Assessment of the 2020 NICE criteria for preoperative radiotherapy in patients with rectal cancer treated by surgery alone in comparison with proven MRI prognostic factors: a retrospective cohort study

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Summary

Background Selection of patients for preoperative treatment in rectal cancer is controversial. The new 2020 National Institute for Health and Care Excellence (NICE) guidelines, consistent with the National Comprehensive Cancer Network guidelines, recommend preoperative radiotherapy for all patients except for those with radiologically staged T1–T2, N0 tumours. We aimed to assess outcomes in non-irradiated patients with rectal cancer and to stratify results on the basis of NICE criteria, compared with known MRI prognostic factors now omitted by NICE.

Methods For this retrospective cohort study, we identified patients undergoing primary resectional surgery for rectal cancer, without preoperative radiotherapy, at Basingstoke Hospital (Basingstoke, UK) between Jan 1, 2011, and Dec 31, 2016, and at St Marks Hospital (London, UK) between Jan 1, 2007, and Dec 31, 2017. Patients with MRI-detected extramural venous invasion, MRI-detected tumour deposits, and MRI-detected circumferential resection margin involvement were categorised as MRI high-risk for recurrence (local or distant), and their outcomes (disease-free survival, overall survival, and recurrence) were compared with patients defined as high-risk according to NICE criteria (MRI-detected T3+ or MRI-detected N+ status). Kaplan-Meier and Cox proportional hazards analyses were used to compare the groups.

Findings 378 patients were evaluated, with a median of 66 months (IQR 44–95) of follow up. 22 (6%) of 378 patients had local recurrence and 68 (18%) of 378 patients had distant recurrence. 248 (66%) of 378 were classified as high-risk according to NICE criteria, compared with 121 (32%) of 378 according to MRI criteria. On Kaplan-Meier analysis, NICE high-risk patients had poorer 5-year disease-free survival compared with NICE low-risk patients (76% [95% CI 70–81] *vs* 87% [80–92]; hazard ratio [HR] 1·91 [95% CI 1·20–3·03]; p=0·0051) but not 5-year overall survival (80% [74–84] *vs* 88% [81–92]; 1·55 [0·94–2·53]; p=0·077). MRI criteria separated patients into high-risk versus low-risk groups that predicted 5-year disease-free survival (66% [95% CI 57–74] *vs* 88% [83–91]; HR 3·01 [95% CI 2·02–4·47]; p<0·0001) and 5-year overall survival (71% [62–78] *vs* 89% [84–92]; 2·59 [1·62–3·88]; p<0·0001). On multivariable analysis, NICE risk assessment was not associated with either disease-free survival or overall survival, whereas MRI criteria predicted disease-free survival (HR 2·74 [95% CI 1·80–4·17]; p<0·0001) and overall survival (HR 2·44 [95% CI 1·51–3·95]; p=0·00027). 139 NICE high-risk patients who were defined as low-risk based on MRI criteria had similar disease-free survival as 118 NICE low-risk patients; therefore, 37% (139 of 378) of patients in this study cohort would have been overtreated with NICE 2020 guidelines. Of the 130 patients defined as low-risk by NICE guidelines, 12 were defined as high-risk on MRI risk stratification and would have potentially been missed for treatment.

Interpretation Compared to previous guidelines, implementation of the 2020 NICE guidelines will result in significantly more patients receiving preoperative radiotherapy. High-quality MRI selects patients with good outcomes (particularly low local recurrence) without radiotherapy, with little margin for improvement. Overuse of radiotherapy could occur with this unselective approach. The high-risk group, with the most chance of benefiting from preoperative radiotherapy, is not well selected on the basis of NICE 2020 criteria and is better identified with proven MRI prognostic factors (extramural venous invasion, tumour deposits, and circumferential resection margin).

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Introduction

The treatment of rectal cancer is complex and reflects the continuing evolution of multimodality treatment. One of the key advances has been the accuracy of preoperative staging by high-quality MRI. Recent evidence shows that MRI can accurately predict pathological findings, including involvement of the circumferential resection margin,[1] extramural vascular invasion,[2] and extranodal

Research in context

Evidence before this study

In the UK, the National Institute for Health and Care Excellence (NICE) guidelines have recently undergone a major change, and now recommend neoadjuvant radiotherapy for nearly all patients with rectal cancers, excluding only those with radiological staging of T1–T2 and N0. This cohort study investigated the impact of these guidelines by assessing oncological outcomes in patients staged by MRI who underwent rectal cancer surgery without preoperative radiotherapy. We first searched PubMed with the terms "rectal cancer" and ("neoadjuvant" or "pre-operative" or "radiotherapy") and ("survival" or "recurrence"), with no date or language restrictions. The evidence cited in the development of the 2020 NICE guidelines was reviewed. The randomised trials that compared preoperative radiotherapy against primary surgery preceded widespread adoption of total mesorectal excision surgery and routine staging with high-resolution MRI, and reported local recurrence rates of 11–40% after primary surgery. A Cochrane review from 2018, investigating the benefits of preoperative radiotherapy in rectal cancer, did a subgroup analysis of patients undergoing total mesorectal excision surgery, and found no survival benefit with radiotherapy. To the best of our knowledge, there have been no new randomised controlled trials since the Cochrane review.

