Quality assurance in rectal cancer treatment

Marcel den Dulk

Cover: The universal symbol of colorectal cancer: the Blue Star. It is a combination of a star and a ribbon, reflecting power, hope, and awareness.

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dr. H.J.T. Rutten (Catharina-ziekenhuis, Eindhoven)
dr. W.H. Steup (HagaZiekenhuis, Den Haag)

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Contents

Chapter 1

General introduction and outline of the thesis

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INTRODUCTION

The incidence of cancer is increasing in Europe.[1,2] With an estimated 3.2 million new cases of cancer and 1.7 million deaths due to cancer in 2006 in Europe, it is an important health problem.[1] Colorectal cancer is the cancer with the second highest incidence and accounts for 412,900 (12.9%) new cases a year.[1] Besides, it is the second cause of cancer death with an estimated 207,400 deaths a year in Europe.[1] In the Netherlands, 10,851 patients were diagnosed with colorectal cancer in 2005.[3] In general, rectal cancer accounts for roughly 35% of colorectal cancers; currently over 3,000 patients are diagnosed with rectal cancer a year.

Quality assurance in surgical oncology

For almost all solid organ cancers, randomised trials have been performed to study new treatment protocols. It is recognised that variability in treatment could influence treatment outcome and consequently this confounder should be minimised. In radiotherapy, several actions have been taken to reduce variation, such as dosimetry or a pre-trial dummy run.[4-10] Moreover, also for systemic treatment such as chemotherapy, several criteria were defined which were used to asses treatment variation in oncological trials.[11-13]

In contrast to drugs, which are reproducible entities, a characteristic of operations is the large variability making it difficult to reproduce the results. A major variable responsible for this variability is the skills of the surgeon. In 1991, McArdle and Hole wrote that "some surgeons perform less than optimal surgery… If by meticulous attention to detail the results of surgery could be improved, and our results suggest that this would not be difficult, the impact on survival might be greater than that of any of the adjuvant treatment therapies currently under study".[14] The skill level of surgeons will not only vary among surgeons, but will increase as a surgeon gains experience. Besides, surgeons with specific interests will perform better and develop more new techniques.[14,15] These new techniques are often tested and analysed in their own centre. This partly explains why so many non-randomised single centre or personal series are reported in surgery.

It is a prerequisite for a randomised trial that the participating surgeons are equally skilled in both techniques. Differences in performances between individual surgeons are rather the rule than the exception. To solve this problem one group of surgeons could only perform the conventional procedure and another group only the experimental operation: a so-called expertise based randomised trial.[16] Another option is to train all surgeons to perform the procedure in the same way and at a similar level. Quality assurance aims at reducing variability and can be defined as the systematic measures required to achieve a treatment result that meets a certain standard. It is a process in which continuous quality improvement is a central issue. Surgical quality assurance measurements were used in the Dutch D1-D2 gastric cancer trial and later in the Dutch TME trial.[17-21]

Quality control in gastric cancer surgery

From August 1989 to June 1993 the Dutch D1-D2 Gastric cancer trial was performed.[17] This trial randomised patients between a limited D1 and an extended D2 lymph node dissection. In the design of this trial, quality assurance measures for both surgery and pathology were incorporated.[17,18,21] Participating surgeons received videotapes and booklets about the technique and were instructed in the operating room by a gastric-cancer surgeon from Japan.[21] This instructing surgeon was present during the first 4 months of the trial, which served as an instruction period. He was also present regularly thereafter. Eight surgeons, from 8 regions, had been specially trained in D2 dissection. These specially trained consulting surgeons attended all operations involving D2 dissections. The study coordinator attended nearly all D1 dissections. The consulting surgeons and the study coordinator monitored the technique and the extend of the lymph node dissection, and after the operation, they divided the perigastric tissue into the proper lymph node stations. Regular meetings about the technique were held with the consulting surgeons, the study coordinator, and the instructing surgeon.[18]

Quality control was also used for pathological examination in the Dutch D1-D2 trial. The number and location of lymph nodes detected at pathological examination were related to the guidelines of the study protocol.[22] If at pathological examination lymph nodes were detected in stations other than those specified by the protocol, this violation of the protocol was called "contamination". If, however, the pathologist could not detect lymph nodes in stations that should have been dissected, this violation was called "non-compliance". These violations could occur in both D1 and D2 dissections. Contamination in the D1 group and non-compliance in the D2 group could blur the distinction between the 2 types of dissection. To account for biological variation, one missing station was allowed.[18]

At the start of the trial, historical data was used to calculate the expected 5-year survival rates after dissection with curative intent: 20% for patients who had a D1 dissection and 32% for patients who had a D2 dissection.[18,23] Although the trial could not demonstrate a difference in overall survival, the 5-year survival rates were much higher than expected: 45% after a D1 dissection and 47% after a D2 dissection.[24] Part of this improved outcome could be explained by an unexpectedly high proportion of pathological T1 (26%) and T2 (47%) tumours, but it could not account for the complete difference. The process of instructing surgeons by videotapes, booklets and instruction sessions, in combination with supervision of dissections by instructor surgeons to standardise the procedure also paid off.

QUALITY CONTROL IN RECTAL CANCER SURGERY

Background

Before the introduction of TME (total mesorectal excision) surgery, blunt digital resection was used, resulting in local recurrence rates of about 20%.[25] In the Swedish Rectal Cancer trial, for example, which included patients from 1987 until 1990, the 5-year local recurrence rate was 27% for patients treated with surgery alone. If the patient was treated with preoperative 5 x 5 Gy radiotherapy, local recurrence rates dropped to 11%.[25]

In the 1990s, the Dutch Colorectal Cancer Group designed a trial using standardised surgery to reduce local recurrence rates: the Dutch TME trial.[19] The surgical procedure used in this trial was new at that time, involving a complete and sharp excision of the mesorectum under direct vision, with preservation of the hypogastric plexus (TME procedure). The approach was advocated by Heald and Enker and resulted in a 5-year local recurrence rate below 10%.[26,27] These rates were almost similar to the recurrence rate found in the Swedish Rectal Cancer trial for conventional surgery combined with preoperative radiotherapy.[25] After the Swedish Rectal Cancer trial had demonstrated the beneficial effect of radiotherapy, the remaining question was whether radiotherapy was still beneficial in combination with standardised, good, TME surgery.[25,28] To standardise treatment and reduce variation, extensive quality control was included in the TME trial for radiotherapy, surgery and pathology.[19,20]

Quality control

Results from a questionnaire which was mailed to all 21 Dutch radiotherapy departments showed that the use of the 5 x 5 Gy scheme, as used in Sweden,[29] was accepted by most institutes. Treatment details, like volume and fields were described meticulously in the protocol, including a mandatory stimulation procedure. All institutes had to use a 3 or 4 fields portal box technique in order to avoid serious non-surgical morbidity which was observed in the Stockholm trial using less fields.[30]

The TME procedure provides an excellent specimen and therefore the pathologist was able to check whether the procedure had been performed according to the protocol, using the transverse slicing method of Quirke.[31] For the pathologists, this way of analysing the specimen was very different from their daily practice. In addition to the TME study protocol, a special pathology protocol was written and distributed to 43 pathology laboratories. A pathology workshop was organised in December 1995 with the attendance of Dr. Quirke. A step-to-step protocol was produced, usable at the dissection table. In addition, the pathology coordinator had set up a Pathology Review Committee to discuss problems and review the slides, reports, and photographs of the specimen.[32]

In the TME trial, a new surgical technique was used by all participating surgeons. For the TME trial, an expertise based randomised controlled trial design was not possible,

as TME surgery was used in both randomisation arms. Besides, due to such a design the change outside the trial would occur at a slower pace, because only part of the surgeons is able to perform the new procedure. Different modalities were used to train the participating surgeons. First, a videotape on radicality and autonomic nerve preservation was produced, with operations performed by professor Moriya. Dr. Heald from Basingstoke (United Kingdom) performed almost 30 operations throughout the Netherlands and produced two videotapes, which were distributed to all participating hospitals. Besides, he has attended all seven workshops, which were organised all over the country from May 1996 to April 2000. A total of 21 instructor surgeons were selected. Their task was to introduce, teach and control the TME operations in their region. In each hospital, the first 5 TME procedures had to be supervised by an instructor surgeon.

Results

A total of 1861 patients were included in the study between January 1996 and December 1999, of whom 1530 from 84 Dutch hospitals.[33] During the TME trial the pathology data were checked.[32] Pathology data from case record forms were compared with hospital pathology reports. Three independent audits were carried out. Special attention was given to the accuracy of parameters, which are important for prognosis and treatment decisions. These quality checks revealed that only one third of the forms were complete and correct. Missing values were most prominent in the number of lymph nodes examined, whereas most errors were made in relation to the circumferential margin. Incorrect and missing data were corrected during these audits. By performing quality checks on all pathology data, the accuracy and completeness of these data were increased, which improved reliability of future analyses.

In the TME trial, the first 5 procedures in each hospital were supervised by an instructor surgeon. This requirement meant that 66% of the TME operations were attended by instructor surgeons during the first year and 58% during the first 500 TME procedures.[19] The pathologist was able to give feedback on the surgical quality of the resection to the surgeon: macroscopic completeness and microscopic circumferential resection margin (CRM) involvement were shown to be good predictors of local recurrence and overall survival.[33,34]

The 5-year local recurrence rates were 5.6% and 10.9% respectively for the group treated with preoperative radiotherapy and for the group treated with surgery alone ($P < 0.0001$), and overall survival rates were 64.2% and 63.5% respectively ($P = 0.90$; median follow up 6.1 years).[33] Compared with historical data derived from trials in which conventional, blunt, non-standardised surgery was used, local recurrence rates were halved and the 5-year overall survival rate improved from 48% to 64% after surgery alone.[25,34] Also in other reports the improved results with standardised surgery for rectal cancer are shown.[35]

The association between CRM involvement and outcome in terms of local recurrence and overall survival, demonstrates the importance of assessing surgical variation: with CRM involvement the 5-year local recurrence rate was 19.7% for patients preoperatively treated with radiotherapy, compared to 3.4% for patients with a negative CRM.[33] If such a parameter of surgical quality is not assessed and used as adjustment in the interpretation of the trial results, drawn conclusions might be made erroneously. Moreover, CRM involvement should be determined in daily clinical practice, as it is an important parameter of outcome and essential for feedback to the individual surgeon.

QUALITY ASSURANCE IN RECENT YEARS

Nowadays, there is a focus on quality assurance. Newspapers publish ranked lists of hospitals with the best care[36,37] and health care insurance companies advertise that they only contract hospitals that provide a certain standard of care. Quantifiable parameters which could be used to determine the quality of care provided are called performance indicators. The Netherlands Health Care Inspectorate has used such performance indicators to protect and promote health and healthcare. An example of interference of the Health Care Inspectorate can be found for oesophageal resections. In literature, an association between volume and postoperative morbidity and mortality was shown: the more oesophageal resections performed in a hospital per year, the lower the complication rate.[38-40] As a result, the Netherlands Health Care Inspectorate nowadays only allows hospitals to perform an oesophageal resection if, annually, 10 or more of these procedures are done. However, to guarantee a certain (high) level of quality of care, it remains important that medical professionals themselves are actively involved in quality assurance. The European Society of Surgical Oncology (ESSO) has recognised the importance of quality assurance and the author of this thesis has received the first Quality Assurance Fellowship. This thesis focuses on quality assurance of rectal cancer treatment, in particular of the surgical treatment. Both oncological short-term and long-term outcome parameters such as circumferential resection margin involvement, local recurrence, and overall survival are studied, but also other end-points which are important for quality assurance are investigated, such as anastomotic leakage and stoma reversal.

OUTLINE OF THE THESIS

Chapter 2 describes the overall survival for resected rectal cancer in the Netherlands before, during and after the TME trial. TME surgery was nationwide introduced during the TME trial in the Netherlands. In the trial, the effects of preoperative 5 x 5 Gy radiotherapy

were studied. In this chapter both the effects of the nationwide introduction of the TME technique and preoperative radiotherapy are investigated.

Chapter 3 and chapter 4 focus on the elderly patients. These patients are underrepresented in most rectal cancer trials, whereas they form the majority of the rectal cancer patient population. It could be questioned whether it is reasonable to apply the guidelines based on relatively younger patients to the elderly. **Chapter 3** discusses this problem, based on analyses of overall survival for elderly patients with rectal cancer. As overall survival failed to improve in the subset of elderly patients since the introduction of TME surgery, in **chapter 4**, postoperative complications and mortality are explored to get more insight in the problems involved.

Apart from the issue of the elderly patients, several studies showed that the type of surgical procedure does also influence outcome: patients treated with an abdominoperineal resection (APR) have a reduced overall survival compared to patients treated with a low anterior resection (LAR).[41-43] In **chapter 5** is studied whether the factors associated with the decision to perform an APR or the APR procedure itself were related to circumferential resection margin involvement, local control, and overall survival. **Chapter 6** describes an in depth analysis in patients treated with an APR in the TME trial to identify tumour and patient related risk factors that contributed to CRM involvement, local recurrence, and reduced overall survival. In both chapters methods which could improve outcome for patients treated with an APR are discussed.

The importance of a resection without involved resection margins or R0 resection has been shown in several studies.[44,45] EORTC trial 22921 compared adjuvant fluorouracil-based chemotherapy to no adjuvant treatment in a 2 x 2 factorial trial with randomisation for preoperative (chemo)radiotherapy in patients with resectable T3-4 rectal cancer. This trial started in April 1993. In 1999, the recommendation to perform a TME procedure was included. In **chapter 7** CRM involvement is investigated in EORTC trial 22921. Furthermore, the effects of CRM involvement on local recurrence and overall survival rates are shown. In **chapter 8**, the same EORTC trial is used to study which subset of patients benefits significantly from adjuvant treatment.

After a resection of the primary rectal tumour, surgeons often create an anastomosis to restore the continuity of the bowel. **Chapter 9** describes a feared complication: anastomotic leakage. Apart from the focus on short-term morbidity, in this chapter long-term end-points are considered including local recurrence, overall survival, disease-free survival, and cancer-specific survival. In **chapter 10**, a protocol for postoperative surveillance after colorectal resection with continuity restoration is described and tested. This protocol aimed at reducing delay in the diagnosis of anastomotic leakage and subsequently at reducing mortality associated with this complication.

Recently, it was shown that the creation of a stoma reduces the rate of symptomatic anastomotic leakage.[46] However, not all stomas that are created with a temporary

intention are reversed. **Chapter 11** describes stoma reversal in the TME trial. Specific attention is given to determine limiting factors for stoma reversal.

Finally, the results of all studies will be summarised and discussed in **chapter 12**.

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Chapter 2

Improved overall survival for patients with rectal cancer since 1990: the effects of TME surgery and preoperative radiotherapy

Marcel den Dulk, Pieta Krijnen, Corrie A.M. Marijnen, Harm J.T. Rutten, Lonneke V. van de Poll-Franse, Hein Putter, Elma Meershoek-Klein Kranenbarg, Marlies L.E.A. Jansen-Landheer, Jan-Willem W. Coebergh, Cornelis J.H. van de Velde

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ABSTRACT

Aim

The aim was to study the effects of the introduction of TME surgery and preoperative radiotherapy on overall survival (OS) by comparing patients treated in the period before (1990-1995), during (1996-1999) and after (2000-2002) the TME trial.

Patients and methods

Patients diagnosed with rectal carcinoma in the region of Comprehensive Cancer Centres South and West were used ($n = 3179$).

Results

Five-year OS was, respectively, 56%, 62% and 65% in the pre-trial, trial and post-trial periods ($P < 0.001$). Preoperative RT was increasingly used over time and significantly related to OS in the post-trial period ($P = 0.002$), but not in the pre-trial and trial periods.

Conclusions

Population-based OS improved markedly since the introduction of TME surgery. With standardised TME surgery, preoperative RT improved OS, whereas withholding preoperative RT was associated with a poorer prognosis. The present study supports that preoperative RT was correctly introduced as a standard treatment before TME surgery in our national guideline.

INTRODUCTION

Since the early 1990s, there have been changes in rectal cancer treatment towards better surgery and/or preoperative radiotherapy (RT). With conventional, blunt dissection of the rectum 5-year local recurrence rates used to be above 20%.[1] However, after total mesorectal excision (TME), which is a sharp dissection under direct vision of the rectum with its mesorectum and the visceral pelvic fascia,[2] local recurrence rates can be less than 10%.[3,4] Moreover, 5-year overall survival (OS) improved from 48% after conventional surgery as performed in the Swedish Rectal Cancer trial to >60% after TME surgery.[1,5,6]

In the Netherlands, a trial was performed between 1996 and 1999 to study the effects of preoperative RT on local control and OS in patients that underwent TME surgery.[7] During this trial, all participating surgeons were trained in the TME technique.[6,8] Instructions were given during workshops, at the dissection table, with booklets and a video tape. Besides, the first five procedures of each participating surgeon were attended by an instructor surgeon. Moreover, RT and pathology examination were also standardised to reduce the variability.[7] The trial resulted in a 5-year local recurrence rate of 5.6% with and 10.9% without preoperative RT, and a 5-year OS rate of 64% in both groups.[6]

TME is now accepted as the golden standard for the curative treatment of rectal carcinoma. In the present study, OS was evaluated in the time periods before, during and after the TME trial to study the effects of the introduction of TME surgery in combination with preoperative RT in the region of Comprehensive Cancer Centres South and West in the Netherlands.

PATIENTS AND METHODS

Patients

Data were derived from the cancer registry of the population-based Comprehensive Cancer Centres South and West. Registration is based on notification of all newly diagnosed malignancies after which data are obtained from clinical records in hospitals. The Dutch regional Cancer Registries have shown to attain a completeness of data exceeding 95%.[9] Patients who underwent a resection for cancer located in the rectum (International Classifications of Diseases-9 154.1) and diagnosed between January 1990 and December 2002 were selected for analysis. Patients with prior invasive adenocarcinoma or with distant metastases diagnosed prior to or during surgery were not included, as were patients who underwent a local excision such as polipectomy or TEM (transanal endoscopic microsurgery). In the Dutch TME trial, patients with T1-T3 and patients with mobile T4 tumours were included. In the registry no details were available on mobility

of the tumour, so all T4 tumours were excluded to limit the current analysis to tumours which could be curatively resected.

The period of study was divided into three periods: 1990-1995 (pre-trial period), 1996-1999 (trial period) and 2000-2002 (post-trial period). Age was categorised into <60 years, 60-74 years and ≥75 years. Data on tumour stage and data on preoperative and postoperative treatment were obtained from the Cancer Registries. Preoperative RT consisted of both the short, 5 x 5 Gy, schedule and the long schedule, such as 25 x 2 Gy. TNM-classification 4 (UICC,1987) was used before 1999.[10] Since 1999, TNM-classification 5 (UICC, 1997) was used, which classifies node negative patients with less than 12 examined lymph nodes as Nx.[11] Survival data were obtained from hospitals, general practitioners and the Central Bureau for Genealogy, which registers all the deceased persons in the Netherlands.

Statistical analysis

Data were analysed with the SPSS package (SPSS 14.0 for Windows; SPSS Inc., Chicago, IL). Univariate comparisons of categorical variables were performed by a χ^2 test. The following variables were considered as potential confounders for period in the analysis for OS: pathological T-stage, lymph node status, age, gender, (neo)adjuvant treatment, and Comprehensive Cancer Centre region. Potential confounder variables were first univariately tested in a Cox regression model. Confounders with a *P*-value ≤ 0.10 in the univariate analysis were selected and entered in a multivariate Cox regression model together with period of diagnosis. Besides, the model was tested for an interaction between period and statistically significant confounders. To test whether the hazard ratios (HR) were constant across time, the assumption of proportional hazards was studied univariately, and subsequently variables with a significant interaction in these analyses (age, pathological T-stage, nodal status, and (neo)adjuvant treatment) were entered in the previously described multivariate Cox regression model. As the estimates of the HR and *P*-values for >6 months post-surgery in the model with time-dependency were comparable to the model without time-dependency, we chose to report the results without time-dependency. Two-sided *P*-values ≤0.05 were considered statistically significant.

RESULTS

Patient characteristics

In total, 3179 patients were included in the analysis. In the pre-trial period 1150 patients, in the trial period 1084 patients and in the post-trial period 945 patients were analysed. In the trial period, 421 patients (39%) were included in the TME trial. All hospitals in both Comprehensive Cancer Centre regions South and West participated in the TME

Table 1. Patient characteristics by period of diagnosis.

Variable	Pre-trial period (%) *n* = 1150	Trial period (%) *n* = 1084	Post-trial period (%) *n* = 945	Total (%) *n* = 3179	*P*-value
Gender					0.195
Female	495 (43)	451 (42)	370 (39)	1316 (41)	
Male	655 (57)	633 (58)	575 (61)	1863 (59)	
Age					0.369
< 60 years	296 (26)	305 (28)	268 (28)	869 (27)	
60-74 years	535 (47)	512 (47)	426 (45)	1473 (46)	
> 74 years	319 (28)	267 (25)	251 (27)	837 (26)	
pT-stage					0.525
T1	110 (10)	96 (9)	74 (8)	280 (9)	
T2	392 (34)	386 (36)	350 (37)	1128 (36)	
T3	648 (56)	602 (56)	521 (55)	1771 (56)	
Lymph node status					0.019
N0/Nx	825 (72)	720 (66)	640 (68)	2185 (69)	
N+	325 (28)	364 (34)	305 (32)	994 (31)	
(Neo)adjuvant treatment					<0.001
No perioperative treatment	705 (61)	591 (55)	241 (26)	1537 (48)	
Preoperative RT	1 (0)	329 (30)	555 (59)	885 (28)	
Preoperative CRT	0 (0)	17 (2)	50 (5)	67 (2)	
Preop. RT and postop. CT	0 (0)	9 (1)	35 (4)	44 (1)	
Postoperative RT	403 (35)	116 (11)	36 (4)	555 (17)	
Postoperative CRT	27 (2)	5 (0)	5 (1)	37 (1)	
Postoperative CT	14 (1)	17 (2)	23 (2)	54 (2)	
Region					<0.001
CCC South	527 (46)	701 (65)	556 (59)	1784 (56)	
CCC West	623 (54)	383 (35)	389 (41)	1395 (44)	

Pre-trial period (1990-1995), trial period (1996-1999) and post-trial period (2000-2002). Percentages may not add up to 100% due to rounding. RT = radiotherapy; CRT = chemoradiotherapy; CT = chemotherapy; CCC = Comprehensive Cancer Centre.

trial. Median follow-up of patients alive was 144 (range 108-191), 86 (range 60-119) and 46 months (range 24-72 months), for the pre-trial, trial and post-trial periods, respectively. Patient characteristics are shown in Table 1. In the pre-trial period more patients were included in the region of Comprehensive Cancer Centre West, whereas in the trial and post-trial periods relatively more patients were included from the region of Comprehensive Cancer Centre South. The patients diagnosed in the three periods differed significantly with respect to (neo)adjuvant treatment: over time less patients were treated with postoperative RT, whereas more patients were preoperatively treated with RT ($P < 0.001$). In the trial and post-trial period more patients were diagnosed with N+ disease compared with the pre-trial period.

Overall survival

Five-year OS in the pre-trial period was 56% (95% confidence interval (CI) 53%-59%), compared to 62% (95% CI 60%-65%) and 65% (95% CI 60%-69%) for the trial and post-trial periods respectively ($P < 0.001$). The increase in OS in the trial period compared with the pre-trial period was significant ($P < 0.001$) and did not change significantly thereafter ($P = 0.31$).

The results of the univariate analyses to select confounding variables for OS are shown in Table 2. In this analysis, only region was not found to be associated with OS ($P = 0.993$) and was not entered in the multivariate analysis. All other variables were entered in the multivariate analysis: the results are presented in Table 3. The effects of period, gender, age, pT-stage, lymph node status, and (neo)adjuvant treatment were found to be independently related to the risk of dying. Furthermore, a significant interaction between period and (neo)adjuvant treatment was found ($P < 0.001$). Consequently, the

Table 2. Results of the univariate Cox regression analyses for overall survival.

