Role of the status of the mesorectal fascia in the selection of patients with rectal cancer for preoperative radiation therapy: a retrospective cohort study

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Background: Patients with rectal cancer in whom the mesorectal fascia is threatened by tumour are more likely than all patients with stage II/III disease to benefit from preoperative radiotherapy (RT). The objective of this study was to assess whether the status of the mesorectal fascia versus a stage II/III designation can best inform the use of preoperative RT in patients undergoing major rectal cancer resection.

Methods: We reviewed the charts of consecutive patients with primary rectal cancer treated by a single surgeon at McMaster University, Hamilton, Ontario, between March 2006 and December 2012. The status of the mesorectal fascia was assessed by digital rectal examination, pelvic computed tomography and, when needed, pelvic magnetic resonance imaging (MRI). Patients whose mesorectal fascia was threatened or involved by tumour received preoperative RT. The study outcomes were rates of positive circumferential radial margin (CRM) and local tumour recurrence.

Results: A total of 153 patients were included, of whom 76 (49.7%) received preoperative RT because of concerns of a compromised mesorectal fascia. The median length of follow-up was 4.5 years. The number of CRM-positive cases in the RT and no-RT groups was 16 (22%) and 1 (1%), respectively ($p < 0.01$), and the number of cases of local tumour recurrence was 5 (7%) and 2 (3%), respectively ($p = 0.2$). Rates were similar when only patients with stage II/III tumours were included. Overall, 26 patients (17.0%) received MRI.

Conclusion: The status of the mesorectal fascia, not tumour stage, may best identify patients for preoperative RT.

Contexte : Plus que tous les patients présentant une maladie de stade II/III, les patients atteints d'un cancer du rectum dont le fascia mésorectal est menacé par la tumeur sont de bons candidats à la radiothérapie (RT) préopératoire. L'objectif de cette étude était d'évaluer ce qui, entre l'état du fascia mésorectal et une désignation de stade II/III, permet le mieux de confirmer le bien-fondé d'une RT préopératoire chez les patients qui doivent subir une résection majeure pour cancer du rectum.

Méthodes : Nous avons passé en revue les dossiers de patients consécutifs atteints d'un cancer rectal primaire traités par un seul chirurgien à l'Université McMaster, à Hamilton, en Ontario, entre mars 2006 et décembre 2012. L'état du fascia mésorectal a été évalué par toucher rectal, tomodensitométrie pelvienne et, au besoin, imagerie par résonnance magnétique (IRM) pelvienne. Les patients dont le fascia mésorectal était menacé ou affecté par la tumeur ont reçu une RT préopératoire. Les paramètres de l'étude étaient : taux de positivité de la marge radiale circonférentielle (MRC) et récurrence de la tumeur locale.

Résultats : En tout, 153 patients ont été inclus, dont 76 (49,7 %) ont reçu une RT préopératoire en raison d'une atteinte du fascia mésorectal. La durée moyenne du suivi a été de 4,5 ans. Dans les groupes soumis et non soumis à la RT, les nombres de cas MRC-positifs ont été respectivement de 16 (22 %) et de 1 (1 %), ($p < 0,01$), et les nombres de cas de récurrence de la tumeur locale ont été respectivement de 5 (7 %) et de 2 (3 %) ($p = 0,2$). Les taux étaient similaires lorsque seuls les patients présentant des tumeurs de stade II/III étaient inclus. Globalement, 26 patients (17,0 %) ont subi l'IRM.

Conclusion : C'est l'état du fascia mésorectal et non le stade de la tumeur qui peut le mieux permettre d'identifier les candidats à une RT préopératoire.

