Original article

doi:10.1111/codi.12931

Scoring the quality of total mesorectal excision for the prediction of cancer-specific outcome

D. Leonard*, F. Penninckx†, A. Laenen‡, A. Kartheuser* and on behalf of PROCARE

*Colorectal Surgery Unit, Cliniques universitaires Saint-Luc, Brussels, Belgium, †Department of Abdominal Surgery, University Clinic Gasthuisberg, Leuven, Belgium and ‡I-Biostat, Katholieke Universiteit Leuven and Universiteit Hasselt, Leuven, Belgium

Received 18 September 2014; accepted 20 December 2014; Accepted Article online 25 February 2015

Abstract

Aim A three-grade system for macroscopic evaluation of the resection plane is used to describe the quality of total mesorectal excision (TME). In several studies, two of the three grades have been combined when analysing the outcome. The aim of our study was to compare the predictive value of the three-graded with that of a two-graded TME score.

Method The quality of TME in 1382 patients who underwent elective resection for mid or low rectal adenocarcinoma was registered by 65 hospitals in PROCARE, a Belgian multidisciplinary improvement project. Prediction of outcome based on the classic three-grade score was compared with a two-grade scoring system in which intramesorectal resection (IMR) was combined with mesorectal (MRR) or with muscularis propria resection (MPR). End-points included the local recurrence rate, distant metastasis rate (DMR), disease-free survival (DFS) and overall survival (OS).

Results Among the 1382 resections, 63% were MRR, 27% IMR and 9% MPR. No significant differences were found in local recurrence between the different grades of TME. A two-grade score distinguishing MRR from the others was found to predict DMR, DFS and OS as well as the three-grade score.

Conclusion The discriminatory and predictive value of a two-grade score, differentiating MRR from the combined IMR and MPR, was as good as the classic three-grade score.

Keywords Rectal cancer, TME quality, oncological outcome

What does this paper add to the literature?
The study has shown that combining intramesorectal and muscularis propria resections into one group is as accurate as when analysed as two groups compared with total mesorectal excision in the mesorectal plane in predicting cancer-specific end-points.

Introduction

The oncological outcome of resectable rectal cancer has improved significantly over the last two decades. Total mesorectal excision (TME) preceded by radiotherapy has been associated with a fall in local recurrence and improved disease-free (DFS) and overall survival (OS) [1,2]. Histopathological analysis of the resected TME specimen has led to the concepts of circumferential resection margin involvement (pCRM) and the quality of the mesorectal excision relating this to the integrity of the mesorectal plane. The latter is based on the pathological assessment of the surgical specimen in which three grades of resection have been defined including mesorectal resection (MRR) (smooth, complete, good quality), intramesorectal resection (IMR) (moderately irregular, nearly complete, moderate quality) and resection in the muscularis propria (MPR) (severely irregular, poor quality) [3,4]. The quality of TME influences local and overall recurrence rates [5]. Evidently, the mesorectal grade extends beyond obtaining statistical significance in individual trials. In the individual patient it can potentially be used to explain the cause of CRM involvement. It is also an excellent way of auditing surgical quality and surgeons going through their TME learning curve can use the feedback to improve the quality of their dissection. IMR has been combined with either MRR or MPR in the analysis in several studies [4–7], but it is unclear whether a two- or a three-scoring system is superior for the prediction of cancer-specific outcome.

We asked the following questions. (i) Is the quality of TME predictive of oncological outcome after

Correspondence to: Dr Leonard Daniel MD, Colorectal Surgery Unit, Cliniques universitaires Saint-Luc, Avenue Hippocrate 10, B-1200 Brussels, Belgium.
E-mail: daniel.leonard@uclouvain.be

The members of PROCARE are in Appendix section.

correction for relevant confounders? (ii) Is the predictive value of the three-grade scoring system better than a two-grade system in which IMR is combined either with MRR or MPR? In an attempt to answer these questions, we conducted a study based on data recorded in PROCARE, a Belgian multidisciplinary improvement project of cancer of the rectum launched in 2006. All hospitals were invited to participate, multidisciplinary guidelines and quality of care indicators were developed [8,9] and multiple data were registered in a specific database [10]. Pathologists were instructed at national meetings and at dedicated workshops, including live demonstrations of TME performance by Heald and the assessment of the quality of TME specimens by Quirke. A *Pathology TME Cookbook* for macroscopic and microscopic TME specimen handling was made available and could be readily downloaded from the PROCARE website at the Belgian Cancer Registry (www.kankerregister.org).