Variable	Hazard ratio	95% CI	*P*-value
Period of diagnosis			<0.001
Pre-trial	1.00		
Trial	0.81	0.72-0.91	<0.001
Post-trial	0.74	0.64-0.86	<0.001
Gender			0.005
Female	1.00		
Male	1.16	1.05-1.29	
Age			<0.001
< 60 years	1.00		
60-74 years	1.60	1.39-1.84	<0.001
> 74 years	3.14	2.72-3.63	<0.001
pT-stage			<0.001
T1	1.00		
T2	1.31	1.04-1.65	0.021
T3	2.44	1.96-3.03	<0.001
Lymph node status			<0.001
N0/Nx	1.00		
N+	1.89	1.70-2.09	
(Neo)adjuvant treatment			<0.001
No (neo)adjuvant treatment	1.00		
Preoperative RT	0.77	0.67-0.89	<0.001
Preoperative CRT	1.35	0.93-1.96	0.111
Preoperative RT and postoperative CT	0.86	0.51-1.47	0.586
Postoperative RT	1.27	1.12-1.43	<0.001
Postoperative CRT	0.84	0.52-1.36	0.478
Postoperative CT	1.21	0.84-1.76	0.311
Region			0.993
CCC South	1.00		
CCC West	1.00	0.90-1.11	

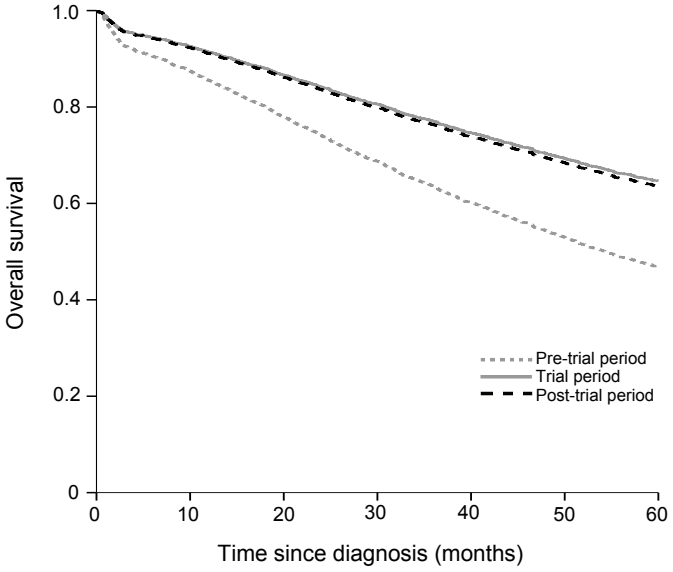
RT = radiotherapy; CRT = chemoradiotherapy; CT = chemotherapy; CCC = Comprehensive Cancer Centre; CI = confidence interval.

Table 3. Results of the multivariate Cox regression analysis for overall survival.

Variable	Hazard ratio	95% CI	*P*-value
Period of diagnosis			<0.001
Pre-trial	1.00		
Trial	0.66	0.56-0.77	<0.001
Post-trial	0.79	0.63-1.00	0.049
Gender			<0.001
Female	1.00		
Male	1.26	1.13-1.40	
Age			<0.001
< 60 years	1.00		
60-74 years	1.71	1.48-1.97	<0.001
> 74 years	3.44	2.96-4.00	<0.001
pT-stage			<0.001
T1	1.00		
T2	1.22	0.96-1.54	0.094
T3	2.02	1.61-2.54	<0.001
Lymph node status			<0.001
N0/Nx	1.00		
N+	1.88	1.68-2.10	
(Neo)adjuvant treatment, pre-trial period *			0.046
No (neo)adjuvant treatment	1.00		
Postoperative RT	0.80	0.68-0.94	0.005
Postoperative CRT	0.58	0.33-1.04	0.069
Postoperative CT	0.99	0.51-1.92	0.972
(Neo)adjuvant treatment, trial period			0.040
No (neo)adjuvant treatment	1.00		
Preoperative RT	1.11	0.90-1.36	0.315
Preoperative CRT	2.38	1.24-4.44	0.007
Preoperative RT and postoperative CT	0.60	0.19-1.84	0.376
Postoperative RT	1.35	1.02-1.75	0.032
Postoperative CRT	1.99	0.75-5.46	0.174
Postoperative CT	1.14	0.62-2.10	0.683
(Neo)adjuvant treatment, post-trial period			0.001
No (neo)adjuvant treatment	1.00		
Preoperative RT	0.64	0.49-0.86	0.002
Preoperative CRT	1.30	0.80-2.17	0.282
Preoperative RT and postoperative CT	0.84	0.45-1.58	0.590
Postoperative RT	1.59	0.97-2.68	0.066
Postoperative CRT	0.41	0.06-2.95	0.375
Postoperative CT	0.82	0.41-1.63	0.562

RT = radiotherapy; CRT = chemoradiotherapy; CT = chemotherapy; CI = confidence interval. * Results for preoperative RT in the pre-trial period not shown ($n = 1$).

effect of (neo)adjuvant treatment is presented separately for each period in Table 3. Moreover, period of treatment itself was significantly associated with OS. Adjusted OS in the trial period was significantly improved compared to the pre-trial period (OR 0.66, $P < 0.001$). In contrast, adjusted OS was lower in the post-trial period compared with the trial period although not statistically significant (OR = 1.20, $P = 0.141$ for post-trial period compared to trial period). Adjusted Cox regression curves for OS are shown in Figure 1.



Numbers at risk							
Pre-trial period	1150	1039	938	857	772	707	646
Trial period	1084	978	909	839	767	718	676
Post-trial period	945	867	815	684	478	268	83

Figure 1. Cox regression curves for overall survival (OS) for resectable rectal cancer by period adjusted for gender, age, pT-stage, lymph node status, (neo)adjuvant treatment, and the interaction between treatment and period.

The effects of period and treatment on overall survival

In the pre-trial period only one patient is treated with preoperative RT, therefore this patient is not included in the following analyses. Unadjusted, 5-year survival rates per period and treatment are shown in Table 4. In Figure 2, Cox regression curves for OS are shown adjusted for gender, age, pT-stage, and lymph node status. The curves are presented separately for patients treated without (neo)adjuvant treatment (Figure 2A), with preoperative RT (Figure 2B) and with postoperative RT (Figure 2C). In the pre-trial period, OS was better for patients treated with postoperative RT compared with patients treated without (neo)adjuvant treatment ($P = 0.005$, Table 3). In the trial period, in which 39% of patients were included in the TME trial and randomised between preoperative

Table 4. Unadjusted 5-year overall survival rate (%) per period for patients treated with no (neo)adjuvant treatment, preoperative radiotherapy (RT), and postoperative RT.

Period	No (neo)adjuvant treatment % (95% CI)	Preoperative RT % (95% CI)	Postoperative RT % (95% CI)
Pre-trial	57.9 (54.2-61.6)	n.a.*	52.6 (47.7-57.5)
Trial	65.0 (61.1-68.9)	62.3 (57.0-67.6)	54.3 (45.3-63.3)
Post-trial	59.5 (66.8-52.2)	70.5 (65.6-75.4)	49.8 (33.3-66.3)

n.a. = not available. *Results for preoperative RT in the pre-trial period not shown ($n = 1$).

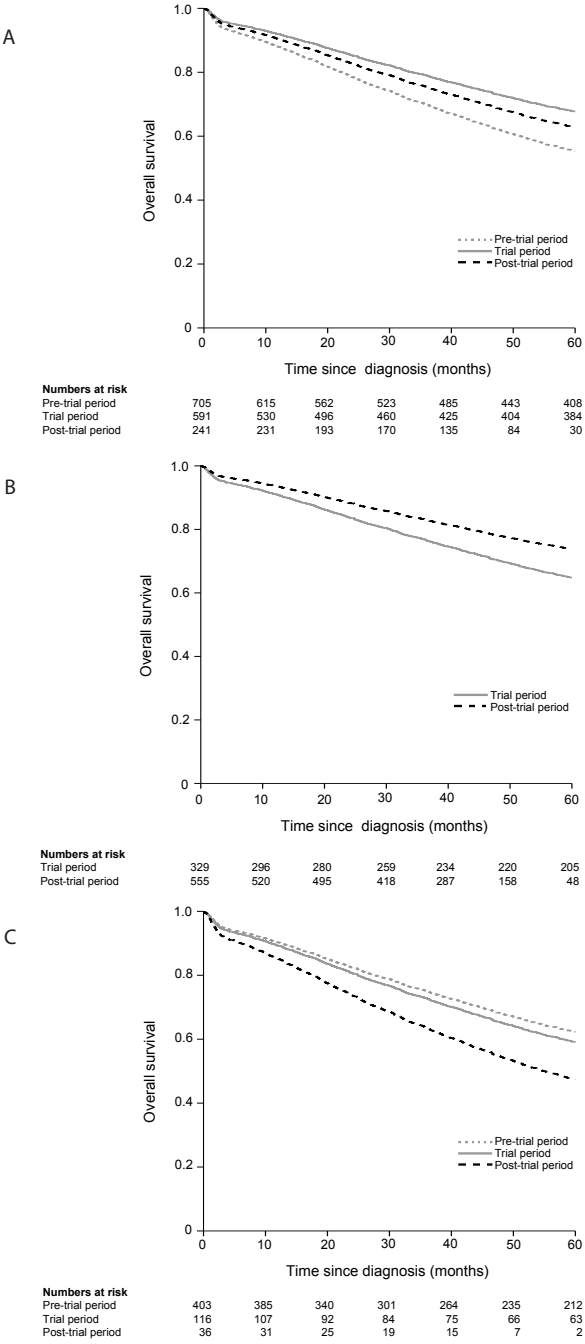


Figure 2. Cox regression curves for overall survival (OS) shown separately for patients treated without (neo)adjuvant treatment (A), with preoperative radiotherapy (RT) (B) and with postoperative RT (C) in the pre-trial, trial and post-trial period. The curves are adjusted for gender, age, pT-stage, and lymph node status. The results for preoperative RT in the pre-trial period is not shown ($n = 1$).

Table 5. (Neo)adjuvant treatments shown separately for patients aged < 75 years, 75-79 years and ≥ 80 years.

Period	(Neo)adjuvant treatment	Age < 75 years *n* (%)	Age 75-79 years *n* (%)	Age ≥ 80 years *n* (%)
Pre-trial	No (neo)adjuvant treatment	465 (56.0)	192 (65.8)	138 (84.1)
	Preoperative RT	1 (0.1)	0 (0.0)	0 (0.0)
	Postoperative RT	326 (39.2)	51 (32.9)	26 (15.9)
	Other (neo)adjuvant treatment	39 (4.7)	2 (1.6)	0 (0.0)
Trial	No (neo)adjuvant treatment	403 (49.3)	95 (66.4)	93 (75.0)
	Preoperative RT	269 (32.9)	37 (25.9)	23 (18.5)
	Postoperative RT	97 (11.9)	11 (7.7)	8 (6.5)
	Other (neo)adjuvant treatment	48 (5.9)	0 (0.0)	0 (0.0)
Post-trial	No (neo)adjuvant treatment	133 (19.2)	53 (37.9)	55 (49.5)
	Preoperative RT	431 (62.1)	72 (51.4)	52 (46.8)
	Postoperative RT	26 (3.7)	6 (4.3)	4 (3.6)
	Other (neo)adjuvant treatment	104 (15.0)	9 (6.4)	0 (0.0)

RT = radiotherapy.

RT followed by TME surgery and TME surgery alone (no (neo)adjuvant treatment), both treatments were comparable, whereas patients treated with postoperative RT did worse. In the post-trial period, preoperative RT was standard treatment, although the treating physician of surgeon could adapt the treatment for each patient. In this period, patients treated with preoperative RT had the best outcome and patients treated with postoperative RT the worst outcome. Moreover, the influence of the introduction of TME surgery can be seen by the improvement of OS in the TME period, which is stable in the post-trial period. Patients treated with preoperative RT did better in the post-trial period compared with the trial period. Patients treated with postoperative RT did worse in both the trial period and post-trial period compared with the pre-trial period. Overall, the lowest survival rate is found for patients in the post-trial period treated with postoperative RT and the highest survival rate is found for patients treated in the same period with preoperative RT.

The relationship between age and (neo)adjuvant treatment per period is shown in Table 5. In general, less (neo)adjuvant treatment is given to patients aged ≥ 80 years. However, over time in all age groups more preoperative RT was given: 47% of patients aged ≥ 80 years and 62% of patients aged <75 years in the post-trial period.

DISCUSSION

Between 1996 and 1999, the TME trial was conducted in the Netherlands, resulting in a nationwide standardised and quality-controlled introduction of TME surgery.[12] Incidentally, preoperative short course RT was already in use in some parts of the Netherlands. In the TME trial, the effects of the addition of preoperative 5 x 5 Gy RT in combination with standardised TME surgery were studied. This cohort study demonstrates that pop-

ulation-based OS of patients with rectal cancer improved over time. An earlier study of Comprehensive Cancer Centre South showed that, compared to the period 1980-1989, OS in this region had already improved in the period 1990-1994, and continued to improve during the study period of the TME trial.[13] Interestingly, the present cohort study shows that the OS improved in the period 1996-1999 and 2000-2002 compared with the period 1990-1995, suggesting that the introduction of TME surgery has improved survival further. Moreover, after adjusting for gender, age, pT-stage, nodal status, and (neo) adjuvant treatment, OS in the post-trial period mainly increased for patients treated with preoperative RT. In other words: with good quality TME surgery survival improves and with good surgery preoperative RT does matter for outcome. In the remaining discussion, we will use the adjusted OS when mentioning OS, unless indicated differently.

Several studies found that preoperative RT resulted in better local control compared with postoperative RT.[14,15] Besides, compliance to postoperative treatment was only about 50% which was often related to surgical complications.[14-16] In a meta-analysis, it was concluded that preoperative RT could be safely used and resulted in a better local control compared to postoperative treatment (37% less local recurrences, $P = 0.002$).[17] In addition, the authors of the meta-analysis found that fewer patients who had preoperative RT died from rectal cancer than did those who had surgery alone (45% versus 50%, respectively, $P = 0.0003$). In the Dutch TME trial, it was found that local recurrence rates could be further reduced with the addition of preoperative RT to TME surgery, whereas OS remained the same.[6,12] These findings resulted in the adjustment of the national treatment guidelines for rectal cancer in the Netherlands: the National Committee on Gastrointestinal Cancer decided to implement 5 x 5 Gy preoperative RT in combination with TME surgery as standard practice in the treatment of resectable T2-4 rectal carcinoma in 2001. The present analysis also showed that patients who were treated with preoperative RT had a better outcome than patients treated with postoperative treatment.

The effect of RT on survival changed over time. In the trial period, 39% of patients were treated within the trial and randomly assigned to preoperative RT followed by TME surgery or TME surgery alone. Similar to the findings in the TME trial,[6,12] treatment with preoperative RT did not significantly improve OS in this period ($P = 0.315$). In contrast, in the post-trial period, preoperative RT was significantly related to OS ($P = 0.002$). In this period, preoperative RT was the standard, although for some patients preoperative RT was omitted according to the judgement of the treating physician or surgeon. For example, preoperative RT was more frequently used in younger patients than in older patients. However, the multivariate analysis showed that after adjustment for age, gender, pT-stage, and lymph node status, preoperative RT was associated with an increased survival in the post-trial period. According to the results, preoperative RT was withheld in 32% (305/945) of patients in the post-trial period, resulting in a poorer prognosis in

this subset of patients. Unfortunately, no information on comorbidity was available in this study. Also for patients treated without preoperative RT but with postoperative RT survival was less, although for these patients selection of tumour related parameters could have played a role. It should be noted that postoperative radiotherapy has been used differently over time: in the trial and post-trial periods it was mainly indicated for patients with a positive circumferential resection margin (CRM), whereas in the pre-trial period it was used for more patients such as patients with pT3 disease or positive lymph nodes. Due to these differences in selection, comparisons between the periods should be done with caution. Nevertheless, the question arises whether patients treated without preoperative RT did receive the most optimal treatment. We think that the aim should be to treat all patients with preoperative RT, although for the elderly patients the effect of preoperative treatment on survival is less clear than for younger patients.[18,19]

Circumferential resection margin (CRM) involvement has been found to be associated with an increased risk of local recurrence and decreased OS in several trials.[20-22] However, not only involvement of the CRM, commonly defined as tumour within 1 mm of the CRM, but even tumour within 1 cm of the CRM is associated with increased local recurrence rates and decreased survival.[22] Therefore, it is necessary to preoperatively identify patients with a tumour that is located in proximity to the mesorectal fascia, the surgical border of the TME resection. The MERCURY study group reported recently that magnetic resonance imaging (MRI) is accurate in predicting whether the CRM will be clear or affected by tumour.[23] Burton et al. showed that if only a MRI-scan is performed but not discussed in a multidisciplinary team meeting, poor prognostic factors were missed in 50% of patients.[24] Therefore, preoperative MRI-based multidisciplinary team meetings are necessary to select patients in whom the treatment plan should be adapted to a more extended resection and/or to a long schedule of (chemo)radiotherapy to downstage or downsize the tumour to perform a curative resection with an uninvolved CRM.[25,26]

In conclusion, population-based OS of patients with curatively resected rectal cancer improved since the nationwide introduction of TME surgery. The training of surgeons in this new technique was done successfully, with lasting effects. Furthermore, after TME surgery, preoperative RT resulted in an increased survival rate, whereas withholding of preoperative RT was associated with a poorer prognosis. In the latest Dutch national guideline, a preoperative MRI scan is recommended as standard preoperative work-up for all patients with a >T1 tumour. Besides, all patients should be discussed preoperatively in a multidisciplary team meeting. Preoperative short-course RT is advised for all patients with a >T1 curable rectal tumour. If all future patients will be treated according to these recommendations, it is likely that further improvements in OS are within reach.

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Chapter 3

Survival of elderly rectal cancer patients not improved: analysis of population-based data on the impact of TME surgery

Harm J.T. Rutten, Marcel den Dulk, Valery E.P.P. Lemmens, Grard A.P. Nieuwenhuijzen, Pieta Krijnen, Marlies L.E.A. Jansen-Landheer, Lonneke V. van de Poll-Franse, Jan-Willem W. Coebergh, Hendrik Martijn, Corrie A.M. Marijnen, Cornelis J.H. van de Velde

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ABSTRACT

Introduction

The incidence of rectal cancer is the highest in elderly patients. However, these patients are often underrepresented in randomised studies. Therefore, it is not clear whether results of rectal cancer studies are equally applicable to both elderly and younger patients.

In this paper, the Dutch Total Mesorectal Excision (TME) study is revisited, focused on patients aged 75 years and above. The rectal cancer databases of the Comprehensive Cancer Centres (CCC) South and West were combined to analyse the effect of the TME study in three different periods: before (1990-1995), during (1996-1999) and after (2000-2002) the trial.

Results

Implementation of preoperative radiotherapy, as investigated in the TME trial, and the introduction of TME surgery resulted in improved 5-year survival during the subsequent periods in patients younger than 75 years, of 60% (1990-1995) to 67% (1996-1999) and 70% (2000-2002) ($P < 0.0001$, log-rank). The older patients did not improve and remained at 41%, 40% and 43% at 5 years in the respective periods.

Furthermore, mortality during the first 6-month period after treatment is significantly raised compared to younger patients: 14% in the elderly, compared to 3.9% in the younger TME study patient ($P < 0.0001$, χ^2). In the CCC database these figures were confirmed at 16% and 3.9% ($P < 0.0001$, χ^2).

Conclusion

Overall survival was not improved in the elderly rectal cancer patient after introduction of preoperative radiotherapy and TME surgery. Non-cancer related mortality is a significant problem in the first 6 months after surgery.

INTRODUCTION

Few data are available about the proper treatment of elderly patients with rectal cancer. The median age of patients that are enrolled in rectal cancer studies is around the mid-60s. Often patients are excluded either because they are too old: i.e. older than 75 years, or they are excluded as a result of co-morbidity or high ASA (American Society of Anaesthesiology) classification. Despite the fact that surgery is the only proven curable treatment for rectal cancer there are no randomised studies focusing on the improvement of rectal cancer surgery in the elderly. The introduction of TME (Total Mesorectal Excision) surgery has led to a major decrease of the local recurrence rate and an improvement in survival rate.[1,2] TME surgery is an explicit improvement of the quality of surgery and therefore not suitable to be investigated in randomised trials: it is impossible to compare 'good' surgery with 'bad' surgery in a randomised fashion. In the Netherlands, a randomised study comparing TME surgery alone to TME surgery preceded by 5 x 5 Gy short course of radiotherapy led to the introduction of this new technique.[3] This introduction happened almost instantaneously in 1996; within 6 months, surgeons in 80 Dutch hospitals were trained through workshops and the attendance of a referent surgeon at the first five procedures. This relative short transition period to TME surgery creates the opportunity to study population-based databases from the Comprehensive Cancer Centres (CCC) South (Eindhoven Cancer Registry) and West in periods before, during and after introduction of TME surgery. The findings of the randomised study can be correlated with the population-based databases. In the CCC databases all older patients are included. Therefore, it was a challenge to research if findings from the TME study permeated equally into the younger and older rectal cancer population.

The authors of this paper were involved in accumulating data of rectal cancer treatment without the exclusion of older patients: the first database being used is the combined population-based database of two Comprehensive Cancer Centres (South and West) in the Netherlands; the second is the database from the Dutch TME study.

Several questions have to be answered. The most important question remains whether it is reasonable to apply the guidelines based on relatively younger patients to the elderly. Secondary questions are: do the same risk-factors apply to the elderly and do subsequent adjuvant treatments yield the same response? And lastly, must special circumstances be taken into account?

PATIENTS AND METHODS

Data were derived from the cancer registry of the population-based Comprehensive Cancer Centres (CCC) South and West. Registration is based on notification of all newly

diagnosed malignancies after which data is obtained from clinical records in hospitals. The Dutch regional Cancer Registries have been shown to attain a completeness of data exceeding 95%.[4] Patients that underwent a resection for cancer located in the rectum (International Classifications of Diseases-9 154.1) and diagnosed between January 1990 and December 2002 were selected for analysis. Patients with prior invasive adenocarcinoma or with distant metastases diagnosed prior to or during surgery were discarded, as well as patients who underwent polypectomy or transanal endoscopic microsurgery.

The period of study was divided into three periods: 1990-1995 (pre-trial period), 1996-1999 (trial period) and 2000-2002 (post-trial period). Age was categorised into younger than 75 years and 75 years or older. A total number 4567 patients, of which 28% was 75 years or older, was included. Data on tumour stage and data on preoperative RT were also obtained from the cancer registries. Survival data were obtained from hospitals, general practitioners and the Central Bureau for Genealogy, which registers all deceased persons in the Netherlands.

The other dataset used came from the Dutch TME study. From January 1996 until December 2000, 1861 patients were randomly assigned to either preoperative radiotherapy (5 x 5 Gy) followed by TME or TME alone in a large, international, multicentre trial. Details of the TME study have been described elsewhere.[5,6] All patients were required to give informed consent before randomisation. Only Dutch patients (n = 1530) were considered in the present analysis because collection and verification of data were, for logistical reasons, feasible for these patients only. Patients with concomitant metastases or who were not resected were excluded. For the underlying study, 1356 patients were selected. Of all the patients in this database, 230 were 75 years or older (17%).

Statistical analysis

Data were analysed with the SPSS package (SPSS 15.0 for Windows; SPSS Inc., Chicago, IL). Univariate comparisons of categorical variables were performed by a χ^2 test. Preoperative treatment, gender, distance, TNM stage, type of resection, preoperative complications, postoperative infectious, general or surgical complications were first univariately analysed for their association with hospital mortality, defined as mortality during the admission in which the TME procedure was performed, and 180-day mortality. All variables with a P-value of ≤ 0.10 were tested in a multivariate logistic regression analysis. Kaplan-Meier curves for overall survival of patients were compared using the log-rank test. All survival data are presented at 5 years. Two-sided P-values ≤ 0.05 were considered statistically significant.

Prognostic groups were created based on significant variables and analysed and presented using a Cox regression survival model.

RESULTS

The combined database of the Comprehensive Cancer Centres South and West showed that survival of rectal cancer patients has improved over time.[7] Interestingly, this improvement was observed in patients younger than 75 years (Figure 1). For younger patients, TME surgery and preoperative radiotherapy were introduced in the second observation period (1996-1999) in the frame of a randomised study, which led to a significant decrease of the hazard ratio to 0.81, and rise of the 5-year survival rate from 60% in the first period to 67% in the second period. After general introduction of TME surgery and 5 x 5 Gy preoperative radiotherapy, the expected survival rate of younger patients increased to 70% and the relative risk decreased further to 0.70 when compared to the first period ($P < 0.0001$). For the elderly rectal cancer patient, the expected 5-year survival rate was 41% in the first period, but it remained 40% and 43% in the respective second and third periods.

