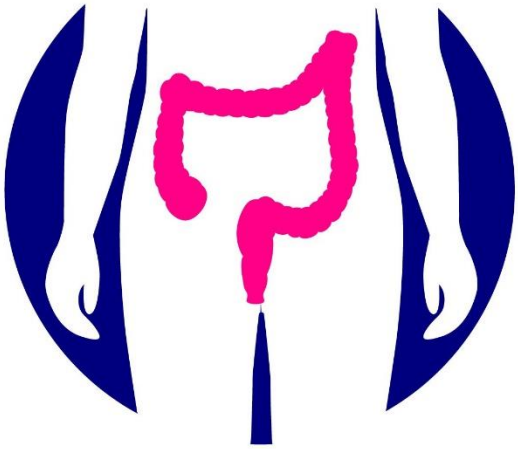

Evaluating concordance with colon cancer NICE treatment guideline recommendations

November 2024

CANCER RESEARCH UK

NHS

Together we are beating cancer

Reference

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About Cancer Research UK

We're the world's leading cancer charity, dedicated to saving and improving lives through research. We fund research into the prevention, detection and treatment of more than 200 types of cancer through the work of over 4,000 scientists, doctors and nurses. In the last 50 years, we've helped double cancer survival in the UK and our research has played a role in more than half of the world's essential cancer drugs. Our vision is a world where everybody lives longer, better lives, free from the fear of cancer.

Our values

Our values help guide our behaviour and culture in an ever-changing world, building on the best of what we do today and what we aspire to be in the future. They unite and inspire us to achieve our ambitious plans and our mission of beating cancer, together.

Our values are:

Bold

Act with ambition, courage and determination

Credible

Act with rigour and professionalism

Human

Act to have a positive impact on people

Together

Act inclusively and collaboratively

Contents

Executive summary

NICE guidelines for cancer treatment set out recommended treatment for patients. However, the levels of concordance to these recommendations are not known. This project aimed to establish levels of concordance to as many colon cancer NICE treatment recommendations as possible, and to investigate variation in concordance by patient characteristic and Cancer Alliance using cancer registration and treatment datasets.

Concordance could only be assessed for two colon cancer treatment recommendations, using currently available routine datasets and the timescale for the project. Inclusion criteria for these recommendations included whether a patient was suitable for surgery and the stage at diagnosis.

Concordance was 98.9% for the recommendation that preoperative chemotherapy alone should not be routinely offered for patients with locally advanced colon or rectal cancer unless as part of a clinical trial and 53.4% for the recommendation that capecitabine as monotherapy or oxaliplatin in combination with 5-fluorouracil and folinic acid are recommended as options for the adjuvant treatment of patients with stage III (Dukes' C) colon cancer following surgery for the condition.

There was no significant association between gender and concordance to either of the recommendations.

Age group was significantly associated with receiving concordant treatment for both recommendations investigated, but the direction of the association was opposite. Patients aged <45 or 45-54 were significantly less likely to receive treatment concordant to the recommendation that preoperative chemotherapy should not be offered compared to those aged 65-74, while those aged 75-84 were more likely. Those aged <45, 45-54 or 55-64 were more likely to receive treatment concordant to the adjuvant treatment recommendation compared to those aged 65-74, while those aged 75-84 or 85+ were less likely.

Deprivation was significantly associated with concordance to the recommendation on adjuvant chemotherapy with those living in the most deprived areas the least likely to be guideline concordant. There was no significant association for the preoperative chemotherapy recommendation.

Ethnicity was significantly associated with receiving treatment in concordance with the recommendation on adjuvant chemotherapy with those of Black, Asian, or 'Other' ethnicity less likely to have concordant treatment compared to those of White ethnicity. There was no significant association for the preoperative chemotherapy recommendation.

Comorbidity score was significantly associated with receiving treatment concordant to the recommendation on adjuvant chemotherapy with patients with increasing comorbidity scores increasingly less likely to receive concordant treatment.

Patients diagnosed at a later stage were less likely to receive treatment concordant to the recommendation that preoperative chemotherapy alone should not be given.

Concordance was significantly associated with year of diagnosis for both recommendations with concordance generally more likely in later years.

The effect of Cancer Alliance was significant for both recommendations investigated. The recommendation that preoperative chemotherapy alone should not be given had a larger standard deviation and coefficient range for the effect of Cancer Alliance compared to the recommendation on adjuvant chemotherapy.

Background

The National Institute for Health and Clinical Excellence (NICE) provides guidelines for promoting good health and preventing and treating ill health in England and Wales (1), including recommendations for the treatment of cancer (2). These guidelines make evidence-based recommendations and, as such, their implementation can be hypothesised to translate to improved outcomes. Investigating the levels of concordance to the treatment recommendations could help to highlight any potential gap between recommended and actual practice and suggest potential areas for improving the delivery of evidence-based treatment.

Yet levels of concordance to the recommendations from the NICE guideline for colon cancer treatment (3) have not been comprehensively investigated in England. An exception is the use of adjuvant chemotherapy for stage III colon cancer which is regularly reported as part of the National Bowel Cancer Audit. The most recent audit (patients diagnosed 2021/22) (4) found that around 62% of eligible patients received relevant adjuvant chemotherapy, with increasing age, lower socioeconomic status, higher comorbidity score, and poorer performance status associated with reduced adjuvant chemotherapy use (5). Variation in the type of adjuvant chemotherapy received by stage III colon cancer patients in England has also been investigated, with the odds of receiving combination therapy rather than monotherapy decreasing with age and lower for the most deprived group, but higher for those with larger tumour size and greater nodal involvement (6). Recently published evidence indicated that use of chemotherapy was lower in colon cancer patients in England and the other UK nations compared to several other countries and sub-national jurisdictions participating in the International Cancer Benchmarking Partnership, suggesting either lower concordance to guidelines or differing guidelines or inclusion criteria for treatment (7).

