

## PDF hosted at the Radboud Repository of the Radboud University Nijmegen

The following full text is a publisher's version.

For additional information about this publication click this link.

<http://hdl.handle.net/2066/185393>

Please be advised that this information was generated on 2022-08-09 and may be subject to change.

# Macroscopic Evaluation of Rectal Cancer Resection Specimen: Clinical Significance of the Pathologist in Quality Control

By Iris D. Nagtegaal, Cornelis J.H. van de Velde, Erik van der Worp, Ellen Kapiteijn, Phil Quirke, and J. Han J.M. van Krieken and the Pathology Review Committee for the Cooperative Clinical Investigators of the Dutch Colorectal Cancer Group

**Purpose:** Quality assessment and assurance are important issues in modern health care. For the evaluation of surgical procedures, there are indirect parameters such as complication, recurrence, and survival rates. These parameters are of limited value for the individual surgeon, and there is an obvious need for direct parameters. We have evaluated criteria by which pathologists can judge the quality or completeness of the resection specimen in a randomized trial for rectal cancer.

**Patients and Methods:** The pathology reports of all patients entered onto a Dutch multicenter randomized trial were reviewed. All participating pathologists had been instructed by workshops and videos in order to obtain standardized pathology work-up. A three-tiered classification was applied to assess completeness of the total mesorectal excision (TME). Prognostic value of this classification was tested using log-rank analysis of

Kaplan-Meier survival curves using the data of all patients who did not receive any adjuvant treatment.

**Results:** Included were 180 patients. In 24% (n = 43), the mesorectum was incomplete. Patients in this group had an increased risk for local and distant recurrence, 36.1% v 20.3% recurrence in the group with a complete mesorectum (P = .02). Follow-up is too short to observe an effect on survival rates.

**Conclusion:** A patient's prognosis is predicted by applying a classification of macroscopic completeness on a rectal resection specimen. We conclude that pathologists are able to judge the quality of TME for rectal cancer. With this direct interdisciplinary assessment instrument, we establish a new role of the pathologist in quality control.

*J Clin Oncol* 20:1729-1734. © 2002 by American Society of Clinical Oncology.

FOR MANY YEARS, pathology has had an important role in the medical audit. There has always been a strong focus on autopsies, but also in surgical pathology the interaction between clinician and pathologist has quality-control aspects (often implicit). In many aspects of medical care, new quality assessment instruments are being developed and tested. Treatment processes are being optimized, standardized, and evaluated to provide evidence-based treatment.

Because the surgeon is a key factor in prevention of the development of local recurrence of rectal cancer,<sup>1,2</sup> various studies have been performed to evaluate the effectiveness of surgical treatment for rectal cancer.<sup>3-7</sup> Perioperative mortality,<sup>4,6</sup> rate of complications,<sup>6</sup> number of local recurrences,<sup>5,6</sup> and 5-year survival<sup>3-7</sup> are often used for quality assessment.

The value of these parameters, however, is often limited because of the large numbers of patients per surgeon and the long follow-up periods needed for reliable data. Therefore, these indirect parameters are of limited value for the individual surgeon. Subsequent changes in practice also take a long time before they can be evaluated, reducing our ability to implement therapy improvement rapidly. Direct evaluation of the result of surgery is potentially much more informative for a surgeon. Recently, we and others<sup>2</sup> showed that an optimal surgical technique is of utmost importance in the treatment of rectal cancer, because a decrease in local recurrence rates from 22%<sup>9</sup> to 8%<sup>8</sup> can be reached.

Total mesorectal excision (TME) has become the surgical treatment of choice,<sup>2</sup> instead of the conventional surgery performed in the past, consisting of partial blunt dissection of the rectum along the presacral fascia cone-wise directed towards the rectal wall. A package around the tumor consisting of a mesorectal fat envelope is created by precise sharp dissection within the true pelvis.<sup>1</sup> Quality control of this procedure can be achieved using the completeness of this mesorectal envelope as a parameter.<sup>10</sup> Both the resection specimen as a whole and the sliced tumor will provide useful information about the completeness of excision. Serious damage to the mesorectal cylinder is an indication of incomplete excision of the tumor and consequently increases the risk of local recurrence. We have shown

---

*From the Departments of Pathology and Surgery, Leiden University Medical Center, Leiden, and Department of Pathology, University Medical Center St Radboud, Nijmegen, the Netherlands; and Department of Pathology, University of Leeds, Leeds, United Kingdom.*

