Original article

doi:10.1111/codi.13254

Review of the quality of total mesorectal excision does not improve the prediction of outcome

P. Demetter* , A. Jouret-Mourin†, G. Silversmit‡, T. Vandendael‡, C. Sempoux†, A. Hoorens§, N. Nagy¶, C. Cuvelier, N. Van Damme‡, F. Penninckx†† and on behalf of PROCARE[b]**

*Department of Pathology, Erasme University Hospital, ULB, Brussels, Belgium, †Department of Pathology, Cliniques Universitaires Saint-Luc, UCL, Brussels, Belgium, ‡Foundation Belgian Cancer Registry, Brussels, Belgium, §Department of Pathology, Universitair Ziekenhuis Brussel, VUB, Brussels, Belgium, ¶Department of Pathology, CHU de Charleroi, Charleroi, Belgium, **Department of Pathology, UG, Ghent, Belgium and ††Department of Abdominal Surgery, UZ Gasthuisberg, KU Leuven, Leuven, Belgium

Received 7 April 2015; accepted 21 October 2015; Accepted Article online 6 January 2016

Abstract

Aim A fair to moderate concordance in grading of the total mesorectal excision (TME) surgical specimen by local pathologists and a central review panel has been observed in the PROCARE (Project on Cancer of the Rectum) project. The aim of the present study was to evaluate the difference, if any, in the accuracy of predicting the oncological outcome through TME grading by local pathologists or by the review panel.

Method The quality of the TME specimen was reviewed for 482 surgical specimens registered on a prospective database between 2006 and 2011. Patients with a Stage IV tumour, with unknown incidence date or without follow-up information were excluded, resulting in a study population of 383 patients. Quality assessment of the specimen was based on three grades including mesorectal resection (MRR), intramesorectal resection (IMR) and muscularis propria resection (MPR). Using univariable Cox regression models, local and review panel histopathological gradings of the quality of TME were assessed as predictors of local recurrence, distant metastasis and disease-free and overall survival. Differences in the predictions between local and review grading were determined.

Results Resection planes were concordant in 215 (56.1%) specimens. Downgrading from MRR to MPR was noted in 23 (6.0%). There were no significant differences in the prediction error between the two models; local and central review TME grading predicted the outcome equally well.

Conclusion Any difference in grading of the TME specimen between local histopathologists and the review panel had no significant impact on the prediction of oncological outcome for this patient cohort. Grading of the quality of TME as reported by local histopathologists can therefore be used for outcome analysis. Quality control of TME grading is not warranted provided the histopathologist is adequately trained.

Keywords Total mesorectal excision, adenocarcinoma, rectum, oncological outcome

What does this paper add to the literature?
The grade of the quality of total mesorectal excision (TME) reported by local histopathologists or by a central review panel can both be used for outcome analysis. Quality control of the assessment of TME is not warranted provided the histopathologist is adequately trained.

Introduction

The macroscopic evaluation of the quality of total mesorectal excision (TME) for rectal cancer [1] has been assessed in randomized trials [2,3] and observational single-centre studies [4–8]. Three grades were introduced by Quirke *et al.* to describe the quality of the TME surgical specmen including mesorectal, intramesorectal and muscularis propria [2,3]. Resection in the muscularis propria plane significantly increases the risk of local recurrence and overall recurrence compared with the mesorectal plane [9]. The impact of a poor-quality TME on overall survival appears to be less pronounced. One study reported decreased survival [2] whereas no difference was observed in another [5].

Correspondence to: Pieter Demetter, Department of Pathology, Erasme University Hospital, Route de Lennik 808, 1070 Brussels, Belgium.
E-mail: pieter.demetter@erasme.ulb.ac.be

[b]The PROCARE steering group members are present in Appendix.

Project on Cancer of the Rectum (PROCARE) a Belgian improvement project on rectal cancer, was launched in 2006. Multidisciplinary guidelines were developed and their implementation was fostered at workshops organized by national scientific and professional organizations. All hospitals were invited to participate on a voluntary basis and to register multiple patient data in a specific PROCARE database at the Belgian Cancer Registry (BCR). Histopathological information was recorded on a standard proforma.