Compared to people of the same age from the general population, the relative risk of dying from rectal cancer increased 5.2 times in younger and 1.6 times in older patients

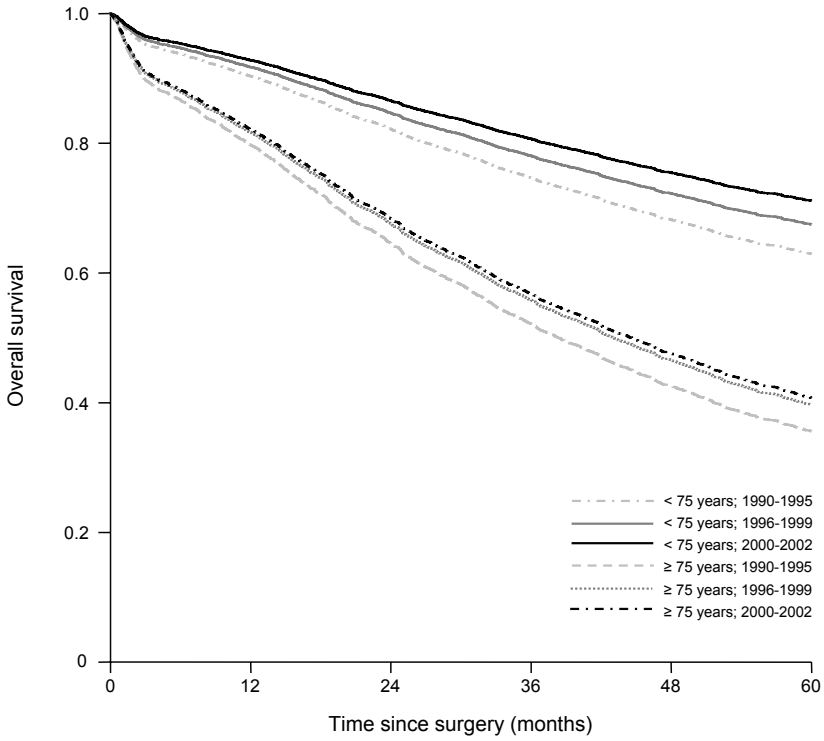

Figure 1. Cox regression overall survival curves in the Comprehensive Cancer Centres combined database. Improved survival over the subsequent periods in the younger patients ($P < 0.0001$), but no improvement in the subsequent periods for the elderly patients.

(data not shown). In the Dutch population, men and women still have a life expectancy of 5 years at the ages of 84 and 87 respectively (Central Bureau of Statistics: www.statline.cbs.nl).

The proportion of patients receiving preoperative radiotherapy in the TME study did not differ between the younger and elderly (younger < 75 years 50% radiotherapy plus TME versus 49% in the elderly, $P = 0.70$). Sex distribution did differ between the age groups: in the younger patients, 65% were male compared to 56% in the elderly ($P = 0.006$). More sphincter conserving procedures were performed in the younger, 66% versus 60% in the elderly ($P < 0.001$). TNM stage distribution also differed: in the young 27% stage 2 and 39% stage 3 whereas in the elderly these figures were 36% and 33% respectively ($P = 0.021$). T-stage distribution differed slightly: 6.0% T1, 34% T2, and 55% T3 in the younger patients versus 2.6%, 33%, and 59% in the elderly ($P = 0.038$). N-stage did not differ between age groups. No patients in this study had metastatic disease. Therefore, mortality during the first month or first 6 months cannot be contributed to cancer progression, but is rather treatment-related. During the first month, the elderly had a significant higher mortality rate, 7.8% versus 2.5% ($P < 0.0001$). However, this difference exaggerates in the ensuing months. The 6-month mortality rate for the elderly was 14% versus 3.3% for the younger patients ($P < 0.0001$). In the TME plus preoperative radiotherapy arm, the 6-month mortality rate for the elderly was 17% compared to 12% in the surgery-alone arm; these figures do not reach statistical significance ($P = 0.27$).

The 6-month mortality rate was also significantly raised in the CCC database: 16% for age 75 and above and 3.9% in the younger patients. For 1-month mortality, these figures were 4.5% and 0.8% respectively. Six-month mortality rates did not decline during the study period. These figures are lower than in the TME study, because the primary date is the date of diagnosis and not the date of surgery, which was unfortunately not recorded in the CCC registries. For the elderly, 6-month mortality was 15%, 18%, and 16% in the consecutive periods. For the younger patients, these figures were 3.9%, 4.1% and 3.6%. No influence on 6-month mortality was found with regard to TNM, T-stage, N-stage, preoperative versus no radiotherapy or type of surgical procedure. Interestingly, those older patients who received postoperative radiotherapy experienced significantly less 6-month mortality, despite the fact that their overall survival was the worst: 37% (postoperative radiotherapy), 40% (no radiotherapy at all) and 48% (preoperative radiotherapy). In younger patients, similar findings were encountered: 6-month mortality was 5.1%, 3.3% and 1.4% ($P < 0.0001$) for no radiotherapy, preoperative radiotherapy and postoperative radiotherapy respectively. Again, an inverse relation with overall survival was noticed: 68%, 68%, and 53% ($P < 0.0001$) for no, preoperative and postoperative radiotherapy.

In the Dutch TME study, patients aged 75 years and older showed a better response in the study arm when compared to younger patients. Younger patients have a significantly

lower local recurrence rate of 5.2% after preoperative 5 x 5 Gy radiotherapy versus 11% for patients without preoperative radiotherapy ($P = 0.001$). However, overall survival at 5 years (respectively 72% and 72%, $P = 0.30$), distant metastases free survival (74% vs. 72%, $P = 0.70$) and cancer-free survival (81% versus 69%, $P = 0.44$) were not improved. Whereas in the elderly, apart from local recurrence rate (5.4% versus 14%, $P = 0.02$), also distant metastases free survival (81% versus 69% $P = 0.07$) and cancer-free survival (81% versus 66%, $P = 0.03$) were improved. The 5-year overall survival rate in the elderly (48% versus 43%, $P = 0.27$), much like in the younger patients, was only slightly improved in the study arm that received 5 x 5 Gy preoperative radiotherapy (Figures 2 and 3).

Complications occurred more frequently in older patients: any postoperative (infectious, general or surgical) complication occurred in 42% of patients aged younger than 75 years compared with 51% in older patients ($P = 0.008$). Pulmonary, renal, neurological, and cardiac complications, and thrombo-embolism, hypertension, line sepsis, and cholecystitis were scored as general complications. Wound infection, abscess, sepsis/febris eci, and haematoma were the infectious complications, and abdominal wound dehiscence, perineal wound dehiscence, intestinal necrosis, ileus, leakage, bleeding,

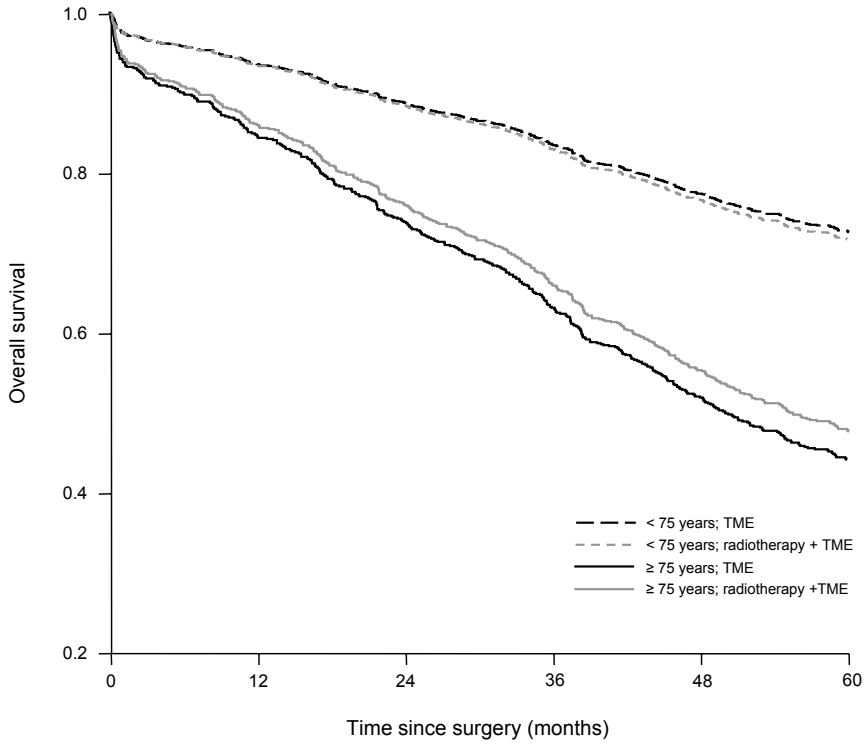

Figure 2. Cox regression overall survival curve in the TME study. A significant increase of the risk of dying for the elderly ($P < 0.0001$), but randomisation within the same age-category was of no influence.

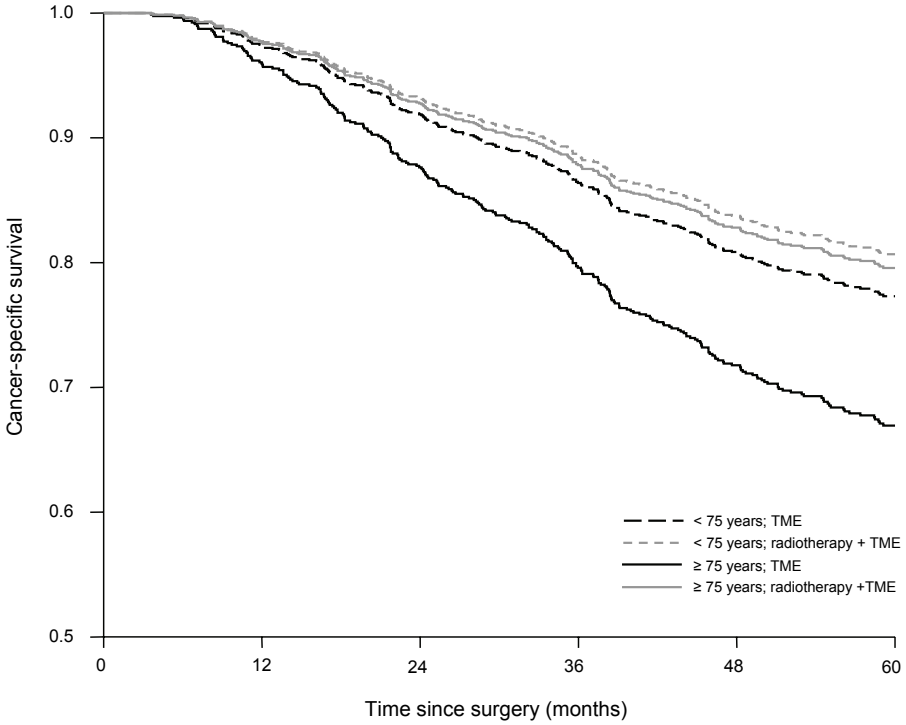

Figure 3. Cox regression survival curve of cancer-specific survival in the TME study. Cancer-specific survival was significantly decreased in the elderly, not receiving preoperative radiotherapy ($P < 0.045$, hazard ratio 1.76). No difference among the other three groups.

fistula, stoma complications, and perforation were considered surgical complications. Six-month mortality was significantly influenced by general (odds ratio (OR) = 3.74, $P = 0.002$) and surgical postoperative complications (OR = 4.93, $P < 0.001$). Radiotherapy, sex, distance, TNM stage, and perioperative complications were not independent contributors. Type of surgical resection was borderline significant ($P = 0.059$). Besides, infectious postoperative complications were not associated with 6-months mortality.

Complications had a greater impact among elderly patients compared to younger patients, i.e. if an anastomotic leakage occurs, the probability of fatal outcome is 50.0% compared to 7.1% in younger patients ($P < 0.001$). However, the overall occurrence of anastomotic leakage is not increased in the elderly: 10% in the elderly compared to 12% in the younger ($P = 0.63$, low anterior resected patients only).

DISCUSSION

From the population-based registries of the Comprehensive Cancer Centre South and Comprehensive Cancer Centre West it is evident that the prognosis of patients with rectal cancer has improved over the last 15 years.[7,8] In Sweden, having the same history of introducing 5 x 5 Gy preoperative radiotherapy and TME surgery, these findings were also made.[9] The major change in the treatment of rectal cancer was the introduction of TME surgery and the introduction of 5 x 5 Gy preoperative radiotherapy for stage 2 and stage 3 rectal cancers. From the registry-based results, it is also obvious that younger patients have more benefited more from the change in cancer treatment than the 75 years and older patients. There is a very evident paradox, as it seems that from the results of the Dutch TME study it can be concluded, that the biological behaviour of rectal cancer in the elderly in response to treatment is better than in the younger patients. Not only is local recurrence rate decreased by the addition of 5 x 5 Gy preoperative radiotherapy, but also the distant metastatic rate and the cancer-specific survival. Unfortunately, this favourable responsiveness comes with a price. The impact of complications in the elderly is more severe. However, neoadjuvant treatment does not lead to statistically significant more complications in the elderly, but this may be due to a power effect. The elderly are a small group within the Dutch TME study and in the whole group of patients treated in the Dutch TME study neoadjuvant treatment did lead to more complications.[10] In the elderly, complications more often have a fatal course. Significant mortality occurs not only during stay in hospital, but is present until 6 months after surgery. Even in the Dutch TME study where elderly patients constitute a highly selected group of patients fit enough to undergo treatment, approximately one out of six will die within 6 months after the treatment.

In the combined CCC database, 6-month mortality was equally high in all periods around 16%, indicating that the changes in therapeutical approach had little impact, and that the surgical trauma by itself, being non-TME or TME, is the most important factor for postoperative mortality. In the general rectal cancer population, the elderly suffer more often from multiple comorbidity, which causes more complications during treatment.[11] Elderly were underrepresented in the Dutch TME study. Age was no exclusion criterion but poor performance status was, and most elderly suffer from comorbidity, influencing performance status. From previous epidemiological studies it is known that older people are less likely to receive adjuvant or neoadjuvant treatment. When elderly are not considered to receive adjuvant or neoadjuvant treatment, they are considered even less for participation in a study investigating (neo-)adjuvant treatment.

Rectal cancer is a disease of the elderly. The chance of developing a rectal cancer increases with age and is highest at the age of 80.[12] The fact that survival did not improve in the older rectal cancer patients casts some doubt as to whether the approach

to rectal cancer in the elderly should be the same as in younger patients. Despite the fact that older patients respond very well to neoadjuvant treatment, the intercurrent mortality not related to cancer obscures any beneficial effect. In the elderly, not only is cancer-related mortality an outcome parameter, but also mortality which is not cancer-related. The relative risk of dying from rectal cancer is 1.6 in the elderly compared to 5.2 in younger patients. Therefore, it can be argued that the focus of treatment should be on preventing non-cancer-related mortality.

Theoretically, two approaches can be followed to achieve reduction of mortality. The first is to optimise the condition of the patient; making him or her more fit for the operation. This approach requires thorough preoperative assessment of amongst others the nutritional, metabolic, cardiac, and pulmonary status of the patient. Standardising risk assessments by the routine use of scorings systems like the P-possum may be a step forward.[13,14] However, this is beyond the scope of this article. The other approach is to reduce the risk or the toxicity of the treatment. This does not mean that a palliative treatment instead of a curative treatment should be offered. If the life expectancy exceeds 1 year, an initially palliative treatment will lead to death from progressive rectal cancer. Moreover, radiotherapy without surgery in potentially curative patients limits the palliative options in case of local progression and secondary curative surgery will certainly be more hazardous. Therefore, curative treatment is the better option.

Combined treatment is more effective than surgery alone, but also carries greater risks. Heald, who has published his excellent personal series, argues that in patients with perfect mesorectal excision, preoperative radiotherapy may be omitted.[15] However, results from the CRO7 study show that even in perfect surgery there is added value of preoperative radiotherapy.[16] An ongoing Scandinavian study investigates the effect of delaying surgery after a short course of radiotherapy.[17] The study goal is to see whether delay leads to downsizing and staging of the tumour. Other effects could be that after a waiting period of 6-12 weeks, the patient recovers from the radiotherapy and avoids the double jeopardy of radiotherapy and a major surgical trauma. Nutritional, metabolic, cardiac, or pulmonary disorders may be optimised in the waiting period.

The surgical approach must also be tailored to the patient. The keywords are optimisation of the patient and individualisation of the treatment to the patient. One of the most feared and life-threatening complications can be avoided by not restoring the continuity of the bowel. However, anastomotic leakage does not occur more often in the elderly.[18] The subsequent complications of anastomotic failure are more serious. Postoperative mortality after complications is substantially higher among the elderly. In addition, this increased mortality persists at least for the first 6 months after surgery.

Apart from a risk factor for recovery, restoration of continuity requires secondary surgery (closure of the temporary colostomy or ileostomy) with its implicit morbidity. Removal of the rectal ampulla and replacing it with the low anterior anastomosis re-

sults in a serious handicap. Most patients will experience a longer period of increased frequency, urge, soiling, fragmented and less solid defecation.[19-21] This often leads to incontinence and subsequently more dependency for care and inclination to social isolation. In a period of life with less mobility, loss of relatives and friends, threats of social isolation must be taken very seriously. Despite this fear, the TME study did not provide data that older patients more often experience worse incontinence than younger ones. At least with regard to the number of patients aged 75 years and older included in the TME study, the 10% difference in worse incontinence did not reach statistical significance.[22] The only finding in the elderly that reached statistical difference was the fact that 21% of the elderly versus 8% of the younger patients had no reversal of their temporary stoma.[23]

The role of local excision after neoadjuvant treatment or even treatment solely with chemoradiotherapy and omitting surgery has not been explored. The elderly patient, especially, is a good candidate for these sorts of studies that focus on reducing the surgical trauma.[24]

CONCLUSION

The paradox in the treatment of rectal cancer in elderly patients is that the treatment is even more effective than in younger patients, but that overall survival is obscured by an increase in non-cancer-related mortality. Improvement of outcome in elderly patients can be realised if non-cancer-related mortality is reduced. This objective can be realised by optimising the condition of the patient or by reducing the toxicity of the treatment. Ideally, randomised studies for elderly patients should be performed. Extrapolation of results of younger patients may not be appropriate. Postoperative or post-treatment mortality should be recorded for at least up to 6 months after the primary treatment. The (in)capacities to take care of themselves and the social environment must bear more weight than the technical possibilities in proposing certain surgical procedures.

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Chapter 4

Controversies of total mesorectal excision for rectal cancer in elderly patients

Harm J.T. Rutten, Marcel den Dulk, Valery E.P.P. Lemmens, Cornelis J.H. van de Velde, Corrie A.M. Marijnen

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ABSTRACT

The cornerstone of treatment for rectal cancer is resectional treatment according to the principles of total mesorectal excision (TME). However, population-based registries show that improvements in outcome after resectional treatment occur mainly in younger patients. Furthermore, 6-month postoperative mortality is significantly increased in elderly patients (≥ 75 years of age) compared with younger patients (< 75 years of age). Several confounding factors, such as treatment-related complications and comorbidity, are thought to be responsible for these disappointing findings. Thus, major resectional treatment is not advantageous for all older patients with rectal cancer. However, the Dutch TME trial showed a good response to a short course of neoadjuvant radiotherapy in the elderly patients. Biological responses to cancer treatment seem to change with age, and, therefore, individualised cancer treatments should be used that take into account the heterogeneity of ageing. For elderly patients who retain a good physical and mental condition, treatment that is given to younger patients is deemed appropriate, whereas for those with diminished physiological reserved and comorbid conditions, alternative treatments that keep surgical trauma to a minimum and optimise the use of radiotherapy might be more suitable.

INTRODUCTION

The effectiveness of surgery for rectal cancer in the elderly (≥ 75 years of age) can be measured by survival, postoperative morbidity and mortality, and the ability of the patient to regain the independence they had before the surgery. The incidence of rectal cancer is highest at around 80 years of age. However the incidence of comorbidity, which renders the patient vulnerable to postoperative complications, is also highest after this age (Figure 1).[1-3]

Population-based studies have shown that the prognosis of patients with rectal cancer has improved over the past few decades. The Danish Nationwide Cancer Registry, a population-based registry with almost complete ascertainment, showed that between 1977 and 1999, 5-year survival gradually improved in all age groups, with the biggest improvement seen in the period between 1977 and 1989. In elderly patients, 30-day and 6-month mortality decreased substantially over time. Better anaesthesia, improved health awareness leading to earlier stage diagnoses, less emergency procedures (surgery within 24 h after first onset of symptoms), improved access to health-care services, and greater availability of effective treatments were considered factors responsible for these findings.[4] In the Netherlands, Dutch cancer registries also noted an improvement in outcome after surgery for rectal cancer, which accelerated in the 1990s.[5]

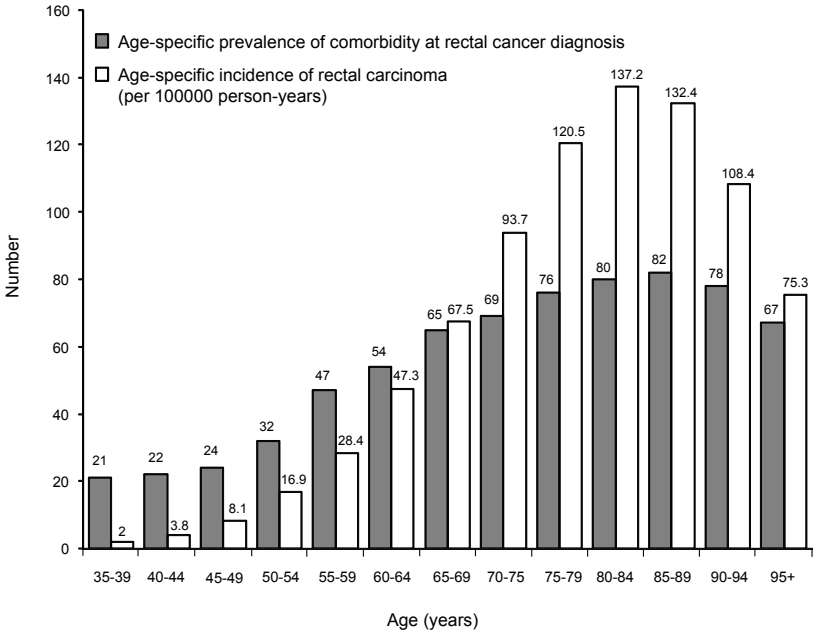

Figure 1. Prevalence of comorbidity and incidence of age-specific rectal cancer.

An explanation for the improvement in the 1990s might be the introduction of total mesorectal excision (TME), which has become the standard for resectional treatment. Heald and colleagues[6] introduced this technique, in which the rectum is removed enveloped within its mesorectal fascia, and Quirke and co-workers[7] provided the anatomical basis for this concept by showing that an uninvolved circumferential margin is the most important independent factor for avoiding local recurrence.

In the Netherlands, TME surgery was introduced as a result of a trial done in 1996 that compared TME surgery with and without a short course of preoperative radiotherapy (5 fractions of 5 Gy).[8] On the basis of the findings of this trial, TME combined with preoperative radiotherapy was rapidly accepted as the standard treatment for rectal cancer. However, the mean age of the patients included in the trial was 63 years, and, although no upper age limit was used, there is concern that the elderly population was underrepresented. In most population-based studies, the mean age of patients with rectal cancer is 70 years and the relative incidence increases with age, reaching a maximum at 80 years of age.[9] Therefore, whether the findings of the TME trial are applicable to the elderly population is unclear.

Other reports of under-representation of the elderly in clinical trials also exist.[10,11] The opinion that geriatric patients do not tolerate cancer treatment well might be a reason for why they are not always included in prospective randomised studies. Other possible explanations are exclusion criteria for comorbidity, which is increasingly present in older patients, and the reluctance of investigators to include frail patients in such trials. Despite this issue, the findings from most studies are presented irrespective of participant age. The exclusion of older populations from these trials leaves important questions unanswered - i.e., are biological behaviour and responsiveness to treatment independent from age; and how do cancer treatments interact with the vulnerability of ageing people? In this paper, we will address the above mentioned topics and propose alternatives for the treatment of elderly patients with rectal cancer.

METHODS

Two datasets were used for our analyses: data from the Dutch TME study and data from the Dutch Comprehensive Cancer Centres (CCC) South and West combined. Both datasets have been published before.[12,13] However, for this review new, unpublished analyses have been done. In the TME study 1356 patients had curative resection (1126 patients aged < 75 years and 230 patients aged ≥ 75 years). 99% of patients had complete follow-up. In this dataset, we focused on mortality in elderly patients. In the Dutch CCC South and West combined dataset, 4567 patients had curative resection during the period 1990-2002, of whom 28% were aged 75 years or more.[12]

Data were analysed with the SPSS package (version 15.0 for Windows; SPSS Inc., Chicago, IL, USA), and SAS (version 9; SAS Institute Inc., Cary, NC, USA). Forest plots were drawn with software from Biostat (Comprehensive Meta-analysis Version 2; Biostat, Englewood, NJ, USA).

The prevalence of comorbidity, including hypertension, in the area of the Comprehensive Cancer Centre South was recorded according to a slightly adapted version of the Charlson Index.[1,2] Patients with missing data were excluded from the comorbidity analysis. European standardised incidence rates of rectal cancer in the Netherlands were downloaded from the website of the Dutch Comprehensive Cancer Centres.[3] Age-specific life expectancy tables were used from the Dutch Central Bureau of Statistics to calculate relative risks of dying for patients with rectal cancer compared with the general population, by means of Cox regression. *P*-values lower than 0.05 were considered significant. All eligible Dutch patients from the Dutch TME trial who underwent a resection and had no evidence of distant metastasis at the time of surgery were included in the analysis of the relative risk of dying from a complication within 6 months of surgery for patients aged 75 years or more compared with those aged less than 75 years.[13] 95% confidence intervals (CIs) not including 1 were considered to indicate significant differences between the respective age groups. No imputation methods of missing values were used because completeness of data in the TME trial exceeded 99%.