*Submitted July 31, 2001; accepted December 14, 2001.*

*Supported by a grant ontwikkelingsgeneeskunde OWG 97/026 from the National Health Council, Amstelveen, the Netherlands.*

*Address reprint requests to Iris D. Nagtegaal, MD, Department of Pathology, University Medical Center St Radboud, PO Box 9101, 6500 HB Nijmegen, the Netherlands; email: i.nagtegaal@pathol.azn.nl.*

*© 2002 by American Society of Clinical Oncology.*

*0732-183X/02/2007-1729/\$20.00*

previously that careful assessment of the circumferential margin (CRM) is a strong instrument with which to predict local recurrence.<sup>11-13</sup> However, there are still many local recurrences that cannot be explained by circumferential margin involvement. We hypothesize that, in addition to an assessment of the CRM, routine determination and reportage of the quality of the mesorectum might improve the prognostic value of the pathologic work-up and eventually improve the quality of the surgical technique.

In the Dutch trial of radiotherapy plus TME, standardization of treatment for rectal cancer was achieved.<sup>8</sup> We evaluated the quality of the mesorectal excision of the patients treated in this trial by examining the resection specimen on arrival at the pathology department. Direct observations by pathologists are described in the pathology reports provided. We report that in the majority of cases pathologists can perform an assessment of the quality of TME surgery and that the result is clinically relevant.

## PATIENTS AND METHODS

### Study Population

Patients were selected from a large multicenter trial, the radiotherapy plus TME trial, in which 1,530 Dutch patients were included from January 1996 through December 1999. This prospectively randomized trial evaluated TME surgery with or without preoperative radiotherapy ( $5 \times 5$  Gy). Patients with a clinically resectable adenocarcinoma of the rectum were included in this study, and were subsequently randomized to radiotherapy followed by TME or TME alone. Radiotherapy, surgical, and pathologic procedures were standardized and quality controlled.<sup>14</sup> Follow-up of all patients was conducted according to the trial protocol for at least 36 months. Outcome measures included local and distant recurrences. These were confirmed by radiographic imaging and histologic diagnosis.

### Patient Selection

For the current study, we analyzed the data of the nonirradiated patients in the trial. The following patient groups were also excluded from the analysis: no rectal adenocarcinoma ( $n = 10$ ), previous other malignancy ( $n = 11$ ), no resection ( $n = 3$ ), and distant metastases at operation ( $n = 28$ ). We analyzed the data of all 180 patients for whom detailed descriptions of the specimen were present in the pathology report. The median follow-up of the patients in this selection was 25.8 months.

### TME Surgery

All patients underwent surgery according to the principle of TME, as has been described before.<sup>1,9</sup> To guarantee a standard surgical operation technique within the trial, instructor surgeons supervised the first five operations by any surgeon.

### Pathologic Procedures

Standardized routine pathology examination was performed in the pathology laboratories of the referring hospitals using the protocol of Quirke et al.<sup>11</sup> Participating pathologists were trained in this technique

by studying videos and newsletters and attending workshops. A pathology review committee was installed to evaluate the pathologic work-up. Together with the pathology quality manager,<sup>13</sup> they ensured constant quality of the pathology data and procedures.

On arrival at the laboratory, the completeness of the specimen was evaluated using the definitions as described below. Pathologists from the referral hospital recorded pathologic information of the resected tumor on a standard form for all patients. Photographic documentation of the resection specimen was required. The resection specimen was photographed at the moment of arrival at the pathology laboratory, and after fixation, inking, and slicing, the coronal sections were subsequently photographed. However, the quality of the images obtained was not sufficient to judge the completeness of the mesorectum reliably. Careful examination of the CRM and investigation of tumor invasion of the bowel wall and surrounding tissue were performed. The largest diameter of the tumor was registered after fixation of the specimen. The specimens were examined for the presence of lymph nodes, and all lymph nodes found were processed for microscopic investigation.

### Macroscopic Judgment of the Resection Specimen

The quality of the mesorectum was determined using pathology reports and scored using three grades:

- Complete: intact mesorectum with only minor irregularities of a smooth mesorectal surface. No defect is deeper than 5 mm, and there is no coning toward the distal margin of the specimen. There is a smooth circumferential resection margin on slicing (Fig 1A and 1B).
- Nearly complete: 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 the insertion of the levator muscles.
- Incomplete: little bulk to mesorectum with defects down onto muscularis propria and/or very irregular circumferential resection margin (Fig 1C and 1D).