Added value of this study

We found that, despite having excellent outcomes (a local recurrence rate of 6%), almost two-thirds of patients undergoing primary surgery would now be treated with preoperative radiotherapy if the 2020 NICE guidelines were implemented. Outcomes were better predicted with proven MRI prognostic markers (extramural venous invasion, tumour deposits, and circumferential resection margin) than with NICE criteria. Moreover, if these MRI high-risk criteria were used instead of NICE criteria, there would be a significant reduction in the use of radiotherapy (121 [32%] of 378 patients treated versus 248 [66%] of 378).

Implications of all the available evidence

Implementing the unselective radiotherapy policy advocated in the NICE 2020 guidelines could cause substantial harm to patients (increased morbidity, increased bowel and sexual dysfunction, and reduced quality of life), as well as stretching an already under-resourced NHS.

tumour deposits,[3] all of which have been shown to substantially affect cancer outcomes. By contrast, preoperative lymph node staging is less prognostically accurate.[3–5]

The purpose of preoperative staging is to facilitate treatment planning by selecting patients who are likely to benefit from preoperative therapy and to assist in determining the optimal surgical procedure. Therefore, if a patient has no adverse prognostic features, it is important to avoid the negative consequences, side-effects, and costs of unnecessary preoperative treatment. Research has shown that downstaging of the tumour by preoperative chemoradiotherapy alters an initial poor prognosis to the prognosis of the final downstaged disease. For example, when a tumour that is circumferential resection margin positive on MRI is downstaged to circumferential resection margin negative on MRI after chemoradiotherapy, with a clear pathological circumferential resection margin after resection, this reduces the risks of local recurrence associated with margin positivity.[6] Likewise, downstaging MRI-detected extramural venous invasion or MRI-detected tumour deposit positive status at primary presentation to a negative status after chemoradiotherapy reduces the likelihood of local recurrence and the distant metastatic potential to that of patients who are negative for these features at primary MRI staging.[3,7] Additionally, a change in tumour depth from more than 5 mm to 5 mm or less invasion after chemoradiotherapy is associated with similar survival outcomes to those seen in patients with T1 and T2 tumours.[8] Conversely, a change in MRI-predicted lymph nodal status before and after neoadjuvant therapy has not been shown to have an impact on survival.[3,9] Despite this, MRI-detected nodes are often the main determinant at multidisciplinary team meetings when recommending neoadjuvant chemoradiotherapy. Neoadjuvant radiotherapy has major disadvantages if used in situations where surgery alone is the optimal treatment. It is well known to be associated with poorer bowel function and quality of life[10] and an increase in sexual dysfunction after rectal cancer surgery. Furthermore, the use of preoperative treatment comes with substantial costs and resourcing implications for health services. Measuring the potential impact of preoperative radiotherapy on outcomes from different policies is therefore important.

In 2020, the National Institute for Health and Care Excellence (NICE) guidelines for the management of rectal cancer[11] in the UK were changed. The guidelines changed from a selective use of preoperative radiotherapy to a recommendation of neoadjuvant therapy for all patients with radiologically predicted T3 or T4 rectal cancers and for all patients in whom lymph node involvement is suspected on imaging. In some centres in the UK, a highly selective approach has been taken, where only patients with predicted circumferential resection margin involvement have been offered preoperative treatment, with the vast majority undergoing primary surgery. In comparison with the NICE guidelines, the National Comprehensive Cancer Network (NCCN) guidelines in the USA[12] advocate preoperative therapy for all but stage I tumours, whereas the European

Society of Medical Oncology (ESMO) guidelines[13] suggest a more selective policy where patients can be treated with primary surgery up to radiologically staged T3b N2 (in the absence of circumferential resection margin involvement or extramural vascular invasion), further highlighting the lack of international consensus.

This study aimed to assess survival outcomes in non-irradiated patients with rectal cancer treated at two institutions in the UK with a policy of highly selective use of preoperative therapy. We compared survival outcomes using the established MRI prognostic risk features with the prognostic accuracy of using more generalised criteria of any T stage with suspicious lymph nodes on MRI or any T3 or T4 tumour as specified in the NICE guidelines. Additionally, we compared the accuracy of known MRI high-risk features with the T and N classification as recommended by the 2020 NICE guidelines in the selection of high-risk patients who might benefit from preoperative therapy.

