Conventional CT for the Prediction of an Involved Circumferential Resection Margin in Primary Rectal Cancer

Steven V.R.C. Wolberink^{a, g} Regina G.H. Beets-Tan^b Danielle F.M. de Haas-Kock^c
Mark M. Span^e Eric J. van de Jagt^d Cornelis J.H. van de Velde^f Theo Wiggers^{a, g}

^aDepartment of Surgery, University Medical Center Groningen, Groningen; ^bDepartment of Radiology, University Hospital Maastricht; ^cDepartment of Radiation Oncology (MAASTRO), Research Institute GROW, University Hospital Maastricht, Maastricht; ^dDepartment of Radiology, University Medical Center Groningen; ^eOffice for Medical Technology Assessment, Groningen, and ^fDepartment of Surgery, Leiden University Medical Center, Leiden; ^gDepartment of Radiology, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands

Key Words

Rectum, computed tomography • Neoplasms • Rectal cancer surgery • Circumferential resection margin

Abstract

Purpose: To determine the accuracy of conventional computed tomography (CT) scan in the preoperative prediction of an involved circumferential resection margin (CRM) in primary rectal cancer. **Methods:** 125 patients with biopsy-proven adenocarcinoma of the rectum underwent CT of the abdomen before undergoing total mesorectal excision. Scans were scored by three observers, differing in experience. The main outcome was yes/no involvement of the CRM. Histology was taken as reference standard. **Results:** For the most experienced observer, observer A, sensitivity was 46.7% and specificity 92.6%. For observer B, sensitivity was 46.7% and specificity 89.5%. For the least experienced observer C, sensitivity was 43.3% and specificity 92.6%. Inter-observer variability was good between observers A and B (κ 0.648), B and C (κ 0.648), and intermediate between A and C (κ 0.542). Discrepancies occurred in a total of 34 patients; 25 had a CT scan of low technical quality, 10 an anteriorly located distal tumor.

Conclusion: Conventional CT scan lacks sensitivity for a clinical use in the preoperative assessment of an involved CRM in primary rectal cancer. Modern multislice spiral CT will probably resolve some of the problems of conventional CT; however, further research is needed to establish its role.

Copyright © 2007 S. Karger AG, Basel

Introduction

Successful treatment of primary rectal cancer means achieving a free circumferential resection margin (CRM). Total mesorectal excision (TME) is now the standard treatment, allowing recurrence rates below 10% [1–5]. In addition to TME, neoadjuvant treatment decreases the local recurrence rate even more to rates as low as 6% [6–15]. To assign the optimal neoadjuvant treatment strategy however, patients with rectal cancer high at risk of local recurrence need to be identified. The CRM is known to be one of the main risk factors in rectal cancer surgery [16]. A reliable prediction of the CRM by preoperative imaging is therefore important.

Recent publications have shown that MRI using phased-array coils can predict the CRM preoperatively with high accuracy [17–19].

Despite the widespread use of computed tomography (CT) in tumor staging, so far its role in the preoperative assessment of the CRM in rectal cancer staging has not been determined. In contrast to MRI, CT is more available, less expensive and less time-consuming. Furthermore, if CT would work for CRM assessment in rectal cancer patients, it would become a potential one-stop shop whole-body staging tool allowing accurate local and distant staging in one single examination.

The aim of this study is to investigate the accuracy of conventional CT for the prediction of an involved CRM in patients with primary rectal cancer.

Materials and Methods

The study was approved by the institutional review board.

Study Population

The study was performed on a retrospective basis. A cohort of patients was drawn from an existing database from the Dutch TME trial [9]. All 600 patients registered to have had a preoperative CT scan were included. All patients had a biopsy-proven, primary adenocarcinoma of the rectum, deemed primarily resectable on the basis of clinical evaluation, endoscopy and/or imaging. All patients underwent a conventional CT scan of the abdomen/pelvis before undergoing either surgery or radiotherapy. All patients underwent TME surgery performed by expert surgeons or surgeons trained by these experts to perform TME surgery. Pathologists were trained to dissect the resection specimen according to the protocol of Quirke et al. [20] and histopathological results were reviewed by a panel of supervising pathologists.

Imaging Techniques

The Dutch TME trial was a multicenter trial in which the imaging protocol was not standardized. The scans were therefore performed on different types of CT scanners and each participating hospital used its own protocol and indications for abdominal/pelvic imaging. Sections were obtained in a range of 5–15 mm with an average of 8.97 mm. All scans were made using intravenous contrast administration and a total of 81 patients had rectal contrast administered (table 1).