### Data Collection and Statistics

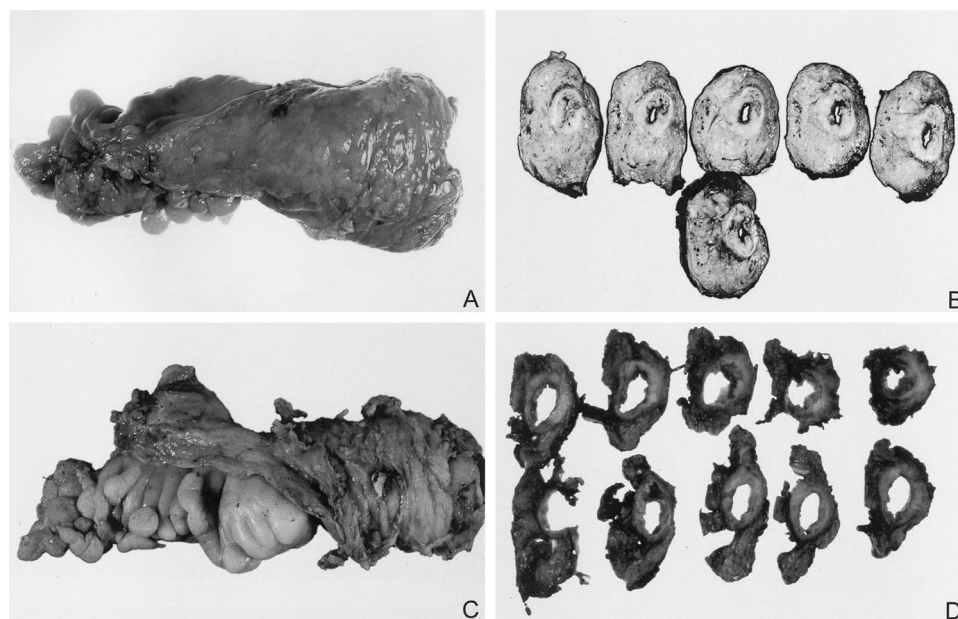
All case record forms were sent to the central data office at the surgery department of the Leiden University Medical Center in Leiden. The data were checked and entered onto a database and analyzed with the SPSS package (Statistical Product and Service Solutions 9.0 for Windows; SPSS, Inc, Chicago, IL).

Relations between various parameters were analyzed using Mann-Whitney and Kruskal-Wallis nonparametric testing procedures. Univariate survival analyses of time to local recurrence, distant metastasis, or death were performed using the Kaplan-Meier method, with the time of surgery as the entry date. Differences in observed survival between groups were tested for statistical significance using log-ranks tests. Multivariate analysis was performed using the forward stepwise elimination method in the Cox proportional hazards regression model;  $P \leq .05$  was considered statistically significant.

## RESULTS

### Patient Characteristics

From the 180 patients for whom information was available about the quality of the mesorectum in the reports, 102 specimens (56.6%) were classified as complete, 35 (19.4%) as nearly complete, and 43 (23.9%) as incomplete mesorec-



**Fig 1.** Illustrations of the definitions used to judge resection specimens. (A and B) Complete mesorectum, with (A) no defects, no coning and (B) smooth circumferential margin. (C and D) Incomplete mesorectum with (C) deep defects and (D) very irregular circumferential margin.

tum (Table 1). The distance of the tumor from the anal verge is strongly associated with quality of the mesorectum. Lower tumors (distal border  $\leq 5$  cm from the anal verge) showed only 39% complete excision, compared with 67% in the group of tumors located more than 10 cm from the anal verge. There is also a related difference regarding the operative technique: abdominoperineal resections showed a complete mesorectum in 34% compared with 73% in the group in which a low anterior resection was performed. There was no relation between age and sex of the patients and the quality of the resection specimen.

#### *Relation With Circumferential Margin Involvement*

Forty-one patients had a positive resection margin, defined as tumor cells within 1 mm of the inked resection margin. In patients with a positive resection margin, 44% of the specimens were incomplete, compared with 11% in the patients with margins greater than 1 cm ( $P < .001$ ) (Table 2). Both lateral tumor extension and positive lymph nodes present in the resection margin can cause a positive margin. In 44% of the tumor, node, metastases (TNM) stage III patients in whom margin involvement was determined by the primary tumor, the mesorectum was incomplete. This is significantly higher than in patients with a negative margin (24%,  $P < .05$ ). No such difference was found in patients in whom the margin was determined by a positive lymph node: 25% had an incomplete mesorec-

tum (CRM-positive) compared with 23% in patients with a negative margin ( $P = .46$ ).

