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Article

Determination of Tumor Location in Rectosigmoid Carcinomas: Difficulties in Preoperative Diagnostics

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Abstract: Differentiation between rectal and sigmoid carcinomas is a diagnostic challenge with important implications for further treatment. Depending on the tumor stage, treatment for rectal carcinoma consists of preoperative (chemo)radiotherapy and surgery. Sigmoid carcinomas are treated with surgery alone. We established the diagnostic accuracy of flexible endoscopy, MRI and/or CT scan, and both modalities combined as reflected by the conclusion of our multidisciplinary team (MDT). Furthermore, we assessed the treatment consequences of misdiagnosis. Consecutive patients were included who underwent surgery from January 2012 to January 2017 for colorectal carcinoma located ≤20 cm from the anal verge as determined by flexible colonoscopy. Diagnostic accuracy of MRI/CT, flexible endoscopy and the final MDT conclusion were analyzed as index test. The location of the tumor during surgery and the type of surgery was the reference standard. We included 293 patients. Flexible endoscopy had a diagnostic accuracy of 90% and for MRI/CT scanning this was 86–87%. Combination of both modalities improved diagnostic accuracy to 96%. Due to misdiagnosis during initial staging, three patients (1%) erroneously underwent neoadjuvant treatment and in two patients neoadjuvant treatment was potentially erroneously omitted. In conclusion, the combination of both flexible endoscopy and MRI/CT (the MDT conclusion) improves diagnostic accuracy. Erroneous clinical diagnosis can lead to under- and overtreatment.

Keywords: rectosigmoid carcinoma; abdominal surgery; multidisciplinary team

1. Introduction

Colorectal cancer is the third most commonly diagnosed cancer in males and the second in females [1]. During the workup for diagnosis and treatment of patients with colorectal carcinomas, rectosigmoid carcinomas are thoroughly discussed during multidisciplinary team (MDT) meetings due to the debatable location of the tumor [2]. All tumors from 0 to 15 cm distance from the anal verge are usually defined as "rectal carcinomas" and all tumors above 15 cm as (distal) sigmoid carcinomas [3]. Internationally there is no agreement about the exact border of rectal cancer [4]. There is often a discrepancy between the distance that is measured by endoscopy, CT/MRI scan and the final location of the tumor during surgery. Anatomically, the upper limit of the rectum is recognized by the splay of taeniae coli and by the absence of epiploic appendices, haustra, and a well-defined mesentery [5]. Radiographically, the sacral promontorium is generally regarded as the upper limit of the rectum. A line drawn from the promontory to the lowest border of the pubic bone forms the border on the MRI. All tumors below this line are radiologically called "rectal tumors." On flexible endoscopy, the upper

limit of the rectum is usually defined as 15 cm from the anal verge, but this distance might differ with examination [4].

Agreement on the definition of rectal cancer is necessary because it has a great influence on tumor staging and preoperative radiotherapy and/or chemotherapy. Depending on the tumor stage, preoperative (chemo)radiotherapy is part of rectal cancer treatment protocols, while resectable sigmoid cancer is treated by surgery alone and sometimes with adjuvant chemotherapy depending on the tumor stage [6].

The purpose of this study is twofold. First, to establish which diagnostic tool is best suited in order to distinguish between rectal and sigmoid cancer. Second, to investigate whether patients with sigmoid cancer had been misdiagnosed as having rectal cancer (or vice versa) and, as a result, received incorrect treatment. In order to achieve this we compared tumor localization measured by flexible endoscopy and radiographically imaging techniques (CT scan and/or MRI). As the gold standard, the tumor location during surgery and the following surgical procedure has been taken.

2. Results

2.1. Patients

In total 293 patients were included. Median age at the time of surgery was 69 (inter quartile range 63–76) and the majority of patients were male (62%, Table 1).

Table 1. Baseline characteristics and pre-treatment diagnostics.

Characteristic	*N* = 293
Age—years	
Median	69
IQ Range	63–76
Male sex—no. (%)	181 (62)
Colonoscopy	293 (100)
CT	293 (100)
MRI	229 (78)
MDT conclusion	
Rectum	220 (75)
Rectosigmoid	60 (21)
Sigmoid	13 (4)
Neoadjuvant treatment	
No neoadjuvant treatment	133 (45)
Radiotherapy, short (5 × 5)	72 (25)
Radiotherapy, long	5 (2)
Chemoradiotherapy	82 (28)
Chemotherapy	1 (0)
MDT advice regarding surgical procedure	
Sigmoidectomy	51 (17)
Anterior resection	14 (5)
Low anterior resection	183 (62)
APR/intersphinteric	34 (14)
APR/LAR	4 (1)

APR: abdominal perineal resection; LAR: low anterior resection.

