Original article

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Need for objective and reproducible criteria in histopathological assessment of total mesorectal excision specimens: lessons from a national improvement project

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Abstract

Aim Data on quality control of the pathologic evaluation of total mesorectal excision (TME) specimens are scarce. We aimed to assess differences between evaluation by local pathologists participating in PROject on CAncer of the REctum (PROCARE; a Belgian improvement project on rectal cancer) and by a review panel of experts.

Method Based on photographic material and histopathology slides, a Review Committee of gastrointestinal expert pathologists re-evaluated the mesorectal plane, the tumour differentiation grade, the (y)pT stage and the tumour regression grade in 444 patients previously routinely assessed by local pathologists.

Results The surgical plane was reported in 89% of patients and the circumferential resection margin in 88% of patients by the local pathologist. The median number of lymph nodes harvested in patients undergoing neoadjuvant radiochemotherapy was 11 and 14 in the other patients. The Review Committee downgraded the surgical plane from (intra)mesorectal to intramuscular in 17% of patients, and upgraded it from intramuscular to (intra)mesorectal in 27%. Tumour differentiation grade, T stage and tumour regression grade differed between local pathologists and the Review Committee in 15%, 10% and 38%, respectively, of patients. T stage was upgraded, mainly from T2 to T3, in 8% of patients. Tumour regression was judged by the Review Committee to be less advanced in 15% of patients.

Conclusion Acknowledging some shortcomings, this study gives a realistic view of clinical practice. There are differences in interpretation with regard to both macroscopic and microscopic analysis of TME specimens. These findings indicate a need for more objective and reproducible criteria in histopathology. Being aware of this is a first step for improvement.

Keywords Total mesorectal excision, adenocarcinoma, rectum

What does this paper add to the literature?
We describe differences in interpretation with regard to macroscopic and microscopic analysis of total mesorectal excision (TME) resection specimens within the framework of the national multidisciplinary improvement project, PROCARE (PROject on CAncer of the REctum). Such analysis of daily pathology practice is not yet available in the literature; it underlines the need for objective and reproducible criteria in histopathology.

Introduction

The development of total mesorectal excision (TME), introduced by Heald and Ryall in the early 1980s, is based on the notion that lateral mesorectal spread of small tumour foci, which are not removed in classic anterior resection, can lead to local recurrence after rectal cancer surgery.

In a TME procedure the rectum and the mesorectum are excised by precise dissection in the avascular 'holy' plane between the visceral and parietal pelvic fascia separating the mesorectal fat from the other pelvic

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[1]The details of the members in PROCARE are present in Appendix A.

structures [1]. Discontinuous tumour deposits and possibly involved lymph nodes present in the mesorectum are hereby removed together with the tumour. The introduction of TME led to the reduction of local recurrence rates from 20 to 45% [1] to around 10% with TME surgery alone and to 2.4–6% after short-term neoadjuvant radiotherapy followed by TME [2,3]. Predicting local recurrence by acknowledging the importance of lateral tumour spread led to the introduction of the circumferential resection margin (CRM) in the evaluation of TME specimens. This margin, which comprises the entire nonperitonealized circumference of the resection specimen, has a relatively short, distally located anterior aspect, whereas posteriorly it has a triangular shape and runs up to the start of the sigmoid mesocolon. Currently, CRM involvement is considered to be one of the key factors in rectal cancer treatment. A large number of studies, pooled in a meta-analysis by Nagtegaal and Quirke and including over 17 500 patients, showed a CRM of ≤ 1 mm to be a strong predictor of local recurrence, distant recurrence and survival. After neoadjuvant therapy, CRM involvement was found to be an even stronger predictor of local recurrence, but not of distant recurrence and survival [4]. However, local and distant recurrences may also develop in patients with an uninvolved CRM.

The plane of resection created by the surgeon is another predictor of outcome that has been investigated by pathologists for almost a decade, and which may explain part of the local recurrences in CRM-negative patients. A meta-analysis revealed that a muscularis propria resection plane increases the risk of local recurrence and overall recurrence compared with an (intra)mesorectal plane [5].

