Factors Predicting the Quality of Total Mesorectal Excision for Rectal Cancer

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Objective: To determine preoperative tumor-, patient-, and treatment-related factors that are independently associated with incomplete mesorectal excision.

Summary of Background Data: Incomplete total mesorectal excision (TME) for rectal cancer is associated with increased local and overall recurrences. Factors predicting incomplete mesorectal excision have scarcely been studied.

Methods: In the context of PROCARE, a Belgian multidisciplinary project on rectal cancer, the quality of 266 consecutive and anonymized TME specimens submitted by 33 candidate-TME-trainers was graded by a blinded pathology review board in a standardized manner. Uni- and multivariable analysis were performed to identify factors that can independently predict incomplete mesorectal excision.

Results: Mesorectal resection was complete in 21%, nearly complete in 47%, and incomplete in 32%. Of 57% of TME specimens the grade of resection had not been reported by the local pathologist. Incomplete TME doubled the incidence of a positive circumferential resection margin ($P = 0.004$). Factors found to be significantly related to incomplete TME in univariate analysis were as follows: surgeon, female gender, pathologic body mass index, low rectal cancer, negative clinical nodal status, the absence of downstaging after long-course chemoradiation, laparoscopic and converted laparoscopic resection, and abdominoperineal resection. Multivariable analysis identified pathologic body mass index ($P = 0.017$), the absence of downstaging after long-course chemoradiation ($P = 0.0005$), and laparoscopic or converted laparoscopic resection ($P = 0.014$) as factors that are independently associated with incomplete mesorectal excision.

Conclusion: Good TME quality cannot be guaranteed. This peer-reviewed TME assessment revealed a number of factors that are independently related to incomplete TME. Both specimen and pathology report need to be audited.

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Total mesorectal excision (TME) has become a standard part of the multidisciplinary treatment of rectal cancer. Measurement of the pathologic circumferential tumor-free resection margin (pCRM) and grading of the quality of TME are important pathologic criteria in the assessment of surgical specimens. Two recent reviews con-cluded that the pCRM status predicts outcome after surgery with or without neoadjuvant radio(chemo)therapy.[1,2] A strong relationship between poor TME quality and a positive circumferential resection margin, recurrence and survival rates has been documented.[3] Together with tumor stage, nodal status, and preoperative radiotherapy, grade of the mesorectal excision was identified as an independent predictor of both local and overall recurrence.[4,5] In the MRC CR07 and NCIC-CTG CO16 trials, the risk of local recurrence was virtually eliminated, that is, it was 1% 3 years after a good quality TME which had been preceded by preoperative radiotherapy. In cases of poor TME surgery, the 3-year local recurrence rate was 10% in the preoperative radiotherapy arm and 16% in the selective postoperative chemoradiation arm.[5,6] Although mesorectal excision grading is relevant and can serve as a surrogate for oncological outcome, reports on factors affecting TME quality are very scarce.

In several countries major efforts have been made to implement and teach the technique of TME and its pathologic assessment.[7–15] In some of them, participating surgeons were trained by expert tutors. In the context of PROCARE, a Belgian multidisciplinary project on cancer of the rectum (available at: http://www.registreducancer.org), workshops for surgeons and pathologists with masterclasses by Heald and Quirke were organized in 2005. After these meetings and a population-based analysis of the outcome after rectal cancer treatment in Belgium,[16] it was decided to offer decentralized TME training to surgeons on a voluntary basis, as an important part of the project. Because of financial constraints, this training could not engage foreign TME experts. As an alternative, Belgian surgeons were invited to act as tutors if they agreed to an external audit of their consecutive TME cases by delegates from the Digestive Pathology Club and the Belgian Section of Colorectal Surgery. This study was based on anonymously reviewed material from 266 consecutive TME specimens submitted by these candidate TME tutors.

The aim of this study was to identify preoperative patient-, tumor-, and treatment-related factors that are independently related to the quality of TME.