Methods

Study design and participants

For this retrospective cohort study, all consecutive patients undergoing primary resectional surgery for rectal adenocarcinoma, without any preoperative therapy, at Basingstoke Hospital (Basingstoke, UK) between Jan 1, 2011, and Dec 31, 2016, and St Marks Hospital (London, UK) between Jan 1, 2007, and Dec 31, 2017, were identified from two prospectively maintained databases (appendix p 1). Patients undergoing exenterative surgery, patients with distant metastases at initial diagnosis, or patients treated by transanal local excision were excluded. There were no exclusion criteria in terms of age, performance status, comorbidities, or previous treatments. Variables examined included demographic data, high-resolution MRI and pathological T stage, N stage, presence of extramural vascular invasion, tumour deposits, and involvement of the circumferential resection margin. Only patients with complete data were included in the study. The project was approved at each participating centre as a retrospective service evaluation and all data used in the analysis were fully anonymised at source, so institutional ethics approval and a requirement for patient consent were waived.

Procedures

Although all treatment decisions were made on an individual basis following multidisciplinary team discussion, both hospitals followed a general policy of predominantly only treating patients with circumferential resection margin involvement with preoperative radiotherapy. A summary of the factors considered in treatment decision making and potential treatments offered is included in the appendix (p 1). This project was part of a service evaluation to assess the effect of instituting updated NICE guidelines in a population of patients who would otherwise not have undergone preoperative radiotherapy.

Patients were defined as having disease that was high risk for poorer local or distant recurrence, or both, and poor overall survival if they had MRI-detected circumferential resection margin involvement, MRI-detected extramural venous invasion, or MRI-detected tumour deposits. Tumour deposits were defined on MRI as irregular nodules within the mesorectum that directly interrupt the course of veins but are discontinuous from the primary tumour. Tumour deposits can be distinguished from lymph node metastases as they cannot be separated from the vein when assessed on two orthogonal views and tend to taper into the vein (described as a comet-tail appearance) rather than being alongside the vein and forming an acute angle. Extramural venous invasion was defined on MRI as a contiguous expansion of perirectal veins with intermediate tumour signal intensity. Circumferential resection margin involvement was defined on MRI as a tumour signal at or within 1 mm of the mesorectal fascia and on pathology as the presence of microscopic or macroscopic tumour at or within 1 mm of the surgical resection margin. Patients who would have received neoadjuvant therapy according to NICE guidelines (T3+ or N+, or both, detected by MRI) were categorised as NICE high risk.

High-resolution MRI scans were re-reviewed by two experienced gastrointestinal radiologists (ACo and ACh), in a blinded setting, to distinguish MRI lymph node metastases from tumour deposits. Both radiologists had received training in diagnosing tumour deposits by MRI and had been shown to have good agreement (κ=0·77 and κ=0·83, respectively) with the radiologist (GB) who first described tumour deposits on MRI, and validated their prognostic importance.[3]

See Online for appendix

Follow-up outcomes assessed were disease-free survival, overall survival, and location of recurrence. Overall survival was defined as the number of patients alive at the date of censor. Disease-free survival was defined as the number of patients alive and free from local or distant cancer recurrence at the date of censor. Recurrence was defined as local if it was confined to the pelvis or distant if it was outside the pelvis. The follow-up period was calculated from the date of surgery to last censor. Demographic, pathological, and follow-up data were collected from electronic patient records.

Statistical analysis

Survival was determined by use of the Kaplan-Meier method. The differences between survival curves and recurrence rates were assessed for statistical significance with log rank (Mantel-Cox) analysis. Comparisons between recurrence rates were assessed with the log-rank test.

A univariable Cox proportional hazards model was used to assess crude local and distant recurrence in relation to MRI prognostic variables, and multivariable Cox

	Patients (n=378)
Median age, years	68 (IQR 59–74)
Sex	
Female	147 (39%)
Male	231 (61%)
T stage diagnosed by MRI	
T1–T2	167 (44%)
T3–T4	211 (56%)
N stage diagnosed by MRI	
N0	252 (67%)
N1–N2	126 (33%)
EMVI status diagnosed by MRI	
Negative	288 (76%)
Positive	90 (24%)
Tumour deposit status diagnosed by MRI	
Negative	300 (79%)
Positive	78 (21%)
CRM status diagnosed by MRI	
Safe (>1 mm)	354 (94%)
Threatened (<1 mm)	24 (6%)
T stage diagnosed by pathology	
pT1–T2	164 (43%)
pT3–T4	214 (57%)
N stage diagnosed by pathology	
pN0	232 (61%)
pN1–N2	146 (39%)
EMVI status diagnosed by pathology	
Negative	264 (70%)
Positive	114 (30%)
Tumour deposit status diagnosed by pathology	
Negative	364 (96%)
Positive	14 (4%)
CRM status diagnosed by pathology	
Negative	364 (96%)
Positive	14 (4%)

Data are n (%) unless otherwise indicated. Data on race and ethnicity were not collected. EMVI=extramural venous invasion. CRM=circumferential resection margin.