2.2. Endoscopy

All 293 patients had pre-treatment diagnostic endoscopy with the distal border of the tumor located ≤20 cm from the anal verge (Figure 1). At endoscopy, the distal boundary of the tumor was located ≤15 cm from the anal verge in 223 patients and >15 cm in 70 patients, who were classified as having a rectal and sigmoid tumor, respectively (Table 2). Of the 223 patients with tumors ≤15 cm

from the anal verge, 212 had rectal resections and 11 had sigmoid resections (96% correctly diagnosed). Of the 70 patients with sigmoid tumors according to endoscopy, 52 had sigmoid resections and 18 had rectal resections (74% correctly diagnosed). This led to an overall diagnostic accuracy of endoscopy of 265 out of 294 patients (90%).

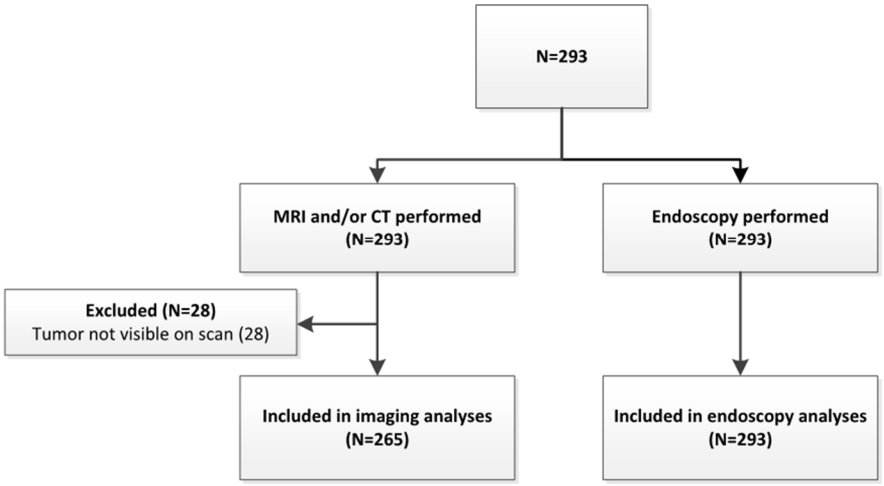

Figure 1. Flowchart for patients included in the analyses.

Table 2. Outcome of different diagnostic modalities in relation to surgical procedure.

Outcome Diagnostic Modality	Performed Resection		
	Sigmoid/Anterior Resection	LAR/APR/Intersphincteric	Total
CT/MRI (distal boundary from anal verge in cm) *			
≤15 cm	21	203	224
>15 cm	28	13	41
Total (%)	49	216	265 ‖
CT/MRI (relation tumor with os promontorium †			
Distal	31	212	243
Proximal	18	4	22
Total (%)	49	216	265 ‖
CT/MRI (relation tumor with mesorectal fascia) ‡			
yes	7	186	193
no	42	30	72
Total (%)	49	216	265 ‖
Endoscopy (distal boundary from anal verge in cm) ¶			
≤15 cm	11	212	223
>15 cm	52	18	70
Total (%)	63	230	293

* $p < 0.001$ (chi-square); † $p < 0.001$ (chi-square); ‡ $p < 0.001$ (chi-square); ¶ $p < 0.001$ (chi-square); ‖ 28 patients had non-visible tumors on CT and/or MRI.

2.3. Imaging

All patients underwent pre-treatment diagnostic CT scan and 229 out of 293 (78%) of patients also had a pre-treatment MRI scan. After discussion in the MDT meeting, 60 patients (21%) were classified as having a tumor located in the sigmoid, 13 (4%) in the rectosigmoid and 220 (75%) in the rectum. Based on the MDT meeting, 65 patients (22%) were diagnosed with sigmoid carcinomas and recommended to undergo a sigmoidectomy or an anterior resection (AR). A total of 228 patients were diagnosed with rectal carcinoma and recommended to undergo a low anterior resection (LAR), intersphincteric resection or abdominal perineal resection (APR) (Table 1). In total, 265/293 (90%) pre-treatment scans could be analyzed (224 MRI and 41 CT), since 28 patients were excluded due to a non-visible tumor (Figure 1).

