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The role of the pathologist in rectal cancer diagnosis and staging and surgical quality assessment

Carmen Faus · Desamparados Roda · Matteo Frasson · Susana Roselló · Eduardo García-Granero · Blas Flor-Lorente · Samuel Navarro

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Abstract Since the introduction of the total mesorectal excision by Heald, many changes in the therapeutic management of rectal cancer have been incorporated. The multidisciplinary approach to colorectal cancer, integrated in a team of different specialists, ensures individualised treatment for each patient with rectal cancer. Therefore the role of the pathologist has acquired an important relevance, not only in diagnosing but also managing and evaluating the surgical specimen. The knowledge of preoperative staging, distance between tumour and anal verge or in patients subjected to a neoadjuvant treatment is necessary for the pathologist to make a detailed, accurate and good-quality report. Parameters such as the macroscopic quality of the mesorectum, the status of the circumferential resection margin and the lymph node harvest are considered basic criteria recommended by the current guidelines for the multidisciplinary team audit.

Keywords Rectal cancer · Diagnosis · Pathologic assessment · Circumferential radial margin

C. Faus (✉) · S. Navarro
Department of Pathology
Hospital Clínico Universitario
University of Valencia. INCLIVA
Av. Blasco Ibáñez, 17
ES-46010 Valencia, Spain
e-mail: mafausal@comv.es

D. Roda · S. Roselló
Department of Haemathology and Oncology
Hospital Clínico Universitario
University of Valencia. INCLIVA
Valencia, Spain

M. Frasson · E. García-Granero · B. Flor-Lorente
Department of Surgery
Hospital Clínico Universitario
University of Valencia. INCLIVA
Valencia, Spain

Introduction

During the last two decades, important changes in the therapeutic management of rectal cancer have been incorporated. In the 1980s, Heald introduced the surgical technique called total mesorectal excision (TME) [1] based on dissection along an embryologic plane comprising avascular areolar tissue between the mesorectal fascia and the fascia of the pelvic sidewall, which results in complete excision of the mesorectum, including lymph vessels, lymph nodes, nerves and blood vessels. This procedure ensures that all avenues of tumour dissemination are included in the specimen. This technique has become the gold standard for surgical treatment of the infiltrating rectal carcinomas located in the middle third and inferior third [2–5], obtaining a dramatic decrease of local recurrences to 4% [6] compared with the 30–40% of relapses previously reported. The current guidelines support the multidisciplinary approach to colorectal cancer [7-9] integrated in a team of specialists that ensures individualised treatment for each patient [10–12].

As a consequence of these changes, the pathologist's role has acquired an important relevance, not only for diagnosing but also for managing and evaluating the surgical

specimen. The pathologist must create a quality report incorporating all parameters of prognostic value, evaluating surgical quality in the same manner in which the pathologist report is audited by the surgeon and the oncologist, whose further clinical and therapeutic decisions will be based on it. This process should ensure analysis of prognostic factors that condition therapeutic strategies.

Preoperative staging and neoadjuvant therapy

Although pathologic analysis is considered the gold standard in diagnosing rectal cancer [13], preoperative staging is necessary to establish therapeutic management with objective criteria [14] and essential for selecting the surgical procedure as well as deciding whether or not neo-adjuvant treatment is necessary.

Using the rigid rectoscopy, rectal cancer is classified into three groups depending on tumour distance to the anal margin: lower third (0–6 cm), medium third (7–10 cm) and upper third (11–15 cm). Endorectal ultrasonography (EUS) and magnetic resonance imaging (MRI) are the most useful techniques for preoperative evaluation. EUS is very accurate for assessing invasion of tumours within the bowel wall. High-resolution MRI predicts with high accuracy circumferential resection margin (CRM) involvement. With the development of MRI, it is now possible to predict tumour stage and other prognostic parameters such as nodal disease, depth of extramural spread and presence of extramural vascular invasion [13-15].

In some cases, such as locally advanced tumours, nodal involvement or affectation of the CRM, the multidisciplinary team decides upon administration of neoadjuvant therapy, which modifies the macroscopic aspect of the tumour and makes managing the specimen difficult from the pathologist's point of view, thus influencing sampling, lymph-node harvest and the microscopic analysis.

Surgical technique and anatomic structures

For optimal management of the surgical specimens, the pathologist should know tumour location and type of surgery performed.

