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The role of pathologists in the quality control of diagnosis and treatment of rectal cancer—an overview

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Abstract

Pathological examination of the rectal cancer resection specimen has an increasingly important role in influencing decisions about clinical management. Standardisation of the examination procedures and reporting are necessary. To evaluate the relevant pathological factors, data from randomised clinical trials with adequate follow-up are necessary. From a recently closed trial on the treatment of rectal cancer (preoperative radiotherapy or total mesorectal excision (TME) surgery alone?), the pathological data were used to evaluate the importance of pathological factors, like circumferential margin and tumour, lymph nodes, metastasis (TNM) stage. Furthermore, it was possible to evaluate the surgical procedures and correlate these findings to clinically relevant endpoints. In this review, we describe the standard evaluation of a rectal cancer specimen with special attention to preoperative irradiated specimens.

Keywords: Rectal cancer; Pathology; Quality; Staging; Circumferential margin; Lymph nodes; Radiotherapy; TME

1. Introduction

In the multidisciplinary approach of patients with rectal cancer, the pathologist plays a role in two phases: the diagnostic phase and the postsurgical phase. The diagnostic role concerns mainly the confirmation of clinically-, endoscopically- and radiologically-suspected rectal carcinoma—although occasional lymphomas, sarcomas or benign tumours diagnosed by endoscopic biopsies radically change the therapeutic approach of the patient. The majority of the pathology textbooks and literature deal with the criteria, classification and techniques necessary to make a reliable diagnosis [1,2]. Indeed, with the exception of villous adenoma, the preoperative biopsy is confirmed, in the great majority of patients, after resection of the tumour. This high quality instrument to select patients for surgery is well developed and leads to a key role for histopathology in the diagnostic process. The present review will therefore not cover this aspect, but will focus on the second phase: the assessment and reporting of the resection specimen.

Accurate pathological reporting of resection specimens has an increasingly important role in influencing decisions about clinical management. Results of clinical trials are compared using various pathological stages of disease to select the appropriate therapy strategies for patients and to prevent overtreatment. New imaging techniques are being introduced and will be compared with the gold standard provided by the pathology report.

The pathological data are important in order to provide a correct and reliable diagnosis that is relevant for prognosis. However, the pathological examination of the rectal resection specimen might also serve as an auditing instrument for the technical quality of the surgeon [3]. In this review, pathological evaluation will be discussed in particular from a quality assurance perspective.

2. Macroscopic evaluation

The total mesorectal excision (TME) technique for rectal cancer surgery is based on the sharp dissection of the avascular plane between visceral structures (rectum and mesorectum) and somatic structures (autonomic

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nerve plexuses). This operation under direct visualisation results in the excision of the rectum enveloped by a mesorectal fat column of 2–3 cm. TME resection specimens should be received fresh, unfixed and unopened for the optimal macroscopic evaluation.

2.1. Completeness of the mesorectum

The first assessment of the specimen deals with the quality of the mesorectum (Table 1). Inspection of the mesorectal surface gives the first indication of its quality. Defects should be classified into three classes: less than 5 mm in depth, 5 mm and more but not reaching the muscularis propria, and defects reaching the muscularis propria, regardless of depth. Full thickness slicing of the tumour and the mesorectum allows a good assessment of the adequacy of excision and the regularity of the circumferential resection margin (CRM), which is the second indicator of the quality of resection. The ideal resection should have a smooth CRM as far as possible away from the muscularis propria. In a poor resection specimen, it is possible to see the muscularis propria forming the CRM and, as such, the recurrence of even tumour, lymph nodes, metastasis (TNM) I tumours might be explained.

For the surgical audit, photographing the intact resection specimen might be desirable, and might be convincing in the discussions afterwards.

Recently, we showed that the evaluation of completeness of the mesorectum provides significant information about prognosis [56]. Patients with an incomplete mesorectum have a higher risk of recurrence, 36% versus 20% in the group with a complete mesorectum ($P = 0.02$). Part of the recurrences can be contributed to the increased number of positive resection margins (CRM), but the prognostic value of the quality evaluation is especially present in patients with negative margins.

The benefit of this direct evaluation of the completeness of the mesorectum is that, unlike other methods of quality evaluation in surgery (perioperative mortality, complication, recurrence and survival rates [4–6]), individual patients can be evaluated and one does not have to wait for long-term follow-up to obtain relevant data.