In 224 out of 266 patients (84%), the tumor was located within 15 cm of the anal verge, as determined by MRI/CT, and classified as a rectal tumor. In 41 patients, the tumor was located >15 cm from the anal verge and classified as a sigmoid tumor. Of the 224 patients classified as having rectal tumors, 203 also had rectal resections, whereas 21 ultimately had a sigmoidectomy or AR (91% correctly diagnosed). Of 41 patients classified as having sigmoid tumors, 28 indeed had sigmoid resections and 13 had rectal resections (68% correctly diagnosed). Overall, the diagnostic accuracy of the distance $\leq$15 cm from the distal tumor boundary to the anal verge measured by CT/MRI was 231/265 (87%).

Out of 265 scans analyzed, 243 showed a lower border of the tumor below the os promontorium line (OPL) and 22 above the OPL. Therefore, 243 tumors (92%) were categorized as rectal tumors and 22 as sigmoid tumors. Of the 243 patients classified as having rectal tumors according to this definition, 212 had rectal resections, whereas 31 had sigmoidectomy or AR (87% correctly diagnosed). Of 22 patients classified as having sigmoid tumors, 18 had sigmoid resections and four had LAR/intersphincteric resection/APR (82% correctly diagnosed). This led to a diagnostic accuracy of the association of the tumor with the OPL, as determined by MRI/CT, of 230/265 (87%).

Relation of the tumor with the mesorectal fascia as determined by MRI/CT was present in 193 of 265 patients and absent in 72. As a result, 193 patients were diagnosed as having rectal tumors and 72 as having sigmoid tumors. Of the 193 patients diagnosed with rectal tumors, 186 had rectal resection and seven had sigmoid resections (96% correctly diagnosed). Of 72 patients with tumors without relation to the mesorectal fascia, 42 had sigmoid resections and 31 had rectal resection (58% correctly diagnosed). Based on these analyses, the accuracy of the association of the tumor with the mesorectal fascia, as determined by CT/MRI, was 228/265 (86%).

2.4. MDT Conclusion

Based on the MDT meeting, 220 patients were classified as having rectal tumors, 13 as having rectosigmoid tumors, and 60 as having sigmoid tumors (Table 3). Of the 220 patients classified as having rectal tumors, 216 underwent rectal resections for rectal cancers and four had sigmoid resections for a sigmoid carcinoma (98% correctly diagnosed by MDT as having rectal tumors). Of the 60 patients diagnosed with a sigmoid tumor, 52 (87%) had a sigmoid resection and eight ultimately had rectal resections. Of these misclassified patients, one underwent a LAR for a sigmoid carcinoma due to adhesions after a previously performed cystectomy, leading to 53/60 (88%) patients who were correctly diagnosed by the MDT as having sigmoid tumors. Therefore, the accuracy of the MDT to differentiate between rectal and sigmoid cancer was 269/280 (96%).

Table 3. Outcome of pre-treatment multidisciplinary team conclusion in relation to surgical procedure.

MDT Conclusion *	Sigmoid/Anterior Resection	LAR/APR/Intersphincteric	Total
Rectal	4	216	220
Rectosigmoid	7	6	13
Sigmoid	52	8	60
Total (%)	63	230	293

* $p < 0.001$ (chi-square).

2.5. Treatment

Neoadjuvant treatment was recommended by the MDT and applied in 160 patients. Neoadjuvant chemoradiotherapy or radiotherapy was the most frequently used treatment regimens (Table 1) [7,8]. The performed surgical procedure was a sigmoidectomy or AR in 63 patients (23%) and a LAR, intersphincteric resection, or APR in 230 (73%, Table 4). Outcomes of pathological staging are shown in Table 3.

Table 4. Surgical outcomes.

Characteristic	*N* = 293
Performed surgical procedure	
Sigmoidectomy	22 (8)
Anterior resection	41 (14)
Low anterior resection	184 (63)
Intersphincteric resection	10 (3)
Abdominal perineal resection	36 (12)
(y)pT-stage	
(y)pTis	6 (2)
(y)pT0	35 (12)
(y)pT1	37 (13)
(y)pT2	86 (29)
(y)pT3	122 (42)
(y)pT4	7 (2)
(y)pN-stage	
(y)pN0	202 (69)
(y)pN1	63 (22)
(y)pN2	28 (10)

2.6. Clinical Consequences of Misdiagnosis

Three out of four patients (75%) who were incorrectly classified as having rectal tumors during the pre-treatment MDT meeting received neoadjuvant treatment (all 5 × 5 Gy radiotherapy). Adjuvant therapy for sigmoid carcinoma was indicated in none of them (pT1N0, ypT2N0, ypT0N0 and ypT3N0).