Method

Between January 2006 and October 2011, 2297 patients with a primary adenocarcinoma of the rectum between 0 and 10 cm from the anal verge underwent TME. Patients (439) with disseminated disease or those having an *en bloc* resection of other organs (322), emergency management (5), patients with a synchronous cancer (61) and patients for whom the quality of TME was not registered (88) were excluded. This left 1382 patients who were included for further study.

Multiple patient, tumour and treatment-related data, prospectively recorded in the PROCARE database by 65 of the 111 Belgian hospitals, were extracted for analysis. The quality of TME was uniformly reported by the pathologists according to the three-grade scoring system [3,4]. The end-points included the local recurrence rate (LRR), the distant metastasis rate (DMR), DFS and OS. Time to local or distant recurrent disease and death was computed from the date of surgery. DFS was defined as the time from surgery to local recurrence, metastasis or death from any cause, whichever occurred first. The current status of all patients was obtained from the Belgian Crossroads Bank for Social Security on 23 November 2012. Patients who were alive and disease free were censored at the time of last follow-up.

Statistical analysis

Kaplan–Meier estimates were used to express survival and were stratified for TME quality scores. A multivariable Cox model was used to test the influence of quality of TME on outcome, adjusting for confounders, such as variables that appeared to be associated with the quality of TME and the oncological outcome. Only records with observation of all model variables were included. A Wald test was used to determine whether TME quality scores differed with respect to the oncological outcome. The robust sandwich estimate of Lin and Wei for the covariance matrix was used to account for clustering by hospital [11].

In order to compare the different TME scoring systems, three measures of goodness of fit or performance were calculated including the Akaike information criterion (AIC), the concordance probability estimate (CPE) and a pseudo R^2 value for time-to-event data. A lower AIC value indicates the model with minimal loss of information, but it provides no information about how well a model fits the data in an absolute sense. CPE is a time-dependent extension of the area under the receiver operating curve for binary responses and has a similar interpretation to an index for the discriminatory power of a model. It includes values between 0.5 (discrimination not better than random) and 1 (perfect discrimination). The pseudo R^2 value is a time-dependent extension of the R^2 measure in linear regression expressing the percentage of variance explained by the model, or the predictive value of the model. It includes values between 0 (no predictive value) and 1 (perfect prediction).

All analyses were performed using SAS software, version 9.2, of the SAS System for Windows (Copyright © 2002 SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, North Carolina, USA).

Results

There were 875 (63.3%) resections in the mesorectal plane, 379 (27.4%) in the intramesorectal plane and 128 (9.3%) in the muscularis propria plane. Kaplan–Meier estimates were quite different for most outcomes when stratified for the quality of TME (Fig. 1), but several patient, tumour and treatment-related characteristics were unevenly distributed across the different TME quality scores (Table 1). The following variables, not mentioned in the table, were not significantly associated with TME quality: American Society of Anesthesiologists score, body mass index, cN, pretreatment imaging-based distance from the outer border of the tumour to the mesorectal fascia, serum carcinoembryonic antigen, year of surgery, peri-operative blood transfusion, anastomotic leakage after sphincter-saving operation, tumour diameter (≤ 5 cm or > 5 cm), pT, pN, number of