Total mesorectal excision techniques adopted worldwide in the last 20 years have improved outcomes for patients undergoing rectal cancer surgery. Certain jurisdictions have seen postoperative local recurrence rates decrease from more than 20% to 10%.[1,2] Units that perform fastidious total mesorectal excision have reported local recurrence rates as low as 5%.[3] Dutch and UK Medical Research Council (MRC) trials that incorporated total mesorectal excision techniques while testing the role of preoperative radiotherapy (RT) showed reductions in local recurrence of 5% and no improvement in patient survival.[4,5] Of relevance, despite the inclusion solely of patients with resectable disease and the intent to provide optimal total mesorectal excision techniques, only about 50% of pathology specimens in both trials could be classified as complete.[6,7] Thus, the utility of preoperative RT in settings where optimal total mesorectal excision is consistently delivered still requires evaluation. Such evaluation would not be needed if preoperative RT did not confer on patients the risks of important adverse effects such as poor sexual and bowel function, bowel obstruction and hip fracture.[8–12] Even in the era of total mesorectal excision, most North American guidelines recommend the use of preoperative or postoperative long-course chemoradiotherapy for patients with stage II or III disease.[13] Many European centres use preoperative short-course RT (delivered over 1 wk) in such patients.[4,5] Most jurisdictions also now recommend the use of pelvic magnetic resonance imaging (MRI) to locally stage rectal tumours, despite evidence showing that pelvic MRI assigns an incorrect T or N category in about 30% of patients.[14] Limited evidence suggests that both MRI and computed tomography (CT) can adequately evaluate the status of the mesorectal fascia.[15,16] In an attempt to influence current approaches to preoperative RT in rectal cancer, investigators have published case series in which recommendations for preoperative RT are driven largely by the status of the mesorectal fascia versus a TNM stage II or III designation, and most investigators have determined the status of the mesorectal fascia using MRI.[17–20]

The objective of this study was to further assess whether the status of the mesorectal fascia versus a stage II or III designation can best inform the use of preoperative RT in patients undergoing major rectal cancer resection.

Methods

Design

This was a nonmatched cohort study involving retrospective review of the charts of consecutive patients who had undergone rectal cancer surgery with and without preoperative radiation.

Population, staging tests and follow-up

Patients with primary rectal cancer were accrued by a single surgeon with a clinical focus on complex colorectal cancer surgery and who works at an academic centre in Ontario (population 14 million). The cohort consisted of consecutive patients who presented with primary rectal adenocarcinoma and who were treated with major resection between March 2006 and December 2012. Most patients were referred by outside surgeons, in most cases because of concerns about tumour operability or sphincter preservation. All patients who underwent major surgery for primary rectal cancer during the study period were included; there were no exclusions for variables such as tumour stage or comorbidities. For distant and local staging purposes, all patients underwent physical examination including a digital rectal examination, chest radiography, CT of the abdomen and pelvis, and colonoscopy. Pelvic MRI was ordered if the digital rectal examination or CT did not provide a clear status of the mesorectal fascia (i.e., definitely clear or definitely threatened or involved). Magnetic resonance imaging information was also considered if the test had already been ordered by the referring surgeon. Transrectal ultrasonography for local staging is not used in our centre and is not relevant to the evaluation of the mesorectal fascia. For follow-up, patients were seen shortly after hospital discharge, every 6 months for 2 years and once a year thereafter. Colonoscopy was performed 1 year and 6 years after surgery unless more frequent examination was clinically indicated. The following surveillance tests were performed annually: blood testing including liver function tests and measurement of carcinoembryonic antigen levels, chest radiography, and CT of the abdomen and pelvis. Ultrasonography of the liver was performed 6 and 18 months after surgery. This surveillance scheme follows an Ontario guideline developed during the time of this study.[21]

Decision-making for pelvic magnetic resonance imaging and preoperative radiotherapy

Following abdominal and pelvic CT imaging and physical examination including a digital rectal examination, patients could be placed into 1 of 3 categories. The first category was patients with a threatened or involved mesorectal fascia who were recommended to receive preoperative RT. These patients had tumour fixation on digital rectal examination, or a primary lesion or abnormal mesorectal lymph nodes that were near or traversed the mesorectal fascia, as seen on CT. Abnormal lymph nodes were defined by signal heterogeneity or extracapsular extension but not by size. The second category was patients with a nonthreatened mesorectal fascia who were recommended to go directly to surgery. These patients had tumour mobility on digital rectal examination or a generous layer of normal

mesorectal fat located between tumour and fascia, as seen on CT. There was subjectivity in identifying "tumour near the mesorectal fascia" or a "generous layer of mesorectum," although, generally, tumour cells 2 mm or less from the mesorectal fascia were considered "near." The third category was patients in whom the status of the mesorectal fascia was not obvious; for these patients, pelvic MRI was ordered. Lower tumours were more likely to prompt MRI since CT is typically of little use to assess the mesorectal fascia at the level of the pelvic floor. If MRI did not show a clear mesorectal fascia or surgical margin, preoperative RT would be recommended. Fig. 1 summarizes our approach.