In order to audit the quality of evaluation of TME specimens, a central pathology review body was organized. A fair to moderate concordance in the interpretation of the resection plane by local histopathologists and the review panel was found, with downgrading of the surgical plane in 17% from (intra)mesorectal to muscular, and upgrading from muscular to (intra)mesorectal in 27% [10].

The aim of the present study was to investigate whether TME grading assessed by a review panel or local histopathologists predict oncological outcome equally well.

Method

A review panel of gastrointestinal histopathologists was appointed to re-assess the resection plane previously reported by local pathologists for 482 TME surgical specimens. The local histopathologists had been informed of the aim of the study and were made aware of the procedures of PROCARE through workshops and communication at national meetings. They were also able to download the national guidelines for macroscopic and microscopic TME specimen handling (the 'Pathology TME Cookbook') from the website of the Belgian Cancer Registry (http://www.kankerregister.org).

Patients treated with TME and entered on the PROCARE database between 2006 and 2011 were identified, and 53 with a Stage IV tumour, four with no known date of treatment and 42 patients without follow-up information were excluded. This left 383 patients from 40 hospitals whose specimens were examined by 65 local pathologists. Neoadjuvant therapy had been administered to 308 (80%) patients all of whom received radiotherapy; this was combined with chemotherapy in 256.

The process of TME review has been described previously [10,11]. In brief, the local histopathologist was invited to send digitized pictures of the uninked anterior and posterior surfaces of the mesorectum and pictures of 5-mm thick transverse slices of the fixed surgical specimen, together with other material. After anonymization of the submitted material, the quality of TME was assessed by the central review committee. The macroscopic assessment of a TME specimen was based on the quality of the resection plane to include mesorectal resection (MRR; smooth, complete, good quality), intramesorectal resection (IMR; moderately irregular, nearly complete, moderate quality) and resection involving the muscularis propria (MPR; severely irregular, poor quality) [2,3].

The end-points in the study were local recurrence, distant metastasis, disease-free survival (DFS) and overall survival (OS). The time to recurrence, metastasis or death was calculated from the date of surgery. Survival data for all patients were obtained from the Belgian Crossroad Bank for Social Security on 6 January 2014.

Statistical analysis

The quality of the TME determined by the local histopathologist and the central review panel as predictors of cancer-specific end-points of local and systemic recurrence and OS and DFS was assessed using a Cox univariable regression model. The Kaplan–Meier method was used to estimate survival 5 years after surgery.

The differences in prediction error between local and review grading were tested following the method of van de Wiel [12]. In brief, this method uses different random training and testing splits of the dataset. For each split, the predictions for both TME gradings were obtained. A signed-rank test was then applied to the paired Brier residuals. The median of the *P*-values over the multiple splits was used as the final summary test statistic. A total of 50 splits was used with a split fraction of 0.80 for the training set and 0.20 for the test set. The Brier score is reported as a measure of the prediction error. A Brier score of zero reflected perfect prediction. In the context of prediction models, a Brier score of 0.25 corresponds to a non-informative model which assigns a probability of 0.5 to each individual; such a model does not perform better than flipping a coin [13].

Exploratory and statistical analyses were performed with SAS version 9.3 (SAS Institute, Cary, North Carolina, USA). The signed-rank test to the paired Brier residuals was performed in R 3.1.1. Statistical conclusions were drawn at the 5% significance level.

Results

Of the 383 TME specimens, 229 (59.8%) were from male patients. The median patient age was 67.2 (interquartile range (IQR) 59.2–75.7) years. In those

having preoperative radiotherapy, the histopathological stage was yp Stage 0 in 44 (11.5%), yp Stage I in 114 (29.8%), yp Stage II in 98 (25.6%) and yp Stage III in 127 (33.1%).

Comparison of local and central grading of the specimen

Of the 383 specimens, concordance in grading was observed in 215 (56.1%) (Table 1). The resection plane as judged by the local pathologist was downgraded by the panel in 139 (36.3%) specimens and upgraded in 29 (7.6%). A pronounced discordance between grades, defined as a shift from MRR to MPR or *vice versa*, was noted in 23 and 2 specimens, representing 6.5% of all specimens.