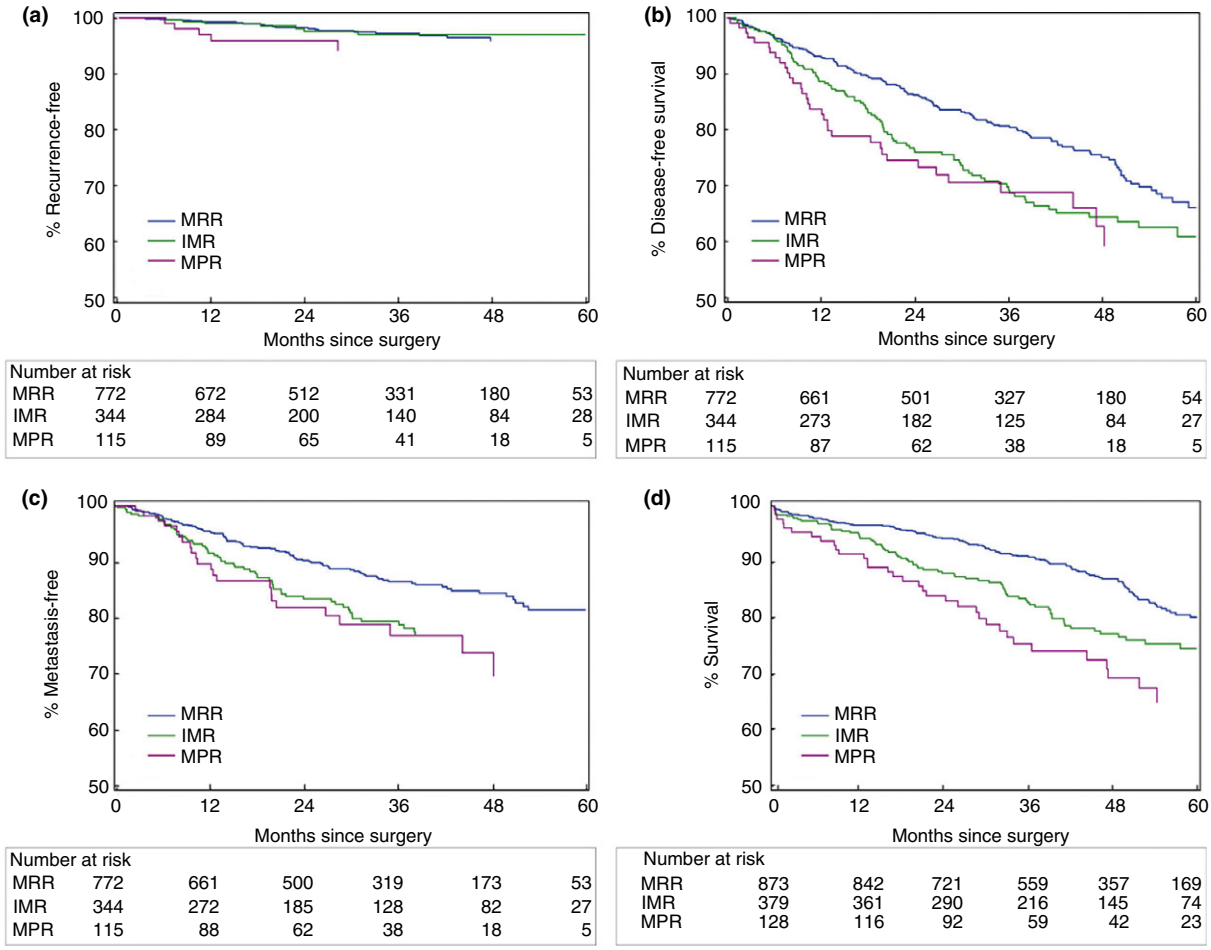


Figure 1 Kaplan–Meier curves for local recurrence-free survival (a), distant metastasis-free survival (b), disease-free survival (c) and overall survival (d), stratified according to quality of the TME resection plane using the three-grade scoring system: mesorectal (MRR), intramesorectal (IMR) and muscularis propria (MPR).

positive lymph nodes, lymph node ratio, extramural tumour deposits, and adjuvant chemotherapy.

The results of univariable analysis testing the influence of the same set of variables on oncological outcomes are summarized in Table 2. Intra-operative perforation and margin positivity were not considered for adjustment because they were deemed to be intervening factors, i.e. poor quality of TME may result in worse outcome through these covariates.

The 5-year LRR was 4%. There were no significant differences between the quality of TME and the risk of local recurrence (Table 3). The three scoring methods were comparable after adjustment for extramural vascular invasion and age, but the degree of fit and the amount of variation of LRR explained by each was low (Table 4).

The 5-year DMR was 21%. The adjusted hazard ratio (HR) for DMR reached a level of statistical significance when surgical specimens with a good quality TME were compared with suboptimal resection planes (Table 3). After adjustment for number of quadrants involved, type of radical resection, histological grade, extramural vascular invasion and age, goodness of fit and performance of the two-grade system distinguishing MRR from IMR combined with MPR was as good as the three-grade system (Table 4, Fig. 2).