Table 1: **Demographic, radiological, and pathological staging data**

proportional hazards models were used to evaluate individual prognostic markers in relation to overall survival and disease-free survival. In multivariable analysis, tumour deposits and extramural venous invasion were combined due to multicollinearity; however, both factors were also evaluated individually through a model where the other factor was excluded to assess their individual effect (appendix pp 3–4). In the combined MRI-detected tumour deposit plus MRI-detected extramural venous invasion model, patients with either an MRI-detected tumour deposit, MRI-detected extramural venous invasion, or both, were included as a single category. A separate model was used to assess overall and disease-free survival in the NICE high-risk and MRI high-risk categories in a simple model.

Statistical significance was defined as a p value less than 0·05. Statistical analysis was done with SPSS software (version 28.0.0.0).

Role of the funding source

There was no funding source for this study.

Results

462 patients with primary rectal cancer were initially identified from the two prospectively maintained databases. Overall, 84 (18%) of 462 patients received preoperative therapy and were excluded from the current analysis. Consequently, 378 patients were included in the study (139 from Basingstoke and 239 from St Marks). The median age was 68 years (IQR 59–74) and 231 (61%) patients were male. Data on race and ethnicity were not collected. 57 (15%) patients were treated by abdominoperineal excision and 321 (85%) treated with restorative anterior resection. A summary of the demographic and staging information for both radiology and pathology is included in table 1.

Patients were followed up for a median of 66 months (IQR 44–95). Overall, 5-year disease-free survival was 80% (95% CI 75–84; 301 of 378 patients) and 10-year disease-free survival 68% (60–75; 256 of 378 patients). 5-year overall survival was 82% (95% CI 78–86; 329 of 378 patients) and 10-year overall survival was 72% (65–78; 271 of 378 patients). Overall recurrence was diagnosed in 79 (21%) of 378 patients, local recurrence was diagnosed in 22 (6%) of 378 patients, and systemic distant recurrence was diagnosed in 68 (18%) of 378 patients. 11 (3%) of 378 patients had both local and distant recurrence.

Overall, 248 (66%) of 378 patients would have been classified as high-risk according to NICE criteria, compared with 121 (32%) of 378 according to the MRI-based risk stratification. Of the 248 patients who were classified as high-risk according to NICE criteria, 109 were also high-risk on MRI risk stratification. A further 139 NICE high-risk patients who were defined as low-risk based on MRI criteria had similar disease-free survival as 118 NICE low-risk patients; therefore, an additional 139 (37%) of 378 patients would have received radiotherapy based on the change in NICE guidelines. Of the 130 patients defined as low-risk by NICE guidelines, 12 were defined as high-risk on MRI risk stratification and would have potentially been missed for treatment.

In Kaplan-Meier survival analysis, when patients were separated into high-risk and low-risk groups as specified by the 2020 NICE treatment guidelines, there was a significant difference in 5-year disease-free survival (76% [95% CI 70–81] *vs* 87% [80–92]; hazard ratio [HR] 1·91 [95% CI 1·20–3·03]; p=0·0051), but not in 5-year overall survival (80% [74–84] *vs* 88% [81–92]; 1·55 [0·94–2·53]; p=0·077; figure 1). Overall, for disease-free survival, 75 (30%) of 248 NICE high-risk patients had an event compared with 24 (18%) of 130 NICE low-risk patients.

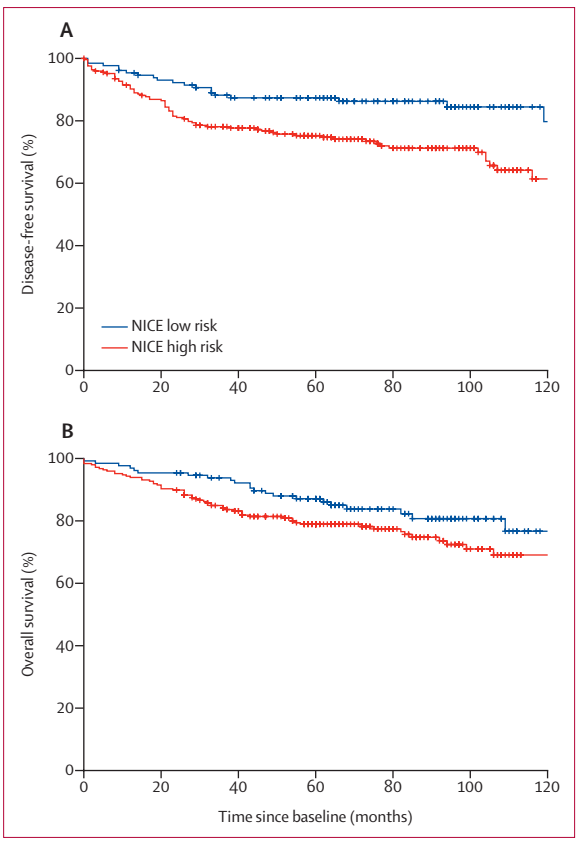

Figure 1: **Disease-free survival (A) and overall survival (B) according to NICE risk assessment**
Crosses denoted censored patients. NICE=National Institute for Health and Care Excellence.