Table 1
Definitions used for the assessment of quality of mesorectal excision or completeness of resection[a]

Quality and completeness of the mesorectum		
Complete	Mesorectum	Intact, smooth
	Defects	Not deeper than 5 mm
	Coning	No coning
	CRM	Smooth, regular
Nearly complete	Mesorectum	Moderate bulk, irregular
	Defects	No visible muscularis propria
	Coning	Moderate
	CRM	Irregular
Incomplete	Mesorectum	Little bulk
	Defects	Down onto muscularis propria
	Coning	Yes
	CRM	Irregular

CRM, circumferential margin.

[a] Both the specimen as a whole and the slices of the resection specimen should be examined to come to a reliable verdict.

2.2. Macroscopic evaluation

After inspection and photographic documentation of the gross specimen, the rectum can be opened anteriorly apart from the area 2 cm above and below the tumour where the anterior part of the rectum is left intact. Margins (proximal, distal and circumferential) and tumour size are recorded. Tumour size is recorded as an element of tumour documentation, which is important for clinicopathological correlation or quality control (for example to compare size measurements by imaging techniques). Tumour size is not related to outcome [7].

Subsequently, the specimen is fixed for at least 48 h, after which the non-peritonealised surfaces should be painted with ink. The area of the tumour which was not opened is transversely sliced into thin sections (0.3–0.5 cm).

2.3. Circumferential margin involvement

The sliced sections can be used to examine circumferential margin involvement macroscopically. If the distance between tumour and resection margin is sufficiently large, i.e. over 1 cm, macroscopic measurement is adequate. Whenever the tumour approaches the resection margin, measurements should be repeated microscopically. For the determination of the CRM, only the relationship between primary tumour and resection margin has to be examined, since we have shown that lymph nodes in the resection margin do not influence the risk of local recurrence [57].

Circumferential margin involvement is one of the most powerful predictors of local recurrence in rectal cancer. Although there has been discussion about the definition of positive margins [8–11], we have recently shown that in order to predict local recurrence, margins smaller than or equal to 2 mm should be regarded as involved with an increased risk of local recurrence (16% versus 6% for patients with margins over 2 mm) (Fig. 1).

Margins of 1 mm or less are predictive of an increased risk of developing distant metastases (37% versus 15% for patients with margins over 1 mm), and shorter survival times (70% versus 90% 2-year survival rates, respectively).

2.4. Distal margin involvement

In recent years, the role of circumferential margin involvement for recurrent disease in rectal cancer has

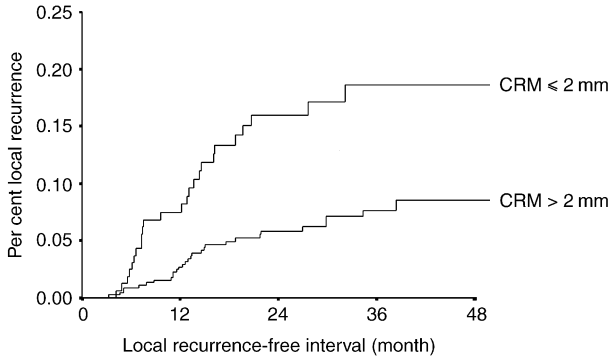

Fig. 1. Prognostic value of circumferential margins (CRM) of over 2 mm compared with less than or equal to 2 mm. In contrast to earlier publications, we showed that 2 mm is the cut-off point for an increased risk of local recurrence.

become clear. Less attention has been given to the distal resection margin. Although in most laboratories the distal margin is routinely examined, the relevance of the tumour close to this margin is less clear. It has been suggested that microscopic examination of this margin is only necessary if the tumour 'approaches' the margin.

Two different aspects are relevant for the definition of an adequate distal margin: intramural and extramural continuous growth and distal spread through the lymph vessels. First of all, it is important to confirm the histological rationale behind an adequate margin. The determination of distal spread should be performed, both the intramural distal spread, as well as the retrograde lymphatic spread. When a large number of lymph node metastases occur along the inferior mesenteric artery, lymphatic flow may change to a downward direction, causing distal spread [12]. In Table 2, an overview of studies concerning distal spread in rectal cancer is given. Large variety exists in the observed distal spread in rectal carcinoma, according to the literature. Recent observations [12] show that in only 3.6% of the cases intramural distal spread is present to an extend of over 2 cm. When regarding the distal spread via the lymphatic system [13], in 20% of the node-positive cases lymphatic spread is present distal to the primary tumour. In 6.4%, the lymph-nodes are more than 2 cm away.