METHODS

The Review Process and Quality Definitions

Surgeons participating in PROCARE submitted multidisciplinary data on consecutive patients with rectal cancer. After anonymization these data were fed into a specific database at the Foundation Belgian Cancer Registry. Registration started in January 2006. The possibility to participate as a candidate TME-trainer was open to all surgeons involved in the PROCARE project. Candidate TME tutors confirmed their willingness to help colleagues with TME surgery and their availability on a written form in January 2007.

Data managers at the Foundation Belgian Cancer Registry requested pathologists of all candidate TME-trainers to submit material for review. After receipt, the material was anonymized. Pathology review was performed at regular meetings by at least 4 pathologists delegated by the Digestive Pathology Club. The following material was required to evaluate a case: (1) good quality photo documentation of the ventral and dorsal aspects of the fresh, unfixed, and unopened resection specimen; (2) good quality photo documentation of serial transverse sections, with a thickness of 3 to 5 mm, through

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the inked non peritonealized part of the specimen; (3) microscopy sections demonstrating the deepest tumor infiltration and pCRM; (4) anonymized report of the local pathologist. Per case a summary report of the pathology audit was made mentioning TME quality, pT category according to TNM classification, and (y)pCRM (pathologic tumor-free circumferential resection margin either with (ypCRM) preoperative radio(chemo)therapy or without (pCRM) preoperative treatment). TME quality was defined as described by Quirke and colleagues.[3,17,18] Complete: intact and smooth mesorectal surface with defects not deeper than 5 mm, no coning; nearly complete: somewhat irregular mesorectal surface with defects deeper than 5 mm but muscular coat not visible or inked, moderate distal coning; incomplete: very irregular mesorectal surface with defects down to the muscularis propria. The (y)pCRM was considered positive when $\leq$1 mm. For abdominoperineal resection (APR) specimens, the quality of resection at the sphincteric level was not considered for the appreciation of the quality of the TME part of the resection although pronounced distal coning ("waist") with dissection down to the muscularis propria were considered poor quality of resection.

Clinicopathologic data of all cases submitted by candidate TME-trainers and the summary report of the pathology review board were assessed by a subcommittee of the Belgian Section of Colorectal Surgeons. In case of inconsistency with clinical data (eg, TME considered to be a partial mesorectal excision) or with the conclusion on TME quality by the local pathologist, a rereview by the pathology board was requested.

Material

Between January 2006 and February 2008, 40 candidate trainers submitted 362 TME specimens. Their pathologists were able to provide all the requested material for central pathology review of 266 cases (73%). The main reasons for the rejection of material for evaluation were as follows: absence or insufficient pathologic material or suboptimal quality of photographic material (N = 87) and inconsistent data without clear explanation obtainable from the surgeon or the pathologist (N = 9). This left 266 TME specimens from 33 candidate trainers, a median of 6 specimens per candidate trainer (range, 1–19). Specimens with complete (good quality) and nearly complete (moderate quality) mesorectal surface were combined for further analysis as no difference in outcome between both subgroups has been reported.[3]

The following patient-, tumor-, and treatment-related data were analyzed to identify factors influencing the quality of TME: age, gender, weight, body mass index (BMI), lower limit of the tumor above the anal verge, tumor size estimated by means of its longitudinal diameter at proctoscopy or colonoscopy, tumor circumferential position and extension (ventral, circular, number of quadrants involved), clinical tumor (cT), and nodal status (cN) according to TNM classification, clinically assessed tumor-free circumferential resection margin (cCRM), neoadjuvant treatment and type of neoadjuvant treatment, surgeon, type of approach for resection (open, laparoscopy, converted laparoscopy), and type of resection (sphincter-saving operation with reconstruction, APR, Hartmann's procedure). BMI was analyzed as a continuous linear or nonlinear variable. The lower limit of the tumor was analyzed as a continuous variable transformed to log scale. Cases with a converted laparoscopic resection were analyzed on the basis of intention to treat, that is, they were included in the laparoscopic resection group. It was anticipated that the relation between cT and TME quality could be a nonsignificant one because neoadjuvant chemoradiation could have resulted in downstaging/downsizing. Therefore, the effect of downstaging after long-course chemoradiation was included as a potential factor. To do so, cT3 and cT4 patients who had received long-course chemoradiation were divided into patients who had been downstaged to $\leq$ypT2 and those who had not responded to chemoradiation, that is, who had remained ypT3/4.