While concordance to NICE colon cancer guidelines has not been widely studied, there have been several studies looking at concordance to the relevant colon cancer guidelines in other countries, mostly relating to patient populations in the United States (8; 9; 10; 11; 12), but also Canada (13), Netherlands (14), Australia (15), Sweden (16) and France (17). These studies largely found that age and comorbidity were associated with guideline-concordance, with other variables including sex and deprivation measures also showing an association in some studies. Interestingly, these studies highlight that the relationship between guideline-concordance and explanatory variables varies depending on whether a guideline is recommending that a treatment be offered or not offered. For early-stage guidelines, which typically indicate that chemotherapy should not be given, concordance is often lower for younger patients (12). However, studies focusing on guidelines for later stages where adjuvant chemotherapy is recommended largely found comparable results to those from the National Bowel Cancer Audit, with older age and increased comorbidity score associated with increased risk of non-concordance (12; 9; 8; 16). Doctors recommending against therapy for older and sicker patients or patients choosing not to have guideline recommended treatment have been identified as important reasons for

non-guideline-concordant treatment (10; 15; 13). Several of these studies also investigated the relationship between survival and concordance and consistently found that concordance to treatment guidelines was associated with improved outcomes compared to non-concordance (8; 9; 11).

Methods

Determining which NICE guideline recommendations were suitable for analysis within this project

The first NICE cancer service guideline for colorectal cancer was published in 2004 (CSG5) and then replaced with a clinical guideline for the diagnosis and management of colorectal cancer in 2011 (CG131). The 2011 guideline has been superseded by a 2020 NICE guideline during the course of this project.

The 2011 guideline makes several recommendations divided into four main themes:

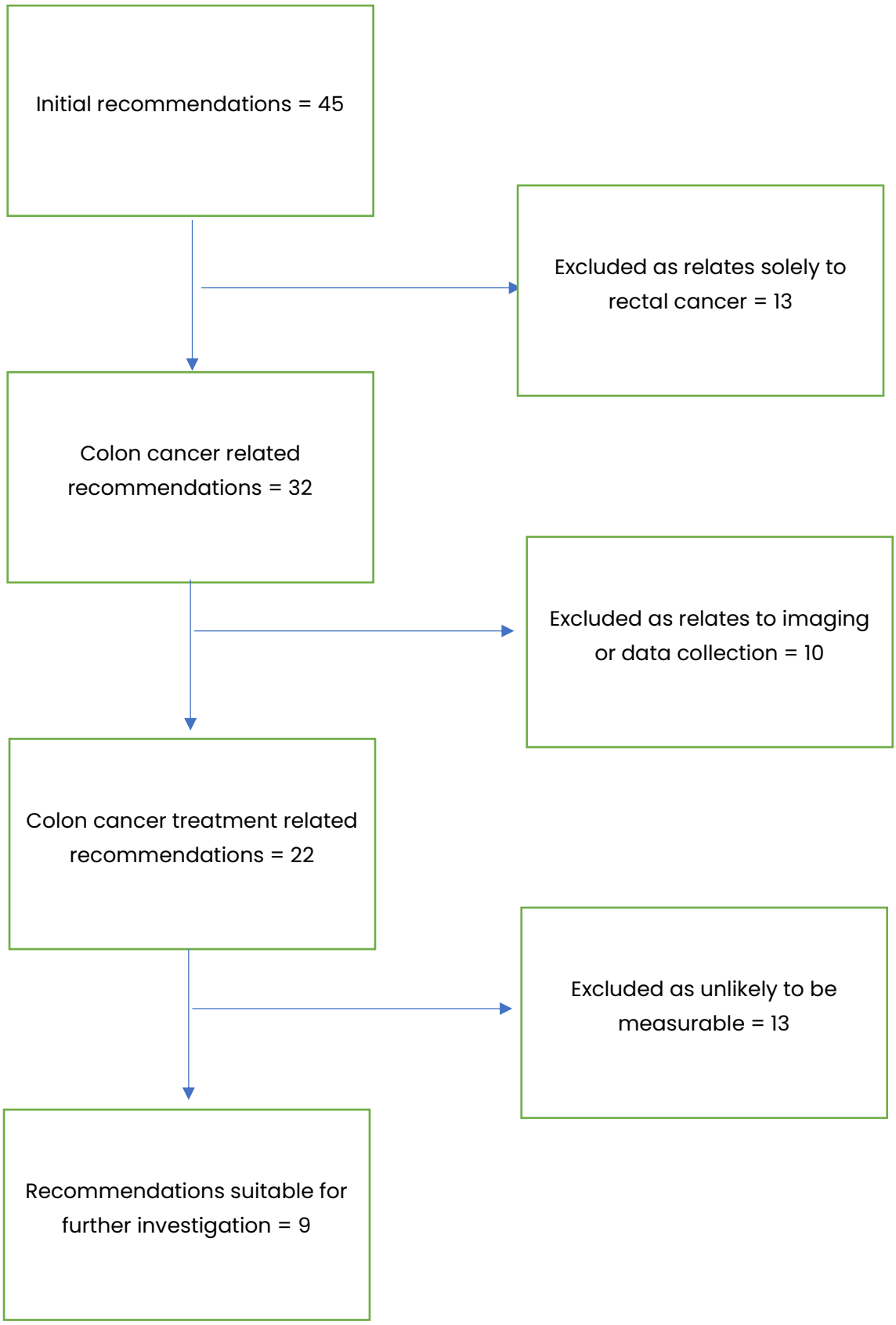
1. Investigation, diagnosis, and staging
2. Management of local disease
3. Management of metastatic disease
4. Ongoing care and support

As this project was focussed on and used treatment datasets, only recommendations from the management of local or metastatic disease ('2' and '3') were considered.

Within these sections, recommendations were divided by several factors including colon or rectal cancer and stage. Several of the rectal cancer treatment recommendations involved a risk classification schema which could not be applied based on the patient data available for the study and hence rectal cancer was excluded from the analysis and only recommendations which pertained to colon cancer or to colorectal cancer were included for consideration.

Of the remaining colon appropriate recommendations, a number of these were found to not be suitable for this investigation because concordance to them was unlikely to be able to be determined from the routinely collected datasets available, such as recommendations on multi-disciplinary team discussions or the importance of communicating with patients. Several recommendations also related to imaging or data collection and so were excluded.