For distal margin examination, it is important to recognise fixation induced shrinkage of the bowel, with the result that adequacy of the resection margin may be underestimated if measurements are taken following fixation. Unfixed colorectal segments with a length of 5 cm *in vivo*, shrink to 3 cm after resection and after fixation, the segment length is 2.2 cm (range 1–4 cm) [14]. When specimens are pinned on corkboards, shrinkage is negligible [15].

Based on these histological data, a recommended margin can be provided, and subsequently tested using clinical data. Interpretation of these data is difficult, since most of the studies do not take circumferential margin involvement, being a very strong prognosticator for local recurrence, into account.

In Fig. 2, distal margins in the TME trial are reported. In almost 40% of the cases the distance between the tumour and the distal resection margin was less than 2 cm. Although there were more local recurrences in the patients with distal margins less than 2 cm compared with the patients with margins over 5 cm (independent of circumferential margin status), these differences were not significant. Thus, an adequate distal margin cannot yet be defined using this trial data.

Table 2
Distance of intra- and extramural spread from the primary tumour towards the distal resection margin[a]

Author (Ref.)	Method		Distal spread (cm)	%
Morkawa [13]	Lymph node mapping (fat clearance)	$n=98$	0.0–2.0	13.5
		N+ only	2.0–4.0	6.4
			>4.0	0
Shiruzu [12]	Intra- and extramural	$n=610$	0.0–1.0	3.8
			1.0–2.0	2.6
			>2.0	3.6
Williams [15]	Intramural	$n=50$	0.0–0.5	10
			0.5–2.0	8
			>2.0	6
Grinnell [50]	Intamural	$n=76$	0.0–0.5	9
			0.5–1.5	8
			1.5–4.0	4
			>4.0	0
Connell and Rottino [51]	Intramural	$n=9$	0.0–4.0	0
			>4.0	44
Quer [52]	Intramural	$n=93$	0.0–1.5	2
			>1.5	3

N+, node-positive.
[a] Only the percentage of cases that shows distal spread is shown. In the majority of cases, no distal spread was present.

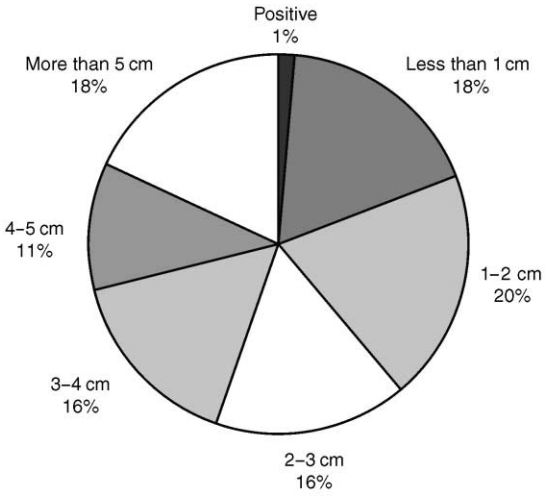

Fig. 2. Distribution of distance from primary rectal tumour to the distal resection margin in the Dutch TME trial population ($n = 1405$).

2.5. Staging

Pathological staging is defined as the evaluation and description of the anatomical extent of cancer assessed by macroscopic and microscopic examination. By worldwide agreement, the definitions for extent are classified in three categories: tumour, lymph nodes, metastasis (TNM). The combined outcome of these categories, the stage of the tumour, is one of the strongest prognostic factors. Survival as well as the development of local and distant recurrences are predicted by the TNM stage. Historically, the Dukes' classification system for rectal cancers [16] forms the basis of the staging systems for colorectal cancers, followed by numerous modifications. Although many pathologists and clinicians are still attached to the Dukes' classification or one of its many modifications, the staging system of choice is the TNM classification [17], since it is a standardised system. Standardisation is essential, since it allows valid comparisons of clinical data and studies among different institutions and treatments.

2.6. Lymph nodes

One of the most important factors in patients' prognosis is the presence of nodal metastases at the time of surgical treatment. Approximately 68% of the patients with no metastatic involvement of the lymph nodes are still alive after 5 years, while in those with lymph node metastases a 5-year survival rate of 40% has been described [18].

Standard guidelines are provided for the number and location of the examined lymph nodes. According to the TNM guidelines [17], ideally 12 lymph nodes should be examined before a patient can be classified as N0. However, in a recent comment [19], it was emphasised that the number of 12 nodes is not a requirement, but rather a guideline. Indeed, in daily practice, this number is hard to reach. When evaluating the number of lymph nodes examined in node-negative patients in the TME trial [20], we found that in 82% of the cases less than 12 lymph nodes were examined (mean number of nodes 7.5, median 6.0). We know that preoperative radiotherapy influences the number of examined lymph nodes [20]; however, in 79% of the non-irradiated N0 patients, the number of 12 nodes was not reached (mean 8.3, median 7.0 nodes).