Statistical Analysis

Proportions were compared between groups with a Fisher exact test. To predict incomplete TME, a univariate logistic regression model was used for each potential risk factor. The set of all factors with $P < 0.10$ was combined into a multivariable model. Data from the 170 patients with complete information for these factors were used in the multivariable model. As a sensitivity analysis, a multiple imputation approach has been used to deal with the missingness in preoperative factors. However, the major conclusions did not differ with those obtained from the analysis on the subjects with complete information (details of analysis and results not shown). No further model reduction strategies were considered. Nonlinear relations were allowed for the continuous predictors by means of restricted cubic splines. The effect of "surgeon" was added in each model as a random one, yielding a so-called multilevel logistic regression model. *P* values were obtained with likelihood-ratio tests and considered significant if <0.05. All analyses were performed with SAS software (version 9.2).

RESULTS

Patient demographic data are presented in Table 1. Of the 266 specimens, 56 were classified as complete (21%), 124 as nearly complete (47%), and 86 as incomplete (32%). In 152 cases (57%), the TME quality was not recorded in the local pathology report. In 53 of 114 cases (46%), the local pathologist's assessment of TME quality was overruled by the pathology review board. Nineteen TMEs originally judged to be of complete (13 cases) or nearly complete (6 cases) quality were found to be incomplete. The grading of another 26 specimens changed from complete to nearly complete, whereas 4 cases were upgraded from nearly complete to complete and 4 cases from incomplete to nearly complete mesorectal excision.

To assess the relation between TME quality and the pCRM with or without neoadjuvant chemoradiation, cases with a complete tumor response were excluded (Table 2). The incidence of a positive (y)pCRM, defined as tumor cells at $\leq$1 mm from a circumferential resection margin, doubled in case of incomplete TME as compared with nearly complete or complete resections ($P = 0.004$). No significant difference was observed between the latter 2 ($P = 0.60$). Stratification for pathologic staging still yielded a significant ($P = 0.012$) relation between incomplete TME and a positive (y)pCRM, indicating that the result is not because of a confounding effect of stage mix.

At univariate analysis the surgeon (Fig. 1), female gender, pathologic BMI, negative clinically assessed nodal status (cN), a lower limit of the rectal cancer, cT 3 to 4 tumors not downstaged after neoadjuvant chemoradiation, laparoscopic resection including laparoscopy converted resections, and APR were all significantly associated with incomplete mesorectal excision (Table 3). A nonlinear significant ($P = 0.003$) association between BMI and TME quality was found (Fig. 2). An incomplete mesorectal excision was more frequently observed in patients with either high or low BMI. There was no evidence that the relation between BMI and incomplete TME differs between men and women ($P = 0.25$). A low tumor level was related to more incomplete TME. In contrast, tumor mass—assessed by means of its longitudinal diameter, number of involved circumferential quadrants, tumor depth (cT), and pretreatment cCRM—was not found to be significantly related to TME quality. The clinically assessed CRM (cCRM) remained not significant after categorization into <2, 2 to 5, and >5 mm classes or when treating cCRM as a continuous predictor. However, it must be emphasized that the amount of missing information about cCRM was high. Rather unexpectedly, a negative cN status was associated with incomplete TME. Although

TABLE 1. Patient-, Tumor- and Therapy-Related Characteristics for the Different Groups