Preoperative RT was delivered as long-course chemoradiotherapy treatment or short-course RT with 25 Gy delivered in 5 equal fractions. Patients who could not tolerate chemotherapy or for whom convenience was a concern (e.g., elderly patients or those who had to travel long distances) received short-course treatment. Randomized trials have shown similar outcomes with short- and long-course RT, although long-course RT is the preferred treatment in Ontario.[13,32,23] All patients who received preoperative RT had an interval of at least 6 weeks between treatment and surgery to allow for tumour downsizing.

Ontario guidelines recommend preoperative RT for patients with stage II or III rectal cancer.[13] Thus, patients with a nonthreatened mesorectal fascia but obvious T3 tumour extension or a positive mesorectal lymph node were encouraged to speak with a radiation oncologist on the risks (e.g., bowel and sexual dysfunction) and benefits (i.e., decrease in risk of local recurrence) of preoperative RT. After surgery, patients with stage II or III cancer who did not undergo some form of preoperative RT were also encouraged to speak with an oncologist regarding potential adjuvant therapy. Most patients with stage III tumours who did not receive preoperative RT received postoperative chemotherapy.

Data collection

We retrospectively collected from relevant clinic, hospital, operative and pathology notes the following information: patient characteristics (age, sex and comorbidities), investigations (CT and MRI) and tumour characteristics (distance from anal verge to distal tumour edge, degree of fixation, closest distance from tumour cells to circumferential radial margin [CRM], size, TNM stage [postoperative pathology only], differentiation, and presence of vascular, lymphatic or perineural invasion). Palpable tumours on rectal examination were defined as mobile, tethered or fixed. Treatment factors abstracted included use of chemotherapy, RT, permanent colostomy and hospital length of stay.

Groups and outcomes

We defined study groups by whether patients did or did not receive preoperative RT. The primary outcomes were