The 5-year DFS was 64% and OS 77% in the whole patient series. After adjustment for c stage, ventral tumour location, number of quadrants involved, type of radical resection, histological grade, extramural vascular invasion and age (quadratic), the HR for death during follow-up was statistically significant when MRR was compared with IMR combined with MPR (Table 3). This two-grade scoring system could replace the classic three-grade system without losing discriminatory or predictive power (Table 4, Fig. 3). Overall, goodness of fit, discriminatory and predictive power of the models were comparable, whatever TME quality scoring system was used.

Table 1 Patient characteristics according to the three-grade assessment of the quality of TME.

Variables	TME plane			*P*
	Mesorectal (*N* = 875, 63.3%)	Intramesorectal (*N* = 379, 27.4%)	Muscularis propria (*N* = 128, 9.3%)	
Gender				
Male	574 (66)	224 (59)	71 (55)	0.017
Female	301 (34)	155 (41)	57 (45)	
Age, median (range)	67.4 (21.8–94.5)	70.5 (22.0–90.4)	70.2 (46.7–89.5)	0.002
LLcm, median (range)	5.0 (0.0–10.0)	5.0 (0.0–10.0)	4.0 (0.0–10.0)	< 0.001
c Stage				
I	121 (14)	41 (11)	23 (19)	0.011
II	128 (15)	81 (22)	17 (14)	
III	603 (71)	246 (67)	82 (67)	
cT				
T ≤ 1	26 (3)	10 (3)	7 (6)	0.042
T2	183 (21)	61 (16)	26 (21)	
T3	614 (71)	270 (73)	82 (67)	
T4	36 (4)	29 (8)	8 (7)	
Ventral tumour location				
No	360 (50)	162 (50)	37 (35)	0.011
Involved	357 (50)	160 (50)	69 (65)	
Number of quadrants involved				
1	388 (54)	154 (48)	33 (31)	< 0.001
2	234 (33)	118 (37)	41 (39)	
3 or 4	95 (13)	50 (16)	32 (30)	
Neoadjuvant RT/RCT				
No	201 (23)	94 (25)	40 (31)	0.12
Yes	674 (77)	285 (75)	88 (69)	
Surgical approach for TME				
Open	597 (68)	258 (69)	79 (62)	0.30
(Converted) Lap	277 (32)	118 (31)	49 (38)	
Type of radical operation				
APER	142 (16)	116 (31)	55 (43)	< 0.001
SSO/Hartmann	733 (84)	263 (69)	73 (57)	
Intra-operative perforation				
No	860 (99)	357 (97)	110 (89)	< 0.001
Yes	10 (1)	10 (3)	14 (11)	
p Stage				
0/I	425 (49)	171 (45)	54 (43)	0.62
II	197 (23)	95 (25)	32 (25)	
III	247 (28)	111 (29)	40 (32)	
Histological grade				
Well	113 (15)	52 (16)	17 (17)	0.022
Moderate	496 (67)	199 (60)	61 (60)	
Poor	76 (10)	60 (18)	17 (17)	
Not applicable	50 (7)	18 (5)	6 (6)	
Margin positivity				
Negative	599 (89)	267 (86)	65 (65)	< 0.001
Positive	75 (11)	45 (14)	35 (35)	
No. of lymph nodes [median (range)]	11 (0–62)	12 (1–135)	11 (0–44)	0.009
Extramural vascular invasion				
No	753 (90)	318 (88)	103 (82)	0.049
Yes	86 (10)	44 (12)	22 (18)	

LLcm, lower limit of the tumour in centimetres from the anal verge; c Stage, clinical TNM stage; cT, clinical tumour stage; RT, radiotherapy; RCT, radiochemotherapy; TME, total mesorectal excision; Lap, laparoscopic; cT, clinical tumour stage; APER, abdominoperineal resection; SSO, sphincter-saving operation; p Stage, pathological TNM stage.

Absolute numbers are given with percentages in parentheses, if not otherwise indicated. *P* values of univariable analysis are presented.