Figure 1: Flow diagram demonstrating how many recommendations were investigated and exclusion reasons



Of the nine recommendations initially identified as suitable for further investigation, four were not suitable for definition upon further investigation of availability of required variables in the routine datasets and discussion with clinicians, leaving five recommendations potentially suitable for inclusion.

Time restrictions meant that only the two most readily definable recommendations were able to be investigated within the remit of this project:

- 1.2.1.8 - Do not routinely offer preoperative chemotherapy alone for patients with locally advanced colon or rectal cancer unless as part of a clinical trial. [2011]
- 1.2.8.1 - The following are recommended as options for the adjuvant treatment of patients with stage III (Dukes' C) colon cancer following surgery for the condition: capecitabine as monotherapy or oxaliplatin in combination with 5-fluorouracil and folinic acid [2006]

Defining the cohorts and concordance

Overall cohort

The overall cohort was defined as patients who had a record of a C18 International Classification of Diseases (10th edition) (ICD10) code tumour diagnosed between 2015 and 2018 within the National Cancer Registration Dataset (NCRD) (18). Further inclusion criteria for patients were applied as standard (19) with only patients resident in England, finalised, non-duplicated cases with a sensible age (between 0 and 200 years old) and known gender included. Patients recorded as death certificate only or with multiple malignant tumours (excluding C44) at any point were excluded due to the likely impact that this would have on their treatment history. This overall cohort was subsequently used for sub-cohort definitions (see below).

Specific sub-cohorts

Cohort for recommendation 1.2.1.8 - Do not routinely offer preoperative chemotherapy alone for patients with locally advanced colon or rectal cancer unless as part of a clinical trial.

Locally advanced colon cancer was defined as stages 1-3, based on discussion with clinicians. Patients with any record of preoperative chemotherapy were defined as non-concordant, irrespective of whether they also had radiotherapy, based on advice from clinicians due to the low use of radiotherapy for colon cancer.

This sub-cohort was defined as patients from the overall colon cancer cohort diagnosed at stage 1 -3 who had a record of major colorectal site-specific surgery (an attempt to surgically remove the whole of the primary tumour defined using colorectal cancer specific Operating Procedure Codes Supplement (OPCS) codes for resection of primary

tumour taken from previous work (20), endoscopic procedures were not included for any stage) within one month pre-diagnosis and six months post-diagnosis recorded in the Hospital Episode Statistics Admitted Patient Care (HES APC) dataset or NCRD treatment datasets and who did not have a record of being involved in a clinical trial in either the systemic anti-cancer therapy (SACT) or NCRD treatment datasets.

Concordance to recommendation 1.2.1.8 was defined as patients with either no record of chemotherapy in the SACT or NCRD treatment datasets within one month pre-diagnosis and 12 months post-diagnosis or who only had chemotherapy recorded after the date of their first surgery.

A sensitivity analysis was also conducted where patients whose first recorded chemotherapy was up to 31 days before surgery were also defined as concordant.

Cohort for recommendation 1.2.8.1 - The following are recommended as options for the adjuvant treatment of patients with stage III (Dukes' C) colon cancer following surgery for the condition: capecitabine as monotherapy or oxaliplatin in combination with 5-fluorouracil and folinic acid.

Adjuvant treatment was defined as chemotherapy within 84 days of surgery, with this definition based on clinician guidance, but only the first treatment post-surgery was chosen so that only first line treatment was used. While this recommendation specified capecitabine or oxaliplatin with 5-fluorouracil and folinic acid (MdG), regimens containing capecitabine with oxaliplatin, 5-fluorouracial alone or raltitrexed were also accepted. The combination of capecitabine and oxaliplatin is now recommended in the 2020 NICE guideline as an adjuvant chemotherapy option for stage 3 colon cancer and including this combination within the definition was agreed through discussion with clinicians.

The cohort for 1.2.8.1 was defined as patients from the overall colon cancer cohort diagnosed at stage 3 who had a record of major colorectal site-specific surgery (an attempt to surgically remove the whole of the primary tumour defined using colorectal cancer specific Operating Procedure Codes Supplement (OPCS) codes for resection of primary tumour taken from previous work (20), endoscopic procedures were not included for any stage) within one month pre-diagnosis to six months post-diagnosis in the HES APC or NCRD treatment datasets.

Concordance to recommendation 1.2.8.1 was defined as patients who had one of the following chemotherapy regimens listed as their first adjuvant chemotherapy regimen in the SACT or NCRD treatment datasets, and within 84 days from their first surgery date:

- CAPECITABINE + OXALIPLATIN
- CAPECITABINE
- OXALIPLATIN + MDG
- RALTITREXED
- FLUOROURACIL

A sensitivity analysis was also conducted where the period of adjuvant chemotherapy occurring within 84 days of surgery was based on the latest date of relevant surgery for a patient, rather than the first relevant surgery. A further analysis was also carried out extending the adjuvant chemotherapy inclusion timeline to 124 days post-surgery, in line with the time frame used in the National Bowel Cancer Audit.

Statistical analysis

All statistical analysis was conducted using R version 4.4.0 with regression models produced using the lme4 package. A p value of <0.05 was considered to be significant. Details of patient demographics and tumour characteristics including stage, gender, age, ethnicity, deprivation, and comorbidity score were extracted from routinely collected datasets held by the National Disease Registration Service (NDRS) with details of chemotherapy treatment extracted from the SACT and NCRD treatment datasets and details of surgical treatment extracted from the HES APC and NCRD treatment datasets.

Age at treatment start date was grouped into six broad categories (<45, 45-54, 55-64, 65-74, 75-84 and 85+ years), deprivation quintile was based on the full 2019 Index of Multiple Deprivation for patient area of residence. For recommendation 1.2.8.1 ethnicity was grouped into Asian, Black, Mixed, White or Other ethnicity based on the Census groupings (20). Due to small number limitations, Asian, Black, Mixed and Other ethnicity were combined to a Minority ethnic groups category for recommendation 1.2.1.8. Comorbidity score was defined based on the Charlson comorbidity index looking at the period from 27 months to 3 months prior to the cancer diagnosis and grouped to a score of 0, 1, 2 or 3+. For non-ordered categorical variables, the most common category was used as the reference category. This meant that male gender, 65-74 age group, White ethnicity, the least deprived quintile, zero comorbidity score and 2015 diagnosis year were the reference groups. Stage 1 was used as the reference for recommendation 1.2.1.8 and the West Midlands was used as the reference Cancer Alliance.