Image Evaluation

In daily practice, primary rectal cancer will mostly be treated by radiotherapists and surgeons. Both these specialties will feel the need to be able to easily interpret the preoperative imaging. A member of both these specialties was therefore chosen as observer, along with a radiologist as reference observer. Images were therefore retrospectively evaluated on film by a radiologist (A), radiotherapist (B) and a surgeon (C), all acknowledged experts in the field of rectal cancer and working in different hospitals. Each

Table 1. Imaging techniques

Sections	Patients	IV contrast	Rectal contrast	Helical
5 mm	16	16	10	16
6 mm	3	3	0	3
7 mm	14	14	13	14
8 mm	9	9	4	9
10 mm	77	77	51	60
12 mm	2	2	0	0
15 mm	4	4	3	0
Total	125	125	81	102

observer had a different level of experience, observer A as an expert on reading both pelvic CT and MRI being the most experienced reader of pelvic and/or abdominal CT scans (having read approx. 5,000 scans), observer B intermediate (having read approx. 2,000 scans) and observer C the least experienced reader (having read approx. 500 scans). All three observers assessed the scans individually and were blinded for each other's and histological results and any other patient data. None of the observers was treating physicians of the patients, and none had previous knowledge of any patient data prior to reading the images.

The scans were scored using a standardized scoring form, in which technical data were registered. The main outcome parameters were yes/no tumor involvement of the mesorectal fascia. The direction of the tumor penetration through the rectal wall was recorded as it is this direction which determines the shortest distance from the tumor to the mesorectal fascia (the CRM). In addition, the distance to the anal verge of the tumor and sites of extramesorectal growth were registered. For the prediction of the involvement, the direction of an involved fascia and the infiltration of mesorectal fat, the following confidence levels were scored: 0 = definitely not, 1 = probably not, 2 = possibly so, 3 = probably so, and 4 = definitely so.

Analysis and Statistics

The distance from the tumor to the mesorectal fascia on pathology was taken as the reference standard against which the CT findings were compared. Overall accuracy, sensitivity and specificity of the prediction of involvement of the CRM were calculated using cross-tabulation statistics. Receiver operating characteristic (ROC) analysis for the prediction of an involved mesorectal fascia were performed on the data generated by the confidence level scoring of the three observers. For each observer the accuracy of the CT for the prediction of an involved CRM was measured by calculating the area under the curve (AUC). Differences in accuracy between the observers were evaluated by a pairwise comparison of their respective areas under the ROC curve. The inter-observer agreement was measured using the linear weighted κ statistic by pairwise comparison of the accuracy of the three observers for the prediction of an involved CRM. Statistical analysis was performed using the software package SPSS® for Windows Version 11.0 (SPSS, Chicago, Ill., USA).

Table 2. Distribution of positive and negative CRM

			CRM neg	CRM pos	Total (%)
pT0	N0	M0	2	–	2 (1.6)
pT1	N0	M0	3	–	3 (2.4)
pT2	N0	M0	28	–	28 (22.4)
pT2	N1	M0	5	–	5 (4.0)
pT2	N1	M1	1	–	1 (0.8)
pT3	N0	M0	31	8	39 (31.2)
pT3	N1	M0	20	9 ¹	29 (23.2)
pT3	N1	M1	3	5 ²	8 (6.4)
pT4	N0	M0	1	–	1 (0.8)
pT4	N0	M1	–	1	1 (0.8)
pT4	N1	M0	1	5	6 (4.8)
pT4	N1	M1	–	2 ³	2 (1.6)
			95 (76%)	30 (24%)	

¹ Two of these 9 patients had a positive CRM due to a positive lymph node.

² One of these 5 patients had a positive CRM due to a positive lymph node.

³ One of these 2 patients had a positive CRM due to a positive lymph node.

Results

Patients

The study population consisted of 125 patients: 90 male (72%) and 35 female (28%). The age of the patients ranged between 32 and 87 with a median age of 64. The study population was a good representation of the population of the TME trial [9], in age and sex as well as in distribution of T stage.

TNM Stage

There were 2 T0 tumors, 3 T1 tumors, 34 T2 tumors, 76 T3 tumors and 10 T4 tumors. Table 2 shows the histological TNM classification of the tumors and the histological CRM assessment: free (e.g. CRM neg) or involved (CRM pos).

Prediction of Involved CRM per Observer

All three observers made 125 predictions. Thus, a total of 375 predictions were made, of which 73 were incorrect (19.5%) and 302 correct (80.5%).