PROCARE (PROject on CAncer of the REctum), a Belgian multidisciplinary national project to improve outcome in patients with rectal cancer, was launched in 2006. Guidelines were produced by a multidisciplinary group [6] and quality-of-care indicators were determined [7]. Decentralized implementation of guidelines was organized by the national scientific and professional organizations. Pathologists were informed of the aims and the procedures by workshops and communications at national meetings. Moreover, they had the possibility to consult and to download the national guidelines for macroscopic and microscopic TME specimen handling (the 'Pathology TME Cookbook'), from the website of the Belgian Cancer Registry (www.kankerregister.org). Overall quality of care was assured by registration in a specific national database. Through feedback, all pathologists and centres are able to position themselves in comparison with national indicators.

Pathologists from participating hospitals record histopathological information of the resected tumour on a standard minimal data form for all patients. Central pathology review was organized to ensure consistent quality of all pathology data and procedures. The aim of the present study was to review the differences in histopathological evaluation performed by local pathologists compared with that of the Central Review Committee. Although some form of quality assurance programmes for histopathological examination exist in the most relevant randomized controlled trials [8,9], such comparison is not yet available in the literature.

Method

Patients

Between January 2006 and December 2010, 2460 patients with invasive adenocarcinoma of the rectum, between 0 and 10 cm above the anal margin, underwent TME and were registered in the PROCARE database.

Histopathological assessment in the participating hospitals

All surgical specimens were assessed according to the protocol of Quirke and Dixon [10]. Before starting the procedure, the fresh specimen was examined grossly and pictures were taken from the anterior and posterior surfaces of the mesorectum. The quality of the mesorectum was scored using three grades, as described: complete (smooth); nearly complete (mildly irregular); or incomplete (severely irregular) [11]. To determine the CRM, the mesorectal surface of the fresh specimen was inked and subsequently the specimen was fixed in formalin for 48 h. Blocks of the tumour in relation to the inked CRM were collected. Measurements of the margin were performed microscopically. Classification of tumours was made using the World Health Organization (WHO) guidelines; only adenocarcinomas were included. Tumours were graded, according to histological differentiation, into well, moderately and poorly differentiated. Radiation-induced tumour regression was assessed according to the grading system described by Dworak *et al.*: Grade 0, no regression; Grade 1, minimal regression (dominant tumour mass with obvious fibrosis and/or vasculopathy); Grade 2, moderate regression (predominantly fibrotic changes with few tumour cells or groups); Grade 3, good regression (very few tumour cells in fibrotic tissue); and Grade 4, total regression (no tumour cells, only fibrotic mass) [12].

Histopathological assessment by the Review Committee

Eighty-one pathologists from 54 participating hospitals were asked to send digitalized pictures of the uninked anterior and posterior surfaces of the mesorectum, as well as pictures of 5-mm-thick transverse slices of the fixed surgical specimen, together with all histopathology slides, the pathology report and the standard pathology checklist of PROCARE for central review. Before central review, all material was anonymized by a data manager at the Belgian Cancer Registry.

The Pathology Review Committee received material from 743 patients for evaluation. In 299, the material was considered insufficient for evaluation, mainly because of the lack of one or more of the required pictures, or insufficiently sharp images (273). Those patients were excluded from the current study, resulting in a study population of 444 patients (354 low anterior resection and 90 abdomino-perineal resection), 323 of whom had received neoadjuvant therapy.

The Central Review Committee, composed of pathologists with a particular interest in colorectal pathology, evaluated the following items: resection plane (based on the photographic material); tumour differentiation grade; (y)pT; and tumour regression grade. For evaluation of the resection plane, two categories were considered: (intra)mesorectal (corresponding to complete and nearly complete mesorectum); and intramuscular (corresponding to incomplete mesorectum). Evaluations of the mesorectum by pathologists from the referring hospitals were converted towards this two-tiered score. All evaluated items were discussed until consensus was reached within the Review Committee.