Table 2 Overview of univariable analysis testing the independent variables against the quality of TME and oncological outcome.

Variable	TME quality	LRR	DMR	DFS	OS
Gender	×				
Age	×	×	×	×	×
ASA score				×	×
BMI					
LLcm	×				
cT	×				
cN			×		
c Stage	×				×
cCRM					
CEA			×	×	×
Ventral tumour location	×			×	×
No. of quadrants involved	×		×	×	×
Neoadjuvant RT/RCT		×		×	×
Year of surgery					
Surgical approach					
Type of radical resection	×		×	×	×
Intra-operative perforation	×	×			
Peri-operative blood transfusion				×	×
Margin positivity	×	×	×	×	×
Tumour diameter		×	×	×	×
pT			×	×	×
pN		×	×	×	×
p Stage		×	×	×	×
Tumour differentiation grade	×		×	×	×
No. of lymph nodes examined	×				
No. of positive lymph nodes		×	×	×	×
Lymph node ratio		×	×	×	×
Extramural tumour deposits		×	×	×	×
Extramural vascular invasion	×	×	×	×	×
Leakage after SSO					
Adjuvant chemotherapy			×		

TME, total mesorectal excision; LRR, local recurrence rate; DMR, distant metastasis; DFS, disease-free survival; OS, overall survival; ASA, American Society of Anesthesiologists; BMI, body mass index; LLcm, distance from the inferior pole of the tumour to the anal verge; cT, clinical tumour stage; cN, clinical nodal stage; c Stage, clinical TNM stage; cCRM, pretreatment imaging-based distance from the outer border of the tumour to the mesorectal fascia; RT/RCT, radiotherapy/radiochemotherapy; type of radical resection, sphincter-saving operation *vs* abdominoperineal resection; pT, pathological tumour stage; pN, pathological nodal stage; p Stage, pathological TNM stage; SSO, sphincter-saving operation. Marked by a cross: variables considered as confounders, i.e. significantly associated with TME quality and oncological outcome.

Discussion

A two-grade system distinguishing MRR from the other forms of surgery was found to predict distant metastasis, DFS and OS as well as the three-grade score. Nevertheless the performance of all models was relatively low and little different. Some authors have combined IMR with either MRR or MPR to analyse the effect of TME quality on outcome. This is the first study to specifically compare the predictive value of the classic three-grade total mesorectal scoring method with that of two-grade methods. The principal weakness of this study is the participation of centres on a voluntary basis with registration bias [12], but biased reporting of the quality of TME could not be assessed.

In contrast with other studies, no significant associations were observed between TME quality and local recurrence [3,13]. Combining two grades increased the chance of reaching a statistically significant difference. Thus the aim of the study of whether IMR can be merged with MPR without a reduction in the prediction of cancer outcome showed a positive result.

When using a two-grade assessment of the quality of TME with good quality (MRR) on the one hand and IMR combined with MPR on the other, a significant association was found with the risk for developing

Table 3 The comparison of systems of the quality of TME including three grades, MRR with IMR and MRR combined and MRR and IMR combined with MPR.