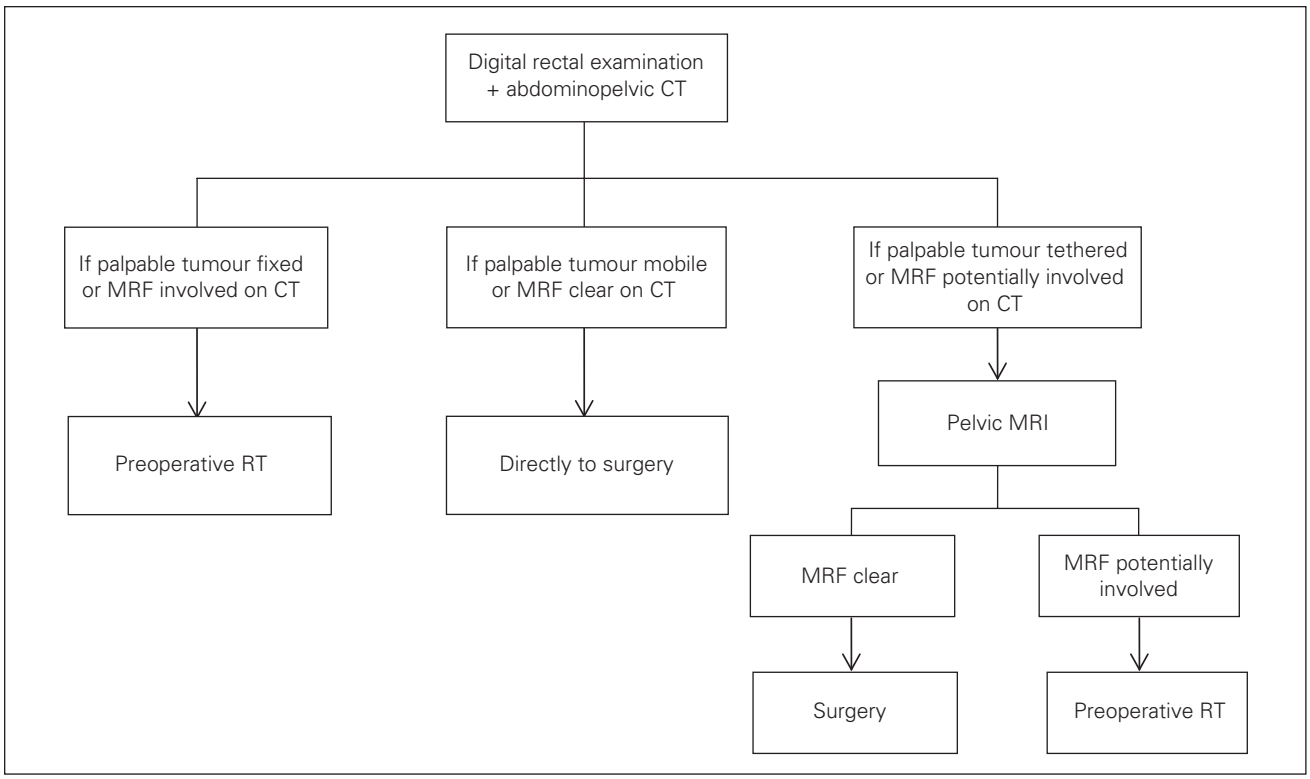

Fig. 1. Decision-making for pelvic magnetic resonance imaging (MRI) and preoperative radiotherapy (RT). CT = computed tomography; MRF = mesorectal fascia.

rate of positive CRM (tumours cells ≤ 1 mm from the CRM) and local tumour recurrence. To determine rates of CRM positivity, we defined the numerator as patients with tumour cells 1 mm or less from the cut edge of the surgical specimen, or a pathology report identifying a positive CRM but with no CRM distance provided; the denominator included patients with CRM distance reported plus patients deemed CRM-positive without a measurement reported. We have used this approach for evaluation of CRM positivity elsewhere.[24] Tumour cells could be from the main tumour, from a positive lymph node, from a discontinuous tumour focus, or from cells in a vascular, lymphatic or neural structure. Local recurrence was defined as recurrent disease anywhere in the pelvis. Local recurrence was confirmed by biopsy. It was also decided a priori that any pelvic mass with associated symptoms of pain or pressure would be classified as a local recurrence.

Statistical analysis

We used the χ^2 and Fisher exact tests for categorical variables, and the Mann–Whitney and Student *t* tests for continuous variables to assess differences between the subcohorts with regard to patient, tumour, treatment and outcome measures. We assessed the odds of local recurrence using a logistic model while controlling for patient (age, sex and comorbidity), tumour (TNM stage, tumour fixation) and treatment (use of radiation, type of surgery) variables. All statistical analyses were carried out with SPSS version 20.0 (IBM Corp.). We considered $p < 0.05$ statistically significant. There were no external funding sources for this work. The study received ethics approval from the Hamilton Health Sciences Research Ethics Board.

Results

We reviewed the charts of 153 patients, of whom 76 (49.7%) received preoperative RT. No patient with likely stage II or III disease and a clear mesorectal fascia elected to receive preoperative RT. One patient in the no-RT group with a clear mesorectal fascia but stage III disease elected to receive postoperative chemoradiotherapy. The median length of follow-up was 4.5 (range 0–10.5) years for the RT group and 6.0 (range 0–10.8) years for the no-RT group (5.3 yr overall). There were no significant differences in median age, sex or comorbidities between the 2 groups (Table 1). All patients underwent staging CT. Twenty-six patients (17.0%) underwent staging MRI; the use of MRI was significantly greater in the RT group than in the non-RT group (19 [25%] v. 7 [9%], $p < 0.01$).