	Quality of Mesorectal Excision			
	Total	Complete	Nearly Complete	Incomplete
No. patients (%)	266	56 (21)	124 (47)	86 (32)
Men	175	43	86	46
Women	91	13	38	40
Age (yr)				
Mean	66	67	65	66
Median	66	66	66	66
Range	35−89	35−89	36−87	39−88
Missing	2	1	0	1
Weight (kg)				
Mean	74	74	75	73
Median	73	77	74	70
Range	42−122	42−104	46−102	43−122
Missing	22	2	15	5
BMI				
Mean	26	26	26	26
Median	25	26	26	24
Range	17−41	18−37	18−36	17−41
Missing	45	7	27	11
Lower limit of tumor				
Mean (cm above anal verge)	5.4	5.9	5.7	4.6
Median	5	5	5	4
No. tumors at <5 cm	107	19	46	42
No. tumors at 5−10 cm	124	28	61	35
No. tumors at >10 cm	15	5	8	2
Level unknown	20	4	9	7
Tumor size (longitudinal)				
Mean (cm)	5	4.9	4.8	5.5
Median	4.3	5	4	5
No. tumors <2 cm	6	1	4	1
No. tumors 2−5 cm	98	20	48	30
No. tumors >5 cm	56	14	24	18
Missing	106	21	48	37
Tumor size (circular)				
1 quadrant involved	92	24	39	29
2 quadrants involved	44	6	19	19
3 quadrants involved	33	4	20	9
Circular	46	14	19	13
Missing	51	8	27	16
Tumor circumferential position				
Ventral quadrant involved	123	31	50	42
Clinical invasion depth (cT)				
cT1	8	0	3	5
cT2	39	10	16	13
cT3	174	37	87	50
cT4	36	8	13	15
Missing	9	1	5	3
Clinical nodal status (cN)				
cN0	84	14	35	35
cN+	173	40	85	48
Missing	9	2	4	3
cCRM				
≤1 mm	25	7	12	6
>1 mm	61	13	27	21
Missing	180	36	85	59
Neoadjuvant radiation				
None	69	16	25	28
Short-course radiation	24	7	11	6
Long-course chemoradiation	173	33	88	52
Surgical approach for resection				
Open	210	47	104	59
Laparoscopic	46	6	15	25
Laparoscopic converted	10	3	5	2
Resection type				
Low anterior resection	218	48	111	59
Abdominoperineal resection	44	8	12	24
Hartmann	4	0	1	3

cCRM indicates clinically assessed tumor-free circumferential resection margin.

TABLE 2. Relation Between the Quality of TME and the Pathologic Circumferential Margin in 227 Cases Without Complete Tumor Response to Chemoradiation and Known (y)pCRM

Quality of TME	No. Patients	(y)pCRM ≤1mm	*P**
Complete	48	7 (14.6%)	–
Nearly complete	108	12 (11%)	–
Incomplete	71	20 (28.2%)	0.004

*As compared with nearly complete + complete TMEs.

TME indicates total mesorectal excision; pCRM, pathologic circumferential tumor-free resection margin.

the administration of neoadjuvant therapy appeared to have no significant effect, larger cT 3 to 4 tumors that were not downstaged by neoadjuvant chemoradiation were significantly associated with lesser TME quality as compared with those that were downstaged ($P < 0.001$).

Multivariable analysis was performed on data of 170 patients, with complete data for all potentially relevant factors related to TME quality as identified by univariate analysis. Pathologic BMI, the absence of downstaging after long-course chemoradiation, and laparoscopic or laparoscopy-converted resection were identified as independent prognostic factors in this patient series (Table 4).