#### *Clinical Implication*

We did not observe any difference in prognosis between the groups with complete and nearly complete mesorectum, and we combined these groups for further analyses. Overall recurrence rates were worse in the group with incomplete mesorectum at 2-year follow-up. In the group with an incomplete mesorectum, the overall recurrence rate after 2-year follow-up was 35.6% compared with 21.5% in the group with a nearly complete mesorectum ( $P = .01$ ) (Fig 2). This could be attributable mainly to the local recurrences (15.0% v 8.7%), although this difference was not significant. No difference was found in survival rates (76% v 86%,  $P = .10$ ).

As mentioned before, incomplete resection leads to more positive margins, but in patients with a positive resection margin, there was no added value of the quality assessment of surgery on prognosis ( $P = .97$ ). However, in patients with a negative resection margin, the overall recurrence rate was increased in the group with incomplete mesorectum (28.6% v 14.9%,  $P = .03$ ), so determination of the quality of the mesorectum does have additional value in patients without CRM involvement (Fig 3). Both local recurrence (11.4% v 5.5%,  $P = .09$ ) and distant recurrence (19.2% v 12.2%,  $P = .11$ ) contributed to this effect. Survival rates

**Table 1. Patient Characteristics for the Different Groups**

	Total No. (N = 180)	Complete (n = 102) (%)	Nearly Complete (n = 35) (%)	Incomplete (n = 43) (%)	P
Sex					.87
Men	117	58.1	18.8	23.1	
Women	63	54.0	20.6	25.4	
Age, years					.90
Mean	64.2	64.0	64.9	64.1	
Range	37-85	38-83	37-84	45-85	
Operation type					< .001
LAR	102	72.5	12.7	14.7	
Hartmann	8	50.0	12.5	37.5	
APR	70	34.3	30.0	35.7	
Tumor location					.007
< 5 cm	61	39.3	32.8	27.9	
5-10 cm	74	64.9	10.8	24.3	
> 10 cm	42	66.7	16.7	16.7	
Unknown	3				
Tumor size, cm					.15
Mean	4.8	4.6	5.2	5.0	
Median	4.5	4.5	5.0	4.5	
Invasion depth					.13
T1	9	55.6	33.3	11.1	
T2	50	68.0	14.0	18.0	
T3	110	53.6	20.0	26.4	
T4	11	36.4	27.3	36.4	
Nodal status					.35
N0	97	59.8	20.6	19.6	
N+	83	53.0	18.1	28.9	

NOTE. Differences were tested with the Kruskal-Wallis test. Data are presented in percentages, except for age (years) and tumor size (cm). Abbreviations: LAR, low anterior resection; APR, abdominoperineal resection.

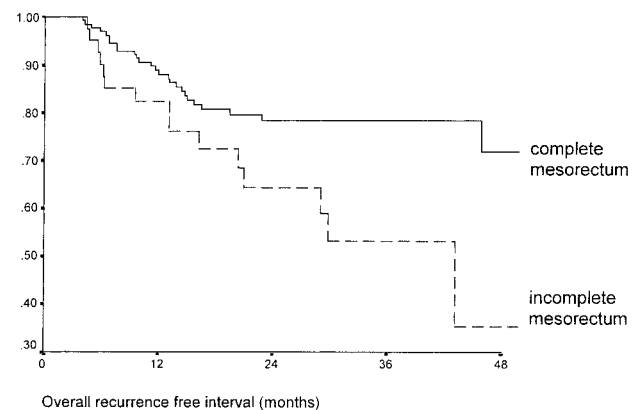
were different between the groups: 90.5% in the patients with a complete mesorectum *v* 76.9% in the patients with an incomplete mesorectum ( $P < .05$ ) (Fig 4).

## DISCUSSION

Our data show that evaluation of the mesorectum by pathologists has prognostic implication: recurrence occurs more often in patients with an incomplete mesorectum. This is only partly explained by the higher frequency of positive resection margin in this patient group. Indeed, we also show that in CRM-negative patients, the determination of the

quality of surgery provides additional prognostic information. Quality of surgery and margin involvement are separate but related issues.