There were differences between the 2 groups in rates of tumour fixation ($p < 0.001$): of the 59 patients with a palpable tumour in the no-RT group, none had a fixed tumour, and 4 (7%) had tethered tumours. In the RT group, palpable tumours were fixed or tethered in 53 (79%) of 67 patients. Patients were more likely to have a higher postoperative TNM stage in the RT group than in the non-RT group ($p < 0.01$). Pathology stage differences were likely even greater since tumour downsizing could have occurred only among patients who had preoperative RT. Five patients (7%) in the RT group had a complete pathologic response. Of note, of the patients who did not receive preoperative RT, 40 (52%) had stage II or III tumours, and 8 (10%) had stage IV tumours.

The CRM distance was reported for 141 patients (92.2%). The rate of CRM positivity in the RT and no-RT groups was 16/73 (22%) and 1/72 (1%), respectively ($p < 0.001$) (Table 2). Among patients with stage II or III disease, the corresponding rates were 9/44 (20%) and 1/40 (2%) ($p = 0.01$). There were 5 local recurrences (7%) among the patients who received preoperative RT and 2 (3%) among those who did not ($p = 0.2$). Among patients with stage II and III disease, the corresponding values were 3/44 (7%) and 2/40 (5%) ($p = 0.7$). Nearly half (34 [45%]) of the patients who received preoperative RT also received a permanent colostomy, compared to 7 patients (9%) in the no-RT group ($p < 0.001$). The anastomotic leak rate, wound infection rate and median length of stay were similar between the 2 groups. When

Table 1. Patient and tumour characteristics

Characteristic	Group; no. (%) of patients* Preoperative radiotherapy *n* = 76	No preoperative radiotherapy *n* = 77	*p* value
Age, yr, median	60.5	63.0	0.2
Male sex	56 (74)	49 (64)	0.2
Comorbidities	21 (28)	21 (27)	> 0.99
Preoperative magnetic resonance imaging	19 (25)	7 (9)	< 0.01
Tumour distance to anal verge, cm, median	7.0	8.0	0.09
Tumour fixation			
Mobile	14 (18)	55 (71)	< 0.001
Tethered	22 (29)	4 (5)	
Fixed	31 (41)	0 (0)	
Not reported†	9 (12)	18 (23)	
Tumour size, cm, median	3.4	4.0	< 0.05
Any vascular, lymphatic, neural invasion	32 (42)	31 (40)	0.2
Tumour–node–metastasis stage			
I	11 (14)	29 (38)	0.003
II	18 (24)	15 (19)	
III	26 (34)	25 (32)	
IV	21 (28)	8 (10)	

*Except where noted otherwise.
†Beyond the reach of the examining finger.

we controlled for patient and tumour variables, the odds of local recurrence with preoperative RT versus no preoperative RT was similar (odds ratio 0.26, 95% confidence interval 0.04–1.57). The small number of local recurrences likely undermines the clinical usefulness of this finding.

Of note, none of the 7 patients with local recurrence had a positive CRM (Table 3). The 5 patients in the RT group with a local recurrence all presented with a fixed tumour, and all were treated with long-course chemoradiation. The 2 cases of local recurrence in the no-RT group are of particular interest. In 1 case, the tumour was tethered to the pelvic sidewalls and prostate, but preoperative RT was precluded by the use of radical RT for prostate cancer 3 years earlier. In the second case, the tumour was mobile, and the presence of 4 of 18 positive lymph nodes led to full-dose adjuvant chemotherapy. Symptomatic local recurrence developed in the left pelvic sidewall, and the patient underwent pelvic chemoradiation, additional full-dose chemotherapy and resective surgery of an isolated positive lymph node. The patient was disease free 3 years after surgery for recurrence and 6 years after the original rectal surgery.