Statistical analysis

The concordance in observations between pathologists in participating hospitals and the Review Committee was studied by calculating the κ coefficient. Perfect agreement equates to $\kappa = 1$, and chance agreement equates to $\kappa = 0$ [13].

Results

Evaluation by local pathologists

Local pathologists evaluated the resection plane in 396 (89%) patients. In 49 (12%), the resection plane was considered intramuscular, whereas in the remaining 347 (88%) it was considered (intra)mesorectal.

The CRM was measured in 340 (88%) of 387 patients with (y)pT1 or more. The CRM was 0 mm in 27 (8%), ≤ 1 mm in 38 (11%) and > 1 mm in 275 (81%).

The number of lymph nodes was reported in 430 (97%) patients. At least 12 lymph nodes were examined in 204 (47%) of these 430 patients. In patients undergoing long-course neoadjuvant radiochemotherapy, the median number of lymph nodes harvested was 11, whereas this was 14 in the other patients.

For 382 (99%) of 387 patients not staged as ypT0 or ypTis, the tumour differentiation grade was mentioned in the pathology report. In 49 (13%) of these 382 patients, the tumour was considered well differentiated, in 266 (70%) it was moderately differentiated and in 67 (17%) it was poorly differentiated.

Fifty-four (12%) of the 444 patients were staged as ypT0, three (< 1%) as ypTis, 29 (7%) as (y)pT1, 113 (25%) as (y)pT2, 222 (50%) as (y)pT3 and 23 (5%) as (y)pT4. For 250 (77%) of 323 patients who received neoadjuvant therapy, the tumour regression grade was evaluated according to Dworak. The regression grade was considered as Grade 0 in 57 (23%) patients, Grade 1 in 31 (12%), Grade 2 in 83 (33%), Grade 3 in 55 (22%) and Grade 4 in 24 (10%).

Evaluation by the Review Committee and discordances with local pathologists

Based on the photographic material provided by local pathologists, the Review Committee considered the dissection plane from 110 (25%) of 444 patients as intramuscular. For the remaining 75%, this plane was considered as (intra)mesorectal. As can be derived from Table 1, in 58 (17%) of 347 patients in whom the surgical plane was considered as (intra)mesorectal by the local pathologist, it was considered as intramuscular by the Review Committee. Inversely, in 13 (27%) of 49 patients, the local pathologist considered the surgical plane as intramuscular, whereas the Review Board considered it as (intra)mesorectal. Statistical analysis

Table 1 Evaluation of the resection plane by local pathologists and the Review Committee.

	Local pathologist			
Resection plane	(Intra) mesorectal	Intramuscular	Missing	Total
Review Committee				
(Intra) mesorectal	289	13	32	334
Intramuscular	58	36	16	110
Total	347	49	48	444

revealed $\kappa = 0.41$ (95% CI, 0.30–0.52) for the concordance in interpretation of the dissection plane by local pathologists and the Review Committee.

Based on a review of the histological slides, in 26 (7%) of 387 patients who were not staged as ypT0 or ypTis, the tumour was considered as well differentiated, in 281 (73%) it was considered as moderately differentiated and in 76 (20%) it was considered as poorly differentiated. In the remaining four (1%), the Review Committee felt it irrelevant to grade the tumours because only a few neoplastic cells were found. As can be derived from Table 2, the tumour differentiation grade differed between local pathologists and the Review Committee in 56 (15%) of 378 patients who were scored by both. In five (10%) of 49 patients with tumours considered as well differentiated by local pathologists, the Review Committee considered the tumour as poorly differentiated; these five tumours were mucinous adenocarcinomas. For the concordance in interpretation of the tumour differentiation grade by local pathologists and the Review Committee, $\kappa = 0.67$ (95% CI, 0.59–0.75).