Concordance was defined as a binary yes or no variable and percentages concordant within each category of the explanatory variables were calculated. Unadjusted logistic regression was then conducted for gender, age, ethnicity, deprivation, comorbidity score, stage and diagnosis year to calculate an unadjusted odds ratio for concordance to the recommendation. A mixed effects model was then produced using Cancer Alliance as the random effect to generate adjusted odds ratios for each potential explanatory variable, accounting for potential clustering of observations within Cancer Alliances. An additional mixed effects model with an interaction term between age and comorbidity score was also produced.

The relationship between Cancer Alliance and concordance to each recommendation was assessed by using an ANOVA test to compare the full mixed effects model to a model including all the predictor variables but no Cancer Alliance random effect.

Results

Recommendation 1.2.1.8 - Do not routinely offer preoperative chemotherapy alone for patients with locally advanced colon or rectal cancer unless as part of a clinical trial

There were 38,501 patients in the sub-cohort for recommendation 1.2.1.8, of whom 38,063 received treatment concordant to this recommendation (98.9%). In the adjusted model, age group was significantly associated with the likelihood of not receiving preoperative chemotherapy, with those in the <45 and 45-54 group being significantly less likely than those in the 65–74-year-old group to receive treatment concordant to this recommendation (adjusted odds ratio (AOR) of 0.54 and 0.64 respectively) and those in the 75–84 age group significantly more likely (AOR of 1.38). There was no evidence for an association between gender, deprivation, ethnicity, or comorbidity score and receiving recommendation concordant treatment. Stage had a statistically significant relationship with the likelihood of not receiving preoperative chemotherapy with individuals diagnosed at stage 2 or 3 significantly less likely than those diagnosed at stage 1 to not receive this (AOR of 0.67 and 0.33 respectively). More recent diagnosis year was associated with concordance with those diagnosed in 2016 or 2017 more likely to receive concordant treatment than 2015 (AOR of 1.41 and 1.35 respectively) although there was not a significant difference for 2018 (Table 1). There was variation in the levels of concordance to this recommendation by Cancer Alliance, both in unadjusted analyses (Figure 2), and the adjusted regression analyses with an overall p value of <0.001 for the inclusion of Cancer Alliance as a random effect in the model. The standard deviation for the Cancer Alliance random effect was 0.307 and the coefficient ranged from -0.590 to 0.428.

There was no statistically significant interaction between age and comorbidity score.

Table 1: Demographic breakdown of the cohort for recommendation 1.2.1.8, number and percentage of the cohort treated in concordance with the recommendation and odds ratios for recommendation-concordance from unadjusted analyses and adjusted for all the other variables

Characteristic	Category	Number in cohort	Percentage of cohort (%)	Number concordant	Percentage concordant (%)	Unadjusted odds ratio (95% CIs)	Unadjusted overall p value[1]	Adjusted odds ratio (95% CIs)	Adjusted overall p value[2]
Total	Total	38,501	100.0	38,063	98.9				
Gender	Female	18,448	47.9	18,256	99.0	1.18 (0.98-1.43)	0.085	1.18 (0.98-1.43)	0.084
	Male (ref)	20,053	52.1	19,807	98.8	1 (ref)		1 (ref)	
Age group	<45	1,543	4.0	1,508	97.7	0.51 (0.35-0.74)*	<0.001	0.54 (0.37-0.79)*	<0.001
	45-54	2,896	7.5	2,841	98.1	0.61 (0.44-0.83)*		0.64 (0.47-0.89)*	
	55-64	7,406	19.2	7,324	98.9	1.05 (0.8-1.38)		1.08 (0.82-1.42)	
	65-74 (ref)	12,144	31.5	12,003	98.8	1 (ref)		1 (ref)	
	75-84	11,331	29.4	11,236	99.2	1.39 (1.07-1.8)*		1.38 (1.06-1.8)*	
	85+	3,181	8.3	3,151	99.1	1.23 (0.83-1.83)		1.22 (0.82-1.81)	
Ethnicity	Minority ethnic groups	2,147	5.6	2,119	98.7	0.87 (0.59-1.28)	0.472	1.05 (0.7-1.58)	0.448
	Not stated or known	1,686	4.4	1,671	99.1	1.28 (0.76-2.16)		1.39 (0.83-2.34)	