Of the seven patients who were incorrectly classified by the MDT as having rectal tumors, four underwent pre-treatment MRI. Based on revision of these MRI scans, neoadjuvant (chemo)radiotherapy would not have been indicated in any of these cases. The remaining three patients did not receive a pre-treatment MRI scan, but based on post-treatment pathological outcome (pT3N2, pT2N1, and pT3N0), neoadjuvant therapy might have been indicated in two of them (i.e., pT3N2 and pT2N1).

Of the 13 patients classified as having rectosigmoid tumors by the MDT, six had a rectal and seven had a sigmoid resection. None of these patients underwent (neo)adjuvant therapy. Based on pretreatment MRI, neoadjuvant (chemo)radiotherapy would not have been indicated in any of these cases.

3. Discussion

Today, endoscopy is still the standard diagnostic tool for the first detection of colorectal cancer, used over 10,000 times a year in the Netherlands [9]. It is feasible, easy to perform, and has a low morbidity rate of 0.3% [10]. In the current study, however, endoscopy could not accurately distinguish distal sigmoid carcinomas from rectal carcinomas in one out of 10 patients. MRI and/or CT scan was accurate in 86–87% of cases, with the association of the tumor with the os promontorium line as the most accurate index test variable. Our study has shown that a combination of the two modalities improved diagnostic accuracy: the conclusion of the MDT was accurate in 96% of cases. These results are comparable to a previous smaller report with 128 patients that found an 88% concordance with endoscopy and 91% for radiological findings. However, in that study it was unclear how many patients mistakenly missed or received preoperative treatment because of diagnostic error [11].

The difficulty starts with the unspecified definition: what exactly is the upper border of the rectum? An overview of national and international guidelines underlines the various definitions of the rectum and the differences in the preferred method to define tumor location [4]. Recently, the European Society for Medical Oncology (ESMO) published revised guidelines on rectal cancer and now uses 0–15 cm as the rectal cancer border and rigid endoscopy as the preferred method to define tumor location [3]. However, endoscopy has a considerable error rate of 6.4% regarding tumor localization [12]. This could

result in an alteration of preoperative treatment or a change to another surgical procedure in 11% to 21% of the cases [13–15]. In the Netherlands, rectal carcinomas are treated differently than sigmoid carcinomas. Rectal carcinomas with positive lymph nodes and/or threatened resection margins on MRI are treated with preoperative therapy, but sigmoid carcinomas are not [6]. Therefore, a correct diagnosis made during the pre-treatment workup is vital.

Another difficulty is that the mesorectum can be very short, with a deep Douglas cave or peritoneal envelope. This can result in a prolapse position of the distal sigmoid under the promontory–pubic line. We call this the "sagging sock" situation; on an MRI or colonoscopy the tumor seems to be much more distal than it actually is. During surgery, the sigmoid is retracted and the tumor is much more proximal than suspected. As a result, a sigmoid resection or partial mesorectal excision (PME) is performed instead of a total mesorectal excision (TME). A complicating factor is that the os promontorium/pubic line does not match the peritoneal envelope that separates the intra- and extraperitoneal parts of the rectum. This means that the radiologist needs to focus more on the peritoneal envelope than on the line between the os promontorium and the os pubis. This had been studied and found feasible in the majority of CT scans [16].

It has been suggested that applying a rectal gel before MRI scan could be beneficial to stretch the distal rectum and detect the lower border of the tumor more accurately [17]. However, a 2012 consensus meeting of the European Society of Gastrointestinal and Abdominal Radiology does not recommend applying rectal gel routinely because the primary goal of an MRI is not to assess the endoluminal part of the tumor, but to assess the extent of transluminal growth [18]. It has not been described whether rectal gel is an advantage when measuring tumor distance.