Table 2. Outcomes

Outcome	Group; no. (%) of patients*		*p* value
	Preoperative radiotherapy	No preoperative radiotherapy	
CRM distance reported on pathologic report	69 (91)	72 (94)	0.5
CRM distance ≤ 1 mm	12 (17) *n* = 69	1 (1) *n* = 72	
CRM not measured but reported as positive	4 (57) *n* = 7	0 (0) *n* = 5	
Positive CRM	16 (22) *n* = 73	1 (1) *n* = 72	< 0.001
Stage I	1 (6)	0 (0)	
Stage II	3 (19)	0 (0)	
Stage III	6 (38)	1 (100)	
Stage IV	6 (38)	0 (0)	
Local recurrence†	5 (7)	2 (3)	0.2
Stage I	0 (0)	0 (0)	
Stage II	1 (20)	0 (0)	
Stage III	2 (40)	2 (100)	
Stage IV	2 (40)	0 (0)	
Permanent colostomy at surgery	34 (45)	7 (9)	< 0.001
Anastomotic leak	8 (10)	8 (10)	> 0.99
Wound infection	4 (5)	5 (6)	0.7
Length of stay, d, median	7	8	> 0.99

CRM = circumferential radial margin.
*Except where noted otherwise.
†Includes any reported positive, probably or positive cases.

Discussion

Guidelines from many jurisdictions related to rectal cancer surgery recommend the use of preoperative RT for patients with stage II or III tumours and the use of pelvic MRI for local staging.[13,25] Our results suggest an opportunity to modify these norms. A total of 52% of patients who did not receive preoperative RT had stage II or III tumours. However, in this group, only 1 patient had a positive CRM, and only 2 patients experienced a local recurrence. One of the patients with local recurrence likely would have received preoperative RT owing to tumour tethering but could not because of recent pelvic RT for prostate cancer. The second patient had a recurrence in a pelvic sidewall lymph node and was free of disease 3 years after therapy for the recurrence and 6 years after the original surgery. The rate of CRM positivity among the patients who received preoperative RT was understandably high (22%). Only patients with a compromised or involved mesorectal fascia on preoperative assessment were recommended to receive RT. As well, only 26 patients overall (17%) received pelvic MRI. Our findings suggest that pelvic CT and digital rectal examination, with the as-needed use of pelvic MRI, can identify patients with a compromised mesorectal fascia who will likely most benefit from preoperative RT. Similarly, patients with a noncompromised mesorectal fascia and thus a much lower risk of negative outcomes can also be identified and can avoid the risks of preoperative RT, even in the presence of stage II or III disease.

Table 3. Summary characteristics of patients with local recurrence

Patient no.	Age at surgery, yr	Sex	Preoperative radiation	Tumour distance from anal verge, cm	Tumour fixation	TNM stage	Surgical procedure	CRM distance, cm	No. of positive lymph nodes
1	63	Female	Yes	4.0	Fixed	IV	LAR	0.8	1/6
2	36	Male	Yes	4.0	Fixed	III	APR	1.0	1/58
3	49	Male	Yes	7.0	Fixed	IV	LAR	0.15	0/7
4	77	Female	Yes	7.0	Fixed	II	LAR	0.5	0/35
5	50	Male	Yes	10.0	Fixed	III	LAR	0.6	5/9
6	73	Male	No	8.0	Tethered	III	Hartmann	0.9	1/16
7	56	Female	No	7.0	Mobile	III	LAR	2.0	4/18

APR = abdominoperineal resection; CRM = circumferential radial margin; LAR = low anterior resection; TNM = tumour–node–metastasis.

In the era of total mesorectal excision, the benefits of RT are confined to a decreased risk of local recurrence; there are no survival benefits. However, the use of RT is associated with major adverse effects including sexual impotence (1 in 6 women, 1 in 11 men) and debilitating bowel function (1 in 8 patients).[8–12] It is possible that such risks can be mitigated or removed with the use of newer conformal RT approaches, but we are unaware of evidence to support this position. In Ontario and other jurisdictions, the use of preoperative RT is recommended for all patients with stage II or III rectal cancer.[13] However, in the era of total mesorectal excision, we suggest that the risk–benefit ratio for preoperative RT should be considered differently for patients with and without a clear mesorectal fascia. We suspect that our results are generalizable to many other surgeons and surgical units, and we encourage surgeons to correlate their own rates of CRM positivity and local recurrence with preoperative mesorectal fascia status.