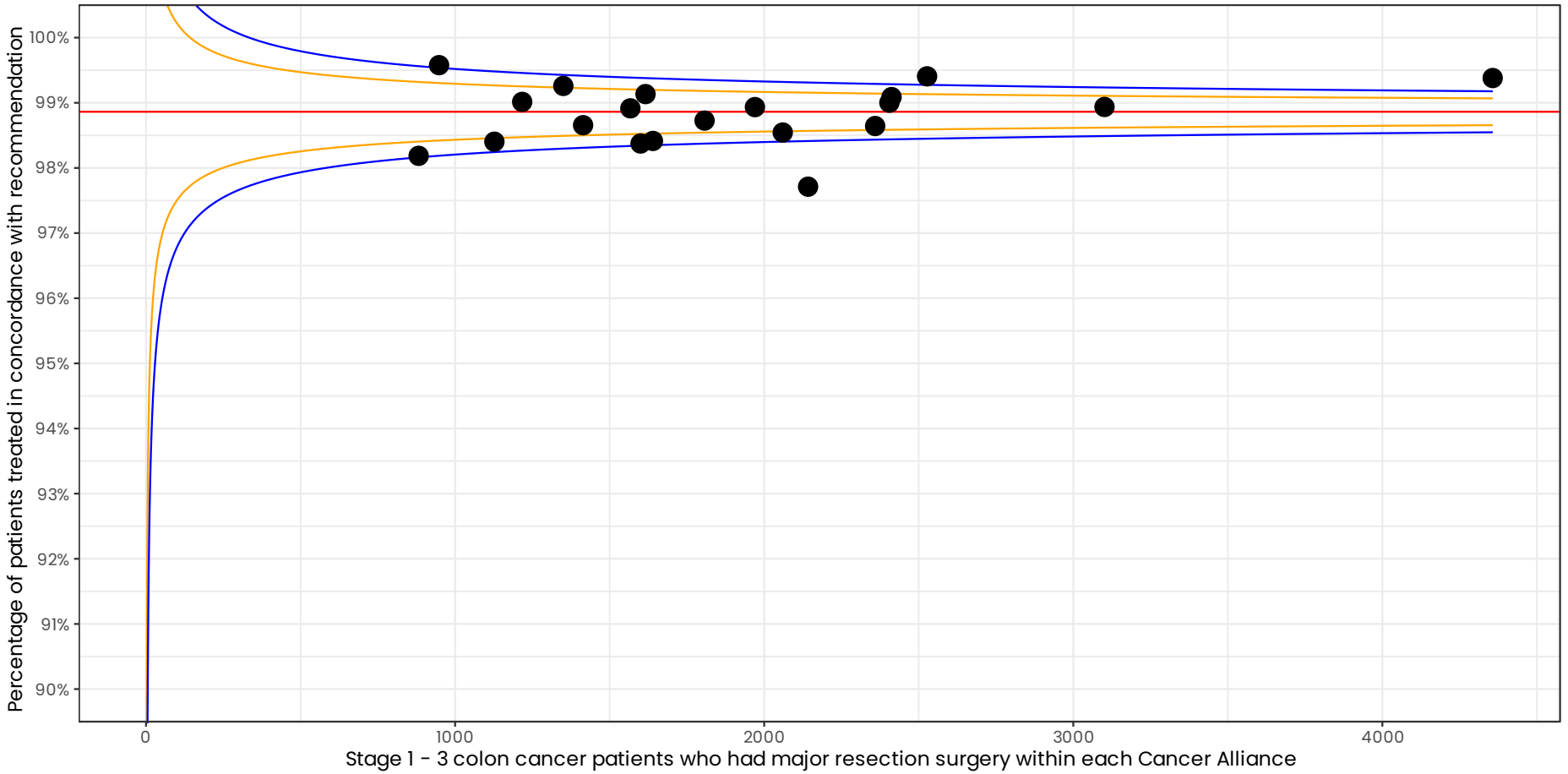
[1] Overall p value calculated using the likelihood ratio test

[2] Overall p value calculated using the chi-squared test

*denotes statistical significance at the p<0.05 confidence interval

Characteristic	Category	Number in cohort	Percentage of cohort (%)	Number concordant	Percentage concordant (%)	Unadjusted odds ratio (95% CIs)	Unadjusted overall p value[1]	Adjusted odds ratio (95% CIs)	Adjusted overall p value[2]
	White (ref)	34,668	90.0	34,273	98.9	1 (ref)		1 (ref)	
Deprivation quintile	1 - most deprived	5,947	15.4	5,893	99.1	1.4 (1.01-1.94)*	0.263	1.38 (0.98-1.93)	0.369
	2	6,908	17.9	6,821	98.7	1 (0.76-1.33)		1.04 (0.78-1.38)	
	3	8,002	20.8	7,913	98.9	1.14 (0.86-1.51)		1.16 (0.87-1.54)	
	4	8,854	23.0	8,757	98.9	1.15 (0.88-1.52)		1.16 (0.88-1.53)	
	5 - least deprived (ref)	8,790	22.8	8,679	98.7	1 (ref)		1 (ref)	
Comorbidity score	0 (ref)	31,852	82.7	31,473	98.8	1 (ref)	0.119	1 (ref)	0.592
	1	3,829	9.9	3,792	99.0	1.23 (0.88-1.73)		1.09 (0.77-1.53)	
	2	1,598	4.2	1,584	99.1	1.36 (0.8-2.33)		1.19 (0.7-2.04)	
	3+	1,222	3.2	1,214	99.3	1.83 (0.91-3.69)		1.53 (0.76-3.09)	
Stage group	1 (ref)	6,577	17.1	6,540	99.4	1 (ref)	<0.001	1 (ref)	<0.001
	2	16,680	43.3	16,540	99.2	0.67 (0.46-0.96)*		0.67 (0.46-0.96)*	
	3	15,244	39.6	14,983	98.3	0.32 (0.23-0.46)*		0.33 (0.24-0.47)*	
Diagnosis year	2015 (ref)	9,512	24.7	9,384	98.7	1 (ref)	0.068	1 (ref)	0.042
	2016	9,505	24.7	9,412	99.0	1.38 (1.06-1.81)*		1.41 (1.08-1.84)*	
	2017	9,551	24.8	9,453	99.0	1.32 (1.01-1.71)*		1.35 (1.03-1.76)*	
	2018	9,933	25.8	9,814	98.8	1.12 (0.88-1.45)		1.14 (0.89-1.46)	

Figure 2: Funnel plot for proportion of patients treated in concordance with recommendation 1.2.1.8 by Cancer Alliance. Black dots represent Cancer Alliances, red line indicates overall mean proportion for the whole cohort, blue line indicates 95% confidence intervals around overall mean and yellow line 80% confidence intervals.



When the sensitivity analyses were conducted there were some changes in odds ratios and p values, but age group, diagnosis year and stage remained significantly associated with receiving treatment concordant to this recommendation. However, gender also had a statistically significant relationship with recommendation-concordance, with those of female gender more likely to receive concordant treatment. The Cancer Alliance random effect remained significant, and the standard deviation was larger (0.432).