Anterior resections

Anterior resections are the most frequently performed procedures. It is recommended that the percentage of surgical anterior resections be superior to 70% of total mesorectal excisions, arriving to 90% of them in referral centres for rectal cancer surgery [16]. The surgeon must ensure a distal margin of 2 cm except in undifferentiated carcinomas, in which the margin should be 5 cm [17]. Moreover, the surgeon should avoid involvement of the CRM, which is considered the main cause of local relapse [16, 18, 19].

Anatomically, one rectal-sigmoid segment should be included, with the surrounding mesorectum, in front of the peritoneal reflection and the Denonvilliers' fascia. In neoplasms of the upper third, subtotal mesorectal excision provides satisfactory oncologic results, allowing a distal margin of 5 cm and lesser morbimortality [20]. In tumours of middle and lower third of the rectum, the appropriate procedure is anterior ultralow resection, the objective being total mesorectal excision.

Abdominoperineal resection (APR), or Miles' operation

APR is considered following regression due to the tendency to preserve sphincters [21]. In specialised centres, APR results do not differ regarding relapse and overall survival [22]. However, for several series, recurrence rates are higher after APR [23, 24]. A change in technical approach by performing cylindrical APR in the prone position has been proposed. The anus and levator muscles are excised, allowing a cylinder of tissue to be removed [25]. This results in the surgical resection margin being farther away from the muscularis propria and sphincters and a lower rate of CRM involvement and intraoperative perforations, which should reduce local disease recurrence [26].

Pathology report

Macroscopic assessment of mesorectum quality

Macroscopic quality of the mesorectum is a fundamental parameter for evaluation by the pathologist. One interesting point is the demonstration that many relapses could not be explained by affectation of the CRM only. Routine analysis of mesorectum quality could improve the prognostic value of the pathologic report as well surgical procedure quality [27–29]. The macroscopic aspect of the specimen could provide information more relevant than other prognostic indicators [10, 28, 30–32]. It has been recently included in the current recommendations of the Royal College of Pathologists and is considered a basic criterion recommended for multidisciplinary team audit [9].

Immediately after surgery, the pathologist should evaluate the quality of the mesorectum on the fresh specimen, first taking photographs from the anterior and posterior sides before opening the specimen. Evaluation of each specimen is based on criteria described by Quirke et al. [8] and also as defined by Nagtegaal et al. [29]:

- Complete excision or mesorectal plane: intact mesorectum with minor irregularities of a smooth mesorectal surface. No defect is deeper than 5 mm, and there is no coning towards the distal margin of the specimen. There is a smooth CRM on slicing.

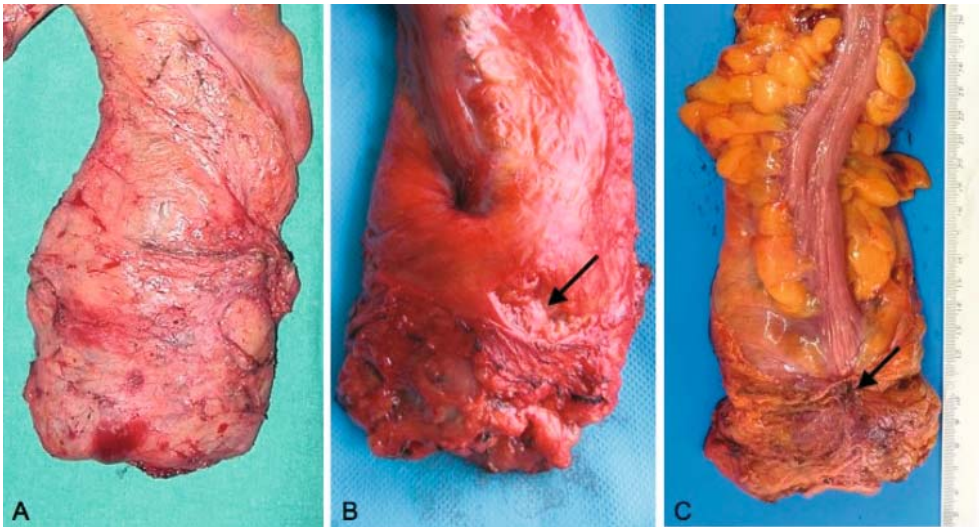

Fig. 1 Macroscopic assessment of mesorectal excision in fresh surgical specimens of rectal cancer (anterior resection): **A** complete excision, smooth mesorectal surface with minor irregularities; **B** nearly complete excision, irregularity of the mesorectum much deeper than 5 mm *(arrow)*; **C** incomplete excision, defect down to the muscularis propria *(arrow)*