Our results add to a growing number of case series reports suggesting that the status of the mesorectal fascia versus a stage II or III tumour designation can largely inform the use of preoperative RT in patients with rectal cancer.[17–20] Strassburg and colleagues[17] used digital rectal examination and MRI to identify patients at low risk who could avoid preoperative RT: those with nonfixed tumours located higher than 6 cm from the anal verge and no evidence of tumour within 1 mm of the mesorectal fascia. This approach was extended to numerous other German centres and is being currently evaluated.[20] In the Magnetic Resonance Imaging and Rectal Cancer European Equivalence (MERCURY) Study, MRI was used alone to identify low-risk tumours: no evidence of tumour within 1 mm of the mesorectal fascia, no extramural vascular invasion and a maximum extent of tumour beyond the bowel wall of 5 mm.[19]

In the MERCURY Study, nodal status (i.e., positive or negative) did not influence the use of preoperative RT.[19] There would be little impetus for clinicians to modify indications for preoperative RT away from the current stage II or III paradigm practised in many jurisdictions, including Ontario, if pre- or postoperative RT did not expose patients with rectal cancer to possible adverse effects.[8–12]

The approach that we outline to identify patients for preoperative RT is practical and efficient. Digital rectal examination and preoperative CT findings allow for most patients to be classified as having or not having a threatened or involved mesorectal fascia. Pelvic MRI can be used in the minority of patients where such classification is not clear. Magnetic resonance imaging and CT can evaluate the status of the mesorectal fascia with high accuracy, with some evidence that MRI is superior for lower tumours.[15,16] An additional issue that we have observed with rectal tumour staging is a propensity to rely on pelvic MRI to assess mesorectal lymph nodes. However, the mesorectal lymph node package extends to the origin of the inferior mesenteric artery, an area not normally assessed by pelvic MRI.[26] Abdominopelvic CT can assess this area, and obviously worrisome nodes can influence surgeon planning (e.g., high ligation in a young patient with nonmetastatic disease) or can lead to a request that pelvic MRI cover the inferior mesenteric artery origin.

Three other relevant findings are presented in our paper. First, in our preoperative RT group, only 5 patients (7%) had a complete pathologic response. This likely resulted from reservation of preoperative RT for patients with advanced tumours that compromised the mesorectal fascia. Second, none of the 7 patients with a local tumour recurrence had a positive CRM on pathologic assessment. Of relevance, the MRC CR07 trial investigators observed that a positive CRM did not predict local tumour recurrence when tumour stage, quality of the mesorectal specimen and other factors were included in multivariable analyses.[6] Finally, all 5 patients in the RT group who experienced a local recurrence had a fixed tumour on digital rectal examination. For patients with fixed tumours on digital examination at presentation, current reliance on long-course chemoradiation alone may not be adequate to minimize the risk of local recurrence.

Limitations

Our study has limitations. First, there was some subjectivity in identifying a threatened mesorectal fascia, although, generally, tumour cells 2 mm or less from the mesorectal fascia were considered near. As noted, in most cases, digital rectal examination and CT alone can identify a threatened, involved or clear mesorectal margin, but, in a small number of cases, this assessment does not provide a clear answer, even with the addition of MRI. However, other investigators have used approaches related to those that we outline to determine the mesorectal fascia status and the need for preoperative RT.[17–20] Regardless, although the low rates of CRM positivity and local recurrence in our no-RT group provide some validation of our approach, we encourage other investigators to replicate or modify our approach and report their results. Second, our low rate of wound infection was derived retrospectively from hospital chart review. It is likely that hospital notes did not capture evidence of all wound infections and that many infections presented following hospital discharge and were managed by family physicians. However, this would not affect our main outcomes of CRM positivity and local tumour recurrence. Finally, cohort studies are associated with inherent biases that can be dealt with only by using a randomized controlled trial design. However, as with many other surgical changes and innovations, the evolution of standards related to preoperative RT in rectal cancer will likely be catalyzed first by cohort studies and then, it is hoped, studies with more robust designs.

Conclusion

Observations from the current series suggest that, in rectal cancer, the status of the mesorectal fascia and not tumour stage can best identify patients for preoperative RT and that mesorectal fascia status can usually be determined by pelvic CT and digital rectal examination with the occasional addition of MRI.

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