Apart from the effects of preoperative radiotherapy, there may be substantial variability in the type of resection performed for rectal cancer, which could lead to variability in the number of nodes removed. Obviously, the larger the amount of mesorectum resected, the more lymph nodes are likely to be found. Systemic analysis of these aspects of lymph node detection (operation technique and size of specimen) has not yet been performed. Additionally, the number of nodes may vary from one patient to another. From elderly patients (over 75 years of age), less lymph nodes are retrieved (6.7 versus 8.2 nodes, $P < 0.01$ [21]).

The extent of pathological examination is one of the most important factors determining the number of examined lymph nodes. This is reflected by the considerable difference in the numbers of lymph nodes retrieved in different laboratories (Fig. 3). In routine diagnostics, lymph nodes are identified and isolated from the perirectal fat using a combination of visual inspection, palpation and dissection. Lymph nodes are examined microscopically using haematoxylin and eosin (H&E) sections, usually one slide from each tissue block. A second review of histological slides can uncover a small number of missed metastases (as described in Ref.

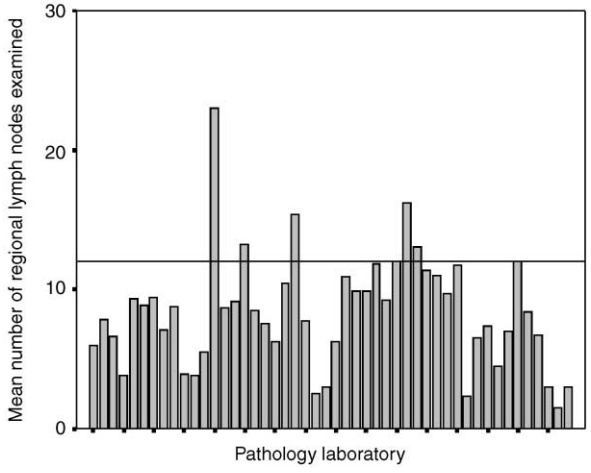

Fig. 3. Distribution of the numbers of examined lymph nodes in non-irradiated node-negative rectal cancer patients treated in the TME trial. Reference line indicates 12 lymph nodes as is described in the International Union Against Cancer (UICC) guidelines. In the larger laboratories (i.e. 9 or more patients in this randomisation arm), mean numbers of lymph nodes varied from less than 4 (22 patients) to over 16 (9 patients). Mean number of examined nodes in this group is 8.3 ($n = 426$). In 7 patients (1.6%), no lymph nodes were retrieved.

[22]). The chance of missed metastases is generally inversely proportional to their size.

Various studies analysed the number of nodes that need to be examined in a routine fashion to accurately reflect the lymph node status of the patient. A retrospective evaluation of the number of nodes necessary for the determination of Dukes' C (TNM III) patients showed that seven lymph nodes were necessary [23]. A more relevant method is the evaluation of prognosis in node-negative and node-positive patients. One study [24] revealed that in patients with less than seven lymph nodes examined, prognosis was comparable to TNM III patients. When comparing the prognosis of node-negative patients, it was found that patients with 14 or more nodes examined [25] showed a better recurrence-free survival compared with patients with less than eight nodes examined.

However, data obtained from colon or colorectal cancer patients, as described above, may not be acceptable for rectal cancer patients. From a retrospective study involving 196 patients [26], it is clear that the mean number of examined nodes in the ascending and descending colon was approximately twice as high as the number of nodes in the rectum (20 versus 11 nodes). A French study confirmed the difference in the number of lymph nodes between the rectum and colon [21]; however, their numbers were much lower (8 versus 6.5 nodes).

Very small lymph nodes that are missed using routine examination can be detected using fat clearance techniques. The specimen is immersed in graded alcohol followed by xylene. A study comparing a traditional and fat-clearing technique [27] revealed that in rectal cancer ($n=41$) initially 6.1 lymph nodes per patient were detected while, after fat-clearing, an additional 12.7 nodes were retrieved. In this study, the fat-clearing technique resulted in a stage migration of 8.6% from TNM II to TNM III. However, the fat-clearing techniques are time-consuming and expensive. They are not recommended since they might interfere with a reliable determination of the circumferential resection margin [28].