DISCUSSION

This is the first report on quality control of the grade of mesorectal excision by an independent and blinded board of pathologists in the context of a nationwide project. In both the Dutch[3] and the UK trial,[5] the macroscopic evaluation of the resection specimen was based on detailed descriptions by the local pathologist. In the report by Nagtegaal et al,[3] the quality of the photographic documentation was not sufficient to allow reliable central pathology review. Such practical problems also occurred in the Belgian project, as illustrated by the high incidence of nonevaluable cases (26.5%). Moreover, in 57% of cases the quality of mesorectal excision was not

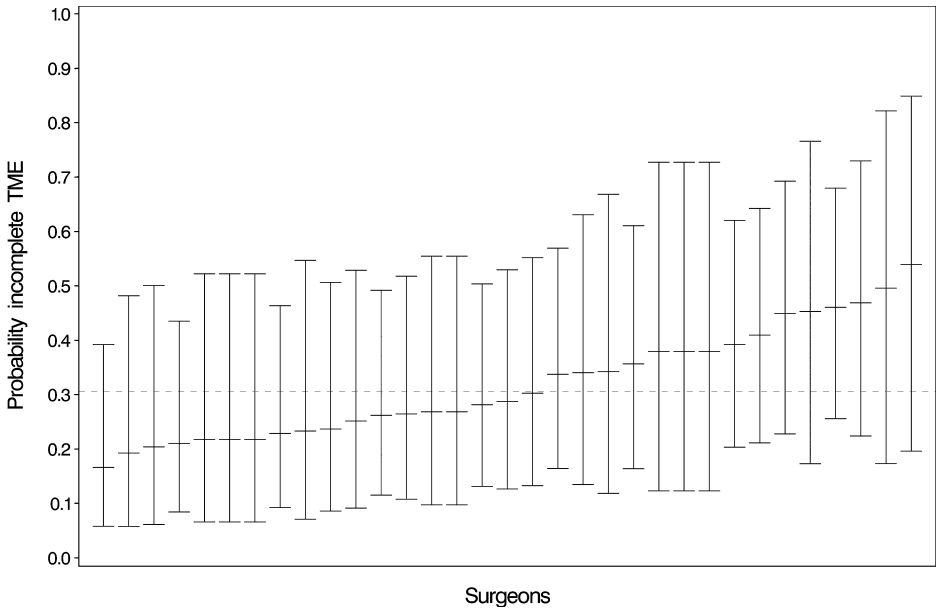

FIGURE 1. Heterogeneity between surgeons derived from the univariable logistic regression model. The figure depicts the estimated probability and 95% confidence interval for an incomplete TME for each surgeon. Surgeons are sorted on their probabilities. The horizontal dashed line represents the average surgeon.

TABLE 3. Results of Univariable Analyses of Prognostic Factors of Incomplete TME

Prognostic Factors	N	$\chi^2(df)$	OR (95% CI)	*P*
Surgeon	266	5.42*	NA	0.01
Age (yr)	264	0.01 (1)	1.00 (0.98; 1.03)	0.91
Pathologic BMI	221	14.2 (3)	NA	0.003
Female gender	266	8.31 (1)	2.35 (1.28; 4.31)	0.004
Lower limit of tumor	246	6.98 (1)	1.86 (0.94; 2.78)†	0.008
Tumor size (longitudinal; cm)	160	1.86 (1)	1.09 (0.96; 1.24)	0.17
Tumor size (circumferential)				
No. quadrants involved	221	2.95 (3)		0.40
Circular vs. 1 to 3 quadrants involved	215	0.59 (1)	0.74 (0.33; 1.66)	0.44
Ventral tumor position	215	0.31 (1)	1.20 (0.62; 2.30)	0.58
cT stage	257	6.17 (3)		0.1
cN negative vs. positive	257	5.11 (1)	2.02 (1.06; 3.83)	0.024
cCRM ($\leq$1 vs. >1 mm)	86	3.10 (1)	2.41 (0.82; 7.09)	0.078‡
Neoadjuvant therapy (yes vs. no)	266	3.19 (1)	0.56 (0.29; 1.09)	0.074
Chemoradiation vs. none or radiotherapy alone	266	0.69 (1)	0.78 (0.41; 1.45)	0.41
Chemoradiation without vs. with downstaging	140	14.2 (1)	8.16 (2.07; 32.2)	< 0.001
Laparoscopy and converted laparoscopy vs. laparotomy	265	4.87 (1)	2.33 (1.10; 5.00)	0.027
APR vs. SSO (Hartmann excluded)	262	12.8 (1)	3.65 (1.72; 7.73)	< 0.001

*To test for surgeon heterogeneity, the reference distribution is a mixture with equal probability mass of 2 χ^2 distributions with 0 and 1 *df,* respectively.