Findings from the analyses were compared with the published work. We searched Medline, Scopus, and the Cochrane database for articles published in English back to January 1997. The following search terms were used: "rectal cancer and elderly (ageing)", "preoperative irradiation", "local excision", and "chemoradiation". Reference lists were used for further search.

RESULTS

The combined cancer registries of the CCC South and West failed to show a beneficial effect of the use of TME surgery in elderly patients (Figure 2). Table 1 provides the relative risk of dying of rectal cancer according to 3-year age groups compared with the general population, and shows that age is an independent risk factor. Therefore, the effectiveness of TME surgery for rectal cancer in the overall population cannot be simply derived from the findings of studies that involve a predominantly younger age group. In a younger patient group with a high relative risk of dying from cancer, a small treatment benefit might be worthwile. However, in elderly patients, such a benefit might be overshadowed by their increased vulnerability and decreased tolerance, resulting in greater postoperative mortality than in younger patients.

Table 1 also shows postoperative 30-day mortality and 6-month mortality for each

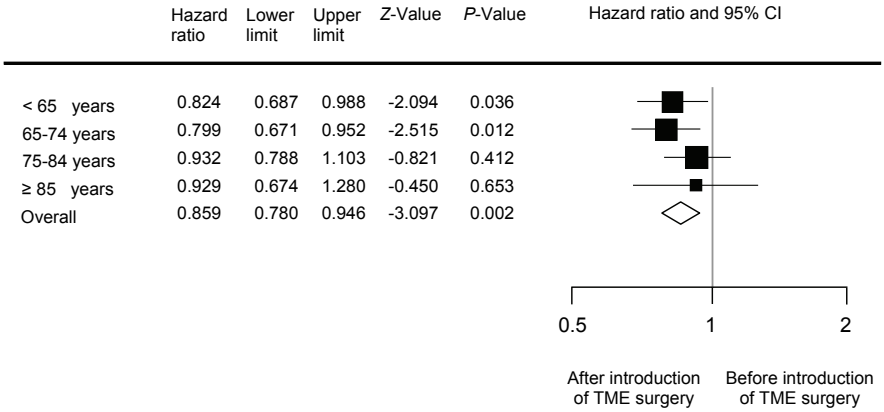

Figure 2. Overall survival per age group before and after the introduction of total mesorectal excision (TME) in the Netherlands. Data from the Dutch Comprehensive Cancer Centres South and West combined database. CI = confidence interval.

Table 1. Relative risk of dying after curative rectal cancer surgery compared with the general population. Data from the Dutch Comprehensive Cancer Centres South and West. CI = confidence interval.

Age (years)	*n*	Relative risk	95% CI	*P*-value	30-day mortality (%)	6-month mortality (%)
< 61	1179	123	56-275	0.0001	1.1	2.1
61-63	354	127	20-806	<0.0001	1.1	3.1
64-66	401	9.0	6.4-12	<0.0001	2.0	4.7
67-69	481	4.7	3.7-6.1	<0.0001	2.5	6.2
70-72	428	3.1	2.5-3.9	<0.0001	1.6	4.9
73-75	452	2.8	2.2-3.4	<0.0001	3.5	8.0
76-78	423	1.8	1.5-2.2	<0.0001	6.9	13.0
79-81	329	1.6	1.3-2.0	<0.0001	7.9	14.9
82-84	321	1.2	0.9-1.6	0.17	10.4	17.7
85-87	169	2.4	1.7-3.2	<0.0001	14.8	27.2
88-90	71	1.5	0.9-2.5	0.09	18.3	26.8
> 90	31	1.5	0.5-2.5	0.14	25.8	38.7

age group after curative surgery for rectal cancer. An increase can be seen in both 30-day mortality and 6-month mortality in elderly patients, representing one of the major drawbacks of surgery for rectal cancer in this population. In patients above 75 years of age, 6-month mortality increases compared with patients aged 75 years or younger. This proportion increases to almost 40% in patients older than 90 years of age. Unfortunately, the introduction of TME surgery has not resulted in a decrease in 6-month mortality.[12] Figure 3 shows 30-day and 6-month mortality per age group for the CCC South and West combined dataset and the Dutch TME trial dataset.

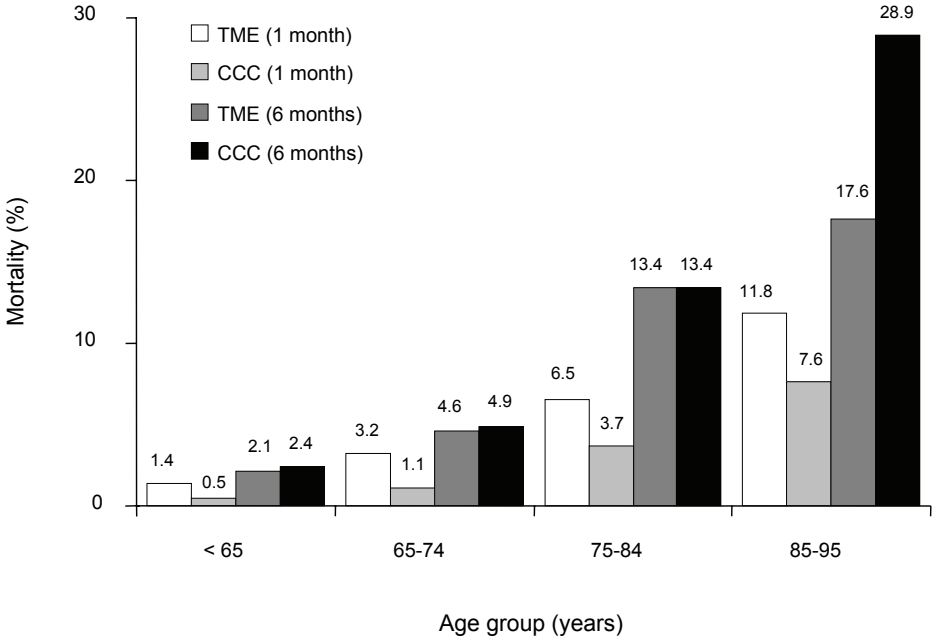

Figure 3. 1-month and 6-month mortality per age group in the Dutch TME study and the population-based Comprehensive Cancer Centres (CCC) database.

DISCUSSION

Rectal cancer surgery is a major procedure, highlighted by the number of postoperative complications. The occurrence of complications is associated with a higher postoperative mortality, which, in elderly patients, persists for at least 6 months, compared with a few weeks after surgery in younger patients.

Table 2 presents the complications that occurred in elderly patients in the Dutch TME trial (unpublished), showing that elderly patients are liable to more complications than their younger counterparts. Furthermore, these complications were associated with higher mortality. Even complications in elderly that occurred at a similar or lower frequency compared with younger patients were associated with more severe consequences. The best example of such a complication is anastomotic leakage. This leakage occurred at a similar rate in younger and elderly patients, but the ensuing mortality in elderly patients was 57% compared with just 8.2% in younger patients. Furthermore, complications including abscesses, sepsis, and postoperative pulmonary and cardiac problems were related to a significantly increased risk of dying within 6 months post-surgery in elderly patients compared with younger patients.

Several studies have addressed the issue of why elderly patients benefit less than younger patients from surgical treatment for rectal cancer. Shahir and colleagues[14]

Table 2. Relation between morbidity and 6-month mortality in the Dutch TME trial.

Variable	Prevalence *n* (%)		6-month mortality *n* (%)		Relative risk*	95% CI
	< 75 years	≥ 75 years	< 75 years	≥ 75 years		
Postoperative infections	208 (18.5)	49 (21.3)	19 (9.1)	11 (22.4)	2.46	1.25- 4.82
Abdominal wound infection	69 (6.1)	17 (7.4)	3 (4.3)	2 (11.8)	2.71	0.49- 14.94
Perineal wound infection (APR only)	35 (10.1)	13 (19.4)	1 (2.9)	0 (0.0)	0	----
Urinary tract infection	96 (8.5)	27 (11.7)	2 (2.1)	3 (11.1)	5.33	0.94- 30.31
Abscess	37 (3.3)	11 (4.8)	1 (2.7)	3 (27.3)	10.09	1.16- 87.57
Sepsis	69 (6.1)	11 (4.8)	15 (21.7)	7 (63.6)	2.93	1.56- 5.51
Fever without known cause	9 (2.0)	0 (0.0)	1 (11.1)	0 (0.0)	0	----
Other	9 (0.8)	1 (0.4)	1 (11.1)	0 (0.0)	0	----
General postoperative complications	163 (14.5)	49 (21.3)	19 (11.7)	15 (30.6)	2.63	1.45- 4.77
Pulmonary complications	78 (6.9)	27 (11.7)	5 (6.4)	7 (25.9)	4.04	1.40- 11.69
Renal complications	8 (0.7)	2 (0.9)	3 (37.5)	1 (50.0)	1.33	0.26- 6.94
Neurological complications	18 (1.6)	3 (1.3)	2 (11.1)	0 (0.0)	0	----
Venous thrombosis	6 (0.5)	0 (0.0)	0 (0.0)	0 (n.a.)	0	----
Embolism	17 (1.5)	2 (0.9)	5 (29.4)	1 (50.0)	1.70	0.35- 8.17
Cardiac complications	35 (3.1)	20 (8.7)	6 (17.1)	10 (50.0)	2.92	1.25- 6.82
Line sepsis	18 (1.6)	1 (0.4)	2 (11.1)	0 (0.0)	----	----
Cholecystitis	13 (1.2)	2 (0.9)	1 (7.7)	1 (50.0)	6.50	0.63- 67.35
Postoperative surgical complications	302 (26.8)	61 (26.5)	25 (8.3)	19 (31.1)	3.76	2.22- 6.39
Abdominal wound dehiscence	35 (3.1)	5 (2.2)	3 (8.6)	2 (40.0)	4.67	1.02- 21.43
Perineal wound dehiscence (APR only)	34 (9.5)	10 (14.9)	1 (2.9)	2 (20.0)	6.80	0.69- 67.46
Intestinal necrosis	10 (0.9)	1 (0.4)	4 (40.0)	1 (100.0)	2.50	1.17- 5.34
Ileus	64 (5.7)	18 (7.8)	6 (9.4)	2 (11.1)	1.19	0.26- 5.38
Anastomotic leakage (LAR only)	85 (11.5)	14 (10.1)	7 (8.2)	8 (57.1)	6.94	2.99- 16.11
Fistula	20 (1.8)	0 (0.0)	3 (15.0)	0 (n.a.)	0	----
Perforation	14 (1.2)	0 (0.0)	6 (42.9)	0 (n.a.)	0	----
Haematoma	9 (0.8)	0 (0.0)	0 (n.a.)	0 (n.a.)	0	----
Bleeding	42 (3.7)	8 (3.5)	6 (14.3)	3 (37.5)	2.63	0.82- 8.39
Stoma complications	23 (2.0)	3 (1.3)	1 (4.3)	2 (66.7)	15.33	1.92-122.39
Other	52 (4.6)	15 (6.5)	3 (5.8)	3 (20.0)	3.47	0.78- 15.44
Any postoperative complications	471 (41.8)	118 (51.3)	33 (7.0)	27 (22.9)	3.27	2.05- 5.21

* Relative risk of 6-month mortality for patients aged ≥ 75 years compared with those aged < 75 years. APR = abdominoperineale resectie; LAR = low anterior resection; CI = confidence interval; n.a. = not available.

showed in a regional setting that older patients (≥ 70 years) were at higher risk of developing treatment-related complications than younger patients (< 70 years). They noted that age, comorbidity, and the number of postoperative complications were sig-

nificantly related with worse outcome. In a subset of patients, the presence of chronic obstructive pulmonary disease and deep vein thrombosis led to a higher occurrence of perioperative complications.[15] An extended study[2] of the Comprehensive Cancer Centre South showed that 65% of patients aged 65-79 years and 70% of patients aged 80 years or over had one or more comorbid conditions, and about half of these patients had two or more comorbid conditions. Additionally, comorbidity was shown to significantly decrease the chance of being treated with TME surgery and was strongly associated with diminished survival.

Similarly, in a systematic review by the Colorectal Cancer Collaborative Group,[16] age was noted to be an important risk factor for 30-day mortality, with a 3.2 times increased risk in the 75-84-year age group and a 6.2 times increased risk in the 85-years-and-older age group compared with younger patients. Although all types of general complications were significantly increased in the older age groups (i.e., pneumonia, thromboembolism, and cerebrovascular complications), anastomotic leakage was not correlated with age.[16]

In addition to the risks of anastomotic leakage, functional outcome after bowel restoration should also be taken into account. When confronted with the choice between a permanent colostomy and restoration of bowel continuity, most patients will opt for the latter choice. Technically, the restoration of bowel continuity is feasible in most patients with rectal cancer. With the protection of a diverting stoma, more than 90% of the anastomoses at the pelvic floor level or lower will heal, and, in elderly patients, the number of anastomotic failures is similar to that in younger patients.[17] However, there are several disadvantages of this procedure. In addition to an increased risk of mortality in case of anastomotic failure, 20% of diverting stomas in elderly patients will not be reversed for many reasons.[18] Furthermore, a return of manageable bowel function is not guaranteed. After removal of the rectal ampulla, bowel function will change and can take up to 2 years before an end stage is reached. Side studies of the Dutch TME trial have shown that, in most patients, a high frequency of defecation, fractionated defecation, urge, and incontinence will occur, at least temporarily. If the anal sphincter was included in the radiation field, incontinence will be a problem in almost all patients.[19] The consequences of the changes in defecation patterns can be grave in elderly patients. The increase and urge of bowel movements can prevent patients from leaving their home and can, therefore, lead to social isolation. Loss of functionality, which is a threat to the delicate balance between living an independent life and depending on others, often leads to a depersonalised, institutionalised life. Several researchers have shown that quality of life can be better with a stoma than with a low anastomosis.[20,21] Multidimensional assessment of individual cases is needed for deciding whether an anastomosis is technically feasible, safe, but above all desirable.

Future perspectives

The current evidence shows that findings from randomised studies on the treatment of rectal cancer cannot be automatically applied to elderly patients, in whom treatment of rectal cancer is a multidimensional issue. Apart from being an oncological problem, this issue is also associated with the physiological changes caused by aging, whereby patients become more vulnerable to noxious effects, which are often exaggerated by comorbid conditions. Population-based studies often claim that elderly patients, who undergo the same cancer treatment as their younger counterparts, have a more favourable outcome than elderly patients who do not have these treatments,[22] and undertreatment of the elderly has been suggested as the reason for decreased rectal-cancer-specific survival in this population.[23] However, these studies do not provide convincing evidence that elderly patients should have the same treatment as younger patients. The factors responsible for the obvious selection bias when recruiting elderly patients into clinical trials are not well explained. Sufficient evidence exists to support the statement that cancer-specific survival after major resection is not age dependent.[24-29] However, all researchers agree that postoperative mortality is at least doubled in elderly patients after resection compared with younger patients after resection and that careful selection should be made. None of the studies provided data for 6-month mortality, but, as can be noted from our analysis presented in Table 1, a further doubling of postoperative mortality at 6 months and thereafter is very likely.

Thus, major surgical treatment might not be the best option for all elderly patients with rectal cancer. However, biological age is not the only factor to be taken into account when including patients in this at-risk group, and more reliable parameters are mandatory when selecting patients for certain treatments. Obviously, in the very fit (i.e., American Society of Anesthesiologists (ASA) grade I) and the very ill (ASA IV-V) the decision to treat with curative intent or to provide palliative care is not difficult to make. The Association of Coloproctology of Great Britain and Ireland (ACPGBI) has developed an excellent scoring system for 30-day mortality on the basis of a prospective survey of more than 8077 patients with colorectal cancer in 79 hospitals (ACPGBI Colorectal Cancer Study).[30,31] Several other scoring systems (i.e., Possum, P-Possum, and CR-Possum) have also been developed, which take into account physiological status and the extent of the procedure, and have produced similar findings. Validation studies have confirmed the usefulness of these systems to predict mortality.[32] For example, the operative mortality risk for patients aged 75-95 years with ASA II-III ranges from 5.4% to 13.5%, as shown in Figure 4 on the basis of the ACPGBI score for resected rectal cancer (Tumour Node Metastasis stage 2 and 3).

Although these scoring systems can help to identify and quantify the risk associated with resectional treatment for a given physiological performance status, they cannot be used as a definite decision aid. A 20% operative mortality risk might be acceptable for a disease that leads to debilitating symptoms if left untreated, but is probably not

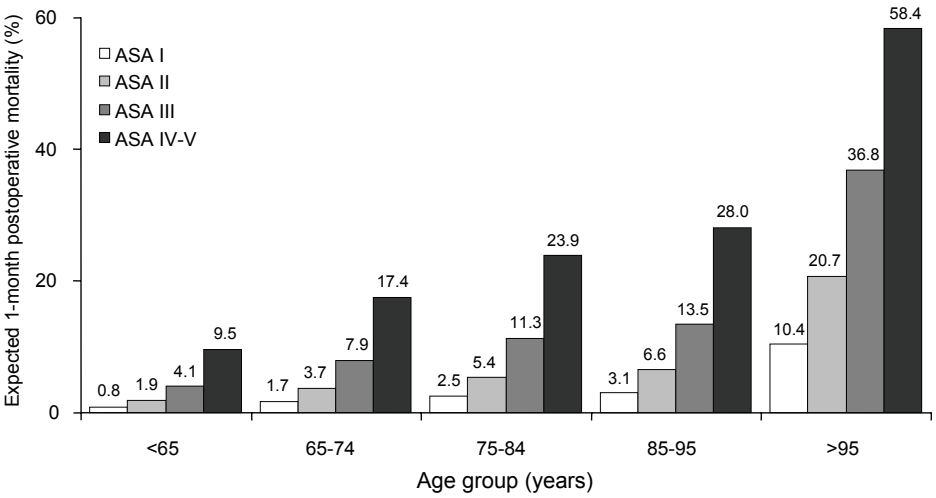

Figure 4. Expected 1-month postoperative mortality for a group of patients with stage 2 and stage 3 rectal cancer according to the Association of Coloproctology of Great Britain and Ireland score. ASA = American Society of Anesthesiologists grade.

acceptable for a small, well-differentiated tumour. Furthermore, the most important question for older patients is not whether they will survive, but, rather, how their quality of life will be affected after surgery - i.e., will their functional status deteriorate and will an independent life still be possible? Mortality scoring systems do not help to answer these questions.

Alternatives for TME surgery for elderly patients

The standardised approach of TME is certainly the best way to avoid local recurrence. However, with the extremely high 6-month postoperative mortality associated with this procedure in elderly patients, the search for safer alternatives is imperative.

In a paper describing the effects of introducing TME surgery in the general population,[12] we showed that radiotherapy was not responsible for the increased mortality in elderly patients and that surgical trauma remained the heaviest burden on mortality. Figure 5 shows cancer-specific survival in the Dutch TME trial. Cancer-specific survival in elderly patients was significantly improved in the study group that received five fractions of 5 Gy preoperative radiotherapy, whereas this improvement did not occur in younger patients.

Future research should take advantage of this finding. The important question is whether radiotherapy can have a more prominent role in the treatment of rectal cancer in the elderly and, thus, avoid the morbidity and mortality associated with major resectional treatments. A concern of omitting mesorectal excision in these patients is the possibility of leaving positive lymph nodes behind, which might cause local recur-

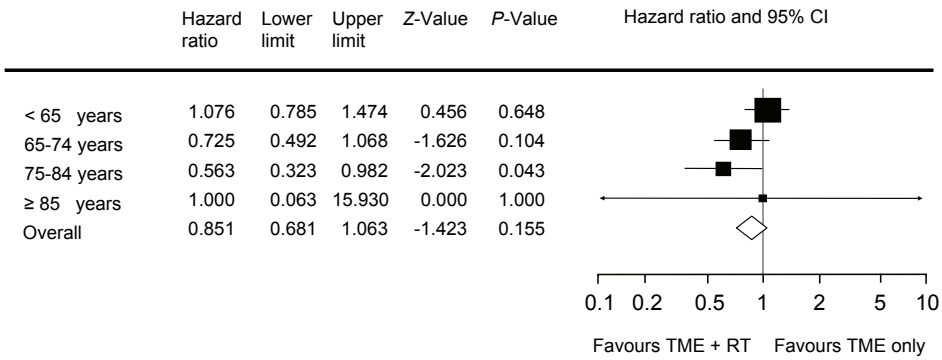

Figure 5. Cancer-specific mortality per age group in the Dutch TME trial. TME = total mesorectal excision; RT = radiotherapy; CI = confidence interval.

rence. However, Read and colleagues[33] showed that in patients whose tumours were downstaged to T0-1 after neoadjuvant radiotherapy and chemoradiotherapy, nodal metastases were rare. Furthermore, publications by Hughes and colleagues[34] and Ratto and colleagues[35] confirm that good responders to neoadjuvant treatment have little chance of persisting nodal metastases. On the basis of these findings, we now discuss several alternative treatment options for rectal cancer in elderly patients.

Chemoradiotherapy alone

In a study by Habr-Gama and colleagues,[36] which included patients with mainly T3 rectal cancers, 71 patients who had a complete clinical response after chemoradiotherapy were closely observed and not operated on. With a mean follow up of 57 months, two patients developed a local recurrence, of which one underwent a successful salvage operation. An additional three patients developed distant metastases. Up to now, no other studies to our knowledge have confirmed these findings.

Radiotherapy in combination with local excision

Less invasive surgical techniques than TME, such as local excision or transanal endoscopic microsurgery (TEM), have resulted in promising findings in the treatment of early rectal cancer, especially in terms of low morbidity and mortality. However, the benefits of these less invasive treatments should be carefully weighed against the increased risk of local recurrence.

For early-stage rectal cancer (T1N0), a trial that randomly assigned patients to either TEM or anterior resection showed significantly less blood loss in the TEM group than in the anterior resection group (143 mL versus 745 mL) and shorter hospitalisation times (5.7 days versus 15.4 days). Local control in the anterior resection group was 100% compared with 95.8% in the TEM group.[37-43] On the basis of these findings, TEM has become a widely accepted treatment modality for T1N0 rectal cancers.

For T2 and T3 tumours, the findings for TEM surgery are less satisfactory, even when combined with postoperative radiotherapy of chemoradiotherapy. Local recurrence of these tumours varies from 10% to 36%,[44-50] suggesting that postoperative radiotherapy or chemoradiotherapy is incapable of eradicating possible lymph node involvement. However, the combination of preoperative radiotherapy or chemoradiotherapy with TEM seems to be more promising.[51] Only one small randomised trial to our knowledge has been done for low T2N0 tumours (situated in the distal rectum), which showed no difference in local control between patients who underwent local excision or laparoscopic resection after chemoradiotherapy.[51] In accordance with this finding, several researchers have reported local control between 90% and 95% for patients with T2 or T3 tumours treated with this approach.[52-56] However, the addition of chemotherapy to radiotherapy, which has produced promising findings in younger patients for downsizing tumours, might become a problem in elderly patients who are unfit for resectional treatment. By contrast, elderly patients respond well to radiotherapy alone, and this might also be an option to be investigated, in terms of a short or long course radiotherapy, without chemotherapy, followed by a longer waiting period before re-evaluation for local excision.

Radiotherapy as radical treatment option

In this context, the role of radiotherapy is limited to the (neo)adjuvant or palliative setting, because a very high dose of radiation (at least 60 Gy, but probably more than 80 Gy) needs to be given for control of rectal carcinomas by radiotherapy alone.[57,58] However, external-beam radiotherapy doses higher than 50 Gy will result in increased late toxic effects, which are the limiting factor for dose escalation in external-beam radiotherapy. To overcome this dose limitation, intracavity irradiation, either by contact X-rays or by intraluminal brachytherapy, which enables the delivery of a high dose of radiation to the tumour with low doses to the surrounding normal tissue, might be explored.

Papillon and Berard[59] described the value of contact X-rays for early rectal cancers (T1 and favourable T2 lesions) and reported 4.5% local failure and 74% survival after 5 years. Several other investigators have confirmed these findings in studies with contact X-rays for patients with T1N0 and small T2N0 rectal cancer.[60-66]

For patients with more advanced tumours, the risk of nodal involvement is high and a combination of contact treatment or interstitial brachytherapy with external-beam radiotherapy is needed to address this problem. Several publications have shown that the combination of local and external radiotherapy leads to 63%-85% local recurrence in T2 and T3 tumours.[66,67]

These findings show that radical radiotherapy might be a good alternative to TME, especially for elderly patients who are unable to undergo any surgical procedure. For patients with small tumours with a low likelihood of nodal involvement, locally applied radiotherapy might be appropriate, as long as the total dose to the tumour is about

80 Gy. For larger tumours with possible lymph node involvement, a combination of external-beam radiotherapy and brachytherapy can be an option.