- Nearly complete or intramesorectal plane: moderate bulk to the mesorectum, but irregularity of the mesorectal surface. Moderate coning of the specimen is allowed. At no site is the muscularis propria visible, with the exception of insertion of the elevator muscles.
- Incomplete or muscularis propria plane: little bulk to the mesorectum, with defects down to the muscularis propria and/or very irregular CRM (Fig. 1). In the cases of abdominoperineal amputation, there are some changes in criteria.
- Complete: the specimen presents a complete circumferential component of striated muscle in the zone of insertion of the elevator muscles.
- Nearly complete: there is no striated muscle. The resection margin is formed by the muscularis propria.
- Incomplete: in the insertion zone, there is no muscularis propria, and perforations of the wall as well as superficial presence of tumour are evident.

It is important that surgeon and pathologist work together to ensure delivery of a high-quality rectal specimen and optimal pathologic assessment.

Macroscopic assessment of mesorectal excision in rectal cancer is a useful tool for improving quality control in a multidisciplinary team [33]. The quality of surgical mesorectal excision should be evaluated by the pathologist and, in turn, the histopathological report should be assessed by the surgeon and the oncologist.

Sampling and analysis of the circumferential radial margin

After evaluating the quality of the mesorectal excision, the pathologist opens the specimen, leaving unopened 2 cm above and below the tumour. The mesorectal tissue is then painted with black ink, and the specimen is fixed in formalin at 10% for a minimum of 48 h. After fixation, sampling consists of transversal consecutives sections of 5 mm, which should include the tumour and the surrounding mesorectum [28, 29]. Tumour measurement, location, macroscopic appearance and distance to longitudinal margins are reported. The whole-mount sections allow measurement of the distance between the tumour and the CRM, which will be confirmed in the microscopic examination. The CRM is regarded as involved when the distance between the malignant cells and the margin is ≤1 mm; such involvement may be through direct continuity with the main tumour, tumour in veins, lymphatics or lymph nodes or tumour deposits discontinuous from the main growth [34–39]. Nagtegaal et al. suggest that the distance between malignant cells and the CRM should be increased to 2 mm for rectal tumours [30].

Cross-sections are then placed on a smooth surface, and digital pictures are taken. The pathologist chooses the most representative section for microscopic analysis. In the report, the pathologist should include the status of the CRM as well the distance in millimetres from the tumour to the CRM, including whether it is a continuous tumoral front, a focal tumoral impact or a lymph node with capsular breakdown (Fig. 2).

We emphasise the importance of understanding the anatomic structure of the specimen to avoid confusion between tumours with CRM involved versus tumours in stage T4b involving serosa without involvement of the CRM.

Lymph-node harvest

An important point of the sampling, always requested by the multidisciplinary team and that reflects the quality of the pathology report, is lymph-node harvest [40]. A minimum of 12 lymph nodes should be obtained to avoid patient infrastaging. Therefore, recent reports recommended harvesting 15–22 lymph nodes depending of tumour staging [40–43]. This is a time-consuming process that must be