Nowadays, MDT meetings are common practice in cancer care. Quality criteria for MDT meetings are drawn up in national guidelines; even the most straightforward cases should be discussed to limit the variation in treatment. Multidisciplinary management of colorectal cancer patients is associated with a more complete preoperative evaluation and results in a substantially higher level of compliance with protocols. Also, it improved access to multimodal therapy [19]. Furthermore, it increases the number of patients receiving neoadjuvant treatment [20]. At our institution, all colorectal cancer patients are discussed in a weekly MDT meeting. Here, we show the importance of combining all diagnostic tools and discussing the outcomes in a multidisciplinary setting to improve accuracy. We believe that most of the benefit of the MDT meeting is from discussing all measured parameters within a dedicated team. Combining each member's expertise, every case is discussed into detail using the national protocol as a guideline. In case the patient does not fit the guidelines, it is checked whether the patient fulfills the criteria for a clinical trial. The meeting allows all the persons present to participate in the discussion to reach a final conclusion. Combining all data and expertise is the strength of the MDT meeting. Despite this, a small number of patients were misdiagnosed. Four patients (2%) clinically diagnosed with rectal cancer were misdiagnosed, which resulted in three cases (1%) of incorrectly applied preoperative treatment. Seven patients were misdiagnosed with sigmoid cancer, of whom three patients (1%) should have received neoadjuvant treatment. In none of the cases did the patient receive preoperative treatment for supposed rectal cancer. Given the accuracy figures of only using endoscopy or MRI/CT, it is safe to conclude that without the MDT meetings these numbers would be significantly higher.

There are some limitations that must be considered when interpreting the results of our analysis. Firstly, this study is designed as a retrospective, observational study. Secondly, endoscopies were performed by a variety of gastroenterologists in our hospital and from referring centers. We cannot review the accuracy when measuring the distance from the anal verge, especially in overweight patients. Nonetheless, we feel that our analysis correctly reflects current clinical practice. CT scans were analyzed in the absence of MRI. It is unlikely that this influenced results, since the measurements can be performed on either MRI or CT. There is also a possibility that the use of neoadjuvant treatment influenced the location of the tumor, as previously determined during pre-treatment staging. Theoretically, this might have impacted the accuracy of the gold standard in patients treated

with neoadjuvant chemo(radio)therapy. Finally, in some centers there is a tendency not to give neoadjuvant treatment in patients with cancers more than 12 cm from the anal verge. However, tumor distances based on endoscopy alone can be inaccurate, as described earlier. It is important to combine radiologic and endoscopic findings and discuss these in the MDT meeting before deciding not to apply neoadjuvant treatment. Only during surgery does one know whether an accurate diagnosis was made, that is, staging the tumor as sigmoid or rectal cancer.

In conclusion, because of major treatment implications, it is very important to accurately differentiate between rectal and sigmoid carcinoma. In our large cohort of 295 patients, endoscopy seems to be the most accurate diagnostic tool. Accuracy is further improved by combining endoscopy and MRI/CT scans, whereby the results of both modalities are discussed in an MDT meeting, underlining the importance of a multidisciplinary approach. If the MDT cannot agree on the exact tumor location, such that there is an impact on pre-operative therapy, it is important to critically evaluate the diagnostic tools used. In this situation it can be helpful to use additional rigid endoscopy or diagnostic laparoscopy in order to determine the final diagnosis and ensure that the patient receives the best treatment.

4. Materials and Methods

4.1. Patients

All patients with a tumor distance from the anal verge $\leq$20 cm as measured by flexible colonoscopy or sigmoidoscopy between 1 January 2012 and January 2017 were included in this study. Data were drawn from the hospital database. This database hosts all colorectal cancer patients' data and is used to serve the Dutch ColoRectal Audit (DCRA). A cutoff distance $\leq$20 cm was used to make sure all proximal rectal carcinomas were included. All patients had a histologically proven left-sided distal colorectal adenocarcinoma; all patients with anal (squamous cell) carcinomas were excluded. All patients were the subjects of discussion in the MDT meeting and all underwent elective surgical resection by one of the three gastrointestinal surgeons at Reinier de Graaf Group teaching hospital in Delft, the Netherlands. Ethical approval was not required for this retrospective study using medical records, according to the Dutch Medical Treatment Contracts Act (WBGO).

4.2. Endoscopy

Endoscopy was performed pre-treatment by gastroenterologists from our center and referring centers. Records were reviewed to identify the distance of the tumor from the anal verge. The distance from the anal verge to the lowest border of the tumor was noted. Tumors from 0 to 15 cm from the anal verge were clinically defined as rectal carcinomas and tumors above 15 cm as (distal) sigmoid carcinomas. In cases of neoadjuvant (chemo)radiotherapy no additional endoscopy was performed.