Recommendation 1.2.8.1 - The following are recommended as options for the adjuvant treatment of patients with stage III (Dukes' C) colon cancer following surgery for the condition: capecitabine as monotherapy or oxaliplatin in combination with 5-fluorouracil and folinic acid

There were 15,296 patients in the sub-cohort for recommendation 1.2.8.1 of which 8,173 were concordant to the recommendation (53.4%). In the adjusted model, there was no evidence for an association between gender and receiving the recommended adjuvant chemotherapy treatment, but all the other variables were associated with receiving the recommended treatment. For age, those in the <45, 45-54, 55-64 age groups were more likely to receive the recommended adjuvant chemotherapy treatment compared to those in the 65-74 age group (AOR of 1.41, 1.59 and 1.45 respectively), while those in the 75-84 and 85+ groups were less likely (AOR of 0.29 and 0.02 respectively). Those of Asian, Black, or 'Other' ethnicity were significantly less likely to receive the recommended adjuvant chemotherapy treatment compared to those of White ethnicity (AOR of 0.62, 0.71 and 0.71 respectively) and those who were in the three most deprived quintiles were significantly less likely to receive concordant treatment compared to the least deprived quintile (AOR of 0.65 for the most deprived quintile). Comorbidity score was also associated with receiving the recommended adjuvant chemotherapy treatment with individuals with a comorbidity score of 1, 2 or 3+ increasingly less likely to receive concordant treatment compared to those with a comorbidity score of 0 (AOR of 0.67, 0.47 and 0.21 respectively). Individuals diagnosed in 2017 or 2018 were more likely to receive recommendation concordant treatment compared to those diagnosed in 2015 (AOR of 1.43 and 1.44 respectively) (Table 2). There was considerable variation in the levels of concordance to this recommendation by Cancer Alliance, both in unadjusted analyses (Figure 3) and the adjusted regression analyses with an overall p value of <0.001 for the inclusion of Cancer Alliance as a random effect in the model. The standard deviation for the Cancer Alliance random effect was 0.190 and the coefficient ranged from -0.354 to 0.330.

There was no statistically significant interaction between age and comorbidity score in the likelihood of a patient receiving the recommended adjuvant chemotherapy treatment

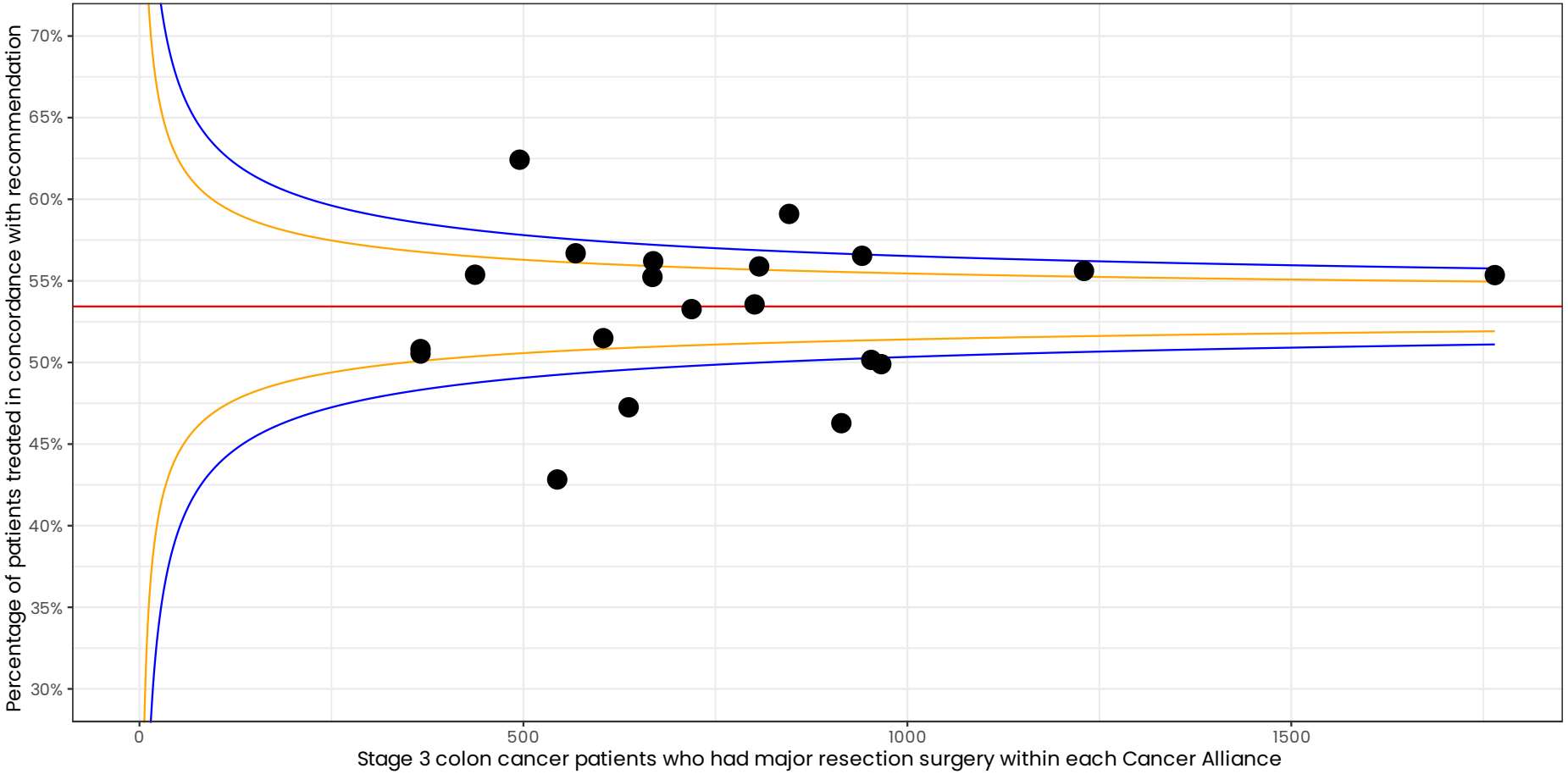
Table 2: Demographic breakdown of the cohort for recommendation 1.2.8.1, number and percentage of the cohort treated in concordance with the recommendation and odds ratios for recommendation-concordance from unadjusted analyses and adjusted for all the other variables