The assessment of the quality of the resection specimen (ie, surgical performance) can be helpful in the determina-



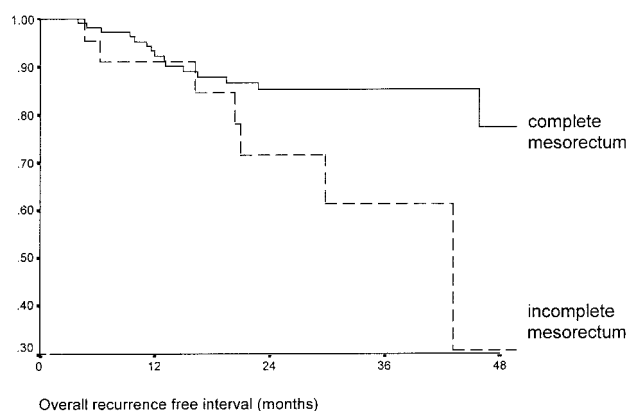
**Fig 2. Relation of completeness of mesorectal excision with overall recurrence rates. Patients with a complete mesorectum show significantly lower overall recurrence rates than patients with an incomplete mesorectum ( $P = .01$ ). Log-rank testing was used.**

**Table 2. Relation Between Completeness of the Mesorectum and Circumferential Margin Involvement**

CRM (cm)	No.	Complete (%)	Nearly Complete (%)	Incomplete (%)
≤ 0.10	41	26.8	29.3	43.9
0.11-0.20	18	50.0	22.2	27.8
0.21-0.50	36	52.8	19.4	27.8
0.51-1.00	31	71.0	16.1	12.9
> 1.00	54	75.9	13.0	11.1

NOTE. Significantly more incomplete mesorectums were present in the group of patients with positive margins (Kruskal-Wallis test,  $P < .001$ ).

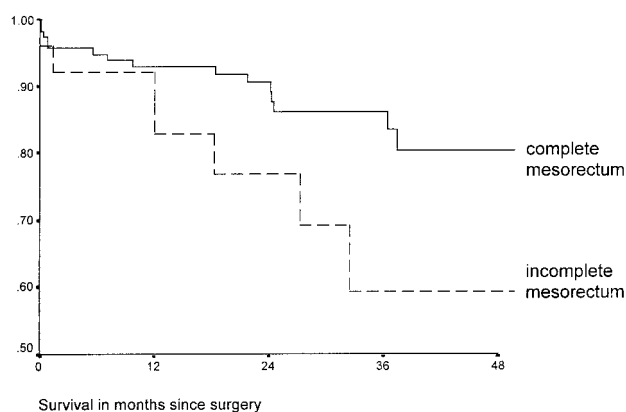




**Fig 3. Clinical implications of quality assessment in patients with negative resection margins.** Patients with a complete mesorectum show lower overall recurrence rates than patients with an incomplete mesorectum ( $P = .03$ ). Log-rank testing was used.

tion of the cause of margin involvement, because margin involvement is not per se a sign of poor surgery, but might be a reflection of advanced tumor growth. In small tumors confined to the muscularis propria without lymph node involvement (TNM stage I), margin involvement is only possible when the mesorectum is incompletely excised. In the current series, in only one patient with a TNM stage I tumor was the margin positive. The mesorectum in this case was indeed classified as incomplete, demonstrating that poor surgery can lead to positive margins even in small tumors.

In advanced tumors, a positive margin can be because of either the tumor characteristics or incomplete surgery. In the



**Fig 4. Clinical implications of quality assessment in patients with negative resection margins.** Patients with a complete mesorectum show higher survival rates than patients with an incomplete mesorectum ( $P < .05$ ). Log-rank testing is used.

patients with margins greater than 1 cm, 11% of the mesorectums are incomplete, reflecting poor surgery. It must therefore be assumed that in patients with positive margins (44% of which showed incomplete mesorectum), a part of the positive margin is most likely caused by a poor surgical technique. Because there are also many cases with complete mesorectum and margin involvement (27% of the total), we can conclude that advanced tumor growth is responsible for at least one third of the positive margins. This implies that CRM has only limited value as a quality assessment instrument for rectal cancer surgery, although it remains very relevant for patient management.

In our analysis, we combined “optimal surgery” cases and cases with nearly complete mesorectum, because we did not find statistical differences between these groups. However, we do not want to give the impression that “coning in” on the rectal specimen is acceptable, and we want to stress that optimal surgery (ie, complete mesorectum) remains the goal.

Recently, a few studies concerning the preoperative imaging of rectal carcinoma have revealed that it is possible to predict the tumor-free resection margin by magnetic resonance imaging.<sup>15,16</sup> A reliable prediction of a tumor-free margin will be possible in those cases with complete mesorectal excision, but not in the group with positive margins because of insufficient surgery.