Observer A was correct in 14/30 patients with positive margins and in 88/95 patients with negative margins. Observer B was correct in 14/30 patients with a positive margin and 85/95 patients with a negative margin. Observer C was correct in 13/30 patients with a positive margin and 88/95 patients with a negative margin. The sen-

Table 3. Sensitivity and specificity per observer for prediction of involved CRM

	Observer A	Observer B	Observer C
Sensitivity, %	46.7	46.7	43.3
Specificity, %	92.6	89.5	92.6

sitivity and specificity for the prediction of an involved CRM per observer are given in table 3.

Inter-Observer Agreement

Inter-observer agreement for prediction of an involved CRM was high between observer A and observer B (κ 0.648), intermediate between observer A and observer C (κ 0.542), and high between observer B and observer C (κ 0.648).

Analysis of Predicted Involvement of CRM

If the confidence level of the prediction of each individual observer is taken into account, there is a rise in the specificity as confidence of the predictions increases for all three observers, as illustrated by the receiver operating curves in figures 1–3. This ROC analysis also shows that the AUC, and thus the overall accuracy is greatest for observer A (the most experienced reader) at 0.813 and the least for observer C (the least experienced reader) at 0.697.

Discussion

Conventional CT scan shows a low sensitivity but high specificity in the preoperative prediction of an involved CRM. An experienced reader performs better than a less experienced reader.

Based on the National Guidelines the main choice before the surgical treatment of rectal cancer is between short-course and long-course radiotherapy. The last one aiming on downsizing and downstaging. Preoperative assessment of the involved circumferential margin should primarily focus on a high sensitivity. A relatively low specificity results in some overtreatment with long-course radiotherapy and is less worse than under treatment in case of an involved margin.

Accuracy of the Prediction of an Involved CRM

Discrepancies between predicted CRM and histology occurred in 34 patients. In 25 of these 34 patients, all

Fig. 1. Receiver operating curve, cut-off points are for a positive prediction by observer A at confidence level definitely not, probably not, possibly so, probably so, and definitely so, respectively.

Fig. 2. Receiver operating curve, cut-off points are for a positive prediction by observer B at confidence level definitely not, probably not, possibly so, probably so, and definitely so, respectively.

Fig. 3. Receiver operating curve, cut-off points are for a positive prediction by observer C at confidence level definitely not, probably not, possibly so, probably so, and definitely so, respectively.

Fig. 4. Example of a CT scan in which all three observers predicted a non-involved CRM. Histology however showed an involved CRM.

three observers judged the CT scan difficult to interpret due to limited spatial resolution. The main reason for the lack of sensitivity therefore seems to be of a technical nature. Most CT protocols in this study made use of thick slices (>8 mm). Therefore, the spatial resolution of the scans were too low to make any reliable predictions on margin involvement.

Most false-negatives also occurred in patients who had a distal tumor located on the anterior side of the mesorectum with a threatened margin anteriorly. In these false-negative cases the margins were often involved only by subtle tumor stranding. Because of the inherent lack of contrast resolution of CT and the insufficient spatial resolution of conventional CT techniques in this study, these tumor strands were not visualized on the CT and therefore missed by all observers (fig. 4).

Second, many disagreements between CT and histology occurred on where the tumor exactly penetrates the bowel wall. The exact location of the site of tumor penetration is essential when the site of the closest CRM has to be anticipated, because it is at this site where the mesorectal fascia should be scrutinized for any possible invasion by tumor stranding. Again, the very low contrast resolution of conventional CT prevents clear distinction between the bowel wall and tumor tissue, making it very difficult to predict the site of bowel wall penetration, resulting in misinterpretations of the site of margin involvement.

MRI being superior to CT in contrast resolution and offering simultaneous imaging in different planes can better distinguish between tumor tissue and rectal wall and is expected to perform better than CT for predicting involvement of the CRM in this specific group of distal rectal cancer. Modern state-of-the-art multislice spiral CT (MSCT) however might probably do better than conventional CT, given the ability to reconstruct thinner sections and to optimally time the bolus contrast, leading not only to an improved spatial but also to an improved contrast resolution. In addition, MSCT offers reconstructions in multiple planes (multiplanar reconstruction) thus allowing an assessment of the rectal tumor in any given plane, analog to MRI. Therefore it seems justified to investigate the role of MSCT in rectal cancer staging, because if MSCT would work, it would become a potential one-stop shop whole-body staging tool allowing accurate local and distant staging in one single examination.

Conclusion

Conventional CT scan lacks sensitivity for a clinical use in the preoperative assessment of an involved CRM in primary rectal cancer. Modern MSCT will probably resolve some of the problems of conventional CT; however, further research is needed to establish its role.