Characteristic	Category	Number in cohort	Percentage of cohort (%)	Number concordant	Percentage concordant (%)	Unadjusted odds ratio (95% CIs)	Unadjusted overall p value[3]	Adjusted odds ratio (95% CIs)	Adjusted overall p value[4]
Total	Total	15,296	100.0	8,173	53.4				
Gender	Female	7,311	47.8	3,843	52.6	0.94 (0.88-1)*	0.04	1.03 (0.96-1.11)	0.411
	Male (ref)	7,985	52.2	4,330	54.2	1 (ref)		1 (ref)	
Age group	<45	742	4.9	529	71.3	1.44 (1.21-1.7)*	<0.001	1.41 (1.19-1.68)*	<0.001
	45-54	1,364	8.9	998	73.2	1.58 (1.38-1.8)*		1.59 (1.39-1.83)*	
	55-64	3,118	20.4	2,218	71.1	1.43 (1.29-1.57)*		1.45 (1.31-1.6)*	
	65-74 (ref)	4,707	30.8	2,981	63.3	1 (ref)		1 (ref)	
	75-84	4,226	27.6	1,408	33.3	0.29 (0.27-0.32)*		0.29 (0.26-0.31)*	
	85+	1,139	7.4	39	3.4	0.02 (0.01-0.03)*		0.02 (0.01-0.03)*	
Ethnicity	Asian	395	2.6	198	50.1	0.88 (0.72-1.07)	0.598	0.62 (0.5-0.77)*	<0.001
	Black	293	1.9	153	52.2	0.95 (0.76-1.2)		0.71 (0.54-0.92)*	

[3] Overall p value calculated using the likelihood ratio test
[4] Overall p value calculated using the chi-squared test
*denotes statistical significance at the p<0.05 confidence interval

Characteristic	Category	Number in cohort	Percentage of cohort (%)	Number concordant	Percentage concordant (%)	Unadjusted odds ratio (95% CIs)	Unadjusted overall p value[3]	Adjusted odds ratio (95% CIs)	Adjusted overall p value[4]
	Mixed	66	0.4	35	53.0	0.98 (0.61-1.6)		0.81 (0.47-1.4)	
	Not stated or known	584	3.8	328	56.2	1.12 (0.94-1.32)		0.84 (0.7-1.02)	
	Other	201	1.3	107	53.2	0.99 (0.75-1.31)		0.71 (0.52-0.96)*	
	White (ref)	13,757	89.9	7,352	53.4	1 (ref)		1 (ref)	
Deprivation quintile	1 - most deprived	2,436	15.9	1,199	49.2	0.79 (0.71-0.88)*	<0.001	0.65 (0.57-0.73)*	<0.001
	2	2,749	18.0	1,472	53.5	0.94 (0.85-1.04)		0.83 (0.74-0.93)*	
	3	3,148	20.6	1,666	52.9	0.92 (0.83-1.01)		0.86 (0.77-0.96)*	
	4	3,484	22.8	1,921	55.1	1 (0.91-1.1)		0.98 (0.88-1.09)	
	5 - least deprived (ref)	3,479	22.7	1,915	55.0	1 (ref)		1 (ref)	
Comorbidity score	0 (ref)	12,824	83.8	7,284	56.8	1 (ref)	<0.001	1 (ref)	<0.001
	1	1,467	9.6	621	42.3	0.56 (0.5-0.62)*		0.67 (0.59-0.75)*	
	2	586	3.8	190	32.4	0.36 (0.31-0.44)*		0.47 (0.38-0.57)*	
	3+	419	2.7	78	18.6	0.17 (0.14-0.22)*		0.21 (0.16-0.28)*	
Diagnosis year	2015 (ref)	3,770	24.6	1,836	48.7	1 (ref)	<0.001	1 (ref)	<0.001
	2016	3,760	24.6	1,915	50.9	1.09 (1-1.2)		1.1 (0.99-1.21)	
	2017	3,810	24.9	2,166	56.9	1.39 (1.27-1.52)*		1.43 (1.29-1.59)*	
	2018	3,956	25.9	2,256	57.0	1.4 (1.28-1.53)*		1.44 (1.3-1.59)*	

Figure 3: Funnel plot for proportion of patients treated in concordance with recommendation 1.2.8.1 by Cancer Alliance. Black dots represent Cancer Alliances, red line indicates overall mean proportion for the whole cohort, blue line indicates 95% confidence intervals around overall mean and yellow line 80% confidence intervals.



In sensitivity analyses where the latest surgery date was used for the adjuvant chemotherapy inclusion period rather than the first surgery date, there were some very slight changes to the odds ratios but no change to which relationships were statistically significant and the

standard deviation for the random effect of Cancer Alliance remained very similar. When the adjuvant chemotherapy period was extended to match that used for the bowel cancer audit the percentage receiving concordant treatment increased to 57.4%. There were some slight changes to the odds ratios, but the overall picture was the same, with a significant association with receiving recommendation-concordant treatment for all investigated variables apart from gender. The Cancer Alliance random effect remained significant, and the standard deviation was smaller (0.156). The Cancer Alliance coefficients ranged from -0.195 to 0.238.

Discussion

Findings from analysis

Concordance with recommendation 1.2.1.8 was very high with only 1.1% of the overall cohort non-concordant. However, age showed a statistically significant relationship with concordance with the percentage of patients treated in concordance with this recommendation generally increasing with age. This agrees with findings from previous studies that younger patients are more likely to be given non-recommendation concordant chemotherapy (12). Patients diagnosed with stage 2 or 3 colon cancer were less likely to receive treatment concordant to this recommendation than patients diagnosed at stage 1 suggesting that a higher proportion of stage 2 and 3 colon cancer patients are given pre-operative chemotherapy than those at stage 1. This recommendation has been updated in the 2020 release (20) to 'consider pre-operative systemic anti-cancer therapy for people with cT4 colon cancer', with the neoadjuvant FOxTROT trial (21; 22) finding that pre-operative chemotherapy can improve surgical outcomes in this cohort. Although the trial findings and updated guidance were published after the inclusion period for our study, the relationship between stage and concordance suggests that the use of pre-operative chemotherapy for later stage patients was already taking place to a certain extent.

Concordance with recommendation 1.2.8.1 was far lower than 1.2.1.8 with 46.6% of the cohort non-concordant, possibly reflecting that this recommendation is for active treatment while recommendation 1.2.1.8 recommends not providing a treatment (14). This proportion is lower than that found for the bowel cancer audit analysis (5), although some of this difference is due to the varied periods for adjuvant chemotherapy, with 57.4% concordant when the period was extended to that used by the audit. However, this analysis focused on a narrower set of regimens laid out in recommendation 1.2.8.1 and so the remaining discrepancy may be due to this narrower definition of relevant adjuvant chemotherapy regimens used here.