CONCLUSION

After major resectional treatment, elderly patients with rectal cancer have an increased 30-day and 6-month mortality compared with younger patients. Treatment-related mortality is an important competitive risk factor, which obscures the positive effect of modern rectal cancer treatment in those aged 75 years and above. Easy and applicable physiological and clinical scoring systems have been developed and validated as instruments for the identification of those with a high operative risk. Additionally, in frail patients, a multidimensional assessment of the relevant medical, functional, social, and mental parameters is necessary to define an appropriate treatment goal. In such an individualised treatment plan, the optimum oncological outcome might not be the most important objective.[68] Less invasive treatment options for rectal cancer in the elderly patients are gaining increased interest. Furthermore, elderly patients seem to respond well to radiotherapy, and might, therefore, become the main beneficiaries from the use of radical radiotherapy in this setting. As such, the elderly population might be a suitable patient group for research in this field.

Despite the fact that we have limited knowledge of the biology of rectal cancer in the elderly patients, treatment options for this population need to be explored, and individualised treatment approaches should be considered in order to maintain a good quality of life for each patient. Such treatment needs to involve specialised services that are capable of obtaining optimum outcomes for this multifactorial issue.

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Chapter 5

The abdominoperineal resection itself is associated with an adverse outcome: the European experience based on a pooled analysis of five European randomised clinical trials on rectal cancer

Marcel den Dulk, Hein Putter, Laurence Collette, Corrie A.M. Marijnen, Joakim Folkesson, Jean-Francois Bosset, Claus Rödel, Krzysztof Bujko, Lars Påhlman, Cornelis J.H. van de Velde

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ABSTRACT

Purpose

The aim of this study is to identify factors associated with the decision to perform an abdominoperineal resection (APR) and to assess if these factors or the surgical procedure itself is associated with circumferential resection margin (CRM) involvement, local recurrence (LR), overall survival (OS), and cancer-specific survival (CSS).

Patients and methods

The Swedish Rectal Cancer trial (SRCT), TME trial, CAO/ARO/AIO-94 trial, EORTC 22921 trial, and Polish Rectal Cancer trial (PRCT) were pooled. A propensity score was calculated, which indicated the predicted probability of undergoing an APR given gender, age and distance, and used in the multivariate analyses.

Results

An APR procedure was associated with an increased risk of CRM involvement (odds ratio (OR) 2.52, $P < 0.001$), increased LR rate (hazard ratio (HR) 1.53, $P = 0.001$) and decreased CSS rate (HR 1.31, $P = 0.002$), whereas the propensity score was not.

Conclusion

The results suggest that the APR procedure itself is a significant predictor for nonradical resections and increased risk of LR and death due to cancer for patients with advanced rectal cancer.

INTRODUCTION

At the end of the 1980s, the 5-year overall survival (OS) rate for curatively treated rectal cancer was around 50%.[1] During the early 1990s it became clear that the previously used bowel margin of 5 cm distal from the tumour could be safely reduced to 2 cm or less.[2] In the same time period, the total mesorectal excision (TME) technique was introduced as the standard of care for rectal cancer.[1,3,4] As a result, less abdominoperineal resections (APR) were performed.[5,6]

Although the general OS improved since the introduction of the TME technique, several studies showed that patients treated with a low anterior resection (LAR) had a 10% better survival rate than patients treated with an APR.[7-10] Recently, Påhlman and colleagues reported the results from 1995 to 2003 of the Swedish Rectal Cancer Registry, a large nationwide Swedish audit.[10] They showed that after the introduction of the TME technique in Sweden, the APR procedure was less frequently performed. However, the APR was still associated with a reduced OS compared to the LAR procedure: 59.8% 5-year survival for patients treated with an APR compared with 70.1% for patients treated with a LAR.[10]

It is not clear if the observed worse outcome of patients undergoing an APR is a result of the surgical procedure itself or solely related to patient- and tumour-related factors that drove the decision to perform an APR in the first place. The aim of the present analyses is first to identify patient- and tumour-related factors associated with the decision to perform an APR, and next, to assess if these patient- and tumour-related risk factors or the type of surgery itself is independently associated with circumferential resection margin (CRM) involvement, local recurrence (LR), OS, and cancer-specific survival (CSS) in a pooled database of treatment variables of five large European trials in rectal cancer.

PATIENTS AND METHODS

Trials and patients

The individual patient data of the following five trials were collated: Swedish Rectal Cancer trial (SRCT)[11], Dutch TME trial[3], German CAO/ARO/AIO-94 trial[12], EORTC 22921 trial[13], and the Polish Rectal Cancer trial (PRCT)[14]. The SRCT randomised 1180 patients between surgery alone and 5 x 5 Gy preoperative radiotherapy followed by surgery (1987-1990).[11] The Dutch TME trial (*n* = 1861, 1996-1999) randomised patients between TME alone and 5 x 5 Gy preoperative radiotherapy followed by TME.[3] The German trial compared preoperative chemoradiotherapy with postoperative chemoradiotherapy (1995-2002, *n* = 823).[12] In EORTC trial 22921 (1993-2003), 1011 patients were randomised in one of four arms: (1) preoperative 45 Gy radiotherapy, (2) preoperative chemoradiotherapy, (3) pre-

operative radiotherapy and postoperative chemotherapy, and (4) preoperative chemoradiotherapy and postoperative chemotherapy.[13] In the PRCT (n = 312), that recruited from 1999 to 2002, preoperative 5 x 5 Gy radiotherapy was compared with preoperative chemoradiotherapy.[14] From this pooled database, all eligible patients, without distant metastases at the time of surgery, treated with LAR or APR were selected. Patients who were treated with a Hartmann's procedure (a LAR in which instead of an anastomosis an endcolostomy is performed) were included in the LAR group. Unless indicated differently, both types of resections will be referred to as a LAR. Because only patients with an advanced tumour stage were included in the German CAO/ARO/AIO-94, EORTC 22921, and PRCT, only the patients with a T3-4 tumour were selected from the SRCT and the Dutch TME trial, and the patients with a T1 or T2 tumour who were entered into these two trials were excluded (TNM classification of malignant tumours fifth edition[15]). As the distance between the tumour and the anal verge was used in the calculations of the propensity score, patients in whom the distance was unknown were excluded. To adjust the survival analyses for different age limits allowed in the various trials, those analyses were restricted to only patients aged 75 year or less.

End-points, variables and statistics

First, the following factors were studied in a multivariate logistic regression analysis for their association with the decision for an APR by preference over an LAR: gender, age, and distance of the tumour to the anal verge. These factors were considered as they were available at the time of the surgical procedure. A propensity score was then calculated from the logistic regression as the predicted likelihood to undergo an APR given gender, age and distance between the tumour and the anal verge; a low score corresponds to a low probability of undergoing an APR and a high score corresponds to a high probability of undergoing an APR. This propensity score was then categorised into quartiles. Second, both the propensity score and the type of surgical resection actually performed were assessed as predictors in four multivariate models predicting, respectively, the risk of CRM involvement (logistic regression), LR, OS, and CSS (Cox regression). The analysis for CRM was adjusted, and the analyses for LR, OS, and CSS were stratified for trial and randomisation arm. A positive CRM was defined as microscopic or macroscopic tumour in the resection margin. The information about CRM was not available for the SRCT, thus patients from this trial were excluded of the analysis of CRM. For the calculation of LR and OS, the time from surgery to, respectively, LR and death was used. CSS was defined as the time from surgery to death due to rectal cancer. LR probabilities are reported as cumulative incidences with death as a competing risk; CSS is reported as one minus cumulative incidence with death due to other causes as competing risk.[16]

Data were analysed with the SPSS package (SPSS 14.0 for Windows; SPSS Inc., Chicago, IL, USA). Statistical significance was claimed at the two-sided 0.05 significance level.

RESULTS

Patients

In total, 5187 patients were included in the SRCT, Dutch TME trial, German CAO/ARO/AIO-94 trial, EORTC 22921 trial, and the PRCT. Of these, 124 were ineligible (2.4%). Besides, 1142 patients with a T1-2 tumour from the SRCT and TME trial were excluded. Another 148 patients had distant metastasis at the time of surgery; 70 patients had other procedures than LAR, Hartmann's procedure or APR. The distance between the tumour and the anal verge was unknown in 70 patients. Therefore, 3633 patients (70.0%) were included in the analyses of the type of surgery and LR. Patient and tumour characteristics are shown in Table 1 separately for patients treated with a LAR (including Hartmann's procedure) and an APR. The median follow-up of patients alive was 5.4 years (range 0.2-14.9 years). The analysis of CRM involvement was restricted to 2760 of these 3633 patients for whom the CRM status was known. OS and CSS were studied in 3330 of 3633 patients who were aged 75 years or less. In all the presented analyses, patients treated with a Hartmann's procedure were included. If, however, patients treated with a Hartmann's procedure were excluded from the analyses, the results of the following analyses were similar (data not shown).

Type of surgery

The following factors were independently associated with the decision to perform an APR: male gender, age above 60 years, and a tumour located within 7 cm from the anal verge (Table 2A). This model was used to calculate the propensity score: the predicted likelihood to undergo an APR or LAR given gender, age, and distance (range 0.053-0.900). The regression coefficients determining the propensity score are shown in Table 2A. Patients were then classified by quartiles of the propensity score and this grouping was used in all further analyses (patients in the lowest quartile have the lowest probability of being selected for an APR, given their age, gender, and tumour localisation; Table 2B).

Circumferential resection margin

Tumour cells were found in the CRM in 188 patients of 2760 (6.8%). In 93 of 1863 patients (5.0%) treated with a LAR and 95 of 897 patients (10.6%) with an APR, the CRM was tumour positive. The multivariate prognostic factor analysis for the end-point CRM involvement is displayed in Table 3: Table 3A shows the model with type of surgical procedure and propensity score; Table 3B shows the impact of the separate variables. The type of the surgical procedure predicted significantly for the risk of CRM involvement. In contrast, neither the propensity score nor any of the individual factors, distance, gender or age, was significantly associated with CRM involvement.

Table 1. Patient and tumour characteristics given separately for patients treated with a LAR including Hartmann's procedure and an APR.

Variable	LAR *n* (%)	APR *n* (%)
Sex		
Female	816 (66)	416 (34)
Male	1464 (61)	937 (39)
Age		
≤ 60 years	886 (68)	410 (32)
61-70 years	829 (61)	540 (39)
> 70 years	565 (58)	403 (42)
Trial		
Swedish Rectal Cancer trial		
Surgery only	150 (42)	209 (58)
5 x 5 Gy RT + surgery	155 (47)	175 (53)
TME trial		
TME surgery only	413 (75)	136 (25)
5 x 5 Gy RT + TME surgery	384 (73)	142 (27)
CAO/ARO/AIO-94 trial		
Preoperative CRT	235 (68)	109 (32)
Postoperative CRT	243 (72)	93 (28)
EORTC 22921 trial		
Preoperative 45 Gy RT	257 (57)	197 (43)
Preoperative CRT	267 (59)	185 (41)
Polish Rectal Cancer trial		
Preoperative CRT	85 (60)	57 (40)
Preoperative 5 x 5 Gy RT	91 (65)	50 (35)
Distance of tumour to anal verge		
≤ 3.0 cm	99 (15)	563 (85)
3.1-7.0 cm	818 (55)	661 (45)
> 7.0 cm	1363 (91)	129 (9)
pN-status [a]		
N0/Nx	1290 (63)	754 (37)
N+	990 (62)	599 (38)
pT-stage [b]		
Tis/T1/T2	641 (61)	404 (39)
T3/T4	1630 (64)	934 (36)
CRM involvement		
No	1770 (69)	802 (31)
Yes	93 (49)	95 (51)
Unknown	417 (48)	456 (52)

LAR = low anterior resection; APR = abdominoperineal resection; RT = radiotherapy; CRT = chemoradiotherapy. [a] Missing for 178 patients. [b] Missing for 24 patients.

Table 2. Multivariate logistic regression analysis for the type of surgery (LAR including Hartmann's procedure versus APR) (A) and number of patients with patients' characteristics (gender, age, and distance from the tumour to the anal verge) shown for each quartile of the propensity score (B).

A

Variable	Odds ratio	95% CI	*P*-value	Regression coefficient for propensity score
Gender			0.001	
Female	1.00			
Male	1.35	1.13- 1.61		0.301
Age			<0.001	
≤ 60 years	1.00			
61-70 years	1.42	1.17- 1.72	<0.001	0.349
> 70 years	1.90	1.54- 2.36	<0.001	0.643
Distance from the anal verge			<0.001	
> 7.0 cm	1.00			
3.1-7.0 cm	8.82	7.15-10.88	<0.001	2.177
≤ 3.0 cm	63.13	47.57-83.79	<0.001	4.145

An odds ratio (OR) >1 indicates an increased likelihood for an APR and decreased likelihood for a LAR/ Hartmann's procedure. CI = confidence interval.

B

Propensity score	Gender	Age	Distance from tumour to anal verge		
			≤ 3 cm	3-7 cm	> 7 cm
Lowest quartile	Male	≤ 60 years			346
	Female	≤ 60 years			202
		61-70 years			171
		> 70 years			144
25-49%	Male	61-70 years			358
		> 70 years			271
	Female	≤ 60 years		176	
50-74%	Male	≤ 60 years		353	
	Female	61-70 years		174	
		> 70 years		148	
Highest quartile	Male	≤ 60 years	143		
		61-70 years	191	400	
		> 70 years	111	228	
	Female	≤ 60 years	76		
		61-70 years	75		
		> 70 years	66		

Table 3. Multivariate logistic regression analyses, adjusted for trial and randomisation arm, for circumferential resection margin (CRM) involvement: with the propensity score for the type of surgery (A) and for all variables given separately (B).

A

Variable	Odds ratio	95% CI	*P*-value
Surgical procedure			<0.001
LAR	1.00		
APR	2.52	1.69-3.76	
Propensity score			0.513
Lowest quartile	1.00		
25-49%	0.68	0.41-1.15	0.153
50-74%	0.90	0.54-1.48	0.667
Highest quartile	0.80	0.50-1.31	0.374

B

Variable	Odds ratio	95% CI	*P* -value
Surgical procedure			<0.001
LAR	1.00		
APR	2.53	1.70-3.78	
Gender			0.474
Female	1.00		
Male	1.12	0.82-1.55	
Age			0.574
≤ 60 years	1.00		
61-70 years	0.83	0.58-1.18	0.295
> 70 years	0.93	0.64-1.37	0.732
Distance from the anal verge			0.919
> 7.0 cm	1.00		
3.1-7.0 cm	1.01	0.68-1.52	0.946
≤ 3.0 cm	0.93	0.55-1.58	0.790

An odds ratio (OR) >1 indicates an increased likelihood for CRM involvement and an OR < 1 indicates a decreased likelihood for CRM involvement. CI = confidence interval; LAR = low anterior resection, including Hartmann's procedure; APR = abdominoperineal resection.

In the presented multivariate model for CRM involvement, no interaction between distance and surgical procedure could be demonstrated. Figure 1 depicts the observed percent of patients with CRM involvement by distance between the tumour and the anal verge (in centimetres) separately for patients treated with a LAR and an APR. The APR procedure appears to be associated with more frequent CRM involvement for almost all distances.

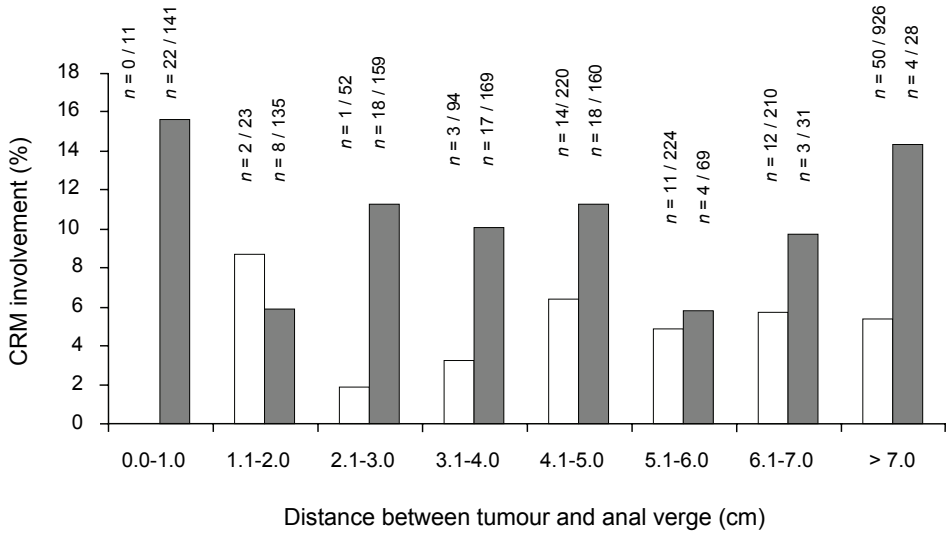

Figure 1. CRM involvement in relation to distance of the tumour to the anal verge, shown separately for patients treated with an abdominoperineal resection (grey bar) and low anterior resection, including Hartmann's procedure (white bar).

Local recurrence

In Figure 2A, the cumulative incidence function for LR is shown separately for LAR and APR with death as competing risk. Five-year local recurrence rates were 11.4% (95% confidence interval (CI) 10.0-12.8%) after LAR and 19.7% (95% CI 17.3-22.1%) after APR ($P < 0.001$). The multivariate model for local control is displayed in Table 4. The type of surgical procedure actually performed, the presence of lymph node metastasis and CRM involvement independently predicted for the risk of LR, but not the propensity score itself. If the analysis was repeated with the component variables of the propensity score (age, gender, and distance) instead of the propensity score, none of these variables predicted for LR (data not shown).

Overall survival

The Kaplan-Meier curves for OS for patients with a LAR and an APR are presented in Figure 2B; 5-year OS rate was 70.1% (95% CI 67.9-72.3%) for patients treated with a LAR and 59.5% for patients treated with an APR (95% CI 56.6-62.4%; $P < 0.001$). The multivariate analysis for OS in Table 4 shows that lymph node metastasis, CRM involvement, surgical procedure, and propensity score were all associated with OS. The results indicate that a higher propensity score (i.e. higher probability to be selected for an APR) was associated with a shorter OS. Studying separately the variables used for the calculation of the propensity score, the three individual variables (gender, age, and distance) all predicted OS

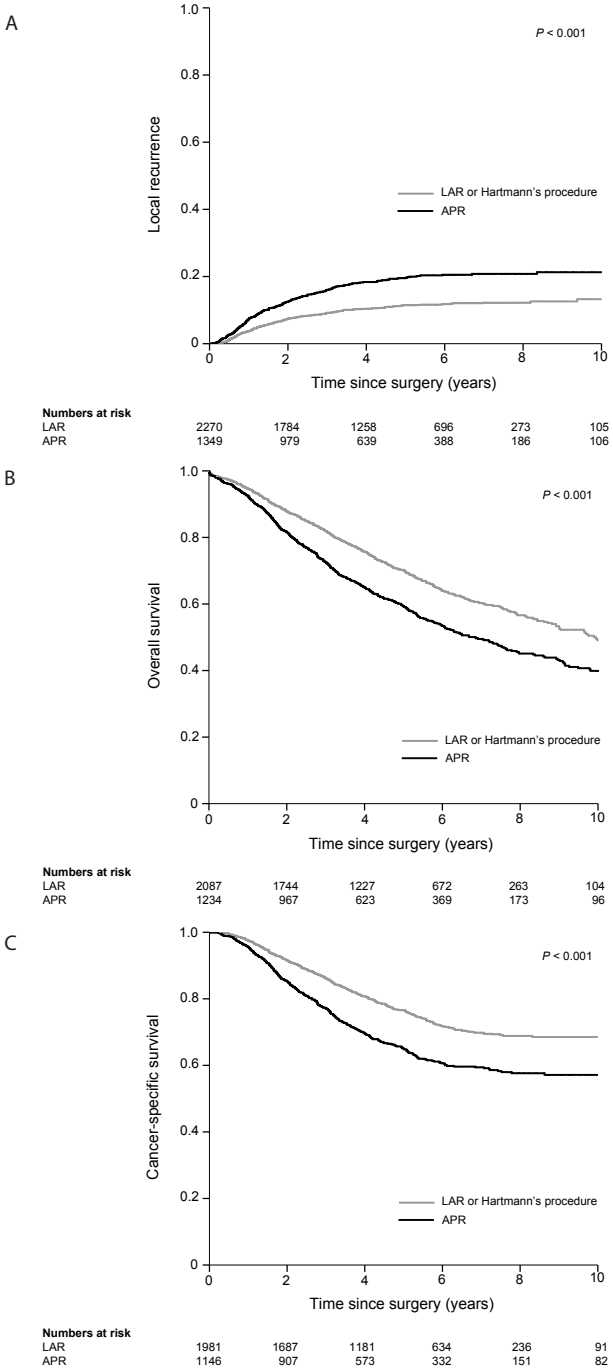

Figure 2. Local recurrence (A), overall survival (B), and cancer-specific survival (C) shown as cumulative incidence (A), Kaplan-Meier survival (B), and one minus cumulative incidence (C) curves separately for patients treated with a LAR (including Hartmann's procedure) and an APR.

Table 4. Multivariate Cox regression analyses for local recurrence, overall survival, and cancer-specific survival with the propensity score for the type of surgery, stratified for trial and randomisation arm.

Variable	Local recurrence			Overall survival			Cancer-specific survival		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value
LN status			<0.001			<0.001			<0.001
N0	1.00			1.00			1.00		
N+	2.26	1.86-2.75		1.99	1.78-2.24		2.97	2.57-3.44	
CRM			<0.001			<0.001			<0.001
Negative	1.00			1.00			1.00		
Positive	3.11	2.26-4.30	<0.001	1.75	1.39-2.19	<0.001	1.84	1.43-2.38	<0.001
Unknown	1.32	0.86-2.04	0.206	1.36	1.05-1.74	0.021	1.36	1.01-1.84	0.043
Surgical procedure			0.011			0.030			0.002
LAR	1.00			1.00			1.00		
APR	1.36	1.07-1.72		1.17	1.02-1.34		1.31	1.11-1.56	
Propensity score			0.440			<0.001			0.101
Lowest quartile	1.00			1.00			1.00		
25-49%	1.02	0.77-1.36	0.887	1.36	1.16-1.60	<0.001	1.20	0.98-1.47	0.076
50-74%	0.94	0.68-1.30	0.706	1.09	0.90-1.32	0.364	1.04	0.83-1.30	0.754
Highest quartile	1.17	0.87-1.57	0.308	1.40	1.17-1.67	<0.001	1.24	1.00-1.53	0.052

HR = hazard ratio; CI = confidence interval; LN = lymph node; CRM = circumferential resection margin; LAR = low anterior resection, including Hartmann's procedure; APR = abdominoperineal resection.

independently of lymph node status, CRM involvement, and type of surgical procedure (data not shown).

Cancer-specific survival

The results for CSS, defined as the time from surgery to death due to rectal cancer, are shown in Table 4: lymph node status, CRM involvement and the type of surgical procedure were independently associated with CSS, whereas the propensity score was not. Focusing on the separate variables, gender ($P = 0.010$) and distance of the tumour to the anal verge ($P = 0.042$) were independently associated with CSS (data not shown). For age such an association could not be found ($P = 0.704$). The estimated cumulative incidences as survival curves with death due to other causes as competing risk are depicted in Figure 2C; 5-year CSS rate was 76.6% (95% CI 74.6-78.6%) for patients treated with a LAR and 65.1% for patients treated with an APR (95% CI 62.0-68.2%; $P < 0.001$).

DISCUSSION

Several studies have documented that patients treated with an APR have a worse local control, and OS than patients treated with a LAR.[8,9] Based on these studies one could debate whether the APR procedure by itself or the difference in the clinical factors that affect the choice to perform an APR in patients is responsible for this adverse outcome. The results of our exploration of a large database of patients treated in five prospective randomised trials suggest that there is an association between the APR procedure itself and a higher risk of CRM involvement, decreased local control and CSS compared to a LAR for patients with advanced rectal cancer, whereas for OS the factors associated with the choice of an APR (age, gender, and distance) seem at least as relevant as the surgical procedure itself. We combined treatment variables of five different European trials on rectal cancer. All of these studies were designed to study the effects of (neo)adjuvant treatments on LR and OS, although in the PRCT these were secondary end-points. The present analyses should thus be interpreted with caution, as the separate trials were not designed to study the effects of different surgical procedures on LR or OS. Moreover, the time-periods of patient recruitment were different. In the mid-1980s when the SRCT was run, 5 cm distal bowel margin below the tumour was considered to be appropriate, resulting in more patients with a mid-rectal tumour to be treated with an APR. Nowadays, a distal margin of 2 cm or less is considered sufficient.[2] Consequently, in comparison more patients were treated with an APR procedure in the SRCT than in the trials that were run later. However, differences between the trials was not the subject of the study. The large number of patients in this study strengthens our conclusion and could be considered representative of a common European experience since patients in our database come from several European countries and were treated over a relatively long period of time.