We also show that when surgeons use the TME technique, which is improved surgical technique with regard to local control, clinically relevant differences exist in quality of surgery performed. It was not possible to relate these outcomes to experience of surgeons, because of the low number of patients with information about the quality of mesorectum per surgeon. However, factors beyond the surgeon’s influence are also important in determining the final quality of resection.

With the direct assessment of the quality of the performed resection by the surgical pathologist, a completely new way of quality evaluation is established. The relevance of this evaluation is clear, because the judgment of the TME resection specimen provides useful information about the prognosis of patients, especially about the probability of local and distant recurrence.

Presently, pathologists provide data to predict the course of disease by diagnosing, classifying, and staging (TNM) the primary tumor. We show that a role in quality assessment may be very valuable in the multidisciplinary approach to patients with rectal cancer. We realize that the direct evaluation of the quality of surgery needs an altered relationship between surgeons and pathologists, on the basis of trust. We believe that pathologists and surgeons need to see this as a challenge.

## APPENDIX

The appendices listing members of the Pathology Review Committee and the Cooperative Clinical Investigators of the Dutch Colorectal Cancer Group are available online at [www.jco.org](http://www.jco.org).

## REFERENCES

1. Heald RJ, Ryall RDH: Recurrence and survival after total mesorectal excision for rectal cancer. *Lancet* 1:1479-1482, 1986
2. Martling AL, Holm T, Rutqvist LE, et al: Effect of a surgical training programme on outcome of rectal cancer in the County of Stockholm. *Lancet* 356:93-96, 2000
3. Hermanek P, Mansmann U, Staimmer D, et al: The German experience: The surgeon as a prognostic factor in colon and rectal cancer surgery. *Surg Oncol Clin North Am* 9:33-49, 2000
4. Hermanek P, Hohenberger W: The importance of volume in colorectal cancer surgery. *Eur J Surg Cancer* 22:213-215, 2000
5. Porter GA, Soskolne CL, Yakimets WW, et al: Surgeon-related factors and outcome in rectal cancer. *Ann Surg* 227:157-167, 1998
6. McArdle CS, Hole D: Impact of variability among surgeons on postoperative morbidity and mortality and ultimate survival. *BMJ* 302:1501-1505, 1991
7. Kingston RD, Walsh S, Jeacock J: Colorectal surgeons in district general hospitals produce similar survival outcomes to their teaching hospital colleagues: Review of 5-year survivals in Manchester. *J R Coll Surg Edinb* 37:235-237, 1992
8. Kapiteijn E, Marijnen CAM, Nagtegaal ID, et al: Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med* 345:638-646, 2001
9. Kapiteijn E, Marijnen CAM, Colenbrander AC, et al: Local recurrence in patients with rectal cancer diagnosed between 1988 and 1992: A population-based study in the west Netherlands. *Eur J Surg Oncol* 24:528-535, 1998
10. Quirke P: Limitations of existing systems of staging for rectal cancer, in Soreide O, Norstein J (eds): *Rectal Cancer Surgery: Optimisation, Standardisation, Documentation*. Berlin, Germany, Springer-Verlag, 1997, pp 63-81
11. Quirke P, Durdey P, Dixon MF, et al: Local recurrence of rectal adenocarcinoma due to inadequate surgical resection: Histopathological study of lateral tumor spread and surgical excision. *Lancet* 2:996-999, 1986
12. Adam JJ, Mohamdee MO, Martin IG, et al: Role of circumferential margin involvement in the local recurrence of rectal cancer. *Lancet* 344:707-711, 1994
13. Nagtegaal ID, Marijnen CAM, Klein Kranenbarg E, et al: Circumferential margin involvement is still an important predictor of local recurrence in rectal carcinoma: Not one millimetre but two millimetres is the limit. *Am J Surg Pathol* (in press)
14. Nagtegaal ID, Klein Kranenbarg E, Hermans J, et al: Pathology data in the central database of multicenter randomized trials need to be based on pathology reports and controlled by trained quality managers. *J Clin Oncol* 18:1771-1779, 2000
15. Blomqvist L, Rubio CA, Holm T, et al: Rectal adenocarcinoma: Assessment of tumour involvement of the lateral resection margin by MRI of resected specimen. *Br J Radiol* 72:18-23, 1999
16. Beets-Tan RGH, Beets GL, Vliegen RFA, et al: Can MRI predict the tumour free resection margin in rectal cancer surgery? *Lancet* 357:497-504, 2001