References

- 1 Heald RJ, Husband EM, Ryall RDH: The mesorectum in rectal surgery: The clue to pelvic recurrence? *Br J Surg* 1982;69:613–606.
- 2 Havenga K, Enker WE, Norstein J, Moriya Y, Heald RJ, van Houwelingen HC, et al: Improved survival and local control after mesorectal excision or D3 lymphadenectomy in the treatment of primary rectal cancer: an international analysis of 1,411 patients. *Eur J Surg Oncol* 1999;25:368–374.
- 3 MacFarlane JK, Ryall RDH, Heald RJ: Mesorectal excision for rectal cancer. *Lancet* 1993; 341:457–460.
- 4 Enker WE, Thaler HT, Cranor ML, Polyak T: Total mesorectal excision in the operative treatment of carcinoma of the rectum. *J Am Coll Surg* 1995;181:335–346.
- 5 Aitken RJ: Mesorectal excision for rectal cancer. *Br J Surg* 1996;83:214–216.
- 6 Colorectal Cancer Collaborative Group: Adjuvant radiotherapy for rectal cancer: a systematic overview of 8,507 patients from 22 randomised trials. *Lancet* 2001;358:1291–1303.
- 7 Investigators Swedish Rectal Cancer Trial: Improved survival with preoperative radiotherapy in resectable rectal cancer. *N Engl J Med* 1997;336:980–987.
- 8 Marijnen CAM, Glimelius B: The role of radiotherapy in rectal cancer. *Eur J Cancer* 2002;38:943–952.
- 9 Kapiteijn E, Marijnen CAM, Nagtegaal ID, Putter H, Steup W, Wiggers T, et al: Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med* 2001;345:638–646.
- 10 Marijnen CAM, Nagtegaal ID, Kapiteijn E, Klein-Kranenberg E, Noordijk EM, van Krieken HJM, et al: Radiotherapy does not compensate for positive resection margins in rectal cancer patients. Radiotherapy in rectal cancer. Thesis. ISBN 9090156356:91–103.
- 11 Marijnen CAM, Nagtegaal ID, Klein-Kranenberg E, Hermans J, van de Velde CJ, Leer JW, et al: No downstaging after short-term pre-operative radiotherapy in rectal cancer patients. *J Clin Oncol* 2001;19:1976–1984.
- 12 Glimelius B, Isacson U: Preoperative radiotherapy for rectal cancer – is 5 × 5 Gy a good or a bad schedule? *Acta Oncol* 2001;40:958–967.
- 13 Steele RJ, Sebag-Montefiore D: Adjuvant radiotherapy for rectal cancer. *Br J Surg* 1999; 86:1233–1234.
- 14 Medical Research Council Working Party: Randomised trial of surgery alone versus surgery followed by radiotherapy for mobile cancer of the rectum. *Lancet* 1996;348:1610–1614.
- 15 Krook JE, Moertel CG, Gunderson LL, Wieand HS, Collins RT, Beart RW, et al: Effective surgical adjuvant therapy for high-risk rectal carcinoma. *N Engl J Med* 1991; 324:709–715.
- 16 Nagtegaal ID, Marijnen CA, Kranenbarg EK, van de Velde CJ, van Krieken JH: Circumferential margin involvement is still an important predictor of local recurrence in rectal carcinoma: not one millimeter but two millimeters is the limit. *Am J Surg Pathol* 2002;26:350–357.
- 17 Beets Tan RGH, Beets GJ, Vliegen RFA, Kessels AG, Van Boven H, De Bruine A, et al: Accuracy of MRI in prediction of tumor free resection margin in rectal cancer surgery. *Lancet* 2001;357:497–504.
- 18 Brown G, Richards CJ, Newcombe RG, Dalimore NS, Radcliffe AG, Carey DP, et al: Rectal carcinoma: thin section MR imaging for staging in 28 patients. *Radiology* 1999; 221:215–229.
- 19 Lahaye MJ, Engelen SM, Nelemans PJ, Beets GL, van de Velde CJ, van Engelshoven JM, et al: Imaging for predicting the risk factors – the circumferential resection margin and nodal disease – of local recurrence in rectal cancer: a meta-analysis. *Semin Ultrasound CT MR* 2005;26:259–268.
- 20 Quirke P, Durdey P, Dixon MF, Williams NS: Local recurrence of rectal adenocarcinoma due to inadequate surgical resection. Histopathological study of lateral tumour spread and surgical excision *Lancet* 1986;ii:996–999.