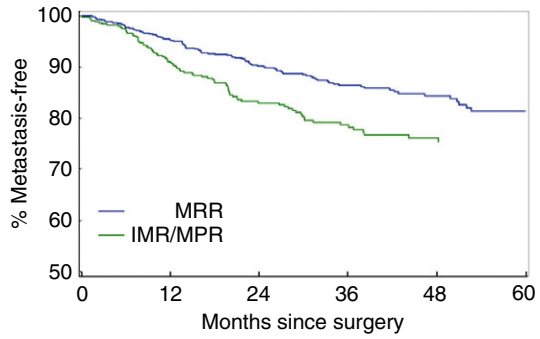
TME quality scoring method	Comparison	Hazard ratio	95% CI lower limit	95% CI upper limit	*P*
Local recurrence					
Three grade	IMR *vs* MRR	0.953	0.410	2.216	0.9107
Three grade	MPR *vs* MRR	1.718	0.635	4.649	0.2866
Three grade	MPR *vs* IMR	1.803	0.579	5.618	0.3093
MRR *vs* IMR + MPR		1.147	0.561	2.345	0.7069
MRR + IMR *vs* MPR		1.745	0.665	4.581	0.2584
Distant metastasis					
Three grade	IMR *vs* MRR	1.454	0.998	2.119	0.0512
Three grade	MPR *vs* MRR	1.547	0.843	2.841	0.1594
Three grade	MPR *vs* IMR	1.064	0.573	1.976	0.8447
MRR *vs* IMR + MPR		1.474	1.034	2.101	0.0321
MRR + IMR *vs* MPR		1.303	0.725	2.344	0.3760
Disease-free survival					
Three grade	IMR *vs* MRR	1.322	0.975	1.792	0.0727
Three grade	MPR *vs* MRR	1.345	0.811	2.228	0.2506
Three grade	MPR *vs* IMR	1.017	0.608	1.702	0.9481
MRR *vs* IMR + MPR		1.327	0.995	1.770	0.0544
MRR + IMR *vs* MPR		1.189	0.730	1.936	0.4867
Overall survival					
Three grade	IMR *vs* MRR	1.356	0.940	1.954	0.1032
Three grade	MPR *vs* MRR	1.688	0.976	2.920	0.0611
Three grade	MPR *vs* IMR	1.245	0.724	2.143	0.4279
MRR *vs* IMR + MPR		1.427	1.010	2.016	0.0435
MRR + IMR *vs* MPR		1.464	0.870	2.464	0.1509

TME, total mesorectal excision; MRR, mesorectal resection; IMR, intramesorectal resection; MPR, mucularis propria resection. *P* values and confidence limits are based on a robust Wald test performed between all possible couples of quality levels.

Table 4 Goodness of fit and performance statistics for models using three TME scoring methods.

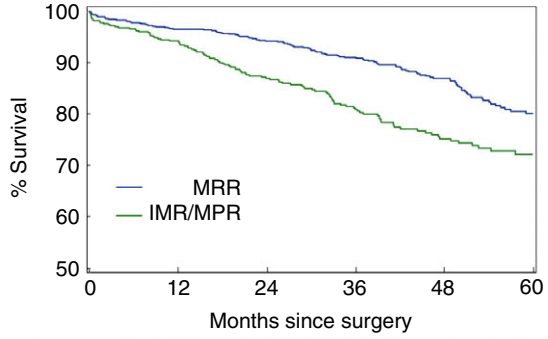
TME quality scoring method for different oncological end-points	AIC	CPE (SD)	Pseudo R^2 (%)
Local recurrence			
Three grade	402.340	0.638 (0.029)	2.692
MRR *vs* IMR + MPR	401.337	0.636 (0.031)	1.850
MRR + IMR *vs* MPR	400.353	0.638 (0.028)	2.648
Distant metastasis			
Three graded	1603.765	0.663 (0.020)	8.857
MRR *vs* IMR + MPR	1601.808	0.663 (0.020)	8.843
MRR + IMR *vs* MPR	1605.357	0.656 (0.021)	8.808
Disease-free survival			
Three-grade	2458.076	0.667 (0.016)	11.393
MRR *vs* IMR + MPR	2456.081	0.667 (0.016)	11.395
MRR + IMR *vs* MPR	2459.186	0.663 (0.016)	11.408
Overall survival			
Three grade	1861.195	0.699 (0.018)	13.879
MRR *vs* IMR + MPR	1859.895	0.701 (0.018)	13.862
MRR + IMR *vs* MPR	1861.887	0.696 (0.018)	13.436

AIC, Akaike information criterion; CPE, concordance probability estimate; MRR, mesorectal resection; IMR, intramesorectal resection; MPR, mucularis propria resection.



Number at risk						
MRR	772	661	500	319	173	53
IMR/MPR	459	360	247	166	100	32

Figure 2 Kaplan–Meier curves showing metastasis-free survival according to a two-grade scoring system comparing outcome after resection in the mesorectal plane (MRR) with outcome after pooling resections in the intramesorectal and the muscularis propria plane (IMR/MPR).