Forty-six (10%) of 444 patients were staged as ypT0, seven (2%) as ypTis, 26 (6%) as (y)pT1, 103 (23%) as (y)pT2, 242 (55%) as (y)pT3 and 20 (4%) as (y)pT4. Staging differed between local pathologists and the Review Committee in 46 (10%) of 444 patients (Table 3). In 36 (8%) of 444 patients, the T stage was upgraded, mainly from T2 to T3. For the concordance in (y)pT staging according to local pathologists and the Review Committee, $\kappa = 0.84$ (95% CI, 0.80–0.88).

The tumour regression grade was considered as Grade 0 in 27 (8%) of 323 patients, Grade 1 in 59 (18%), Grade 2 in 140 (43%), Grade 3 in 56 (17%) and Grade 4 in 41 (13%). An overview of the grading by local pathologists and the Review Committee indicates that grading differed between both in 95 (38%) of 250 patients (Table 4). In 37 (15%) of 250 patients, tumour regression was considered as less advanced by the review panel. Statistical analysis revealed $\kappa = 0.50$ (95% CI, 0.43–0.58) for the concordance in interpretation of the tumour regression grade by local pathologists and the Review Committee.

Table 2 Evaluation of the tumour differentiation grade by local pathologists and the Review Committee.

Differentiation grade	Local pathologist				
	Well	Moderate	Poor	Missing	Total
Review Committee					
Well	24	2	0	0	26
Moderate	20	244	13	4	281
Poor	5	16	54	1	76
Missing	0	4	0	0	4
Total	49	266	67	5	387

Table 3 (y)pT stage according to local pathologists and the Review Committee.

	Local pathologist						
(y) pT	yp T0	yp Tis	(y)p T1	(y)p T2	(y)p T3	(y)p T4	Total
Review Committee							
ypT0	46	0	0	0	0	0	46*
ypTis	3	3	1	0	0	0	7
(y)pT1	3	0	21	2	0	0	26
(y)pT2	2	0	7	92	2	0	103
(y)pT3	0	0	0	19	218	5	242
(y)pT4	0	0	0	0	2	18	20
Total	54	3	29	113	222	23	444

*Five of these were staged ypT0 on the total mesorectal excision (TME) resection specimen after transanal polypectomy or mucosectomy; these patients did not receive neoadjuvant radiochemotherapy.

Discussion

The quality of TME according to Quirke, the status of the CRM and the number of harvested lymph nodes illustrate the potential effectiveness of TME and affect the patient's oncological outcome [11,14,15]. Together with other prognostic factors, they should be mentioned in the pathology report. The present study illustrates that this does not occur systematically.

Numerous studies have shown that the integrity of the mesorectum correlates with the rate of local recurrence [15–17]. Although in the first systematic description of the macroscopic quality of the mesorectum in rectal resection specimens these were called complete, nearly complete or incomplete [11], more recent publications describe evaluation of mesorectal quality based on the surgical plane of resection, which is more objective [16,18]. The resection plane is therefore said to be in the mesorectal plane (previously good/complete), the intra-mesorectal plane (previously moderate/nearly complete) or the muscularis propria plane (previously poor/incomplete), thereby going back to the initial definitions that were developed for the MRC CR07 trial that started in 1998 [16]. As data from a recent meta-analysis show that avoiding a muscularis propria plane of resection significantly reduces the risk of local recurrence and overall recurrence after TME surgery [5], we preferred to consider two groups: intramuscular *vs* (intra) mesorectal plane of resection. Achieving a mesorectal

Table 4 Tumour regression grade according to local pathologists and the Review Committee.

	Local pathologist						
Dworak grade	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Missing	Total
Review Committee							
Grade 0	14	1	0	1	0	11	27
Grade 1	5	21	7	13	0	13	59
Grade 2	14	9	74	13	0	30	140
Grade 3	20	0	2	24	2	8	56
Grade 4	4	0	0	4	22	11	41
Total	57	31	83	55	24	73	323

plane of surgery also significantly improves local recurrence rates compared with a suboptimal (intramesorectal or muscularis propria) plane, but for overall recurrence there is only a trend towards significance [5]. In our study, the surgical plane was reported in 89% of patients by the local pathologist. Several studies have shown that pathologist reports of mesorectal integrity have been highly inconsistent, with significant variations between institutions ranging from 40 to 99% [18–21]. In our study, differences in evaluation of the resection plane between local pathologists and the Review Committee might be related to the fact that the Review Committee evaluated the plane based on photographic material instead of 'handling' the specimen for macroscopic inspection and appraisal of the surface integrity. In fact, no valuable alternative exists; such photographic-based central assessment of the resection plane has also been performed in the ROLARR trial, a pan-world trial of robotic-assisted *vs* standard laparoscopic surgery for the curative treatment of rectal cancer [22].