In this study, distance of the tumour to the anal verge, gender, and age were the factors that influence the choice of the surgical procedure. However, it must be stressed that some other factors, that were not available in the present study because they were not collected in any or some of the trials, may also have influenced the selection of the surgical procedure. Moreover, patients' or surgeons' preferences could have affected the type of surgical resection actually performed: variability between surgeons and patients exists.[17] The variables that were considered in the present analysis for propensity score were known at the time of surgery, as otherwise they could not have affected the choice for a certain surgical procedure: pathological T-stage and nodal status were therefore not considered as variables for this end-point. It is important to note that the decision to perform an APR is influenced by multiple factors. The worse outcome for the APR procedure after adjustment for the propensity score in the current analyses is therefore also multi-factorial. However, the analyses for LR, OS and CSS are adjusted for the factors involved in the propensity score, lymph node status, and CRM involvement. Therefore,

in our opinion the quality of the surgical procedure is a crucial factor contributing to the poor results of patients treated with an APR.

The APR procedure is still associated with a high risk for a nonradical resection. Due to changes in time, such as the changed thoughts about a free distal margin, nowadays less patients are treated with an APR than many years ago. For very distal tumours, however, an APR will remain the only treatment of choice and therefore further improvement of this technique is necessary. Several groups have studied the surgical APR specimen.[8,9,18] Marr and colleagues reported on 190 patients who were operated on in Leeds and described that with an APR less tissue was removed around the tumour than after a LAR.[8] Similarly, in the TME trial, the high rate of CRM involvement after an APR was ascribed to the surgical resection plane: the plane of surgical resection most frequently followed the mesorectal fascia and then passed over the surface or into the sphincter muscles providing little in the way of tissue to protect the surgical margin from direct spread of tumour circumferentially.[9] Furthermore, the plane of surgical resection was associated with LR and OS.[9,18] These results indicate that a more anatomical and selectively widened resection should be performed in order to improve CRM negativity.

Holm and colleagues described a different surgical approach for the APR resulting in a lower risk of bowel perforation and CRM involvement, used in a selected group of patients: the extended posterior perineal approach.[19] The main differences with the conventional approach are that the mesorectum is not dissected off the levator muscles, the perineal part of the operation is done with the patient in the prone jack-knife position and the entire levator muscle is resected *en block* with the anal canal and lower rectum.[19] The result is a more cylindrical resection with more tissue covering and surrounding the tumour in low rectal cancer. To reduce the rate of local complications observed after primary closure, a gluteus maximus flap is used to reconstruct the pelvic floor. Holm and colleagues selected the following patients: patients in whom a MRI scan indicated a T3-4 tumour within 6 cm of the anal verge or a low tumour fixed or tethered at rectal examination.[19] In practice, the APR is more difficult in the smaller pelvis of male patients and in tumours growing anteriorly where the distance to the mesorectal fascia is smallest. Although neither in the pooled database (Table 3B) nor in a previous analysis in the TME trial an association between gender and CRM involvement in the multivariate analysis could be shown, anteriorly located tumours were indeed found to be more frequently associated with an involved CRM in the TME trial independent from confounders such as T-stage.[20] With the cylindrical technique, the amount of tissue present anteriorly beyond the internal sphincter or muscularis propria almost doubled compared to the conventional APR.[21] Therefore, we feel that even patients with an anteriorly located T1-2 tumour might benefit from a cylindrical resection.

Apart from a more cylindrical resection, preoperative treatment with radiotherapy or chemoradiotherapy and delayed surgery may be an alternative option to reduce CRM

involvement and to improve both local control and OS. Chemoradiotherapy and delayed surgery have been shown to downstage and downsize tumours.[14,22] Short course 5 x 5 Gy radiotherapy followed by immediate surgery does not result in downstaging or downsizing,[23] whereas if 5 x 5 Gy is used with delayed surgery, the effect is probably of the same magnitude as found for chemoradiotherapy.[24,25] Unfortunately, the present pooled database cannot be used to study the question which preoperative treatment is associated with more radical resections: observed differences could also be explained by differences between the several trials instead of solely a treatment effect. However, in the PRCT, preoperative chemoradiotherapy is compared with 5 x 5 Gy radiotherapy. Bujko and colleagues reported that CRM involvement was 4.4% after chemoradiotherapy compared with 12.9% after 5 x 5 Gy radiotherapy followed by immediate surgery ($P = 0.017$).[14,26] Despite this difference in CRM involvement, no statistically significant difference in local control or OS could be found.[26] The reason for this finding might be due to the short interval between radiotherapy and surgery in the 5 x 5 Gy group. It should, however, be noted that the PRCT did not had LR or OS as a primary end-point. The absence of statistical significance in this study regarding LR or OS may be related to the relatively small number of patients to study these end-points. Nevertheless, downstaging and downsizing are not the only contributors to free resection margins. In the EORTC 22921 trial, with the same delay in all groups between preoperative treatment and surgery, it was shown that no significant difference in CRM involvement was obtained after preoperative chemoradiotherapy compared to preoperative radiotherapy despite an impact on tumour stage and size.[27] Therefore, improving the surgical procedure to reduce CRM involvement remains necessary to structurally improve the number of R0 resections.

In conclusion, the results suggest that the APR procedure itself is associated with nonradical resections, and later reduced local control, OS, and CSS for patients with advanced rectal cancer. For many patients an APR is the only and best surgical option, and therefore we should focus on how to improve treatment outcome for these patients. The debate about the optimal (preoperative) treatment for patients who undergo an APR is still ongoing. At present there is no official guideline to advise preoperative treatment with a long schedule of chemoradiotherapy for all patients who have planned to undergo an APR or to advise that an extended resection should be performed to prevent CRM involvement. One can speculate whether patients subjected to an APR should not have delayed surgery independent from the type of preoperative treatment given. Nevertheless, our exploratory study supports the view that the quality of the APR procedure needs improvement and stresses the importance to find other means to improve the outcome of patients treated with an APR procedure. Until the debate is ended, preoperative imaging and multidisciplinary team meetings should be used to discuss the optimal treatment for each individual patient.

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Chapter 6

Risk factors for adverse outcome in patients with rectal cancer treated with an abdominoperineal resection in the total mesorectal excision trial

Marcel den Dulk, Corrie A.M. Marijnen, Hein Putter, Harm J.T. Rutten, Geerard L. Beets, Theo Wiggers, Iris D. Nagtegaal, Cornelis J.H. van de Velde

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ABSTRACT

Objective

This study was performed to identify tumour- and patient-related risk factors for distal rectal cancer in patients treated with an abdominoperineal resection (APR) associated with positive cirumferential resection margin (CRM), local recurrence (LR), and overall survival (OS).

Background

The introduction of total mesorectal excision (TME) has improved the outcome of patients with rectal cancer. However, survival of patients treated with an APR improved less than of those treated with a low anterior resection (LAR). Besides, an APR is associated with a higher LR rate.

Methods

Patients were selected from the TME trial, which is a randomised, multicentre trial, studying the effects of preoperative radiotherapy (RT) in 1861 patients. Of the Dutch patients, 455 underwent an APR. Location of the bulk of the tumour was scored with surgery, pathology, or other reports. CRM was available from pathology reports.

Results

A positive CRM was found in 29.6% of all patients, 44% for anterior, 21% for lateral, 23% for posterior, and 17% for (semi)circular tumour location ($P < 0.0001$). In a multivariate analysis, T-stage, N-stage, and tumour location were independent risk factors for CRM. If a (partial) resection of the vaginal wall was performed in women, 47.8% of patients still had a positive CRM. T-stage, N-stage, and CRM were risk factors for LR and age, T-stage, N-stage, CRM, and distance of the inferior tumour margin to the anal verge for OS.

Conclusion

Age, T-stage, N-stage, CRM, distance of the tumour to the anal verge, and tumour location were independent risk factors for adverse outcome in patients treated with an APR for low rectal cancer. Anterior location, specifically in women, more often requires downstaging and/or more extended resection to obtain free margins.

INTRODUCTION

The change from digital, blunt dissection of the rectum to total mesorectal excision (TME) in rectal cancer patients has played a major role in reducing local recurrence (LR) rates and improving overall survival (OS).[1-3] The TME procedure aims at free circumferential resection margins (CRM), which has been found to be an acceptable surrogate end-point for LR and disease-free survival.[4-6] LR rates have dropped by 50% with TME surgery compared with conventional surgery (respectively, 11% and 27% at 5 years).[2,7]

With the introduction of the TME technique, a decline in the ratio of abdominoperineal resections (APR) compared with low anterior resections (LAR) was observed, without a rise in hospital mortality.[8] LR and OS rates for rectal cancer have improved.[7,9] However, several groups have shown that the improvement for APR was less than for LAR.[10,11] In LAR, 12% of excisions had a positive CRM compared to 29% after APR.[11] Radiotherapy (RT) was not effective in patients with a positive CRM.[12] Five-year OS rates in patients with a positive CRM after LAR and APR were, respectively, 57.6% and 38.5% ($P = 0.008$).[11]

In the standard TME technique for APR, the mesorectal fascia is followed onto the sphincter complex. The anterior mesorectum below prostate and vesicles is thin. In theory, this area is at risk for nonradical resections. In women, the tumour could grow ventrally in the vagina. This study aimed to determine whether tumour location or other tumour and patient related characteristics were risk factors for CRM, LR, or OS. We evaluated this in the Dutch TME trial.[2] This trial included 1861 patients and examined the effects of short-course (5 x 5 Gy) preoperative RT.

PATIENTS AND METHODS

Study population

The Dutch TME trial included 1861 patients from January 1996 to December 1999.[2] This randomised multicentre trial evaluated TME surgery with or without preoperative RT (5 x 5 Gy). Patients with clinically resectable adenocarcinoma of the rectum were included and were subsequently randomly assigned to either RT followed by TME surgery or to TME surgery alone. Stratification was used for institution and expected operation type. RT, surgery, and pathology were standardised and strictly quality controlled. Follow-up of all patients was conducted according to trial protocol. Outcome measures included local and distant recurrences. The study was approved by all institutes and ethics committees. All patients gave informed consent.

Patient selection

For the current study, data of eligible patients who underwent an APR were analysed.[13] Only Dutch patients were selected because detailed information about the CRM was available for these patients. Patients with distant metastases at surgery and patients who died during the admission for the TME procedure were excluded from analyses for LR and OS. Patients with macroscopic nonradical resections (R2) were excluded from analyses for LR.

Preoperative radiotherapy

Patients assigned to preoperative RT received a total dose of 25 Gy in 5 fractions over 5 to 7 days. The irradiated volume included the primary tumour and the mesentery with vascular supply containing perirectal, presacral, and the internal iliac nodes.

Surgery

All patients underwent surgery according to the principles of TME, as previously described.[1] The main principles of this technique involve sharp dissection of the rectum and mesorectum within the true pelvis around the endopelvic fascia under direct vision with nerve preservation.

Pathological procedure

Standardised pathology examination was performed in the pathology laboratories of referring hospitals using the protocol of Quirke et al.[6,14,15] Pathologists from referring hospitals recorded pathologic information of the resected tumour on a standard form for all patients. A pathology quality manager and a pathology review committee were installed to ensure consistent quality of all pathology data and procedures. The lateral resection margin of the fresh received specimen was inked and subsequently the specimen was fixated for 48 hours. After fixation, the resected specimen was sliced transversely to provide multiple coronal sections through the tumour and the mesorectum. The macroscopic CRM was measured using a ruler. Sufficient blocks of the primary tumour and lymph nodes in relation to the CRM were taken; and when the tumour or a suspected lymph node approached the margin (i.e., distance from the margin <1 cm) measurements were repeated microscopically. Any specimen that had tumour (i.e., primary tumour or lymph node metastasis) ≤ 1 mm from the CRM was recorded as having tumour margin involvement. If the tumour was more than 1 mm but less than 2 mm from the CRM, deeper levels were cut to exclude involvement.

Data collection

During the trial, T-, N-, M-stage, and maximum tumour size were recorded. Information on tumour location was collected retrospectively from surgery reports. The investiga-

tor who studied the reports was blinded for the outcome. If no information could be found related to the location, the pathology report was examined, and if necessary, reports from radiologic, digital, or endoscopic examination were studied. A tumour was scored as located anterior if the bulk of the tumour was located anterior or anterolateral. Similarly, if the bulk of the tumour was located either posterior or posterolateral, the tumour was scored as posterior. If the tumour was located lateral or (almost) circular, these locations were used. The variables were analysed for their relation with CRM, LR, and OS, which were collected prospectively during the follow-up of the trial.

Statistical analyses

Data were analysed with the SPSS package (SPSS 12.0 for Windows; SPSS Inc., Chicago, IL). Unless indicated differently, univariate analyses with categorical variables were performed with a χ^2 test, whereas continuous variables were analysed with an unpaired *t*-test. LR and OS were univariately tested with log-rank tests. The following variables were studied for CRM, LR, and OS: assigned treatment, sex, age, body mass index, T-stage, N-stage, maximum tumour diameter, distance of the tumour to the anal verge, and location of the tumour. CRM was included as variable in analyses for LR and OS. Only variables with a *P*-value ≤ 0.10 in the univariate analyses were selected and studied in the multivariate analyses. Multivariate analyses were performed with logistic regression analyses for CRM and with Cox regression analyses for LR and OS. Assigned treatment was always in the multivariate analysis to adjust for trial design. A *P*-value of ≤ 0.05 was considered statistically significant.

RESULTS

Patient characteristics

The median follow up was 7.1 year (range 2.5-9.8 years). In total, 455 Dutch patients underwent an APR, of whom 441 were eligible at randomisation. Seven patients had no invasive tumour at the time of surgery, leaving 434 patients evaluable. Twenty-seven patients with distant metastases at surgery and 10 patients who died during the admission for the TME procedure were excluded from analyses on LR and OS. Two patients with macroscopic nonradical resections (R2) were excluded for analyses from LR.

Patient characteristics are summarised in Table 1 for the selected APR patients in comparison to patients that had a LAR or Hartmann's procedure. A significant difference was found in maximum tumour size, which was larger in APR operated patients ($P = 0.01$). Significantly more lymph nodes were examined after a LAR or Hartmann's procedure (median 8; range 0-60) than after an APR (median 7; range 0-36; $P < 0.001$, Mann-Whitney *U* test). Slightly more APR patients were node negative ($P = 0.04$). In men, significantly more often an APR was performed ($P = 0.02$).

Table 1. Patient characteristics of studied eligible patients who had a LAR or Hartmann's procedure in comparison with patients who underwent an APR.

Variable	LAR and Hartmann's procedure (%)	APR (%)	Total	*P*-value
Total	978 (69.3)	434 (30.7)	1412	
Radiotherapy				0.80
No	484 (49.5)	218 (50.2)	702	
Yes	494 (50.5)	216 (49.8)	710	
Sex				0.02
Female	372 (38.0)	137 (31.6)	509	
Male	606 (62.0)	297 (68.4)	903	
Age				0.82
Mean	64.0	64.5		
Standard deviation	11.0	11.1		
BMI [a]				0.20
< 25 kg/m^2	341 (46.5)	127 (40.7)	468	
25-29 kg/m^2	322 (43.9)	148 (47.4)	470	
≥ 30 kg/m^2	71 (9.7)	37 (11.9)	108	
T-stage				0.10
T1	59 (6.0)	15 (3.5)	74	
T2	307 (31.4)	155 (35.7)	462	
T3	579 (59.2)	246 (56.7)	825	
T4	33 (3.4)	18 (4.1)	51	
N-stage [b]				0.04
N0	563 (57.6)	265 (61.2)	828	
N1	258 (26.4)	88 (20.3)	346	
N2	156 (16.0)	80 (18.5)	236	
Maximum tumour diameter [c]				0.01*
Median	4.0	4.0		
Range	0.3-13.0	1.0-10.5		
Distance of tumour from anal verge [d]				<0.001
≤ 2.0 cm	12 (1.2)	159 (41.3)	171	
2.1-4.0 cm	60 (6.2)	143 (37.1)	203	
> 4.0 cm	893 (92.5)	83 (21.6)	976	

[a] Missing for 366 patients. [b] According to UICC TNM stage 1997; data missing for 2 patients. [c] Missing for 7 patients. [d] Missing for 62 patients. * Mann-Whitney test. BMI = body mass index.

Location of the tumour

The bulk of the tumour was located anteriorly in 172 patients (40%), laterally in 53 patients (12%), and posteriorly in 103 patients (24%). In 47 patients (11%), the tumour was described as (semi)circular. In 59 patients (14%), the location of the tumour was not specified. Location of the tumour was not significantly different between the randomisation groups ($P = 0.69$).

Sex differences

Table 1 demonstrates that men relatively more frequently were subjected to an APR than women ($P = 0.02$). Low rectal tumours for which an APR was performed in women were significantly more often T4 tumours ($P = 0.01$). For N-stage, no significant difference could be found ($P = 0.23$). Of all Dutch women in the TME trial who had an APR, 33.6% (46 of 137) had a partial resection of the vaginal wall. If the vaginal wall was included in the resection, 47.8% (22 of 46) of these patients had a positive CRM. In Table 2, the association between T-stage, partial resection of the vaginal wall and CRM is shown. In 10 out of 50 female patients (20%) with a T1 or T2 tumour, a resection of the vaginal wall was performed. The indicated reasons for vaginal wall resection in these patients were: suspicion of infiltrating tumour growth ($n = 1$), adhesions ($n = 2$), adjacent tumour location ($n = 3$) and unspecified ($n = 4$). Of the patients with a T3 or T4 tumour in whom a partial resection of the vaginal wall was performed, 62% and 50%, respectively, still had a positive CRM. Surprisingly, in most patients, CRM involvement was not located at the resection margin of the vagina, but in the surrounding tissue. The rate of positive CRM after partial resection of the vaginal wall did not differ significantly between the randomisation groups ($P = 1.00$; data not shown). In contrast to the results in women, a (partial) resection of the prostate was only performed in 8 of 297 (2.7%) men who underwent an APR, of whom 3 (37.5%) had a positive CRM.

Table 2. Number and percentage of circumferential resection margin (CRM) involvement per T-stage for female patients who underwent an APR without and with (partial) resection of the vaginal wall.

		T1 + T2 *n* (%)	T3 *n* (%)	T4 *n* (%)	Total
No (partial) resection of vagina	CRM negative	33 (83)	25 (51)	0 (0)	58 (64)
	CRM positive	7 (18)	24 (49)	1 (100)	32 (36)
	Total	40	49	1	90
(Partial) resection of vagina	CRM negative	9 (90)	10 (39)	5 (50)	24 (52)
	CRM positive	1 (10)	16 (62)	5 (50)	22 (48)
	Total	10	26	10	46

CRM status was missing for 1 female patient. $P = 0.003$ for women without a resection of the vaginal wall, and $P = 0.02$ for patients with a (partial) resection.

Circumferential resection margin

CRM status was available for 433 of 434 patients. The results of the univariate analyses are shown in Table 3. In total 29.6% (128 of 433) patients had a positive CRM. Of the anteriorly located tumours, 44% (75 of 171) of patients had a positive CRM. The frequency of positive CRM was significantly lower in tumours located laterally, posteriorly, circularly or with unspecified location, respectively, 21% (11 of 53), 23% (24 of 103), 17% (8 of 47), and 17% (10 of 59) ($P < 0.001$). In a multivariate analysis (Table 4), advanced T-stage,

Table 3. Univariate analyses for circumferential resection margin (CRM) involvement.

Variable	Positive CRM *n* (%)	Negative CRM *n* (%)	OR (95% CI)	*P*-value
Radiotherapy				0.74
No	66 (30.3)	152 (69.7)	1.00	
Yes	62 (28.8)	153 (71.2)	0.93 (0.62-1.41)	
Sex				0.002
Female	54 (39.7)	82 (60,3)	1.00	
Male	74 (24.9)	223 (75.1)	0.50 (0.33-0.78)	
Age				0.11+
≤ 50 years	10 (20.0)	40 (80.0)	1.00	
51 – 70 years	76 (29.7)	180 (70.3)	1.69 (0.80-3.55)	
> 70 years	42 (33.1)	85 (66.9)	1.98 (0.90-4.34)	
BMI				0.24
< 25 kg/m^2	31 (24.4)	96 (75.6)	1.00	
25-29 kg/m^2	48 (32.7)	99 (67.3)	1.50 (0.88-2.56)	
≥ 30 kg/m^2	13 (35.1)	24 (64.9)	1.68 (0.76-3.69)	
T-stage				<0.001
T1 + T2	17 (10.0)	153 (90.0)	1.00	
T3 + T4	111 (42.2)	152 (57.8)	6.57 (3.76-11.5)	
N-stage				<0.001
N0	46 (17.4)	218 (82.6)	1.00	
N1	27 (30.7)	61 (69.3)	2.10 (1.21-3.65)	
N2	54 (67.5)	26 (32.5)	9.84 (5.59-17.3)	
Maximum tumour diameter				0.14+
≤ 3.0 cm	30 (31.9)	64 (68.1)	1.00	
3.1-4.0 cm	29 (22.1)	102 (77.9)	0.61 (0.33-1.10)	
4.1-5.0 cm	22 (24.7)	67 (75.3)	0.70 (0.37-1.34)	
5.1-6.0 cm	21 (36.8)	36 (63.2)	1.24 (0.62-2.48)	
> 6.0 cm	21 (38.2)	34 (61.8)	1.32 (0.66-2.64)	
Distance of tumour from anal verge				0.59+
≤ 2.0 cm	45 (28.5)	113 (71.5)	1.00	
2.1-4.0 cm	44 (30.8)	99 (69.2)	1.12 (0.68-1.83)	
> 4.0 cm	20 (24.1)	63 (75.9)	0.80 (0.43-1.47)	
Tumour location				<0.001
Anterior	75 (43.9)	96 (56.1)	1.00	
Lateral	11 (20.8)	42 (79.2)	0.34 (0.16-0.70)	
Posterior	24 (23.3)	79 (76.7)	0.39 (0.23-0.67)	
Circular	8 (17.0)	39 (83.0)	0.26 (0.12-0.60)	
Unspecified	10 (16.9)	49 (83.1)	0.26 (0.12-0.55)	

$^+ \chi^2$ test for trends. OR = odds ratio; BMI = body mass index; CI = confidence interval.

higher N-stage, and anterior tumour location were independent risk factors for a positive CRM. Although sex was significant in the univariate analysis, after adjustment for T-stage, N-stage, and tumour location, no significant difference could be found.

Table 4. Results of the multivariate logistic regression analysis for positive circumferential resection margin (CRM).

Variable	OR	95% CI	*P*-value
Radiotherapy			0.90
No	1.00		
Yes	0.97	0.59 – 1.59	
Sex			0.11
Female	1.00		
Male	0.65	0.38 – 1.10	
T-stage			<0.001
T1 + T2	1.00		
T3 + T4	4.93	2.68 – 9.06	
N-stage			<0.001
N0	1.00		
N1	1.55	0.85 – 2.85	0.15
N2	8.31	4.39 – 15.7	<0.001
Tumour location			<0.001
Anterior	1.00		
Lateral	0.26	0.11 – 0.63	0.003
Posterior	0.46	0.25 – 0.88	0.02
Circular	0.17	0.06 – 0.45	<0.001
Unspecified	0.32	0.14 – 0.74	0.008

All variables with a *P*-value of ≤ 0.10 in the univariate analysis were included in the multivariate analysis. OR = odds ratio; CI = confidence interval.

Local recurrence

The results of the univariate analysis for LR are shown in Table 5. Randomisation, sex, T-stage, N-stage, distance of the tumour to the anal verge, and CRM had a *P*-value ≤ 0.10 in the univariate analysis and were entered in the multivariate analysis (Table 6). Significantly higher LR rates were found for higher T-stage, positive lymph node status, and positive CRM.

Overall survival

Similar to LR, OS was studied (univariate Table 5, multivariate Table 6). A *P*-value of ≤ 0.10 was found in the univariate analyses for sex, age, T-stage, N-stage, distance of the tumour to the anal verge, CRM, and tumour location. Increased age, advanced T-stage, positive lymph node status, distal location of the tumour, and positive CRM were independent risk factors for OS in the multivariate analysis.

DISCUSSION

This study investigated risk factors associated with positive CRM, increased LR rates, and decreased OS rates in abdominoperineal resected patients in whom TME surgery was

Table 5. Results of the univariate analyses for local recurrence and overall survival.