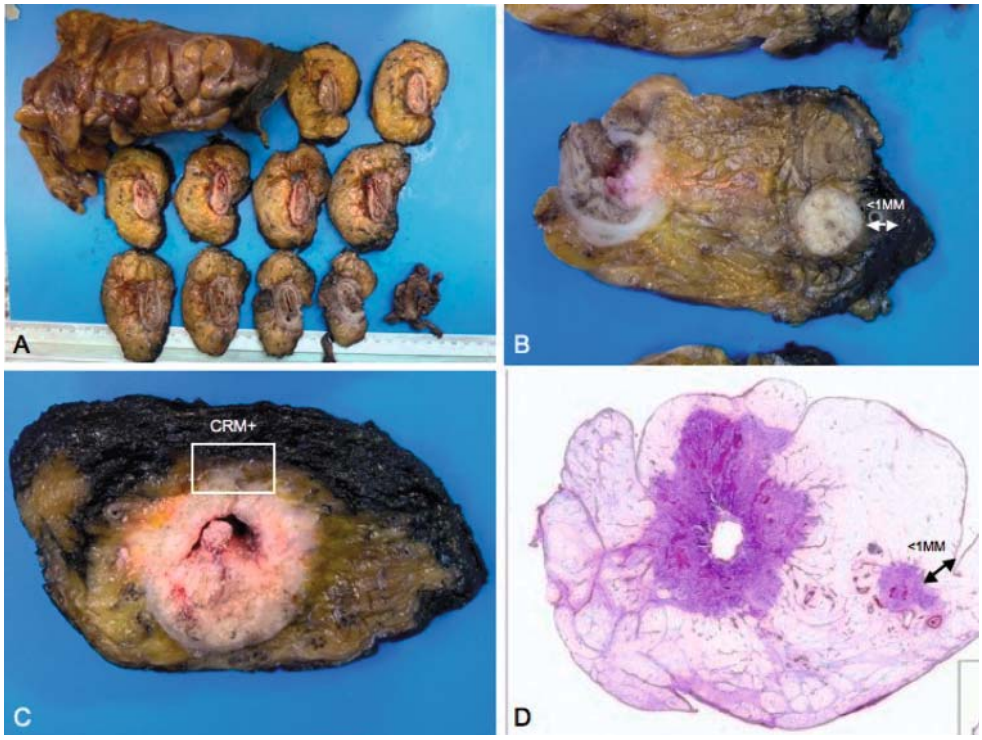

Fig. 2 Whole-mount sections of surgical specimens of rectal cancer: **A** cross-sections. **B** circumferential margin focally involved by a lymph node with capsular break down (arrow); **C** circumferential resection margin involved by the tumoral front; **D** margin focally involved by a lymph node on the slice

done carefully. The pathologist should identify the maximum number of nodes, a difficult task in cases that have received preoperative radiotherapy. In order to improve the number of lymph nodes obtained in the sampling, new studies have proposed the intravascular injection of methylene blue in the fresh specimen [44]. This procedure stains the lymphoid structures, which are then easily identified.

An important, difficult issue in the routine microscopic examination is to distinguish between mesorectal tumour impact and lymph node metastatic deposits. It is a controversial topic; the 3-mm rule proposed in TNM 5 [45] was not based on trial data or even survival data but is quantitative. In TNM 6 [46], if metastatic nodules in the perirectal fat are smooth, they are considered as lymph-node metastases; however, this has the problem of being a qualitative feature. Goldstein and Turner [47] considered a nodule as a lymph node if it was grossly palpable, supported by clinical trial evidence and survival data.

Postadjuvant therapy tumour analysis

In our institution, tumours in advanced stage diagnosed by endorectal ultrasonography or MRI as uT3 advanced and uT4, with clear metastatic nodal disease and specially when the CRM is threatened or affected, are treated with neoadjuvant radiotherapy. Preoperative concurrent chemoradiation has been shown to improve outcomes with local recurrences [48–51]. Adjuvant therapy has some implications on the pathological study, not only in the macroscopic configuration of the tumour but also in the microscopic features.

In cases treated with short-term radiotherapy, some features affecting tumoral size as well the growing front of the tumour and peritumoral lymphoid inflammation can change, with reduction of tumoral diameter or even disappearance of the tumour [52, 53]. Likewise, tumours undergoing long-term radiotherapy can disappear in 15% of cases, so the pathologist must make an exhaustive sampling from the fibrosis zone and a careful study of the slices to identify residual malignant cells [54].

Also, is important to recognise histological changes occurring in tumoral and peritumoral tissue, as well as necrosis, fibrosis, decrease of tumour differentiation or mucinous differentiation [52–54]. Dworak et al. proposed a gradation system based upon desmoplastic reaction and the presence of malignant cell nests [55] to evaluate effectiveness of adjuvant treatment (Fig. 3):

- Grade 0: lack of regression
- Grade 1: minimal regression. There are more tumoral nests than fibrosis; vasculopathy is clear.
- Grade 2: moderate regression. Fibrosis dominates the tumoral mass.
- Grade 3: good regression. Difficulty finding scanty tumoral cells, surrounded by fibrosis, with or without mucin.
- Grade 4: complete regression. Lack of tumoral cells, only fibrosis or mucin. If the tumour is considered in this category, the pathologist must do an exhaustive sampling of the suspicious zone and, if necessary, make immunohistochemical markers to rule out viable malignant cells.