In our study the CRM was reported in 88% of patients by the local pathologist. CRM is a strong predictor of local and overall recurrence [4,23,24] and should therefore be mentioned in the pathology report. In this series, at least 12 lymph nodes were examined in 47% of patients. Over the past 10 years, standards for lymph node harvests in colorectal cancer have been proposed. Several studies have recommended examination of at least 12 lymph nodes in the specimen and this number is now used as a reflection of surgical and pathological quality [7,25,26]. Higher numbers are, however, desirable and achievable in most cases, even after short-course neoadjuvant radiotherapy with a short interval to surgery [27]. Examining a higher number of nodes increases the likelihood of proper staging [28]. Harvests vary in relation to several factors: they are lower in older patients and increase with increasing local invasion and stage of tumour; however, they can be maximized through high-quality surgery and diligent pathological examination [28]. Nevertheless, recent reports have identified significantly decreased lymph node harvests in patients treated with neoadjuvant long-course (chemo)radiation with a long interval to surgery [29,30]. In the current study, the median number of lymph nodes harvested in such patients was 11, whereas it was 14 in the other patients. Examination of six or fewer lymph nodes is related to poor prognosis [31]. Central reviews with feedback to the referring hospitals might be useful to overcome, at least in part, this problem by raising awareness in the local pathologists as well as in others involved in patient care.

Although tumour differentiation grade is consistently recognized as an important prognostic parameter, there is, at present, no consensus on a grading system, with different proposals based on two-, three- or four-tiered stratifications and significant degrees of interobserver variability [32,33]. Another source of variation derives from the differences in tumour grading between the superficial part of a tumour and the invasive front, where tumours are generally less differentiated [34]. In practice, the method for assessing the differentiation grade varies greatly, as it can be based solely on the percentage of gland formation or on the worst pattern, regardless of its relative amount [33]. These factors might explain differences in grading between local pathologists and the Review Committee, especially because the differentiation grading method to be used was not well defined before the start of the study.

Grading of tumour regression is important because outcome is better in complete regression than in residual microscopic disease, which, in turn, is associated with better prognosis than cases without, or with only minor, regression [12,35–37]. In the TNM supplement booklet in use during the study period, it is mentioned that only viable tumour cells should be taken into account for staging purposes and not signs of regressed tumour tissue such as scars, fibrotic areas, fibrotic nodules, granulation tissue and mucin lakes in intestinal wall, perivisceral fat or regional lymph nodes [38]. This is in stark contrast to what was previously stated in the

second edition of the *TNM Supplement* [39], which reports that 'ypTNM should consider not only viable tumour cells but also signs of regressed tumour tissue such as scars, fibrotic areas, fibrotic nodules, granulation tissue, mucin lakes, etc.' An important consequence of this statement is that tumours with the same histologic characteristics could undergo different staging (as might be the case in this work) or inappropriate adjuvant treatments if pathologists are not aware of these practical implications.

As reported by an international study group on rectal cancer regression grading [40], we found little concordance for the regression score according to Dworak between local pathologists and the Review Committee. Unfortunately, other systems also lack precision and clarity for reproducible, accurate regression grading [40]. There seems to be a need for another system with a uniform method of sampling of specimens, clear criteria and a cumulative or composite score, taking into account all sections of the tumour bed. Moreover, the difficulties encountered in the present systems raise the question of whether an all-or-nothing score could be more accurate in terms of reproducibility and prediction of tumour recurrence.