Oncological outcome

Among the 383 patients, 106 deaths were observed during 1881 patient-years of follow-up (5.6 events per 100 patient-years). Death and distant metastasis were competing events for local recurrence and patients were considered censored for local recurrence in this circumstance. Local recurrence was detected in 27 patients during 1662 patient-years of follow-up (1.6 events per 100 patient-years). Likewise, death and local recurrence were competing events for distant metastasis which was then detected in 78 patients during 1662 patient-years (4.7 events per 100 patient-years). Disease-free survival was defined as the time until death, local recurrence, distant metastasis or censoring, whichever came first, and resulted in 145 events during 1660 patient-years of follow-up.

The oncological outcome according to TME grading by the local pathologist and the review panel

There was a major increase in local recurrence in MPR specimens (Table 2), although no significant differences were found between the local recurrence-free survival curves for the three grades of quality of the TME specimen ($P = 0.0697$ and $P = 0.2778$ for local pathologist and review panel, respectively). In contrast, local recurrence rates for MRR and IMR were similar. Distant metastasis was not associated with the quality of TME ($P = 0.5842$ and $P = 0.6927$ for local pathologist and review panel, respectively), while OS decreased with decreasing quality of TME ($P = 0.0054$ and $P = 0.0203$ for local pathologist and review panel, respectively). The oncological outcomes according to the quality of TME as judged by local pathologist and review panel were similar. As this could be related to the fact that only some of the patients had been reclassified by the panel in each TME quality grade, the outcome in reclassified patients was compared with that of patients for whom the judgement of the quality of TME by local and central review was concordant.

Table 1 Grading of total mesroectal excision according to local pathologists and the review panel.

	Review panel		
Local pathologists	MRR	IMR	MPR
MRR	123	86	23
IMR	12	59	30
MPR	2	15	33

MRR, mesorectal resection; IMR, intramesorectal excision; MPR, muscularis propria resection.

The relevance of downgrading by panel

A MRR plane as judged by the local pathologists was downgraded by the review panel to IMR in 86 cases and to MPR in 23 cases. Survival in these 109 patients was not significantly different from the 123 patients with a TME judged to be in MRR by both local and central review. The 5-year survival rates are given in Table 3.

Downgrading from MRR to IMR could have a smaller effect on the oncological outcome, in contrast with downgrading from MRR to MPR. Therefore, the effect of downgrading from MRR to MPR (23 cases) and from MRR or IMR to MPR (53 cases) on outcomes was analysed and compared with those after MRR or IMR as judged by both local pathologists and the review panel (182 cases) as well as with outcomes after MPR according to both local and reviewer pathologists (33 cases). Although no statistically significant differences were found, downgrading from MRR or IMR to MPR resulted in worse outcome for all end-points that were relatively close to those of patients in whom a TME with MPR plane was performed according to both local and review pathologists. The corresponding DFS curves are presented in Fig. 1 as an example.

The relevance of upgrading by the central review panel

A MPR grade judged by local pathologists in 50 cases was upgraded by the review panel in 17 (34%) to either IMR (15 cases) or MRR (2 cases) (Table 1). The oncological outcome in these reclassified patients was found to be similar to those of the 33 patients with a MPR

Table 2 The cancer-specific outcome according to the total mesorectal excision (TME) specimen grade judged by local pathologists and the review panel. Estimated 5-year survival rates are given with 95% confidence intervals in parenthesis.