Immunohistochemical and molecular determination of metastases in lymph nodes are interesting developments, however, the relevance of metastases detected by these techniques is not yet clear. Some studies show no effect, while others have demonstrated a significant correlation with tumour recurrence [29]. There is no routine protocol for these methods, and therefore their discussion is outside the scope of this review.

2.7. Grading

Although many studies of observer variation have shown inconsistent results within the pathology community for determining well-differentiated and moderately differentiated adenocarcinoma of the colon and rectum [30,31], there is a strong consistency between observers for the identification of poorly differentiated tumours [31]. In addition, multivariate analysis in which histological tumour differentiation is dichotomised into poorly differentiated versus others has demonstrated an independent prognostic value.

2.8. Typing

The histological type of the tumour is always designated in the pathology report, based on the internationally accepted histological classification of colorectal carcinomas by the World Health Organization [32]. Aside from those histological types that are always classified as poorly differentiated or undifferentiated (i.e. signet ring cell carcinomas and neuroendocrine or small-cell carcinomas [7]), tumour type has been repeatedly shown to lack independent prognostic significance.

In general, pathologists have assumed that mucinous carcinomas have a worse prognosis. In fact, these patients have a worse prognosis [33–36] as they often present a more advanced stage of disease. The population-based studies that provide prognosis data that have been corrected for tumour stage show no differences in prognosis [33,34,37].

3. Effects of radiotherapy on pathology

Short-term preoperative radiotherapy in combination with TME surgery has become the treatment of choice in many European countries, like Sweden and The Netherlands, based on the results of the TME trial [38]. The effect of this treatment on the histopathology of rectal cancer is thus an important feature. Previously, adjuvant therapy for rectal cancer consisted of postoperative radiotherapy and/or chemotherapy, which inevitably does not influence the pathological examination of the resection specimen.

3.1. Margins

Radiotherapy did not influence the number of positive resection margins, both circumferential and distal. Positive circumferential resection margins were present in 16% of the patients in the radiotherapy group, compared with 19% in the surgery only group ($P=0.22$). For distal margin involvement, the percentages are 1.5 and 1.3%, respectively ($P=0.82$).

3.2. Staging

Although preoperative radiotherapy has been associated with a downstaging of tumours, these treatment regimes, used to facilitate surgical removal, are completely different from the current protocol (reviewed by Marijnen and Glimelius in this issue [39]). Both the

actual time of the treatment and the interval between the end of the treatment and the surgery are considerably longer in the radiotherapy treatment group aimed at downstaging. We have described that downstaging does not occur in the 5×5 Gy regimen [20]. Nevertheless, one of the early reports of the Swedish Rectal Cancer Trial [40] suggests that even the 5×5 Gy scheme can cause downstaging of tumours. When examining these results in more detail, it becomes clear that in patients with an overall treatment time (i.e. time from start of radiotherapy until operation) of more than 10 days downstaging is observed. However, in patients with an overall treatment time of 10 days or less no downstaging was observed.

3.3. Lymph nodes

The numbers of lymph nodes decrease due to short-term radiotherapy [20]. While the mean number of examined lymph nodes in the TME trial was 9.7 in the surgery only group, in the radiotherapy group the mean number of nodes was 7.7 ($P<0.001$). There was no difference in the number of positive lymph nodes (1.9 and 1.6, respectively). This is explained by the fact that lymphocytes can undergo cell death within hours after radiotherapy, whereas tumour cells need more time to undergo cell death and are less sensitive.

The numbers of lymph nodes which should be retrieved in irradiated specimens remains to be determined. In analogy to the studies mentioned before, long-term prognosis of irradiated patients should be taken into consideration. The follow-up of the TME trial is, at the moment, not long enough to answer the questions about numbers of lymph nodes, but this will be a point of study in the future.

3.4. Grading

In the TME trial, preoperative irradiated rectal carcinomas more often showed poor differentiation than non-irradiated carcinomas (35% versus 23%, respectively $P<0.001$) [20]. This difference has been observed before [41,42], and might be explained by the changes in the microenvironment of the tumour cells. Both the disappearance of inflammatory infiltrate in and around the tumour [58] and the increase in fibroblastic reaction might contribute to the observation of a more solid type of tumour growth.

3.5. Typing

In the radiotherapy group of the TME trial significantly more mucinous carcinomas were observed, 13% versus 7% in the non-irradiated group ($P<0.001$) [20]. Other trials investigating preoperative radiotherapy do not report tumour types, but the same phenomenon has been described in a small study with long-term preoperative radiochemotherapy [43]. The mechanisms behind this phenotype switch in carcinomas after irradiation is still the subject of ongoing research.