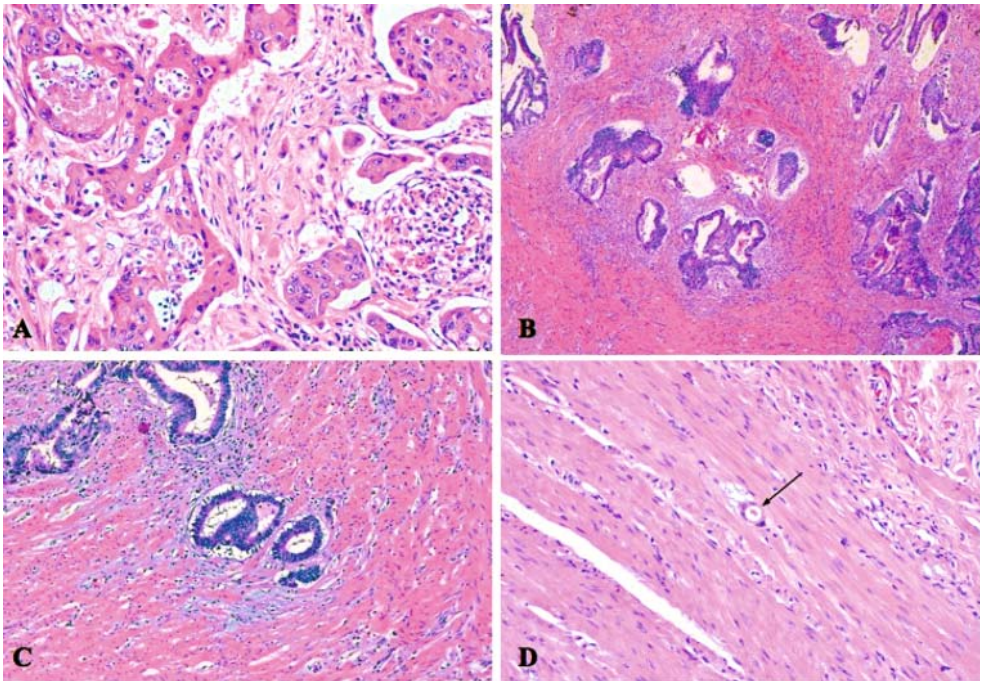

Fig. 3 Grade of tumour regression in rectal cancer after preoperative chemoradiation, according to Dworak et al. [53]: **A** grade 0: lack of regression; **B** grade 1: minimal regression –tumoral mass dominates fibrosis reaction; **C** grade 2: moderate regression –fibrosis dominates tumoral mass; **D** grade 3: good regression, difficulty finding scanty tumoral cells *(arrow)*

Microscopic tumoral parameters

To achieve a correct evaluation and an accurate diagnosis of rectal neoplasms, actual guidelines advise fulfilling a pro forma (Appendix A), because its use has been demonstrated to bring benefits and ensure more reproducibility to report the key features of the neoplasms [56].

Histological classification

Adenocarcinomas are the most frequent primary colorectal tumours and are graded on the extent of glandular appearances. The World Health Organization (WHO) recommends dividing them into (1) well-differentiated (lesions exhibiting glandular structures in >95% of the tumour), (2) moderately differentiated (adenocarcinoma has 50–95% glands), (3) poorly differentiated (adenocarcinoma has 5–50% glands) and (4) undifferentiated (<5% of tumour are glands structures). Grading is subjective, but the distinction between low-grade (well and moderate) vs. high grade (poor and undifferentiated) has been shown to be useful for prognosis [57]. It is suggested that grading should be based on the worst area, even if this does not predominate [58].

Besides adenocarcinomas, there are other histological types: mucinous adenocarcinoma (>50% of the lesion is composed of mucin), signet-cell carcinoma (tumour cells with prominent intracytoplasmic mucin), adenosquamous carcinoma, medullary carcinoma, spindle cell, small cell, and others.

Lymphatic, venous and perineural invasion

Lymphatic, venous and perineural invasion has shown to be of prognostic importance in rectal cancer [59, 60]. The pathologist must report the presence of neoplastic nests inside vascular and lymphatic lumen, paying special attention to the retraction artefacts produced by tissue processing. In some cases, immunohistochemistry to identify endothelial cells such CD31, CD34 or D2-40 can be used to distinguish them.