Variable	Local recurrence			Overall survival		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Radiotherapy			0.07			0.53
No	1.00			1.00		
Yes	0.57	0.31-1.05		0.91	0.67-1.23	
Sex			0.01			0.07
Female	1.00			1.00		
Male	0.48	0.27-0.87		0.75	0.55-1.03	
Age			0.72			0.001
≤ 50 years	1.00			1.00		
50-70 years	0.71	0.31-1.65		1.54	0.86-2.76	
> 70 years	0.75	0.30-1.90		2.48	1.36-4.51	
BMI			0.37			0.16
< 25 kg/m^2	1.00			1.00		
25-29 kg/m^2	1.21	0.57-2.56		1.46	0.99-2.17	
≥ 30 kg/m^2	2.02	0.76-5.37		1.36	0.73-2.54	
T-stage			<0.001			<0.001
T1 + T2	1.00			1.00		
T3 + T4	5.28	2.23-12.5		2.86	2.00-4.10	
N-stage			<0.001			<0.001
N0	1.00			1.00		
N1	6.34	2.82-14.5		1.89	1.27-2.81	
N2	13.61	6.05-30.6		6.62	4.63-9.48	
CRM			<0.001			<0.001
Negative	1.00			1.00		
Positive	4.89	2.67-8.94		3.03	2.23-4.13	
Maximum tumour diameter			0.82			0.21
≤ 3.0 cm	1.00			1.00		
3.1-4.0 cm	1.08	0.44-2.65		1.19	0.76-1.88	
4.1-5.0 cm	1.17	0.45-3.04		1.06	0.64-1.76	
5.1-6.0 cm	0.96	0.29-3.18		1.64	0.96-2.81	
> 6.0 cm	1.69	0.64-4.51		1.59	0.95-2.68	
Distance tumour from anal verge			0.06			0.09
≤ 2.0 cm	1.00			1.00		
2.1-4.0 cm	0.51	0.25-1.04		0.72	0.50-1.03	
> 4.0 cm	0.41	0.16-1.07		0.67	0.43-1.05	
Tumour location			0.42			0.05
Anterior	1.00			1.00		
Lateral	0.70	0.26-1.86		0.85	0.54-1.36	
Posterior	0.90	0.44-1.83		0.71	0.48-1.05	
Circular	0.35	0.08-1.49		0.51	0.27-0.96	
Unspecified	0.47	0.16-1.38		0.54	0.32-0.90	

HR = hazard ratio; CI = confidence interval; BMI = body mass index; CRM = circumfential resection margin.

Table 6. Results of the multivariate Cox regression analyses for local recurrence and overall survival.

Variable	Local recurrence			Overall survival		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Radiotherapy			0.16			0.77
No	1.00			1.00		
Yes	0.61	0.31-1.21		0.95	0.68-1.33	
Sex			0.15			0.82
Female	1.00			1.00		
Male	0.61	0.31-1.19		0.96	0.67-1.38	
Age			----			0.003
≤ 50 years				1.00		
51-70 years				1.91	0.98-3.72	
> 70 years				2.98	1.49-5.93	
T-stage			0.004			<0.001
T1 + T2	1.00			1.00		
T3 + T4	4.13	1.58-10.8		2.22	1.48-3.33	
N-stage			<0.001			<0.001
N0	1.00			1.00		
N1	3.16	1.32-7.57		1.54	0.99-2.40	
N2	8.04	3.40-19.0		5.23	3.48-7.86	
CRM			0.01			0.008
Negative	1.00			1.00		
Postive	2.41	1.20-4.87		1.66	1.14-2.40	
Distance tumour from anal verge			0.08			0.02
≤ 2.0 cm	1.00			1.00		
2.1-4.0 cm	0.49	0.23-1.03		0.66	0.45-0.96	
> 4.0 cm	0.44	0.17-1.17		0.55	0.34-0.88	
Tumour location			----			0.53
Anterior				1.00		
Lateral				0.81	0.49-1.36	
Posterior				0.88	0.57-1.35	
Circular				0.63	0.32-1.26	
Unspecified				0.67	0.38-1.18	

HR = hazard ratio; CI = confidence interval; CRM = circumferential resection margin.

performed. Data were derived from the TME trial that investigated the efficacy of short-term preoperative RT in patients with rectal cancer treated by TME. Stratification for type of surgery took place, but the trial was not set up to answer any question regarding problems related to APR. Therefore, any statement based on data from the trial must be regarded with care. However, the present analysis is informative and identified risk factors for adverse outcome of patients treated with an APR. It showed that tumour location is an independent risk factor for nonradical resections in APR patients. Recently, other studies have been published in which tumour location in rectal cancer was studied. In these studies, however, patients with a LAR were also included. Lee et al. published a retrospective study of ultrasound localisation of rectal tumour, but could not show

an effect of tumour location on recurrence or survival.[16] Chan et al. used a prospective hospital register to study location of rectal tumours.[17] They found that if part of the tumour was located anteriorly the LR rate was 15.9%, compared with 5.8% if the tumour was not located anteriorly ($P = 0.009$). Although we could not demonstrate a significant association between tumour location and LR, a significant correlation between tumour location and CRM was found.

The outcome for patients undergoing an APR has improved less than for patients who are treated with a LAR.[2,10,11] In low rectal cancer, CRM is positive in more than 30% of patients if an APR and in 10.7% if a LAR is performed.[11] CRM involvement increases the more distally the tumour is located.[11] The present analysis showed that CRM is of prognostic value for both LR and OS in patients treated with an APR, similar to previously published results demonstrating the importance of CRM for all patients.[14] In the present analysis, the definition as described by Quirke et al. was used to define CRM involvement in which both distance from tumour and metastatic lymph nodes were regarded.[6,15] However, if CRM involvement was defined as ≤ 1 mm from tumour only, the results of the analyses were similar (data not shown). Glynne-Jones et al. recently performed a literature search studying alternative clinical end-points in rectal cancer.[5] They concluded that CRM is an acceptable alternative end-point, predicting the risk of both LR and disease-free survival. Consequently, the large proportion of CRM positive resections found in the TME trial after an APR is an important explanation of the poor outcome of these patients.

Remarkably, our results showed a difference between men and women. In the univariate analysis, it was found that women treated with an APR were more likely to have a positive CRM than men ($P = 0.002$). In women, less frequently an APR procedure was performed and more often for a T4 tumour, suggesting that in women a T4 tumour was considered to be primarily resectable. Although the TME trial was primarily aimed at resectable tumours, patients with T4 tumours that were considered to be resectable could be included. We have previously shown that the schedule of preoperative 5 x 5 Gy RT followed by surgery within 1 week (short-course) does not lead to downstaging and downsizing.[13] In addition, we demonstrated that short-course preoperative RT cannot compensate for positive CRM.[12] Our present results reveal that margin positivity in women with vaginal wall involvement is a relatively common problem. Apparently, vaginal wall involvement merely reflects a large tumour as CRM is often positive at other sites than the vagina itself. From the previous results, it cannot be expected that 5 x 5 Gy is an appropriate RT schedule for these patients. Therefore, if vaginal wall involvement is suspected on MRI or digital rectal/vaginal examination, the tumour should be downstaged and/or the resection widened.

Several different treatment options have been described to achieve downstaging. The effect of delaying surgery on downstaging was studied in the Lyon R90-01 trial.[18]

The results of this trial demonstrated that delaying surgery for 6 to 8 weeks after 13 x 3 Gy RT was more efficient in terms of downstaging than operating within 2 weeks after completion of the RT ($P = 0.007$). Bujko et al. showed in a randomised trial that delayed chemoradiotherapy with surgery after 4 to 6 weeks was superior for downstaging compared with short-course RT followed by immediate surgery.[19] Finally, both the EORTC 22921 and the FFCD 9203 trial demonstrated that chemoradiotherapy is more efficient than RT alone in downsizing and downstaging rectal cancer, resulting in improved local control in the chemoradiotherapy arm.[20,21] These results indicate that preoperative treatment aiming at downstaging should consist of chemoradiotherapy with an interval of several weeks between RT and surgery. Currently, a trial is being conducted in Sweden, addressing the issue of postponing surgery after 5 x 5 Gy. In this trial, patients are randomised between 5 x 5 Gy RT with a short (<1 week) interval between RT and surgery, 5 x 5 Gy RT followed by surgery after a delay and 25 x 2 Gy RT with delayed surgery.

Apart from neoadjuvant treatment, an improvement could be made in the surgical treatment. Preliminary results of the MRC CR07 trial showed that the rate of CRM involvement from 1998 to 2005 gradually declined from above 20% to below 10%.[22] Furthermore, the plane of the surgical dissection was related to CRM, LR, and disease-free survival, which is in accordance with our previous results.[11] Clearly, a strong association exists between the quality of surgery on one hand and CRM, the rates of LR, and disease-free survival on the other hand. Therefore, the resection in APR patients should be widened to resect the complete mesorectal plane and aim for a free CRM. Besides, evidence is available that patients with rectal cancer should be treated in specialised centres.[23] From a national audit in Sweden, it was concluded that survival of patients with rectal cancer treated in a designated centre improved and is currently better than survival of patients with colon cancer, which is not treated in such designated centres.[9] The improvement in outcome was thought to be a combination of increased quality of the resections after the introduction of TME surgery and the introduction of preoperative RT in a multidisciplinary team setting. Therefore, it might be advisable to treat patients with rectal cancer by specialised surgeons, especially if they have to undergo an APR.

Although both downstaging with chemoradiotherapy and widening of the resection might be used in patients with a threatened CRM, both treatments cause associated morbidity. Short-term side effects of chemoradiotherapy have been often described, but long-term complications are not extensively studied.[24] Bujko et al. compared chemoradiotherapy with 5 x 5 Gy RT in 351 patients and found a borderline non-significant lower complication rate after chemoradiotherapy (22% versus 31% overall postoperative complications, expressed in number of events, $P = 0.06$).[25] However, in the same trial, acute irradiation toxicity was significantly higher after chemoradiotherapy than after the short scheme (85% versus 24% for all complications, $P < 0.001$; 18% versus 3% for serious complications including death, $P < 0.001$). More complications will also be seen

after a widened resection, mainly problems associated with perineal wound healing and closure. Hence, preoperative imaging should be used to select patients for whom 5 x 5 Gy is sufficient and for whom advanced treatment is necessary.

CONCLUSION

Anterior tumour location, advanced T-stage, and higher N-stage were independent risk factors for CRM. Positive CRM, higher T-stage, and higher N-stage were risk factors for LR. In addition to the risk factors for LR, distal tumour location, and older age were associated with reduced OS. To further improve the outcome of patients treated with an APR, tumours should be properly preoperatively staged, including an assessment of CRM. The surgical treatment should primarily be aimed at adequate resection margins. For patients with a threatened CRM preoperatively, 5 x 5 Gy RT alone is insufficient and treatment should preferentially consist of chemoradiotherapy and/or extended resection.

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Chapter 7

Quality of surgery in T3-4 rectal cancer: involvement of circumferential resection margin not influenced by preoperative treatment. Results from EORTC 22921 trial

Marcel den Dulk, Laurence Collette, Cornelis J.H. van de Velde, Corrie A.M. Marijnen, Gilles Calais, Laurent Mineur, Phillippe Maingon, Ljiljana Radosevic-Jelic, Alain Daban and Jean-Francois Bosset

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ABSTRACT

Purpose

The present analyses aimed to determine risk factors for rectal cancer patients associated with circumferential resection margin (CRM) and number of examined lymph nodes and to correlate these parameters of surgical quality with local recurrence (LR), disease-free and overall survival (DFS and OS).

Material and methods

Data of 884 eligible patients, who underwent a resection and had no metastases at time of surgery, were analysed.

Results

Age, period of treatment, distance, and pT-stage were associated with surgical quality. CRM involvement, but not number of examined lymph nodes, was associated with a higher risk of a LR, reduced DFS and OS. An abdominoperineal resection (APR) was a risk factor for adverse outcome.

Conclusion

Surgical quality is an important predictor of outcome, also for patients treated with conventional RT or chemoradiotherapy (CRT). Preoperative CRT results in downstaging and downsizing of the tumour, but not in less CRM involvement.

INTRODUCTION

Surgery is the cornerstone of the curative treatment of rectal cancer. However, in 1991, McArdle and Hole reported that surgical variability could influence outcome to a large extent.[1] Afterwards, several groups reported that the surgeon is an important prognostic factor for outcome in patients with rectal cancer.[2-4] Havenga and colleagues studied cohorts of patients treated with different surgical techniques.[5] Standardised surgery resulted in 30% survival and 25% local control benefit. Quality assurance aims to reduce this variability and can be defined as the systematic measures required to achieve a treatment result that meets a certain standard.

From the end of the eighties, surgeons and pathologists started to be interested in the lateral spread of rectal cancer.[6,7] Quirke and colleagues observed that the amount of excised tissue varied from surgeon to surgeon and found that circumferential resection margin (CRM) involvement was an important predictor for local recurrence (LR) and described a method to study CRM.[6,7] Also in the standardised TME trial, CRM was found to be an important predictor of outcome.[8] Consequently, CRM can be considered as a determinant of surgical quality. Another prognostic factor for outcome of rectal cancer is the number of examined lymph nodes.[9-11] Although the pathologist also influences the number of reported lymph nodes,[12] the number of removed and examined lymph nodes could be considered as a measure of the extent of surgery. Recently, Quirke and colleagues found that CRM and the number of examined lymph nodes were related, and therefore number of examined lymph nodes can be regarded as a measurement of quality of surgery as well (P. Quirke, St James's University Hospital, Leeds).

The EORTC 22921 trial studied the addition of pre- and/or postoperative chemotherapy (CT) to preoperative radiotherapy (RT) followed by surgery in T3 or resectable T4 rectal cancer.[13] The present analyses aimed to determine risk factors associated with quality of surgery in EORTC 22921 trial, defined by CRM and the number of examined lymph nodes, and to correlate these parameters of surgical quality with LR, disease-free and overall survival (DFS and OS) in RT or chemoradiotherapy (CRT) treated patients.

PATIENTS AND METHODS

Trial design

The trial design and eligibility criteria are reported previously[13] and therefore only the main features are summarised. Patients were randomised between preoperative RT or CRT and to either postoperative CT or no further treatment (Figure 1). Inclusion criteria were T3 or resectable T4 M0 adenocarcinoma of the rectum located within 15 cm from the anal verge, aged 80 years or less, and a WHO performance status of 0 or 1. The study

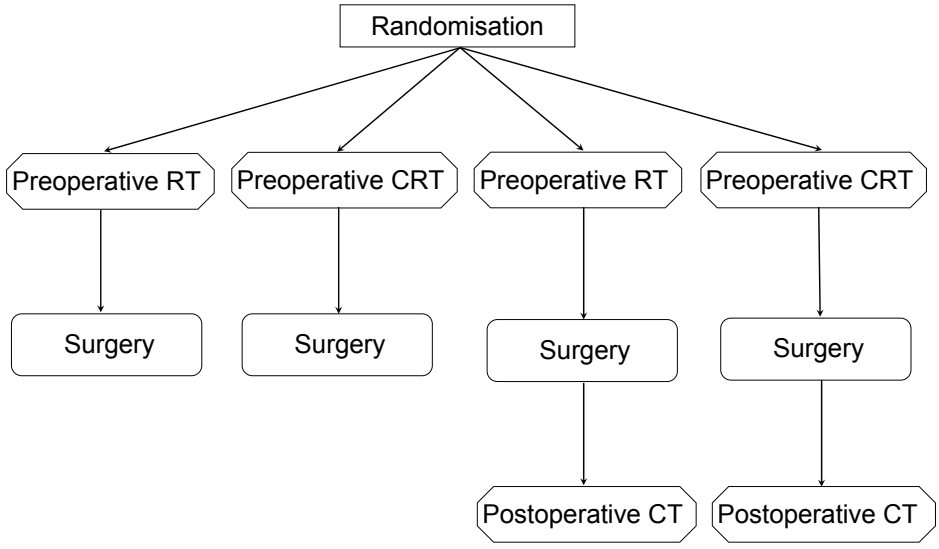

Figure 1. Treatment groups in the trial. RT = radiotherapy; CT = chemotherapy; CRT = chemoradiotherapy.

was approved by the ethics committees of the participating centres. Informed consent was obtained from all patients before their inclusion. The present analyses were restricted to eligible patients who underwent a resection and had no distant metastases at the time of surgery. Patients treated with a Hartmann's procedure (n = 22) were excluded from some analyses due to small patient numbers.

RT consisted of 45 Gy delivered in 25 fractions of 1.8 Gy to the posterior pelvis.[14] Variability of the treated volume and dose homogeneities have previously been studied and reported.[15] Preoperative CT (fluorouracil, 350 mg/m^2/d and leucovorin, 20 mg/m^2/d) was administered in two 5-day courses. Surgery was planned 3-10 weeks after the end of the preoperative treatment. It was recommended to maintain the surgical technique that was planned upfront (low anterior resection (LAR) or abdominoperineal resection (APR)), to perform a total mesorectal excision (TME; included in the recommendations in 1999), to create a protective colostomy in the case of a low-lying anastomosis, and to primarily close the perineum after an APR. When allocated, four courses of postoperative CT had to be delivered starting between 3 and 10 weeks after surgery.

Pathology procedures

Macroscopic and microscopic characteristics of the resected specimen were prospectively recorded by the local pathologists on a standard case report form. Macroscopic examination was performed on the fixated specimen. The total number of lymph nodes examined and total number of lymph nodes involved were registered. Tumour staging was performed according to TNM classification 4 (UICC,1987).[16] For pathological (p)T3-4

tumours (beyond the muscularis propria), the status of the CRM was determined according to the recommendations of Quirke and colleagues.[6] In this study, CRM was considered positive only if the tumour was microscopically abutting the resection margin.

End-points studied and variables considered

All recurrences were confirmed with radiological or histological examination. DFS is defined as the time from the day of surgery to the first event of loco-regional or distant recurrence or death of any cause, or to the date of the most recent follow-up for censored cases. Local control was calculated from the day of surgery to the day of LR, defined as tumour regrowth within the pelvis or perineum. OS is calculated from the day of surgery to the day of death of any cause or the day of most recent information if alive. The end-points and variables studied are shown in Table 1. In the analysis for the number of examined lymph nodes as end-point, this variable was analysed as a numerical variable, whereas in analyses where the number of examined lymph nodes was used as covariate, this variable was analysed as a categorical variable.

Table 1. Relationships that were assessed during the analyses.

End-points	Variables									
	Randomised treatment	Sex	Age	Distance tumour to anal verge	Period of treatment	Type of surgery	CRM	Pathological T-stage	Pathological N-stage	Number of examined lymph nodes (categorical)
Type of surgery (LAR versus APR)	yes	yes	yes	yes	yes	n.a.	no	no	no	no
CRM	yes	yes	yes	yes	yes	yes	n.a.	no	no	no
Number of examined lymph nodes (numerical)	yes	yes	yes	yes	yes	yes	no	yes	no	n.a.
Local recurrence	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Disease-free survival	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Overall survival	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes

LAR = low anterior resection; APR = abdominoperineal resection; CRM = circumferential resection margin; n.a. = not applicable.

Statistics

Data were analysed with Statistical Analysis Software (SAS®, Cary, NC, USA). A multivariate backward selection model was used for all analyses whereby all variables were initially in the model and then the least significant variables were sequentially removed from the model until all remaining variables were significant at the 0.05 level. All models were adjusted for allocated treatment. Local control, DFS, and OS were studied by Cox regression models. Logistic regression was used to study the probability of APR surgical

procedure and CRM involvement, whereas rank ANOVA was used to study the number of examined lymph nodes. The two-sided 0.05 significance level was used for all analyses.

RESULTS

Patients

From April 1993 to March 2003, 1011 patients entered the trial, of whom 884 were included in the present analyses. The reasons for excluding patients were distant metastases at surgery ($n = 46$), unknown status of distant metastases ($n = 62$), no resection ($n = 11$), and ineligibility ($n = 8$). The characteristics of the 884 patients are shown in Table 2.

Table 2. Patient characteristics.

Variable	Preoperative RT	Preoperative CRT	Preoperative RT and postoperative CT	Preoperative CRT and postoperative CT	Total
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Sex					
Male	162 (73)	163 (73)	159 (72)	161 (74)	645 (73)
Female	59 (27)	61 (27)	62 (28)	57 (26)	239 (27)
Age					
Median	63.0	62.0	63.0	62.0	62.0
Range	23.0-79.0	36.0-79.0	31.0-78.0	22.0-78.0	22.0-79.0
pT-stage					
T0	15 (7)	32 (14)	10 (5)	28 (13)	85 (10)
T1	16 (7)	24 (11)	17 (8)	25 (12)	82 (9)
T2	69 (31)	80 (36)	66 (30)	71 (33)	286 (32)
T3	107 (48)	77 (34)	116 (53)	84 (39)	384 (43)
T4	13 (6)	7 (3)	9 (4)	6 (3)	35 (4)
Tx	1 (1)	4 (2)	3 (1)	4 (2)	12 (1)
pN-stage					
N0	144 (65)	157 (70)	143 (65)	165 (76)	609 (69)
N+	73 (33)	61 (27)	74 (34)	46 (21)	254 (29)
Nx	4 (2)	6 (3)	4 (2)	7 (3)	21 (2)
Distance tumour to anal verge					
≤ 3.0 cm	51 (23)	58 (26)	52 (24)	55 (25)	216 (24)
3.1-6.0 cm	88 (40)	79 (35)	79 (36)	83 (38)	329 (37)
6.1-9.0 cm	46 (21)	48 (21)	57 (26)	46 (21)	197 (22)
> 9.0 cm	36 (16)	39 (17)	33 (15)	34 (16)	142 (16)
Surgical procedure					
APR	93 (42)	94 (42)	92 (42)	84 (39)	363 (41)
LAR	122 (55)	125 (56)	122 (55)	130 (60)	499 (56)
Hartmann	6 (3)	5 (2)	7 (3)	4 (2)	22 (2)

Percentages may not sum to 100 because of rounding. T-stage and N-stage are pathological stages. RT = radiotherapy; CT = chemotherapy; CRT = chemoradiotherapy; APR = abdominoperineal resection; LAR = low anterior resection.

The median follow-up at the time of analysis was 5.0 years (range 0.3-10.6 years). The 22 cases with a Hartmann resection were excluded from all further analyses.

Type of surgery

An APR was performed in 363 patients (41%), whereas 499 (56%) and 22 (2%) were treated with a LAR and a Hartmann's procedure, respectively. To evaluate prognostic factors determining the type of surgery, preoperative treatment (RT or CRT), age, sex, distance between tumour and anal verge, and period of treatment were included in the initial step of the multivariate analysis. Preoperative treatment was kept in the model to adjust for trial design. All variables but age were retained in the final model (Table 3). Compared to LAR, APR was more frequently applied in males, in patients treated in the period 1993-1996, and in tumours located within 3 cm from the anal verge.

Table 3. Final model of multivariate logistic regression analysis for the probability of an abdominoperineal resection (APR) compared to a low anterior resection (LAR).

Variable	OR	95% CI	*P*-value
Preoperative treatment			0.28
RT*	1.00		
CRT	0.83	0.60-1.16	
Sex			0.03
Male*	1.00		
Female	0.67	0.46-0.98	
Period of treatment			0.008
1993-1995*	1.00		
1996-1999	0.51	0.33-0.79	0.003
2000-2003	0.54	0.33-0.86	0.010
Distance			<0.001
≤ 3.0 cm*	1.00		
3.1-6.0 cm	0.21	0.14-0.32	<0.001
6.1-9.0 cm	0.05	0.03-0.08	<0.001
> 9.0 cm	0.01	0.01-0.03	<0.001

* Reference group; RT = radiotherapy; CRT = chemoradiotherapy; OR = odds ratio; CI = confidence interval; OR < 1 indicates an increased likelihood of LAR and decreased likelihood of an APR.

Circumferential resection margin (for pT3-4 tumours)

CRM involvement was studied pathologically only in pT3-4 tumours, whereas patients with a pT0-2 tumour were assumed to have a negative CRM. Information on the status of the resection margin was unknown for 115 patients (14%) who were treated with a LAR or APR. In total, 778 patients could be analysed, of whom 42 patients (5.4%) had a positive CRM; 6.5% for patients treated with preoperative RT and 4.9% for patients treated with preoperative CRT ($P = 0.35$). In the multivariate analysis, treatment after 1999 was associated with a significantly lower risk of margin involvement (Table 4). In Figure 2, the

Table 4. Final model of multivariate logistic regression analysis for the probability of a positive CRM in patients with LAR or APR.

Variable	OR	95% CI	*P*-value
Preoperative treatment			0.33
RT*	1.00		
CRT	0.73	0.39-1.37	
Period of treatment			0.04
1993-1995*	1.00		
1996-1999	0.81	0.40-1.71	0.56
2000-2003	0.29	0.10-0.75	0.01

* Reference group; RT = radiotherapy; CRT = chemoradiotherapy; OR = odds ratio; CI = confidence interval; OR < 1 indicates a decreased risk of positive circumferential resection margin compared to the reference level.

