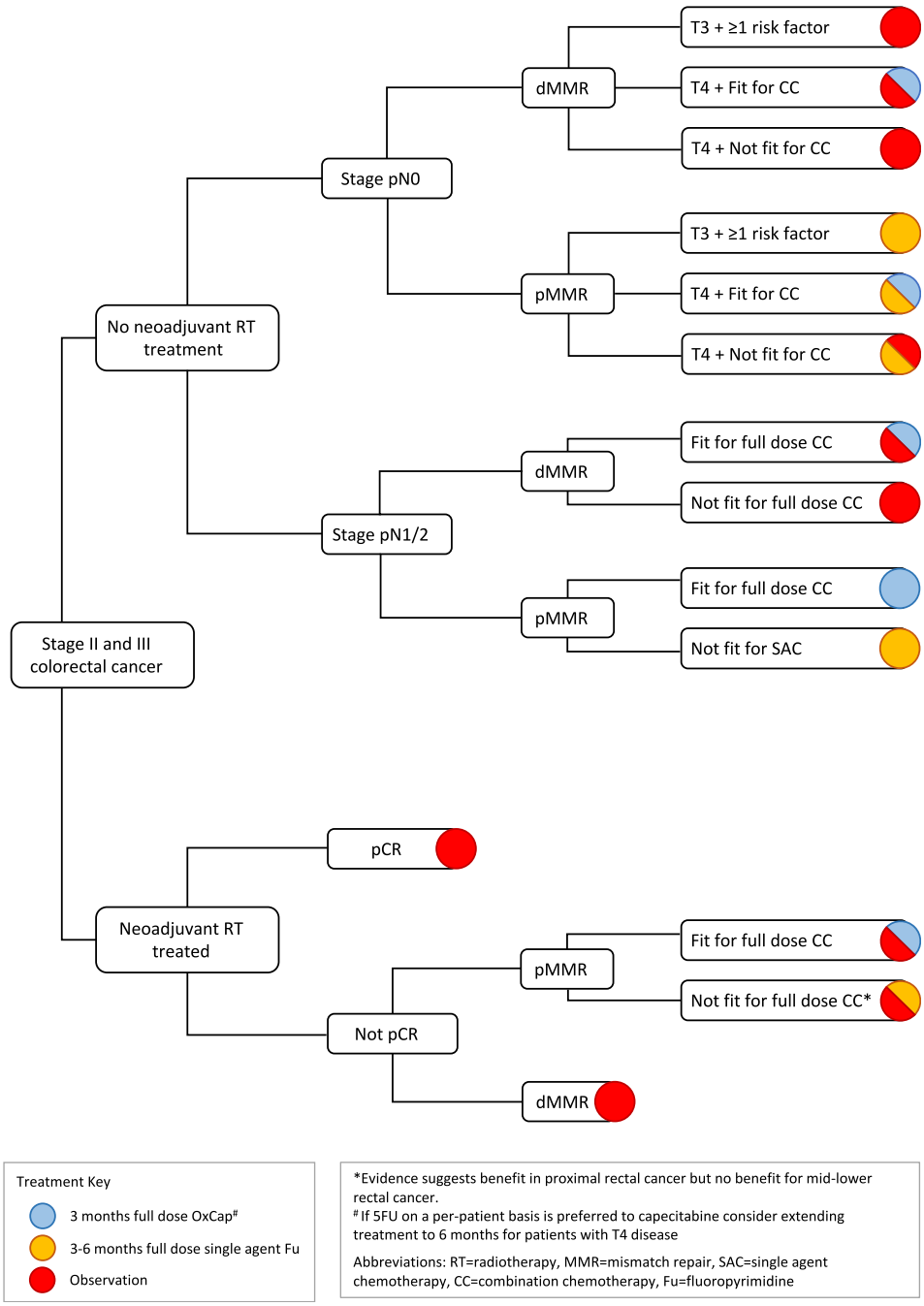

FIGURE 5 Treatment guidelines algorithm for colorectal cancer patients agreed by oncologists in the Yorkshire Cancer Research Bowel Cancer Improvement Programme [Color figure can be viewed at wileyonlinelibrary.com]

NCCN guidance. NICE is the only National body to mention age but does not specify a cut point around which to pivot decision making. We also did not include a specific age cut point. Sporadic dMMR occurs more commonly in the elderly and the algorithm recommends a more conservative approach in the absence of T4 or node positive disease for this molecular type. For those with more advanced T or N stage combination chemotherapy at full dose or observation is recommended on the understanding that comorbidity and performance status will be taken into account in accordance with NICE guidance. Hence, an older patient is less likely to be treated given the higher rate of dMMR, comorbidity and frailty related lower performance status. We limited treatment duration to 3 months when using OxCap for all patients including those with higher risk-stage III disease in accordance with NICE but discordant with NCCN and ASCO guidance. The absolute difference in 3-year survival for these patients treated for 3 and 6 months of OxCap in the IDEAL data set was 0.1% against an increase in Grade 3 neurotoxicity of 6%. We provided guidance on patients with rectal cancer who had received neoadjuvant chemoradiotherapy, which was more conservative than NICE, ESMO, NCCN and ASCO guidance and more akin to Dutch guidance.