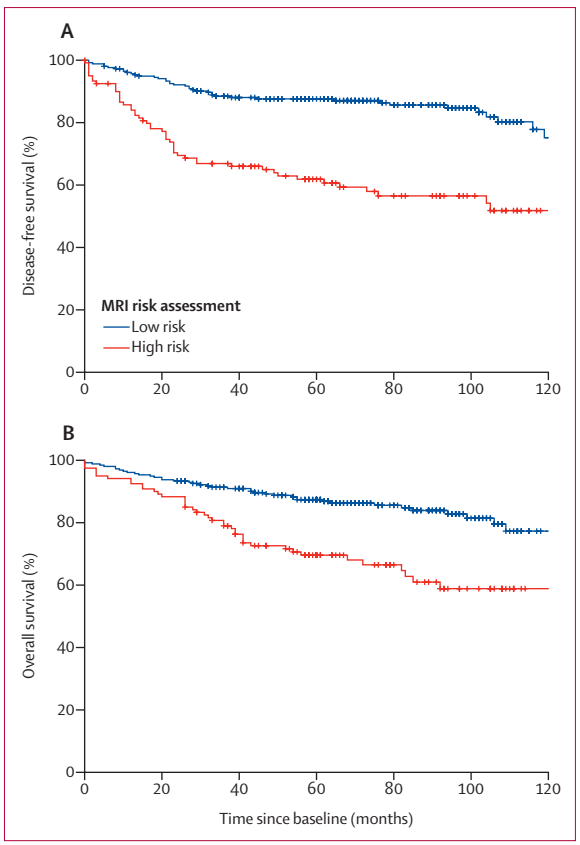

Figure 2: **Disease-free survival (A) and overall survival (B) according to MRI risk assessment**
Crosses denoted censored patients.

For overall survival, 60 (24%) of 248 NICE high-risk patients had an event compared with 22 (17%) of 130 NICE low-risk patients. Use of MRI risk assessment (based on circumferential resection margin status, extramural venous invasion, and tumour deposits) separated patients into high-risk and low-risk groups that predicted both 5-year disease-free survival (66% [95% CI 57–74] *vs* 88% [83–91]; HR 3·01 [95% CI 2·02–4·47]; p<0·0001) and 5-year overall survival (71% [62–78] *vs* 89% [84–92]; HR 2·59 [95% CI 1·62–3·88]; p<0·0001). Overall, 53 (44%) of 121 MRI high-risk patients had a disease-free survival event during follow-up compared with 46 (18%) of 257 MRI low-risk patients. 42 (35%) of 121 MRI high-risk patients died compared with 40 (16%) of 257 MRI low-risk patients (figure 2). In Cox regression analysis (using a separate model to that used to assess the other prognostic factors), the 2020 NICE risk assessment predicted disease-free survival only on univariable analysis (hazard ratio [HR] 1·91 [95% CI 1·20–3·03]; p=0·0060) and was not significantly associated with overall survival (table 2). On multivariable analysis, it was not significantly associated with either disease-free survival or overall survival. The MRI risk assessment predicted disease-free survival on both univariable (HR 3·01 [95% CI 2·02–4·47]; p<0·0001) and multivariable (2·74 [1·80–4·17]; p<0·0001) analyses, and overall survival on both univariable (2·59 [1·62–3·88]; p<0·0001) and multivariable (2·44 [1·51–3·95] p=0·00027) analyses (table 2).