†The variable is transformed (natural logarithm after adding a constant) and used as a continuous predictor. To interpret the effect, the OR refers to the increased risk for incomplete TME of a low (25 percentile = 3 cm) value versus a high (75 percentile = 8 cm) value of the lower limit of the tumor.

‡Due to the low number of patients, cCRM is not considered in the multivariable model.

N indicates number of patients; χ^2, likelihood-ratio test statistic; *df,* degrees of freedom; OR, odds ratio; CI, confidence interval; NA, not applicable; APR, abdominoperineal resection; SSO, sphincter saving operation with reconstruction; cN, clinical nodal status; cT, clinical invasion depth; BMI, body mass index.

reported by local pathologists. Apparently, workshops and meetings or written information do not suffice for the majority of teams to ensure the implementation of current standards. This may be explained by the system of remuneration not covering costs or by the absence of sufficient staff required for the standardized evaluation of TME specimens. Comparison of the pathology board's assessment with the local pathology report resulted in a downgrade of TME quality to incomplete resection in 16.7% (19/114) and in an upgrade from incomplete to nearly complete or complete in 3.5% (4/114) of the specimens. As already suggested by Nagtegaal et al[3] for CRM determination, these data indicate that as long as a preset level of quality of care has not been reached a prospective national project including TME quality control by a pathology peer review committee and feedback to all participating teams is useful.

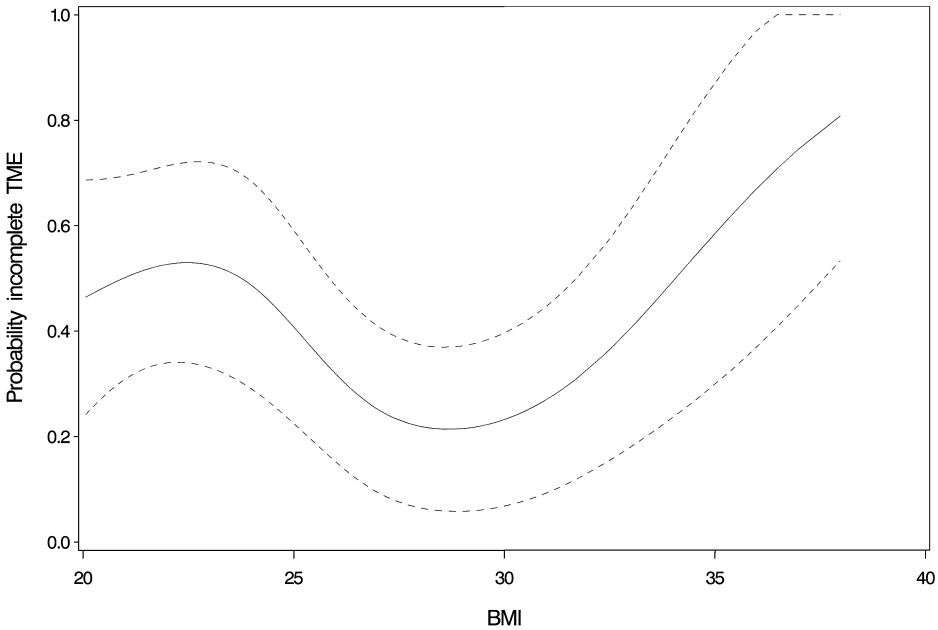

FIGURE 2. Relation between BMI and the probability of an incomplete TME for the average surgeon. Dotted lines represent the 95% pointwise confidence interval for the mean prediction.