	TME quality grades		
	MRR	IMR	MPR
Local pathologists			
Local recurrence-free	92.8% (88.0–95.7)	94.7% (86.3–98.0)	84.3% (69.7–92.2)
Distant metastasis-free	78.7% (72.4–83.8)	74.9% (64.5–82.7)	75.1% (59.4–85.4)
Disease-free survival	67.9% (61.2–73.7)	63.5% (52.8–72.4)	54.6% (38.6–68.1)
Overall survival	78.9% (72.5–84.0)	79.6% (69.7–86.5)	57.2% (40.1–71.0)
Central review panel			
Local recurrence-free	94.0% (87.7–97.1)	93.8% (88.4–96.7)	85.6% (73.4–92.4)
Distant metastasis-free	80.0% (71.6–86.1)	76.9% (69.1–83.0)	73.4% (61.2–82.3)
Disease-free survival	68.5% (59.6–75.8)	67.5% (59.3–74.3)	55.3% (43.5–65.6)
Overall survival	76.8% (67.5–83.8)	81.0% (73.6–86.5)	66.1% (54.0–75.7)

MRR, mesorectal resection; IMR, intramesorectal resection; MPR, muscularis propria resection.

Table 3 The cancer-specific outcome of patients with concordant, downgraded or upgraded TME grade as judged by the review panel.

	Estimated survival proportion at 5 years since surgery, % (95% CI)			
	Local recurrence	Distant metastasis	Disease-free survival	Overall survival
MRR concordant (n = 123)	4.8 (2.0–11.2)	18.7 (12.5–27.4)	69.9 (60.4–77.5)	75.8 (65.6–83.3)
Downgraded from MRR to IMR or MPR (n = 109)	9.7 (5.1–18.0)	23.7 (16.3–33.5)	66.0 (56.1–74.2)	81.5 (72.4–87.8)
Downgraded from MRR to MPR (n = 23)	17.5 (5.8-46.1)	37.8 (20.8–61.8)	59.5 (36.3–76.7)	81.5 (57.6–92.7)
Downgraded from MRR or IMR to MPR (n = 53)	14.2 (6.0–31.6)	27.4 (16.4–43.7)	56.1 (41.1–68.7)	71.4 (56.3–82.1)
MRR or IMR concordant (n = 182)	3.2 (1.3–7.7)	21.3 (15.8–28.4)	69.8 (62.2–76.2)	79.1 (71.6–84.9)
Downgraded from IMR to MPR (n = 30)	10.7 (2.7–37.4)	17.7 (6.8–41.9)	53.5 (33.2–70.1)	63.5 (42.2–78.7)
MPR concordant (n= 33)	14.0 (5.5–33.1)	24.5 (12.5–44.7)	53.8 (33.8–70.2)	56.9 (35.9–73.3)
Upgraded from MPR to IMR or MRR (n = 17)	18.9 (6.5–48.1)	26.0 (10.5–55.7)	55.0 (26.9–76.1)	57.4 (26.8–79.1)

MRR, mesorectal resection; IMR, intramesorectal resection; MPR, muscularis propria resection.

reported concordantly by both local and central histopathologists and worse than in the 123 MRR specimens judged concordantly by both local and central histopathologists (Table 3).

Comparison of prediction models

There were no significant differences in the accuracy of prediction of the TME grade between local pathologists and a central panel of experts. Both predicted the outcome equally well or equally badly, as illustrated by the very similar Brier scores for both models (Table 4).

Discussion

This is the first study to compare the accuracy of grading of the quality of the TME specimen between local pathologists and a central panel of experts. There was concordance between them in assessing the quality of the specimen in 56% of cases, with severe disagreement in only 6.5%. This may be explained by the effectiveness of the implementation of guidelines for histopathological examination of the specimen through the workshops organized by PROCARE. Our findings indicate that neither downgrading nor upgrading of the quality of the TME by the review panel had a significant effect on any of the oncological outcome measures. Admittedly, a relatively small number of patients were studied and not all TME specimens were reviewed. Indeed, central review was intentionally limited as it would have required a major organizational effort and cost had it not been. Selection bias may have been present because participation in PROCARE was incomplete [14] and some of the TME specimens were submitted by centres