4. Specimen handling

The number of tissue blocks taken from the primary tumour is very variable, but will affect staging, grading, the detection of sufficient numbers of lymph nodes and circumferential margin involvement. In a study performed by Halvorsen [44], it was found that if two routine sections were taken both from superficial and deep parts of the tumour, provided that they are of a reasonable size (2–3 cm), they will be sufficient to grade colorectal carcinomas reliably. However, it is questionable whether these two sections will also provide the necessary information on the various other tumour characteristics.

5. Pathology reporting

Histopathological reporting of resection specimens provides important information for both the clinical management of the affected patient and for the evaluation of health care as a whole. For healthcare evaluation, pathology reports provide information for cancer registration, clinical audits, assessing the accuracy of new diagnostic and preoperative staging techniques and for ensuring compatibility of patient groups in clinical trials.

As a result of the many significant correlations established over the years between morphological parameters and the clinical course of disease, the constant increasing individualisation of therapeutic approaches and the strict requirements of quality insurance regulations and clinical protocols, pathologists are expected to report an ever-increasing amount of information on final reports in a consistent and systemic fashion [45]. Standardised pathology forms are frequently proposed for the reporting of the major tumour types, to ensure that the essential morphological information is present in the reports [46,47]. In Table 3, required items for the reporting of rectal carcinoma are shown.

Studies concerning the effect of the introduction of proformas for pathology reports all show an increase in the reporting of certain parameters (for example, circumferential margins and apical lymph node involvement) [47,48]. However, in the use of these forms, there are disadvantages. Simple forms are not sufficient and expansion of the list of items present occurs frequently as a result of the evaluation of the forms. It should be determined which items are really necessary for the various goals. Data directly influencing patient management are of course

Table 3
Summary of required items for the reporting of rectal carcinoma

Required items for the reporting of rectal carcinoma [46,53–55]	
Tumour size	Maximum diameter
Gross tumour configuration	E.g. polypoid, fungating, annular; plaque-like ulcerative
Gross assessment of tumour invasion	Stalk, bowel wall layers, perirectal tissue
Gross assessment of distance of tumour from resection margins	Distal and proximal margins, circumferential margin. For circumferential margin examination, there is no need to include suspicious lymph nodes
Histological type of carcinoma	Adenocarcinoma n.o.s. Adenocarcinoma with mucinous component Mucinous adenocarcinoma Signet ring cell carcinoma Neuroendocrine carcinoma Undifferentiated carcinoma
Tumour grade of differentiation	Distinguish between good/moderate and poor; grading should be based on the worst area
Histological assessment of invasion depth and distance to distal and circumferential margins	Invasion depth should be described in terms of the T classification (TNM) Circumferential margin should be measured in millimetres
Total numbers of histologically-confirmed examined lymph nodes	
Total number of histologically-confirmed positive lymph nodes and their distance to the resection margins	Including tumour deposits over 3 mm in size

n.o.s., not otherwise specified.

obligatory. Some data, although not significant in altering patients' management, are important to note because they reflect how closely the pathologist has examined the specimen, as well as potentially confirming pre-operative endoscopic or radiological findings (like the length of specimen, size and appearance of tumour), which might be of use for quality evaluation in several other departments.

Individual preferences of pathologists may conflict with the items on the forms. There is still disagreement among pathologists as to the preferred terms for various tumours, the best way to subclassify them and the clinical significance of the various morphological parameters. Furthermore, writing errors may easily occur when using the forms and, in contrast to reports, there is no context from which they can be corrected (discussed in Ref. [49]).

Both distribution of guidelines [47] and participation in clinical trials [28] (when pathologists are required to record their findings on specific forms) improve the completeness of the pathology report, but are not as good as template proformas.

6. Conclusions

Active participation of pathologists in clinical trials has many benefits, as can be observed in the recently published RT + TME trial. Not only can pathological parameters be tested in nationwide populations, but also the effects of surgical quality can be studied. We showed that circumferential margin involvement is still one of the most important predictors of local recurrence, despite the improved surgical techniques. Furthermore, we established a clinically relevant method of classification for the quality of the performed excision, or the completeness of the mesorectum using the data and the reports collected in this trial. Participation of pathologists in this trial has led to the introduction of a standardised method of pathological examination of rectal carcinoma in The Netherlands.

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