Number at risk						
MRR	873	842	721	554	357	169
IMR/MPR	507	477	382	275	187	97

Figure 3 Kaplan–Meier curves showing overall survival according to a two-grade score where outcome after resection in the mesorectal plane (MRR) is compared with outcome after pooling resections in the intramesorectal and the muscularis propria plane (IMR/MPR).

distant metastasis, with OS, as well as a trend for DFS. These associations did not reach a level of statistical significance when using the alternative two-graded scoring system. Therefore, resection in the IMR plane should not be combined with good quality TME in the mesorectal plane. This is in line with the concept of TME whereby dissection in the mesorectal plane is the most appropriate means of avoiding a positive CRM.

It was unexpected to observe that the quality of TME was not related to LRR while it was to the other outcome measures. This may be due to the low number of events (31 local recurrences in 1178 patients with complete case information). An effect of a three-graded TME quality system on LRR was observed in the MRC CR07 study, although no statistical significance for the 3-year DFS was reached [3]. Also an independent effect of the grade of MRR on both local and overall recurrences was reported in 130 patients [13]. In contrast and similar to the observation in the present study, the Leicester Colorectal Specialist Group using the three-graded TME scoring system found no effect of the quality of TME on LRR in 287 patients [14]. Two studies merged data from patients with MRR and IMR [4,7]. Nagtegaal *et al.* [4] observed an effect on the overall recurrence rate but not on LRR in 180 patients from the Dutch TME trial. Leite *et al.* [7] reported a significant effect on LRR and DFS in 127 patients. Other authors combined IMR and MPR and found an association with LRR but not with overall recurrence [6]. Overall survival was addressed in two studies. Nagtegaal *et al.* reported survival rates of 86% and 76% ($P < 0.05$) for MRR combined with IMR *vs* MPR, whereas Maslekar *et al.* found no difference in survival in patients stratified according to the three grades of the quality of TME [4,13]. The fact that we did not observe an association between the quality of TME and LRR is most probably due to the low number of events. Indeed, 5-year LRR was only 4%. This may be related to the frequent use of neoadjuvant radiochemotherapy in Belgium, a high percentage of MRR and negative resection margins. Similarly, a 3-year LRR of 1% was observed in the MRC CR07 trial after neoadjuvant radiotherapy and MRR with negative CRM [2,3]. According to a recent meta-analysis, preoperative RCT has a larger impact on local control in resectable Stage II and III rectal cancer than preoperative radiotherapy [15]. The effect of suboptimal quality of TME on DMR, DFS and OS observed in the present study could be related to the fact that pelvic dissection in difficult circumstances (small pelvis, large tumour burden, obesity etc.) frequently results in more 'tumour manipulation', suboptimal resection planes and worse outcome.

In conclusion a two-grade TME quality scoring system with MRR on the one hand and combined IMR and MPR on the other performed as well as the three-grade score for prediction but was more significantly associated with OS and the risk for DMR. IMR should be regarded as suboptimal surgery increasing the risk for an adverse outcome and should not be combined with MRR for analysis.

Acknowledgements

The authors thank all teams and professionals participating in the PROCARE project. The list of participating

centres can be found at www.kankerregister.org under PROCARE. The pathology review board members (C. Cuvelier, G. De Hertogh, P. Demetter, N. Ectors, A. Hoorens, A. Jouret-Mourin, N. Nagy, Ch. Sempoux) and T. Vandendael, data manager at the Belgian Cancer Registry (Dr E. Van Eycken, director), hosting the PROCARE database are acknowledged for their input. PROCARE thanks the Foundation against Cancer and the RIZIV/INAMI for their financial support. D. Leonard is grateful for the financial support granted by the Fondation Saint-Luc, Cliniques universitaires Saint-Luc, Brussels, Belgium.

Conflict of interest

The authors have no disclosures.