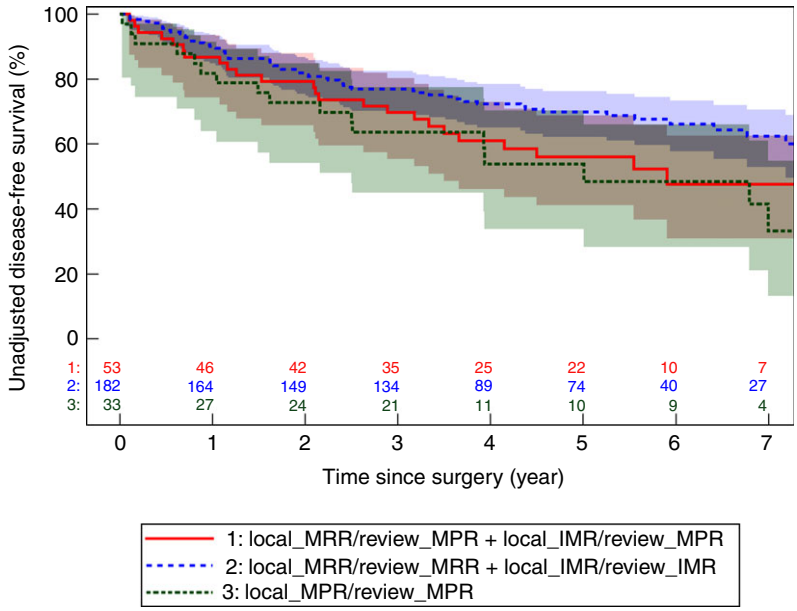

Figure 1 Disease-free survival of patients downgraded by the review panel from mesorectal resection (MRR) or intramesorectal resection (IMR) to muscularis propria resection (MPR) compared with patients in whom MRR or IMR and MPR were judged concordantly by local pathologists and the central review panel. The shaded areas represent the 95% CI.

Table 4 Comparison of the prediction of local pathologists and the central review panel with Brier scores at 1, 3 and 5 years.

		Prediction error (Brier score)					
		Grading by local pathologists			Grading by the review panel		
Outcome variable	*P*-value	1 year	3 years	5 years	1 year	3 years	5 years
Local recurrence	0.249	0.03	0.06	0.08	0.03	0.07	0.08
Distant metastasis	0.549	0.06	0.15	0.18	0.06	0.15	0.18
Disease-free survival	0.383	0.10	0.20	0.23	0.10	0.20	0.23
Overall survival	0.507	0.04	0.11	0.18	0.04	0.11	0.18

where the surgeon was a candidate to become a TME-trainer [11]. Also, the review process relied on photographic material of the whole specimen and transverse sections. The reviewers were therefore unable to handle the specimen for macroscopic inspection or directly examine the integrity of its surface (although there was no practical alternative). If the quality of the photograph was inadequate or a photograph was not available, the specimen was classified as not evaluable by the review panel. This factor might be expected to result in underestimation of the grade, but in the event downgrading occurred six times more than upgrading, possibly because reviewers were trying to find a defect if possible. Nonetheless a MPR grade was identified by the panel in 9.9% of the 232 specimens that were judged by local pathologists to have been of grade MMR. There was, however, no evidence that downgrading affected the outcome, and furthermore there are many other factors besides the quality of the TME specimen that influence the cancer-specific results, as demonstrated in a recent study from our group [15].

In conclusion, the findings of the study indicate that the quality of the TME specimen as reported either by local pathologists or by a central review panel can be used for the prediction of cancer-specific outcome. Thus, quality control of the assessment of the TME specimen does not seem warranted if the histopathologist is adequately trained.

Acknowledgements

K. Charels, C. Cuvelier, G. De Hertogh, P. Demetter, N. Ectors, A. Hoorens, G. Jacomen, A. Jouret-Mourin, N. Nagy, X. Sagaert, C. Sempoux, M. Vivario and H.

Woestenborghs participated in the pathology review panel meetings. The authors thank all surgeons and pathologists who participated in the PROCARE project. The list of participating centres can be found at http://www.kankerregister.org/procare. PROCARE was supported by the Foundation against Cancer and the RIZIV/INAMI, Belgian Ministry of Social Affairs, which had no role in the design or conduct of the study and played no part in the analysis and writing.

Conflicts of interest

All authors declare that they have no conflict of interest.