To assess whether the MRI risk assessment could miss high-risk patients who would have been classified as high-risk by the NICE guidelines (since only half the number of patients were deemed high risk), a further analysis was carried out by separating patients into four groups: those who were low risk on both NICE and MRI assessments, those who were only high risk on the NICE assessment, those who were only high risk on the MRI assessment, and those who were high risk on both assessments. In those classified at MRI staging as low risk, there was no difference in either disease-free survival or overall survival in the NICE high-risk versus low-risk groups (p=0·41 for disease-free survival and p=0·31 for overall survival; figure 3). Adjuvant chemotherapy was given to 116 (58%) of 246 patients in the NICE high-risk group compared with 64 (53%) of 119 in the MRI high-risk group (data on adjuvant therapy were missing for two patients). There was no difference in disease-free survival between the NICE high-risk and MRI low-risk patients who did and did not receive adjuvant

	Disease-free survival				Overall survival			
	Univariable HR (95% CI)	p value	Multivariable HR (95% CI)	p value	Univariable HR (95% CI)	p value	Multivariable HR (95% CI)	p value
Age	1·02 (0·99–1·04)	0·074	(1·00–1·02)	0·019	1·07 (1·05–1·09)	<0·0001	1·03 (1·02–1·04)	<0·0001
Male sex	1·04 (0·69–1·56)	0·85	0·98 (0·76–1·26)	0·86	1·10 (0·70–1·73)	0·66	1·08 (0·81–1·43)	0·60
Radiological prognostic markers								
T3–T4 on MRI	2·01 (1·31–3·09)	0·0014	1·30 (0·80–2·10)	0·28	1·82 (1·14–2·90)	0·012	1·24 (0·73–2·11)	0·43
N1–N2 on MRI	1·38 (0·92–2·09)	0·12	0·98 (0·65–1·53)	0·99	1·52 (0·97–2·37)	0·066	1·24 (0·78–1·97)	0·36
EMVI positive on MRI	3·69 (2·45–5·55)	<0·0001	2·93 (1·88–4·56)	<0·0001	1·92 (1·21–3·03)	0·0055	2·05 (1·25–3·38)	0·0048
Tumour deposit positive on MRI	2·51 (1·65–3·81)	<0·0001	2·93 (1·88–4·56)	<0·0001	1·96 (1·21–3·16)	0·0060	2·05 (1·25–3·38)	0·0048
CRM threatened on MRI	1·94 (1·04–3·65)	0·039	1·58 (0·84–2·99)	0·16	1·84 (0·92–3·68)	0·085	1·46 (0·72–2·98)	0·30
Risk assessment								
NICE high risk	1·91 (1·20–3·03)	0·0060	1·36 (0·83–2·22)	0·22	1·55 (0·94–2·53)	0·080	1·07 (0·62–1·84)	0·80
MRI high risk	3·01 (2·02–4·47)	<0·0001	2·74 (1·80–4·17)	<0·0001	2·59 (1·62–3·88)	<0·0001	2·44 (1·51–3·95)	0·00027

HR=hazard ratio. EMVI=extramural venous invasion. CRM=circumferential resection margin. NICE=National Institute for Health and Care Excellence.

Table 2: **Effect of demographic and MRI variables on disease-free survival and overall survival**

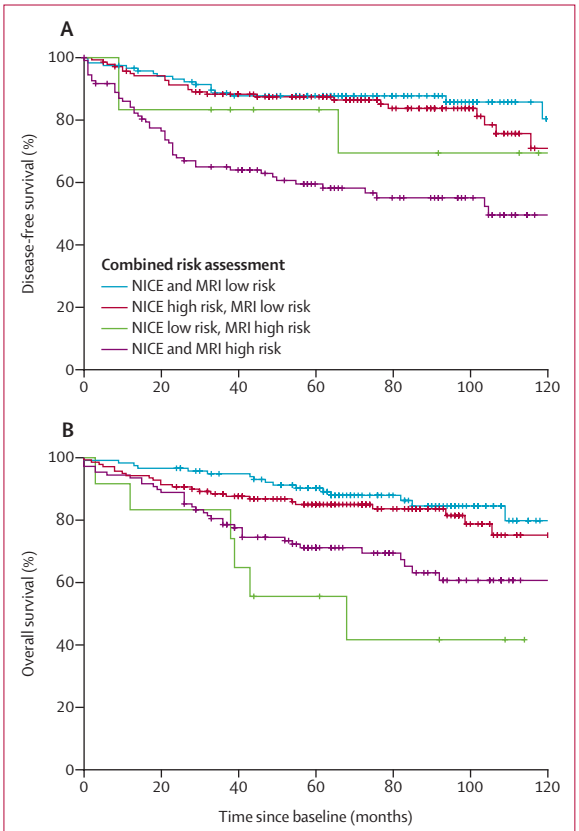

Figure 3: **Disease-free survival (A) and overall survival (B) according to combined NICE and MRI risk assessment**
Crosses denoted censored patients. NICE=National Institute for Health and Care Excellence.

chemotherapy (HR 0·93 [95% CI 0·42–2·03]; p=0·85; appendix p 2). Patients who were classified as low-risk according to MRI risk assessment but high-risk according to NICE (and therefore would be recommended for preoperative therapy if the NICE guidelines were followed) had a 5-year disease-free survival of 87% [95% CI 80–92] and a 5-year local recurrence rate of 3% [95% CI 2–6]. Of the 248 patients classified as high-risk by NICE 2020 criteria, the MRI risk stratification separated these into significantly different prognostic groups (disease-free survival: HR 2·89 [1·80–4·63]; p<0·0001; overall survival: 2·02 [1·20–3·40]; p=0·0067; figure 3).