In conclusion, despite some shortcomings (comparison between a photographic evaluation and an evaluation on a fresh specimen, lack of systematic analysis of the CRM and nodal assessment by the Review Committee), our analysis reveals differences in interpretation with regard to macroscopic and microscopic analyses of TME resection specimens within the framework of the national multidisciplinary improvement project PROCARE, although national pathology guidelines exist [6]. Possible explanations are given and can help involved surgeons, clinicians and pathologists in interpreting histopathological analyses in their centre as well as at the Central Review Committee. Our study underlines the need for objective and reproducible criteria in histopathology. Being aware of this is the first step for improvement.

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Author contribution

All authors contributed significantly to the conception and design of the study, and to the acquisition of the data. Data were analysed and interpreted by PD, TV and AJ-M. PD and AJ-M drafted the article; all authors revised it critically and gave final approval of this version to be published.

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Appendix A

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 (E. Danse, B. Op de Beeck, P. Smeets), the Société Royale Belge de Gastro-entérologie (M. Melange, J. Rahier), the Vlaamse Vereniging voor Gastro-enterologie Flemish Society for Gastroenterology (M. Cabooter, P. Pattyn, M. Peeters) and 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 (J. P. Dercq, A. Thijs). F. Penninckx chairs the PROCARE Steering Group.

Commentary on Demetter *et al.*

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The level of interest in as well as the quality of colorectal cancer pathology has changed markedly over the last 30 years, but the data from Demetter *et al.* [1] issue a timely challenge to pathologists and also indirectly to the rest of the multidisciplinary team (MDT). Whilst this is a relatively small study of 444 selected cases from a total of 2460 cases registered in the Belgium PROCARE study and is limited in its scope by omitting the reporting of some of the key prognostic factors, e.g. extramural vascular invasion, peritoneal involvement, tumour perforation and distance of extramural spread, it does make points of major importance for pathologists and the MDT.

Due to the selection process it is possible that this study shows the pathology reporting in PROCARE in a better light than might be seen were all the cases to have been available for review. Only 743, with submitted pictures and slides, out of the total of 2460 cases were reviewed centrally and of these 444 were felt to be of a standard where the quality of surgery could be assessed by the review panel. What was the data completeness in the non-submitted cases or the cases with poor photographic evidence? It is unlikely to be better than the pathologists work now reported, who had made the effort to take good quality photographs. In the cases that reached the review stage, one in 10 had no record of the circumferential resection margin status with a similar number not recording the grade of the plane of surgery. Furthermore one in five had no record of regression grading after preoperative therapy. Pleasingly the number of lymph nodes identified was recorded in 97% of specimens, but the majority failed to dissect at least 12 lymph nodes, again an area of concern. Whilst preoperative therapy does reduce nodal yield we should expect better performance from the reporting pathologists.

The failure to capture the key data systematically in all patients is unforgivable and is still all too frequent worldwide. There is extensive evidence that proforma reporting improves data capture [2–6], yet proformas were used here, showing that they are not the total solution. Is it time to apply a degree of supervision of pathology reporting? This could be immediate, with modern IT systems prompting pathologists when they have omitted data. Local named pathologists could be responsible for cancer data completeness with a further tier of independent regional or national audit of cancer pathology data as the final layer. By failing to bring pathologists to task by formal supervision or by MDT acceptance of incomplete data, patients may suffer suboptimal management from a poorly informed MDT.

Indeed, should we go further and demand that full data collection occurs from the entire MDT. Pathologists have been at the forefront of standardization of practice, guidelines, data collection and audit whereas other clinicians still fail to capture any data routinely apart from the bare minimum. Radiologists and others have much to learn from the process of change that pathologists have been through even though we have not yet reached our required destination.

The second point that emerges from this paper is the continuing tolerance by pathologists of systems of grading of differentiation (kappa = 0.67) and tumour regression (kappa = 0.50) with relatively poor interobserver agreement. We need to strive for better, more consistent and preferably quantitative criteria, to grade tumours