Tumour staging

Tumours are staged according to the following:

- Dukes and Bussey modification of the original Dukes classification of resection specimens is recommended, subdividing the tumours into A, B, C1 and C2, depending on tumour spread and presence of metastatic lymph nodes. If lymph nodes are positive, it is necessary to report the location of the node; if the lymph node involved is it the highest (the first located under the vascular tie).
- TNM; the T component of TNM is based on the depth of invasion:
  - T1: invasion of submucosa but not the muscularis propria
  - T2: invasion into but not through the muscularis propria
  - T3: invasion through the muscularis propria into subserosal adipose tissue and/or mesenteric fat. At our institution, depending on the extent of mesorectal invasion (<5 mm or ≥5mm), we subdivide T3 into T3ab (<5mm) and T3cd (≥5mm) because it has been shown to be an independent risk factor for recurrence in some studies [61, 62].
  - T4: subdivided in T4a when the tumour invades an adjacent organ and T4b if it invades though the serosa.

Surname: …… Forenames: …… Date of birth: ……

Hospital…… …… Hospital no: …… NHS no: ……

Date of receipt: …… Date of reporting: …… Report no: ……

Pathologist: …… Surgeon: …… Sex: ……

Specimen type: Total colectomy / Right hemicolectomy / Left hemicolectomy / Sigmoid colectomy / Anterior resection / Abdominoperineal excision / Other (state) ……

Gross description

Site of tumour ……

Maximum tumour diameter: ……mm

Distance of tumour to nearer cut end ……mm

Tumour perforation (pT4) Yes ☐ No ☐

If yes, perforation is serosal ☐ retro/infra peritoneal ☐

For rectal tumours:

Relation of tumour to peritoneal reflection (tick one):

Above ☐ Astride ☐ Below ☐

Plane of surgical excision (tick one):

Mesorectal fascia ☐

Intramesorectal ☐

Muscularis propria ☐

For abdominoperineal resection specimens:

Distance of tumour from dentate line..... mm

Histology

Type

Adenocarcinoma Yes ☐ No ☐

If No, other type .....

Differentiation by predominant area

Well / moderate ☐ Poor ☐

Local invasion

No carcinoma identified (pT0) ☐

Submucosa (pT1) ☐

Muscularis propria (pT2) ☐

Beyond muscularis propria (pT3) ☐

Tumour invades adjacent organs (pT4a) ☐

AND/OR

Tumour cells have breached the serosa (pT4b) ☐

Maximum distance of spread beyond muscularis propria ……mm

Response to neoadjuvant therapy

Neoadjuvant therapy given Yes ☐ No ☐ NK ☐

If yes:

No residual tumour cells / mucus lakes only ☐

Minimal residual tumour ☐

No marked regression ☐

Tumour involvement of margins

	N/A	Yes	No
Doughnuts	☐	☐	☐
Margin (cut end)	☐	☐	☐
Non-peritonealised 'circumferential' margin	☐	☐	☐

Histological measurement from tumour to non-peritonealised margin .....mm

Metastatic spread

No of lymph nodes present.....

No of involved lymph nodes.....

(pN1 1–3 nodes, pN2 4+ nodes involved)

Highest node involved (Dukes C2) Yes ☐ No ☐

Extramural venous invasion Yes ☐ No ☐

Histologically confirmed distant metastases (pM1):

Yes ☐ No ☐ If yes, site: ……

Background abnormalities: Yes ☐ No ☐

If yes, type: (delete as appropriate)

Adenoma(s) (state number ……)

Familial adenomatous polyposis / Ulcerative colitis / Crohn's disease / Diverticulosis / Synchronous carcinoma(s)

(complete a separate form for each cancer)

Other ..... ……

Pathological staging

Complete resection at all surgical margins

Yes (R0) ☐ No (R1 or R2) ☐

TNM (5th edition)

(y) pT …… (y) pN ……(y) pM ……

Dukes

Dukes A ☐ (Tumour limited to wall, nodes negative)

Dukes B ☐ (Tumour beyond M. propria, nodes negative)

Dukes C1 ☐ (Nodes positive and apical node negative)

Dukes C2 ☐ (Apical node involved)

Signature: …… **Date** …../…../…… **SNOMED Codes** T…… / M……

Appendix A Pro forma of the Royal College of Pathologist for colorectal cancer resections. Extracted from [62]

– N and M components of TNM are based on the lymph node and distant metastasis.

Conflict of interest The authors declare that they have no conflict of interest relating to the publication of this manuscript.

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