Table 2 shows univariable and multivariable HRs for the effect of each MRI prognostic factor on overall survival and disease-free survival. On univariable analysis, MRI-detected T stage, MRI-detected extramural venous invasion, and MRI-detected tumour deposit status predicted poor disease-free survival and overall survival. MRI-detected circumferential resection margin status predicted poor disease-free survival but not poor overall survival. On multivariable analysis, only MRI-detected extramural venous invasion and MRI-detected tumour deposit status remained significant in predicting both disease-free survival and overall survival (HR 2·93 [95% CI 1·88–4·56], p<0·0001, for disease-free survival; and 2·05 [1·25–3·38], p=0·0048, for overall survival). MRI-detected lymph node status was not prognostic for disease-free survival or overall survival in either univariable or multivariable analyses. Table 2 also shows the univariable and multivariable hazard ratios for a simple model including only the two risk assessment systems. This model showed that although the NICE risk assessment was significantly associated with poorer disease-free survival on univariable analysis, this was not true for overall survival, and did not remain significant on multivariable analysis. MRI risk assessment remained significant on multivariable analysis for both disease-free survival and overall survival (table 2).

Table 3 shows the association between each MRI prognostic factor and both crude local and distant recurrence. None of the MRI prognostic factors was significantly associated with local recurrence (possibly due to a low event rate), but MRI-detected T stage,

MRI-detected extramural venous invasion status, MRI-detected tumour deposit status, and MRI-detected circumferential resection margin status were all significantly associated with distant recurrence.

Discussion

This study reports that 139 (37%) of 378 patients undergoing primary surgery with no poor prognostic features on MRI would have been defined as high risk according to the 2020 NICE guidelines, despite having a 5-year disease-free survival of 87% and a local recurrence rate of 3%. It is unlikely that these 139 patients would have gained any benefit from preoperative radiotherapy. These patients could in fact be more likely to undergo irreversible and unnecessary harm from preoperative radiotherapy in terms of additional morbidity, poor quality of life, impaired sexual function, erratic bowel function (including stool frequency, urgency, and incontinence), as well as the inability to receive pelvic radiotherapy again for any future malignancies. Furthermore, treating patients according to these criteria, when compared to an evidence-based MRI risk assessment, could have substantial implications for resource allocation and costs to the NHS.

In 2020, NICE changed its 2011 guidelines, recommending a change from MRI-based criteria, used since 2011, to far more liberal preoperative radiotherapy or chemoradiotherapy for all patients with rectal cancer unless staged at imaging as T1 or T2 and N0. It appears that the evidence evaluated for the 2020 NICE guidelines was predominantly from historic trials, including the Swedish Rectal Cancer Trial, which to date was the only trial to have reported a survival benefit with the use of preoperative therapy.[14] This trial was completed before the general adoption of total mesorectal excision surgery, and the reported local recurrence rate in the Swedish Rectal Cancer trial of 17% was far in excess of the rates reported in surgical practice.[15–17] With the combination of high-quality MRI and optimal total mesorectal excision surgery, a highly selective use of preoperative therapy is safe and effective in reducing local recurrence, with a rate of 6% reported in the present study. The Dutch TME trial, which took place before widespread use of high-quality MRI imaging, showed that in unselected patients preoperative therapy reduced local recurrence from 11% to 5%, but with no effect on overall survival.[18] Selecting patients who can safely proceed to primary surgery is now a more exacting process, mainly as a consequence of advances in the assessment of pelvic and mesorectal anatomy initiated in the MERCURY studies.[9,19] Given that the 5% local recurrence rate in the preoperative radiotherapy group from the Dutch TME Trial is very similar to the local recurrence rate reported without preoperative therapy in this study, it is questionable whether any margin for improvement exists and whether this would justify the numbers needed to treat when taking into account the potential harm caused by preoperative radiotherapy.

	Crude local recurrence		Crude distant recurrence	
	Patients (%)	p value	Patients (%)	p value
T stage on MRI				
T1–T2 on MRI (n=167)	7 (4%)	0·15	48 (23%)	0·0016
T3–T4 on MRI (n=211)	15 (7%)	..	18 (11%)	..
Lymph node metastases on MRI				
Negative (n=252)	12 (5%)	0·14	40 (16%)	0·16
Positive (n=126)	10 (8%)	..	26 (21%)	..
EMVI status on MRI				
Negative (n=288)	15 (5%)	0·14	32 (11%)	<0·0001
Positive (n=90)	7 (8%)	..	34 (39%)	..
Tumour deposits on MRI				
Negative (n=300)	17 (6%)	0·44	39 (13%)	<0·0001
Positive (n=78)	5 (7%)	..	27 (36%)	..
CRM status on MRI				
Safe (n=354)	19 (5%)	0·10	58 (17%)	0·027
Threatened (n=24)	3 (13%)	..	8 (33%)	..