TABLE 4. Multivariable Analysis of Prognostic Factors of Incomplete TME Based on 170 Patients With Complete Information on Univariable Factors With $P < 0.1$

Prognostic Factors	$\chi^2(df)$	OR (95% CI)	P
Surgeon	0.58∗	NA	0.22
Pathologic BMI	10.2 (3)	NA	0.017
Female gender	2.09 (1)	1.81 (0.78; 4.20)	0.15
Lower limit of tumor	0.96 (1)	1.46 (0.35; 2.58)†	0.33
cN negative	1.15 (1)	1.62 (0.64; 4.09)	0.28
Neoadjuvant therapy (yes vs. no)	1.41 (1)	0.42 (0.10; 1.90)	0.24
Chemoradiation without vs. with downstaging	12.1 (1)	10.8 (2.12; 54.5)	0.0005
Laparoscopy and converted laparoscopy vs. laparotomy	6.09 (1)	3.62 (1.28; 10.3)	0.014
APR vs. SSO	2.21 (1)	2.33 (0.62; 8.72)	0.14

∗To test for surgeon heterogeneity, the reference distribution is a mixture of 2 ξ^2 distributions with 0 and 1 *df,* respectively.

†The variable is transformed (natural logarithm after adding a constant) and used as a continuous predictor. To interpret the effect, the OR refers to the increased risk for incomplete TME of a low (Q1 = 3 mm) value versus a high (Q3 = 8 mm) value of the lower limit of the tumor.

χ^2 indicates likelihood-ratio test statistic; *df,* degrees of freedom; OR, odds ratio; CI, confidence interval; BMI, body mass index; NA, not applicable; cN, clinical nodal status; APR, abdominoperineal resection; SSO, sphincter saving operation with reconstruction.

The clinical relevance of complete or nearly complete mesorecta excision for oncological outcome of rectal cancer has been well documented.[3–6] Apart from its relation with pCRM positivity, as reported by others and confirmed in this study, TME quality has proved to be an independent predictor of local recurrence in patients with negative circumferential resection margins.[3,5] Therefore, mesorectal excision grading can serve as a surrogate for oncological outcome. The incidence of 32% of incomplete mesorectal resections in our study is higher than the 24% (43/180; $P = 0.056$) and 13% (154/1156; $P < 0.0001$) reported in the Dutch and UK trials, respectively.[3,5] The difference may be related to the central audit in our study and the fact that all surgeons had been trained individually in the Dutch multicenter trial.[19] Improving surgical skills and the quality of the mesorectal resection plane can be achieved by appropriate training.[7–15] In analogy with other national projects, workshops have been organized in the context of PROCARE, and direct side-by-side tuition by a qualified TME trainer has just started. However, high quality of TME cannot be guaranteed. Reports on factors affecting TME quality are scarce. Better understanding of these factors may help improve quality of care in patients with rectal cancer. Tumors at ≤10 cm from the anal verge,[3,20] abdominoperineal or Hartmann resection,[3,20,21] male[22] or female gender,[21] as well as obstetric conjugate and interspinous distance[22] have been associated with poor quality of a TME specimen in univariate analyses. In our study, uni- and multivariable analysis were used. Pathologic BMI, and the absence of downstaging after long-course chemoradiation and laparoscopic resection were identified as factors independently related to incomplete TME.

Variation in CRM-positivity and outcome between surgeons has been documented repeatedly and has been shown to persist after implementation of TME.[23] Our study illustrates variation of TME quality between surgeons. However, the surgeon factor was not found to be an independent factor in multivariable analysis.

High and low BMI values were associated with incomplete TME both in uni- and multivariable analysis. These findings indicate and confirm that adequate TME is more difficult to achieve in obese patients. In contrast, dissection closer to the tumor is unavoidable in patients with low BMI and less mesorectal fat.