4.3. Imaging

All patients had a pre-treatment abdominal CT scan for cancer staging. In general, patients with tumors located $\leq$15 cm from the anal verge also had a pre-treatment MRI scan. Pre-treatment MRI scans were used for the imaging analyses when available. When not available pre-treatment CT scans were analyzed instead. One expert gastrointestinal radiologist, who was blinded for the surgical outcome, reviewed raw imaging data from CT and MRI scans retrospectively to assess the radiological location of each tumor. MRI and CT scans were performed separately, but in the same preoperative period. Also, an MRI was taken six weeks after ending chemoradiation to evaluate the response of neoadjuvant chemotherapy.

The equipment used for MRI scans was a Philips MR Initial Achieva 3.0T or Philips 1.5T MRI (Philips, Best, the Netherlands) converted to a Smarthpath Conversion to D-stream 1.5R MRI. T2-weighted sequences were made in the sagittal, axial, and coronal plane. The equipment used for CT scans was a Philips Ingenuity Core 128 slices CT scanner (Philips, Best, the Netherlands) or Toshiba Aquillion One 320 slices CT scanner (Canon Medical Systems Europe BV, Zoetermeer, the Netherlands).

Patients were prepared with both oral and intravenous contrast and 5 mm slices were made in the axial, coronal, and sagittal plane. There was no contrast in the rectum for either the MRI or CT scan. The distance from the anal verge to the distal border of the tumor was described ($\leq$15 cm or not); it was noted if the tumor was beneath the imaginary line of os pubis/os promontorium, and the localization in relation to the mesorectum was described. Tumors located $\leq$15 from the anal verge, beneath the imaginary line of the os pubis/os promontorium or connected to the mesorectal fascia, were classified as rectal tumors in the different analyses.

4.4. Multidisciplinary Team Meeting

All patients were discussed in the MDT meeting, where definitive diagnosis was made based on the available diagnostic modalities. A specialized radiologist, gastroenterologists, colorectal surgeons, a nuclear medical specialist, a pathologist, radiation and medical oncologists, a geriatrician, physicians in training, and dedicated nurses attended the meeting. We compared this conclusion with the performed surgical procedure. Records were reviewed to check whether patients received preoperative radiotherapy and/or (adjuvant) chemotherapy. Preoperative neoadjuvant treatment started within one to two weeks of diagnosis.

4.5. Surgery

Surgical records were reviewed to identify the type of surgical procedure performed (sigmoidectomy, anterior resection, low anterior resection, (intersphincteric) abdominal perineal resection (APR)), whether a different procedure was performed than initially planned, or whether the tumor was located unexpectedly lower or higher in the rectum or sigmoid. All procedures were intended to be minimally invasive. In patients who did not have neoadjuvant treatment, surgery was performed within five weeks of diagnosis (Treek standard) or after six weeks when they were included in a special training program for patients older than 75 years or who needed rehabilitation before surgery. In patients treated with neoadjuvant chemo(radio)therapy, surgery was performed within two weeks after a short period of radiation and after 10–12 weeks of chemoradiation.

4.6. Histology

Patient records were reviewed to collect histological data. All tumors were histologically examined and the TNM stage was scored according to the Union for International Cancer Control TNM Cancer Staging, 5th edition [21]. In the presence of mesorectal fat, the circumferential margin was measured in mm.

4.7. Statistics

The diagnostic accuracy of MRI (or CT when no MRI was available), flexible endoscopy, and both modalities combined, as reflected by the conclusion of the MDT, was calculated. The performed surgical procedure was used as the reference (gold standard). Tumors treated with sigmoidectomy and anterior resection (AR) were classified as sigmoid carcinoma, whereas tumors treated with low anterior resection (LAR), resection or abdominal (intersphincteric) perineal resection (APR) were classified as rectal carcinoma. The number of patients correctly diagnosed by each modality was described. The relationships between distance from the anal verge as measured by colonoscopy, distance as measured by CT/MRI, and surgical location were examined using a chi-square test.

Statistical analyses were performed using Statistical Package for Social Sciences (SPSS, IBM, Chicago, IL, USA). A p-value < 0.05 was considered statistically significant.

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