EMVI=extramural venous invasion. CRM=circumferential resection margin.

Table 3: **MRI prognostic factors and association with crude local and distant recurrence**

This study had some limitations, mainly due to its retrospective nature. Use of retrospective data prevented capture of the entire process of decision making. Additionally, both hospitals involved in the study are centres of excellence in rectal cancer surgery. Although these potential limitations must be acknowledged, we do not feel they substantially affect the applicability of the results to the UK, where total mesorectal excision surgery has been standardised with pathology audit of the quality of specimens to monitor surgical standards. Furthermore, the national training of colorectal multidisciplinary teams and specialist radiologists in rectal cancer staging was pioneered in the UK.

Despite the overall excellent outcomes reported in this study cohort, the subset of patients with high-risk features on MRI clearly have significantly poorer disease-free and overall survival. However, the main problem appears to be distant rather than local recurrence, and efforts should be focused on reducing systemic recurrence. Previous evidence has shown that patients who have high-risk features, but are successfully downstaged after a long course of chemoradiotherapy, have similar outcomes to those who did not have high-risk features at baseline,[3,6–8] but this has not been observed in patients receiving neoadjuvant chemotherapy alone.[20] Therefore, the role of pelvic radiotherapy in blocking the pathways of distant spread might still be important in patients with vascular invasion and vascular mediated tumour deposits. If we consider that in current clinical practice, patients also need to make an informed choice about their risk of recurrence (be it local or distant),

having detailed staging information that gives them this information will help them to decide whether or not to receive pelvic radiotherapy. Downstaging of the tumour when there are poor prognostic features might be a key consideration. In the absence of randomised trials that have stratified patients by validated prognostic factors, it is important to have a discussion with patients about the benefits and risks of radiotherapy based on their individual clinical and MRI prognostic features as well as their own wishes. This is currently absent from the NICE 2020 guidelines.

Use of MRI-based prognostic risk stratification instead of the 2020 NICE guidelines results in better prediction of outcomes, and maintaining a selective policy could prevent a major and potentially harmful increase in the number of patients undergoing preoperative radiotherapy (rising from 32% to 66% in our cohort). There is now a move to offer patients all of their treatment before surgery (the so-called total neoadjuvant therapy approach). If this approach starts to be followed, in accordance with the NICE 2020 guidelines, this could be highly damaging for patients. Therefore, there is a need to carefully identify which patients will not be cured by surgery alone rather than employ a blanket approach.

Future trials are needed to assess and quantify the effect of different preoperative therapy regimes on distant recurrence and survival, using evidence-based MRI risk stratification to target the true high-risk patients. Intensification of treatment for high-risk tumours that are not downstaged on standard neoadjuvant therapy might be of benefit. Whether radiotherapy has a role to play in reducing distant recurrence, or whether intensification of treatment with systemic chemotherapy is more important, remains a priority area for future research. The proposed new routine policy of recommending radiotherapy for large numbers of patients without any additional benefit is likely to cause substantial harm at great personal expense to patients and wider expense to the NHS. The multidisciplinary community should maintain focus on ensuring high-quality image interpretation by specialist gastrointestinal radiologists who apply evidence-based prognostic staging information available from high-resolution preoperative MRI scans. This will help to ensure continued refining of preoperative treatment strategies and provide more accurate information for patients to facilitate informed, evidence-based consent. A selective approach to preoperative therapy optimises outcomes and reduces harm. We advocate that cancer multidisciplinary teams continue to ensure that "decisions are more important than incisions"[21] and that individualised therapy is the most clinically effective curative treatment of rectal cancer.

Contributors

AL contributed to study conceptualisation, data collection, data analysis, writing the original draft of manuscript, and reviewing and editing the manuscript. ACo and ACh contributed to study conceptualisation, MRI interpretation and data collection, and reviewing and editing the manuscript. NH contributed to data analysis, rewriting of manuscript after initial peer review, and reviewing and editing the manuscript. EP and CA-F contributed to data collection, and reviewing and editing the manuscript. BM, JTJ, and FDF contributed to study conceptualisation, and reviewing and editing the manuscript. GB contributed to study conceptualisation, data analysis, writing the original draft of manuscript, and reviewing and editing the manuscript. AL and GB have accessed and verified the data. All authors had access to the data reported in the study. The corresponding author had full access to all of the data in the study and all authors had final responsibility for the decision to submit the manuscript for publication.

Declaration of interests

We declare no competing interests.

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