References

1 Kapiteijn E, Marijnen CA, Nagtegaal ID *et al.* Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med* 2001; **345:** 638–46.
2 Sebag-Montefiore D, Stephens RJ, Steele R *et al.* Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. *Lancet* 2009; **373:** 811–20.
3 Quirke P, Steele R, Monson J *et al.* Effect of the plane of surgery achieved on local recurrence in patients with operable rectal cancer: a prospective study using data from the MRC CR07 and NCIC-CTG CO16 randomised clinical trial. *Lancet* 2009; **373:** 821–8.
4 Nagtegaal ID, van de Velde CJ, van der Worp E *et al.* Macroscopic evaluation of rectal cancer resection specimen: clinical significance of the pathologist in quality control. *J Clin Oncol* 2002; **20:** 1729–34.
5 Bosch SL, Nagtegaal ID. The importance of the pathologist's role in assessment of the quality of the mesorectum. *Curr Colorectal Cancer Rep* 2012; **8:** 90–8.
6 Garcia-Granero E, Faiz O, Munoz E *et al.* Macroscopic assessment of mesorectal excision in rectal cancer: a useful tool for improving quality control in a multidisciplinary team. *Cancer* 2009; **115:** 3400–11.
7 Leite JS, Martins SC, Oliveira J, Cunha MF, Castro-Sousa F. Clinical significance of macroscopic completeness of mesorectal resection in rectal cancer. *Colorectal Dis* 2011; **13:** 381–6.
8 Penninckx F, Roels S, Leonard D *et al. Quality Assurance for Rectal Cancer Phase 1: Good Clinical Practice for the Treatment of Rectal Cancer*. KCE Reports 69B (D/2007/10273/55). Brussels: Health Care Knowledge Centre (KCE), 2007.
9 Vlayen J, De Gendt C, Stordeur S *et al. Indicators for the Management of Upper Gastrointestinal Cancer. KCE Reports 200 (D/2013/10273/15)*. Brussels: Health Care Knowledge Centre (KCE), 2013.
10 Vandendael T, Penninckx F, Bertrand C *et al.* Exploring limits for data registration in the context of PROCARE, a quality improvement project on rectal cancer. *Acta Chir Belg* 2012; **112:** 15–23.
11 Lin DY, Wei LJ. The robust inference for the proportional hazards model. *J Am Statist Assoc* 1989; **84:** 1074–8.
12 Jegou D, Penninckx F, Vandendael T *et al.* Completeness and registration bias in PROCARE, a Belgian multidisciplinary project on cancer of the rectum with participation on a voluntary basis. *Eur J Cancer* 2014; http://dx.doi.org/10.1016/j.ejca.2014.02.025.
13 Maslekar S, Sharma A, Macdonald A *et al.* Mesorectal grades predict recurrences after curative resection for rectal cancer. *Dis Colon Rectum* 2007; **50:** 168–75.
14 Jeyarajah S, Sutton CD, Miller AS, Hemingway D. Leicester Colorectal Specialist Group. Factors that influence the adequacy of total mesorectal excision for rectal cancer. *Colorectal Dis* 2007; **9:** 808–15.
15 De Caluwe L, Van Nieuwenhove Y, Ceelen WP. Preoperative chemoradiation versus radiation alone for stage II and III resectable rectal cancer. *Cochrane Database Syst Rev* 2013; **2:** CD006041.

Appendix: Collaborators

The PROCARE steering group consists of delegates from all Belgian scientific organizations involved in the treatment of rectal cancer, i.e. the Belgian Section of Colorectal Surgery, a section of the Royal Belgian Society of Surgery (Bertrand C., De Coninck D., Duinslaeger M., Kartheuser A., Penninckx F., Van de Stadt J., Vaneerdeweg W.), the Belgian Society of Surgical Oncology (Claeys D.), the Belgian Group for Endoscopic Surgery (Burnon D.), the Belgian Society of Radiotherapy – Oncology (Haustermans K., Scalliet P., Spaas Ph.), the Belgian Society of Pathology and the Digestive Pathology Club (Demetter P., Jouret-Mourin A., Sempoux C.), the Belgian Society of Medical Oncology (Demey W., Humblet Y., Van Cutsem E.), the Belgian Group for Digestive Oncology (Laurent S., Van Cutsem E., Van Laethem J. L.), the Royal Belgian Society of Radiology (Op de Beeck B., Smeets P.), the Société Royale Belge de Gastro-Entérologie (Melange M., Rahier J.), the Vlaamse Vereniging voor Gastro-enterologie (Cabooter M., Pattyn P., Peeters M.), the Belgian Society of Gastro-intestinal Endoscopy (Buset M.). Also represented are the Belgian Professional Surgical Association (Mansvelt B., Vindevoghel K.), the Foundation Belgian Cancer Registry (Van Eycken E.) and the RIZIV/INAMI (Daubie M., Thijs A.). Penninckx F. chairs the PROCARE Steering Group.