The opposite pattern to recommendation 1.2.1.8 was found for the relationship between age and receiving treatment in concordance with recommendation 1.2.8.1, with younger patients more likely to receive this and older patients less likely, and age had the widest range of odds ratios from 1.59 for those aged 45-54 to 0.02 for those aged 85+. There were several other significant associations with receiving treatment in concordance to recommendation 1.2.8.1. Comorbidity score showed an independent relationship with concordance to recommendation 1.2.8.1 with patients with increasing comorbidity score being less likely to receive concordant treatment, potentially reflecting contraindications or increased complexity for treatment to be given. This relationship also had a large effect size, with an AOR of 0.21 for those with a comorbidity score of 3+. Patients living in the three most deprived quintiles were more likely to have treatment that was not concordant to recommendation 1.2.8.1 compared to those in the least deprived quintile. These results

agree with previous studies which found that increased age, comorbidity score and levels of deprivation were associated with increased risk of treatment being in non-compliance with guidelines recommending adjuvant chemotherapy (12; 9; 16; 8) and the findings of the national bowel cancer audit (5) analysis, validating these findings, and extending them to 2018. Patients of Asian, Black, or 'Other' ethnicity were more likely than those of White ethnicity to have treatment that was not concordant to recommendation 1.2.8.1. The association between ethnicity and adjuvant chemotherapy use for stage III patients was not investigated in the bowel cancer audit analysis so further analysis would be useful to verify this new finding.

We also found that concordance to both recommendations was associated with diagnosis year, with concordance increasing with increasing diagnosis year for recommendation 1.2.8.1 and for 2016 and 2017 compared to 2015 for recommendation 1.2.1.8, perhaps representing greater awareness or acceptance of recommendations.

For both recommendations there was evidence for significant variation by Cancer Alliance. The Cancer Alliance random effect was statistically significant, and the alliances had a range of coefficients. This suggests that there may be geographical variation in the use of optimal treatments and could potentially highlight areas for improvement. Recommendation 1.2.1.8 had a larger standard deviation and coefficient range compared to recommendation 1.2.8.1.

Limitations

This project has several limitations. As detailed above, only a small fraction of even the treatment related colon cancer recommendations were able to be analysed based on the currently available data and in the timescale of the project, one of which has been investigated to a certain degree previously, and so this prevented a comprehensive investigation of what proportion of colon cancer patients overall are treated in concordance with the guideline. Our analyses of both recommendations are based on a cohort of patients who had major resective surgery, and so may incorrectly characterise some patients who have more minor surgery. Additionally, the percentage of patients receiving surgery varies by demographics and geography (23) so the percentage of patients receiving both appropriate surgery and recommendation concordant treatment is likely to be lower. The role of surgery would be useful to investigate to provide a fuller picture of whether overall treatment for a patient was as recommended.

This study used data from 2015-2018 and looked at the 2011 NICE guideline which has been superseded by a more recent guideline in 2020. In addition, further significant changes to guidelines are likely to have been introduced during the COVID-19 pandemic, all of which potentially limit the findings that could be taken from this study to current practice.

The comprehensiveness of this analysis relies on availability and completeness of treatment data, with missing data potentially leading to incorrect concordance status for an individual. Additionally, the analytical approach taken here places population wide restrictions on treatment such as timings between treatment events whereas real-world

treatment decisions might have more flexibility i.e., longer time to starting adjuvant treatment if longer is needed for surgical recovery or multiple surgeries potentially meaning chemotherapy began later. Some of these issues were investigated in sensitivity analyses, with using latest surgery date for the analysis of recommendation 1.2.8.1 having very limited impact on the proportion concordant. Extending the adjuvant period had more of an impact on the proportion meeting the recommendation but did not change the overall relationships between demographics and concordance.

An additional potential limitation is around the stage variable. This variable is derived using all the appropriate registry data available within a 4-month period from the date of diagnosis or until the date of the first post-treatment MDT (whichever is shorter). However, this may also include staging from pathology reports and so may not accurately reflect the staging information that the clinicians had when deciding on treatment options for the patient.

No statistically significant interaction between age and comorbidity score was found for either recommendation and both age and comorbidity score remained independently associated with concordance. However, the relatively small numbers available for these analyses mean that analyses splitting by multiple variables may be underpowered and comorbidity score has limitations as a proxy for how well someone is likely to tolerate treatment (24). However, the finding of an independent contribution of age could illustrate that there are genuine inequalities in treatment by age that could be improved. There are several potential reasons why this could be the case including differential assessment of the potential benefits and risks of treatment for patients of different ages, either by clinicians or patients themselves and that older patients tend to be underrepresented in clinical trials, resulting in less evidence on the effect of treatment in this age group, something which the FOxTROT2 trial is aiming to address (25).

There are also several wider questions that were not within the scope of this project, but which are important for understanding the wider context of recommendation-concordance, such as the association between recommendation-concordance and survival and the reasons for non-concordance with recommended treatment and the role that patient choice may play in the variation in concordance identified. Reasons for non-concordance and patient choice could be explored through qualitative analysis or clinical audits of a cohort of patients who received non-concordant treatment (13; 10; 15). We excluded patients with multiple tumours from the cohort for this study, but further research could potentially analyse whether patients with multiple tumours are more or less likely to be treated in concordance with guideline recommendations compared to patients with a single tumour. It would also be useful to investigate what treatment, if any, patients are having if they are identified as not having recommendation concordant treatment.

What would be needed for a more comprehensive analysis?

The high proportion of recommendations that were identified here as currently unsuitable for their concordance to be assessed suggests that there is the potential for improving the quality and scope of data collection or the potential for future NICE guidelines to have more of an explicit focus on how the implementation and concordance to these recommendations could be measured. This includes information about excision margins after surgery, which is collected but has low completeness and information about whether and when MDT meetings were held. It would also be useful to have data on reasons for a patient not having treatment, including whether patient choice played a part in non-concordant treatment and the potential contribution of barriers patients face to taking up an offer of treatment.

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