4 | DISCUSSION

This study has demonstrated both national and regional variations in the use of adjuvant chemotherapy treatment across MDTs managing colorectal cancer in England. This variation was not explained by differences in simple case mix factors at a national level nor more detailed factors at a regional level. The study has highlighted a number of inconsistencies in clinical practice across a large representative region of England, specifically, on the use of adjuvant treatment for Stage II high-risk dMMR patients, and the choice of single agent or combination therapy for Stage II T4 pMMR patients and Stage III pMMR patients aged ≥70. After consultation meetings with oncologists, a consensus treatment guideline has been developed.

Recently the benefits of chemotherapy over and above the presence of modern multidisciplinary care in Stage II disease, and for some Stage III disease patients, have been questioned.[34] Given that it is not currently possible to identify the high-risk stage II patients within the national registry data, some variation in treatment rates for these patients may have been anticipated. The extent of this variation appears, however, to be surprisingly high and so unlikely to be explained by differences in patient and tumour characteristics but rather a result of clinician preference. This view is supported by the results of the questionnaire with regard to Stage II high-risk dMMR patients. Given the lack of evidence for improved outcomes for low-risk dMMR patients,[35] the algorithm developed here recommends adjuvant treatment over surveillance only for those dMMR patients with the strongest adverse risk factor, T4 stage. Poor differentiation is not a risk factor of dMMR tumours and the improved outcomes seen with dMMR counter the adverse prognosis attributed to the presence of vascular invasion. The evidence base guiding which regimen to use for dMMR tumours is mixed, but provided concerns that single-agent fluoropyrimidines are ineffective and combination chemotherapy is recommended. If patients are not fit for such, then surveillance is recommended.

For Stage III patients, some form of adjuvant treatment was suggested by oncologists for most patients regardless of MMR status or age. Hence, differences in opinion of oncologists do not explain significant variation seen in adjusted rates across MDTs in the regional and national data. There were differences in opinion for the choice of single agent or combination chemotherapy for elderly Stage III patients. The majority of clinicians recommended single-agent chemotherapy for Stage IIIA patients in keeping with evidence, suggesting patients over 70 years do not benefit from the addition of oxaliplatin but more clinicians recommended combination chemotherapy for Stage IIIB patients. The algorithm does not specify age cut off but focuses on fitness for full-dose chemotherapy and disease biology. The reasons for the lack of benefit observed in patients over 70 years are unclear but we recognize that sporadic dMMR is more frequently observed in older patients and therefore may be a contributing factor.

This study has a number of limitations, which we were unable to fully address. Although SACT data submission has been mandatory for all NHS providers in England from 2014,[36] it appears this is not fully complied to for the period covered here, as two MDTs were found to have no adjuvant chemotherapy-treated patients. Additionally, the cancer registry data do not provide full information on characteristics to identify high-risk patients and other potentially important factors relating to treatment decisions such as comorbidities not recorded through the Charlson comorbidity index. However, the additional data collection in this study compensates somewhat for these omissions and emphasises the variation shown in national data sets. Patient choice is also likely to be factor here, but it was not possible to account for this in the data used in this study. Previous studies have demonstrated that an increased travel burden is associated with a decreased likelihood of receiving adjuvant chemotherapy.[37,38] It was not possible to assess this within our data, however, a systematic review in the United Kingdom concluded that while variation between healthcare boundaries were observed, other factors such as capacity and treatment policy were more influential than geographical factors.[39]

The patient scenarios in the questionnaires used age as a patient group. Although in some cases this may be a suitable proxy for frailty and fitness to undergo chemotherapy treatment, discussions among the regional oncologists made it clear that a more appropriate measure would be ideal. The algorithm has used the relatively bland term “fit for chemotherapy” based on the expectation that clinicians will factor a patient's comorbidity, performance status and preference during decision making in keeping with NICE guidance. We recognize that ASCO have released guidance on assessment of older patients receiving chemotherapy.[40] The tools highlighted in this guidance document have been developed largely in patients with advanced disease and are not tumour site specific.[41-43] There is a need to develop a tool to help predict which patients are likely to tolerate and complete adjuvant chemotherapy for colorectal cancer. The linked datasets accessed through this work provides an opportunity to further explore this area.

The algorithm developed here provides general guidance to adjuvant treatment; however, it is not expected to provide a definite

stratification of patients as it is not possible to take in account all patient characteristics at such a level. Care must be taken if extending the algorithm for use in other populations, for instance, this study used National Health Service data where access to treatment is good and therefore it was not necessary to take into account factors such as health insurance status and patient access.

In summary, this study has identified considerable variation in the management of adjuvant chemotherapy for colorectal cancer at regional and national levels. Bringing this information to the attention of clinicians through the YCR BCIP enabled a consensus agreement on a proposed algorithm to reduce treatment variation across a large representative region of England. Such a process could be replicated in other regions.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICS STATEMENT

The YCR BCIP study was granted ethical approval (17/WM/0374) by the West Midlands - Solihull Research Ethics Committee in December 2017. The study was approved by the Health Research Authority and granted approval for inclusion in the National Institute for Health Research's portfolio of studies in December 2017 (Project ID 227673).

DATA AVAILABILITY STATEMENT

Access to cancer registration data and the other routine health datasets used in this study is controlled by the Public Health England Office for Data Release. The data supporting the results of the questionnaires are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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