Female gender was found to be associated with poor TME quality, as reported recently.[21] In contrast, others reported no effect of gender on the quality of TME.[3,4] In another study, narrow pelvic diameters, measured on MRI images, was the only independent factor affecting TME quality.[22] In our multivariate model, gender was not found to be an independent predictor.

An effect of the tumor mass on the TME quality has been reported.[24,25] We did not observe an effect of the circumferential or longitudinal extension of the tumor, as reported by others.[21] However, effective tumor shrinkage after chemoradiation resulted in better TME quality. To our knowledge, the influence of long-course

chemoradiation on TME quality has not been reported previously. Although others did not observe an influence of cN stage on TME quality,[4] we found the absence of enlarged nodes (cN0) to be associated with incomplete TME in univariable analysis. This finding is difficult to explain, but cN0 did not come out as an independent predictor in multivariable analysis.

Several studies reported worse quality of resection in APR specimens[4,5,21,26,27] with perforation in up to 36.1% of the specimens.[20] Our results confirm these findings, but only in univariate analysis. Nonetheless, poor prognosis after APR could be improved by adopting the surgical technique, striving at a cylindrical resection specimen, for which surgeons in our study were not trained. A low tumor level was significantly related to TME quality as reported by others.[3,4] Albeit not significant at multivariate analysis, a lower level still had an increased risk (OR = 1.46) for incomplete TME as compared with a higher level.

Laparoscopic and laparoscopy-converted resections were associated with a higher risk of intramesorectal resection. In the CLASICC trial, nonsignificantly higher rates of CRM positivity and local recurrences were observed after laparoscopic resections.[28] However, the authors of a recent meta-analysis warned against drawing conclusions, because of the limited number of randomized trials.[29] Experts agree that laparoscopic TME is a challenging procedure with a long learning curve. The approach for resection explains an important part of the heterogeneity between surgeons in the present study. The χ^2 statistic for the surgeon factor drops from 5.42 to 2.80 after correction for laparotomy versus laparoscopy and converted laparoscopy, but the effect of surgeon remains significant ($P = 0.047$). These data suggest that laparoscopic rectal resection should remain in expert hands with audit of TME quality.

The results of our study need to be interpreted with caution. They evidently apply only to those Belgian surgeons and pathologists who participated in the national PROCARE project on a voluntary basis. This may, however, be an advantage as it is a better reflection of actual clinical practice than observations made in the context of randomized controlled trials. Also, the results do not reflect the performance of all potential experts because some of them declined application for trainer status because of practical reasons. It can be argued that photo-documentation of the specimen might be difficult to interpret. For audit, high quality photographs of the specimen and of consecutive macro-sections were requested. However, this documentation was only part of the central audit and was never used alone as a criterion. Only 73% of the 362 submitted cases were evaluable for pathology review. Selection bias is unlikely because the material was anonymized before being assessed by the pathology review board. Although pronounced distal coning and dissection down to the muscularis propria were part of the pathology review, the additional classification system for the evaluation of APR resection specimens at the anal level[20] was not used as surgeons were not trained to perform cylindrical resections. Our study aimed to evaluate the mesorectal part of the resection only. A logistic-regression approach was used to assess the effect of individual (univariable) and multiple factors simultaneously (multivariable analysis). One may question the validity of a multivariable analysis restricted to patients with complete information on preoperative factors. As a sensitivity analysis, a multiple imputation approach has been used to deal with the missingness in preoperative factors. The major conclusions did not differ with those obtained from the analysis on the subjects with complete information. Therefore, we deemed it more appropriate to report the results from the less complicated analysis. Finally, our findings should be validated in larger prospective studies.

In conclusion, our data indicate that a specific effort is required to improve the quality of surgery and of the pathology report. Appropriate remuneration, further (re)training, and audit with feedback to participating teams are needed.

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