References

1 MacFarlane JK, Ryall RD, Heald RJ. Mesorectal excision for rectal cancer. *Lancet* 1993; **341:** 457–60.
2 Nagtegaal ID, van de Velde CJ, van der Worp E, Kapiteijn E, Quirke P, van Krieken JH. Macroscopic evaluation of rectal cancer resection specimen: clinical significance of the pathologist in quality control. *J Clin Oncol* 2002; **20:** 1729–34.
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* 2002; **373:** 821–8.
4 Herzog T, Belyaev O, Chromik AM *et al.* TME quality in rectal cancer surgery. *Eur J Med Res* 2010; **15:** 292–6.
5 Maslekar S, Sharma A, Macdonald A, Gunn J, Monson JR, Hartley JE. Mesorectal grades predict recurrences after curative resection for rectal cancer. *Dis Colon Rectum* 2007; **50:** 168–75.
6 Jeyarajah S., Sutton C.D., Miller A.S., Hemingway D, Leicester Colorectal Specialist Group. Factors that influence the adequacy of total mesorectal excision for rectal cancer. *Colorectal Dis* 2007; **9:** 808–15.
7 García-Granero E, Faiz O, Muñoz 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.
8 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.
9 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.
10 Demetter P, Vandendael T, Sempoux C *et al.* Need for objective and reproducible criteria in histopathological assessment of total mesorectal excision specimens: lessons from a national improvement project. *Colorectal Dis* 2013; **15:** 1351–8.
11 Leonard D, Penninckx F, Fieuws S *et al.* Factors predicting the quality of total mesorectal excision for rectal cancer. *Ann Surg* 2010; **252:** 982–8.
12 van de Wiel MA, Berkhof J, van Wieringen WN. Testing the prediction error difference between 2 predictors. *Biostatistics* 2009; **10:** 550–60.
13 Graf E, Schmoor C, Sauerbrei W, Schumacher M. Assessment and comparison of prognostic classification schemes for survival data. *Stat Med* 1999; **18:** 2529–45.
14 Jegou D, Penninckx F, Vandendael T, Bertrand C, Van Eycken E, on behalf of PROCARE. Completeness and registration bias in PROCARE, a Belgian multidisciplinary project on cancer of the rectum with participation on a voluntary basis. *Eur J Cancer* 2015; **51:** 1099–108.
15 Leonard D, Penninckx F, Laenen A, Kartheuser A, on behalf of PROCARE. Quantitative contribution of prognosticators to oncologic outcome after rectal cancer resection. *Dis Colon Rectum* 2015; **58:**566–74.

Appendix
The PROCARE steering group

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 (C. Bertrand, D. De Coninck, M. Duinslaeger, A. Kartheuser, F. Penninckx, J. Van de Stadt, W. Vaneerdeweg), the Belgian Society of Surgical Oncology (D. Claeys), the Belgian Group for Endoscopic Surgery (D. Burnon), the Belgian Society of Radiotherapy – Oncology (K. Haustermans, P. Scalliet, Ph. Spaas), the Belgian Society of Pathology and the Digestive Pathology Club (P. Demetter, A. Jouret-Mourin, C. Sempoux), the Belgian Society of Medical Oncology (W. Demey, Y. Humblet, E. Van Cutsem), the Belgian Group for Digestive Oncology (S. Laurent, E. Van Cutsem, J.L. Van Laethem), the Royal Belgian Society of Radiology (B. Op de Beeck, P. Smeets), the Société Royale Belge de Gastro-entérologie (M. Melange, J. Rahier), the Vlaamse Vereniging voor Gastroenterologie [Flemish Society for Gastroenterology] (M. Cabooter, P. Pattyn, M. Peeters), the Belgian Society of Gastro-intestinal Endoscopy (M. Buset). Also represented are: the Belgian Professional Surgical Association (L. Haeck, B. Mansvelt, K. Vindevoghel), the Foundation Belgian Cancer Registry (E. Van Eycken) and the RIZIV/INAMI (M. Daubie, A. Thijs). F. Penninckx chairs the PROCARE Steering Group.