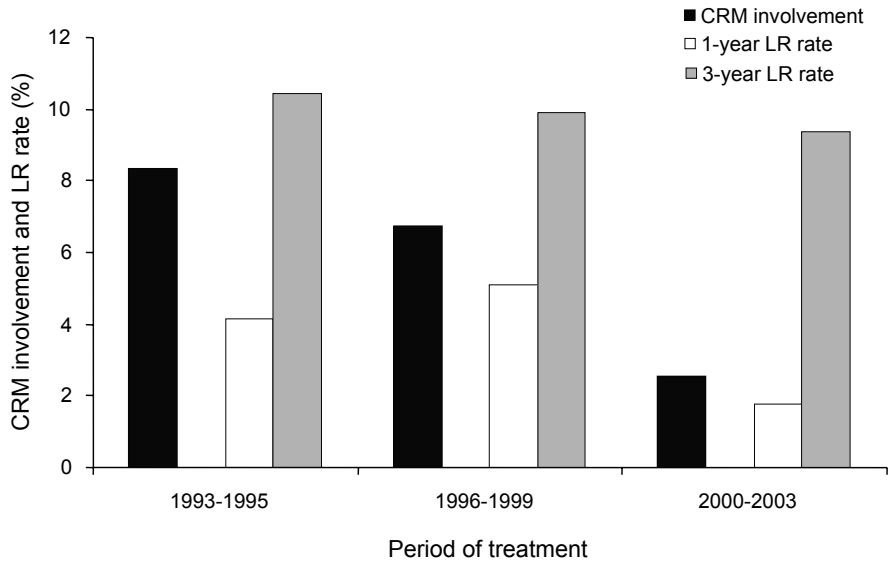

Figure 2. CRM involvement, 1-year and 3-year local recurrence (LR) rate shown per period of treatment. *P*-value for CRM involvement is 0.01 (χ^2-test), for LR 0.79 (log-rank test).

relation between CRM and period of treatment is shown ($P = 0.01$ in univariate analysis, χ^2 for trends).

Number of examined lymph nodes

The lymph node status was known for 831 patients treated with a LAR or APR. The median number of examined lymph nodes was 8 (range 0-45). The results of the multivariate analysis are displayed in Table 5. Younger age, treatment after 1995, proximal tumour location, and advanced tumour stage (pT3-4) were independently associated with a larger number of examined lymph nodes.

Table 5. Final model of multivariate rank ANOVA analysis for the number of examined lymph nodes.

Variable	Difference in number of examined lymph nodes	95% CI	*P*-value
Preoperative treatment			0.41
RT*	0.00		
CRT	-0.38	-1.28 to 0.51	
Age			0.04
≤ 50 years*	0.00		
51-60 years	-0.87	-2.29 to 0.55	
61-70 years	-1.77	-3.11 to -0.43	
> 70 years	-1.73	-3.31 to -0.14	
Period of treatment			<0.001
1993-1995*	0.00		
1996-1999	2.65	1.47 to 3.83	
2000-2003	3.58	2.31 to 4.85	
Distance			0.02
≤ 3.0 cm*	0.00		
3.1-6.0 cm	0.87	-0.39 to 2.13	
6.1-9.0 cm	1.18	0.06 to 2.30	
> 9.0 cm	0.99	0.98 to 4.87	
Pathological T-stage			<0.001
T0-T2*	0.00		
T3-T4	1.90	0.99 to 2.80	

RT = radiotherapy; CRT = chemoradiotherapy; CI = confidence interval. The average number of examined lymph nodes for a reference patient aged ≤50 years, treated with preoperative RT, year of entry before 1996 and a pT1-2 tumour located within 3 cm from the anal verge was 4.86.

Prognostic factors for outcome

Most LR were found in the group treated with preoperative RT alone[13] and were located in the presacral area (42%). LR occurred in 99 (12%) of the 862 patients with a LAR or APR. The local recurrence rate per period is shown in Figure 2 ($P = 0.14$). The results of the multivariate analysis are presented in Table 6: younger age, APR surgery, advanced pT-stage, and positive CRM were independent predictors of an increased risk of LR. Of the 862 patients treated with a LAR or an APR, 346 (40%) had a local or distant recurrence or died during follow-up. The results of the multivariate analysis stratified for treatment are presented in Table 6 and show that an APR procedure, advanced pT-stage, positive lymph node status, and positive CRM are independent prognostic factors for a shorter DFS. During follow-up, 247 patients treated with an APR or a LAR died (29%). The final multivariate model for OS is presented in Table 6. The same variables as for DFS were independent prognostic factors for OS.

Table 6. Final multivariate Cox models for local recurrence (LR), disease-free survival (DFS) and overall survival (OS), stratified for the four treatment arms.

Variable	Local recurrence			Disease-free survival			Overall survival		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age			0.02			----			----
≤ 50 years* versus 51-60 years versus 61-70 years versus > 70 years (linear trend)	0.75	0.60-0.95							
Surgical procedure			0.007			0.008			0.001
APR* versus LAR	0.54	0.34-0.85		0.72	0.57-0.92		0.60	0.45-0.81	
pT-stage			<0.001			<0.001			0.002
T0-T2* versus T3/T4	3.08	1.84-5.16		1.90	1.46-2.46		1.64	1.20-2.25	
pN-stage			----			<0.001			0.02
N0* versus N+				1.71	1.31-2.23		1.48	1.07-2.04	
CRM			<0.001			0.02			<0.001
Negative* versus positive	3.81	2.12-6.86		1.67	1.09-2.57		2.40	1.50-3.84	

CI = confidence interval; APR = abdominoperineal resection; LAR = low anterior resection; CRM = circumferential resection margin. A hazard ratio (HR) < 1 indicates a decreased and a HR > 1 indicates an increased risk of an event compared to the reference category (*).

DISCUSSION

In this analysis, we investigated risk factors associated with quality of surgery in EORTC 22921 trial, which assessed the efficacy of adding pre- and/or postoperative CT to a conventional schedule of preoperative RT for T3 and resectable T4 rectal cancer. In the present analyses, it was found that the period of treatment was associated with CRM and the number of examined lymph nodes. Besides, preoperative treatment was not found to be associated with CRM involvement.

The results indicate that the quality of the surgical resections improved during the trial. In the second half of the eighties, both surgeons and pathologists became interested in the lateral spread of rectal cancer and consequently CRM.[6,7] In addition, results from the TME trial demonstrate that RT is even beneficial for tumours located >1 cm from the CRM, indicating that lateral tumour spread is present in these tumours.[17] In the mid-1990s, after the start of EORTC 22921 trial, it became evident that excision of the total mesorectum should be considered as the gold standard.[18] In EORTC 22921 trial, CRM involvement decreased in the period 2000-2003 compared to the period 1993-1999, which correlates with the addition of the recommendation to perform a TME procedure in the protocol in 1999. A limitation of the present analyses was that CRM status was determined only for pT3-4 tumours; all tumours that were downstaged to pT0-2 were considered to have a negative margin. Although patients with T0-2 tumours in general will have a negative CRM, a few patients might have had a positive CRM similar to findings in the Dutch trial (18% overall margin involvement; 2% margin involvement for T1-2 tumours).[8] Another parameter of surgical quality also improved: over time more lymph nodes were examined. However, in the period 2000-2003, 8.4 lymph nodes were on average examined, whereas in the 5th TNM-classification (UICC, 1999), it was recommended to remove at least 12 lymph nodes.[19] Part of this difference could be explained by the use of preoperative (chemo)radiotherapy, which might have resulted in a reduced number of examined lymph nodes.[20] In daily clinical practice, patients in whom no sufficient lymph nodes are removed are often considered as high risk stage II patients and consequently treated with postoperative chemotherapy. However, by examining an adequate number of lymph nodes, a number of these patients could be considered as low risk patients, without the need to be treated with chemotherapy.

Surgical quality has been shown to be an important predictor of outcome in TME operated patients.[21,22] For patients in the TME trial, an incomplete mesorectum at pathological examination was associated with an increased risk of local and distant recurrence.[21] These results were confirmed in the MRC CR07 trial: an incomplete mesorectum was associated with more CRM involvement and subsequently with decreased local control.[22] However, in the present trial, recommendations to perform a TME were included in the protocol halfway through the trial in 1999. Consequently, in many patients,

no TME surgery was performed. Compared to before 2000, CRM involvement decreased in the period 2000-2003. Patients in this trial were treated with preoperative 45 Gy RT with or without pre- and/or postoperative CT. Several studies have investigated CRM involvement after CRT,[23-25] whereas only few studies report on the association between CRM involvement and outcome after preoperative CRT.[23] As far as we know, the association between CRM and outcome for curatively treated patients in whom postoperative chemotherapy has been administered in addition to preoperative RT or CRT, has not been reported before. Our analyses for LR, DFS and OS, which were stratified for the four treatment arms, indicated that CRM involvement was still an independent predictor of outcome, even though patients were treated with RT and/or pre- or postoperative CT. Moreover, the highest hazard ratio for OS was found for CRM, indicating that CRM was the most important prognostic factor for survival.

The type of surgical resection was found to be a prognostic factor for LR, DFS and OS. Factors which increased the likelihood to undergo an APR were male sex, inclusion in the trial in the period 1993-1995, and tumour location within 3 cm from the anal verge. In the nineties, it was shown that a tumour free distal margin of 5 cm was unnecessary, and that a clear margin of at least 1 cm was sufficient in TME operated patients.[26] Consequently, less patients were treated with an APR and more with a LAR since the introduction of TME surgery.[27] In addition, an APR was associated with a higher risk of CRM involvement and reduced local control and DFS.[28,29] Therefore, it is often advised to treat patients preoperatively with CRT before an APR. Significant more downstaging and downsizing was observed after CRT compared with RT.[14] Despite this downstaging, no significant difference for CRM status could be found when comparing CRT with RT in the present multivariate analysis. Apparently, increased downstaging and downsizing after CRT did not result in more radical resections. To reduce CRM involvement, the surgical procedure should change, especially for APR. For this procedure, it could be an option to perform a so-called cylindrical resection by widening the resection near the sphincter, an area were the resection is often incomplete.[29]

In the early 1990s, endo-rectal ultrasound was commonly used for rectal cancer. Consequently, endo-rectal ultrasound was advised in the EORTC trial protocol. In the same time period, the importance of a negative CRM became clear. However, it is found that CRM involvement cannot be appropriately assessed with ultrasound.[30] Nowadays, it is possible to predict CRM involvement preoperatively with a MRI-scan.[30] In patients who are found to have an involved or threatened CRM on a MRI scan, treatment could be adapted. CRT, for example, could be administered to downstage and downsize the tumour and subsequently the resection should be widened to obtain a negative CRM. In that way, individualisation of treatment with preoperative imaging could improve surgical resection quality.

In conclusion, important surgical parameters improved over time: less APR procedures were performed, the rate of CRM involvement decreased and the number of examined lymph nodes increased. However, an APR procedure was still a risk factor for an adverse outcome, even though all patients were preoperatively treated with 45 Gy RT (or CRT) followed by delayed surgery after 6 weeks. Although downstaging might be helpful in the treatment of these advanced tumours, the ultimate aim of the treatment should still be to perform a radical operation.

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Chapter 8

Patients with curative resection of cT3-4 rectal cancer after preoperative radio- or radiochemotherapy: does anybody benefit from adjuvant fluorouracil-based chemotherapy? A trial of the European Organisation for Research and Treatment of Cancer Radiation Oncology Group

Laurence Collette, Jean-Francois Bosset, Marcel den Dulk, France Nguyen, Laurent Mineur, Phillippe Maingon, Ljiljana Radosevic-Jelic, Marianne Piérart, Gilles Calais

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ABSTRACT

Purpose

European Organisation for Research and Treatment of Cancer (EORTC) 22921 trial compared adjuvant fluorouracil-based chemotherapy (CT) to no adjuvant treatment in a 2 x 2 factorial trial with randomisation for preoperative (chemo)radiotherapy in patients with resectable T3-4 rectal cancer. The results showed no significant impact of adjuvant CT on progression-free or overall survival, although a difference seemed to emerge at approximately, respectively, 2 and 5 years after the start of preoperative treatment. We further explored the data with the aim of refining our understanding of the long-term results.

Patients and methods

Data of 785 of the 1011 randomly assigned patients whose disease was M0 at curative surgery were used. Using meta-analytic methods, we investigated the homogeneity of the effect of adjuvant CT on the time to relapse or death after surgery (disease-free survival [DFS]) and survival in patient subgroups.

Results

Although there was no statistically significant impact of adjuvant CT on DFS for the whole group ($P > 0.5$), the treatment effect differed significantly between the ypT0-2 and the ypT3-4 patients (heterogeneity $P = 0.009$): only the ypT0-2 patients seemed to benefit from adjuvant CT ($P = 0.011$). The same pattern was observed for overall survival.

Conclusion

Exploratory analyses suggest that only good-prognosis patients (ypT0-2) benefit from adjuvant CT. This could explain why, in the whole group, the progression-free and overall survival diverged only after the poor-prognosis patients (ypT3-4) had experienced treatment failure. Patients in whom no downstaging was achieved did not benefit. This also suggests that the same prognostic factors may drive both tumour sensitivity for the primary treatment and long-term clinical benefit from further adjuvant CT.

INTRODUCTION

The European Organisation for Research and Treatment of Cancer (EORTC) 22921 trial was a 2 x 2 factorial plan, four-arm, randomised trial that questioned the value of preoperative radiochemotherapy (RT-CT) versus preoperative radiotherapy (RT) alone and the value of adjuvant chemotherapy (CT) versus none with respect to overall survival and progression-free survival in patients with potentially resectable cT3-4 M0 rectal cancer.

From April 1993 to March 2003, 1011 patients were allocated to one of the following treatment arms: arm 1, preoperative RT; arm 2, preoperative RT-CT; arm 3, preoperative RT and adjuvant CT; and arm 4, preoperative RT-CT and adjuvant CT.

The main trial results were recently published with a median follow-up of 5.4 years.[1] A first analysis showed that the addition of CT to preoperative RT induced a significant increase of the downstaging rate.[2] The long-term results[1] failed to demonstrate a significant impact of CT (either before or after surgery) on progression-free or overall survival, the primary trial end-points. The 5-year overall survival rate was 63.2% in the no-adjuvant CT and 67.2% in the adjuvant CT arms ($P = 0.12$) with a hazard ratio (HR) of 0.85 for adjuvant CT (95% confidence interval (CI), 0.68-1.04). The 5-year progression-free survival rates were 52.2% and 58.2% in the no-adjuvant and adjuvant arms, respectively ($P = 0.132$; HR = 0.87; 95% CI, 0.72-1.04). However, the progression-free and overall survival curves started to diverge at approximately, respectively, 2 and 5 years after entry onto study, suggesting that a subset of patients of better prognosis who survive 2 to 5 years after the initiation of the first treatment might benefit from the adjuvant treatment in the long-term.

We now further explore the data with the aim of refining our understanding of the long-term results. For that purpose, we will focus on the group of eligible patients whose disease had not spread to distant sites before or at surgery and in whom a complete resection was performed. This subgroup should be disease free after surgery. We will then investigate whether we can identify, on the basis of baseline patient and treatment factors as well as of preoperative and surgical treatment and outcome characteristics, a subgroup of patients who benefit significantly from the adjuvant treatment in the long-term.

PATIENTS AND METHODS

Trial design

The trial design and eligibility criteria have been reported previously,[1] and we will summarise only the main features herein. Patients age up to 80 years with resectable T3 or T4 M0 (1987 International Union Against Cancer (UICC) staging) adenocarcinoma of the

rectum,[3] located within 15 cm of the anal margin, with a WHO performance status of 0 or 1, and without previous history of cancer, angina pectoris, or inflammatory disease of the ileum or colon were eligible for the trial. Disease staging was by clinical examination, rigid sigmoidoscopy, chest X-ray, and abdominopelvic computed tomography scan. Endorectal ultrasonography was optional.

The trial was approved by the medical ethics committees of all participating centres. Informed consent was obtained from all patients before random assignment. The patients were centrally randomised at the EORTC Data Centre to RT or RT-CT as preoperative treatment and to CT or nil as adjuvant treatment.

RT consisted of a 45-Gy dose delivered in 25 fractions of 1.8 Gy to the posterior pelvis.[2,4] Irradiation techniques and treatment volumes have been reported previously.[2,4] Preoperative CT was delivered in two 5-day courses during the first and fifth weeks of RT. Surgery was planned 3 to 10 weeks thereafter, and total mesorectal excision was recommended from 1999 onwards. When allocated, the four 3-week courses of adjuvant CT had to start 3 to 10 weeks after surgery. Preoperative and adjuvant CT consisted of fluorouracil (350 mg/m^2/d) and leucovorin (20 mg/m^2/d) administered as a short intravenous infusion.

The toxicity was monitored during treatment.[4] Patients were then followed at 6-month intervals for at least 5 years by clinical examination, abdominal ultrasound, and chest x-ray; coloscopy was performed annually. Recurrences were confirmed radiologically or histologically. Local recurrence was defined as a tumour regrowth within the pelvis or perineum.

Analysis set and end-points

Only the 785 eligible patients whose disease did not spread to distant sites before or at surgery and in whom a microscopically complete (R0) resection was performed are included in the analysis (77.6% of 1011). Complete resection was defined in this study as resection with negative resection margin by both macroscopic and microscopic examination. Disease-free survival (DFS) is defined as the time from the date of surgery to the first event of locoregional or distant recurrence or death resulting from any cause; or to the date of the most recent follow-up for excluded cases. This end-point corresponds to progression-free survival in the study protocol, but is counted from the date of surgery. Survival is counted from the date of surgery to the date of death resulting from any cause or the date of most recent information if alive.

Statistical methods

The analysis is exploratory. The association between classifications and outcome are assessed by log-rank test for heterogeneity and effects represented on forest plots,[5] and the distribution of time-to-event end-points is estimated by means of Kaplan-Meier.[6]

Interaction between factors and treatment effects is summarised by the interaction HR and its associated 95% CI.[7] The interaction HR represents the ratio of the treatment HR for one level of the explanatory variable to the treatment HR in the reference level of the covariate, and thus measures how much the relative treatment effect is modulated by the covariate. For grouping patients, continuous variables were dichotomised at the sample median or at published values. Adjacent levels of discrete variables with small numbers were lumped together. Two-sided tests were used with a 5% significance level. All analyses but those of the preoperative treatment were stratified for the allocated preoperative treatment.

RESULTS

A total of 226 patients were excluded from the analysis (102 initially allocated to no adjuvant CT and 124 to adjuvant CT): 15 were ineligible, 45 had metastatic progression before surgery, 57 have unknown metastatic status, 10 were not resected despite disease being M0, and 78 had an incomplete resection; in 21, the information regarding completeness of the resection was unknown.

Of the 785 patients included in the analysis, 199 had been randomly assigned to the RT arm without adjuvant CT, 204 to RT-CT arm without adjuvant CT, 190 to the RT arm with adjuvant CT, and 192 to the RT-CT arm with adjuvant CT. In the analysed set, all patients allocated adjuvant CT received at least one adjuvant CT cycle. The four adjuvant CT cycles were delivered to 140 (73.7%) of 190 patients and 142 (73.9%) of 192 patients allocated adjuvant CT in the RT and RT-CT arms, respectively.

Of the patients in the RT arm, 233 (57.8%) were alive and free of disease at a median follow-up of 5.2 years from surgery, compared with 237 (62.0%) in the RT-CT arm (Figure 1). The first relapse was locoregional in 37 patients receiving RT versus 19 patients receiving RT-CT, distant relapse occurred in 98 versus 91 patients, the two types of events occurred concurrently in five versus eight patients, a death without relapse occurred in 28 versus 25 patients, and relapse at unspecified localisation occurred in two patients in each arm.

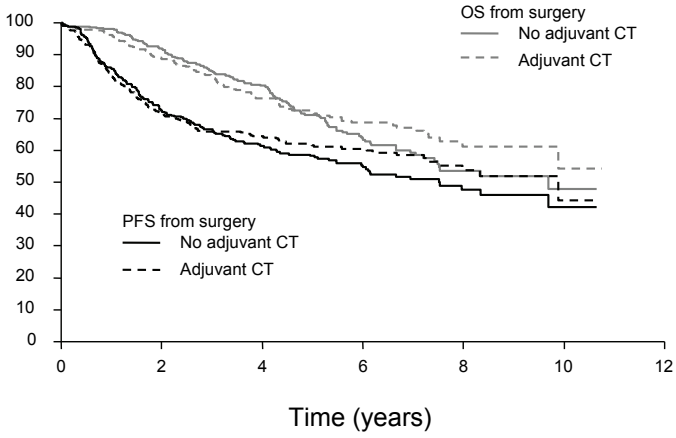
The patients and the potential predictors considered in the analysis are described in Table 1. Because only 5.2% of the cases had mucinous tumours, this variable was not analysed. Although the treatments were randomly assigned, some factors were slightly imbalanced between the two adjuvant treatment groups: WHO performance status more than 1 was more frequent in the adjuvant treatment group (32.2% versus 25%), whereas in the no-adjuvant group, treatment downstaging to ypT0-2 was less frequent (51.8% versus 55.8%) and pN+ cases were less common (25.4% versus 29.5%). The imbalances in prognostic factors seemed to average out: The adjuvant treatment HR for DFS

Table 1. Patient, disease and treatment characteristics considered in the analysis and univariate interaction tests (testing for heterogeneity of treatment effect between levels of the tested classifications).

Characteristics	Frequency		Univariate interaction tests			
	No adjuvant CT (*n* = 403)	Adjuvant CT (*n* = 382)	Disease-free survival		Overall Survival	
	n (%)	*n* (%)	*P*	Interaction HR (95% CI)	*P*	Interaction HR (95% CI)
Patient and disease characteristics at study entry						
Age						
Median	62.5	63.2				
Range	23.3-79.6	22.0-78.6				
≤ 60 years	175 (43.4)	161 (42.1)				
> 60 years	228 (56.6)	221 (57.9)	0.983	1.01 (0.64-1.58)	0.989	1.00 (0.58-1.72)
Sex						
Male	295 (73.2)	285 (74.6)				
Female	108 (26.8)	97 (25.4)	0.588	1.16 (0.68-1.97)	0.965	1.01 (0.52-1.98)
Distance between the tumour and the anal verge						
0-5 cm	198 (49.1)	185 (48.4)				
> 5 cm	205 (50.9)	197 (51.6)	0.202	0.75 (0.48-1.17)	0.026	0.54 (0.31-0.93)
Clinical T category						
T3	368 (91.3)	345 (90.3)				
T4	35 (8.7)	37 (9.7)	0.757	0.90 (0.44-1.81)	0.962	1.02 (0.48-2.18)
Preoperative treatment						
RT	199 (49.4)	190 (49.7)				
RT-CT	204 (50.6)	192 (50.3)	0.763*	1.07 (0.69-1.67)	0.482*	1.21 (0.71-2.06)
Worst WHO grade toxicity during preoperative treatment						
0-1	212 (52.6)	197 (51.6)				
≥ 2	178 (44.2)	176 (46.1)	0.764	0.93 (0.59-1.47)	0.879	0.96 (0.56-1.67)
Missing	13 (3.2)	9 (2.4)				
Surgery						
WHO performance status prior to surgery						
0	294 (73.0)	242 (63.4)				
> 0	101 (25.1)	123 (32.2)	0.984	1.01 (0.62-1.63)	0.398	0.78 (0.43-1.39)
Missing	8 (2.0)	17 (4.5)				

Time from end of the preoperative treatment to surgery						
≤ 6 weeks	271 (67.2)	262 (68.6)				
> 6 weeks	132 (32.8)	120 (31.4)	0.398	0.81 (0.50-1.32)	0.283	0.72 (0.39-1.31)
Surgical procedure						
APR	163 (40.4)	149 (39.0)				
AR or other	240 (59.6)	233 (61.0)	0.146	0.72 (0.46-1.12)	0.023	0.54 (0.32-0.92)
Histopathology						
Tumour length						
≤ 30 mm	244 (60.5)	238 (62.3)				
> 30 mm	143 (35.5)	132 (34.6)	0.474	0.85 (0.53-1.34)	0.780	0.92 (0.53-1.60)
Missing	16 (4.0)	12 (3.1)				
WHO differentiation						
Well	174 (43.2)	153 (40.1)				
Poor/moderate	213 (52.9)	205 (53.7)	0.419	0.83 (0.52-1.31)	0.778	0.92 (0.53-1.60)
Missing	16 (4.0)	24 (6.3)				
Histology						
Mucinous	23 (5.7)	18 (4.7)		Not tested		Not tested
Other	380 (94.3)	363 (95.0)				
Missing	0 (0.0)	1 (0.3)				
Pathologic tumour stage						
ypT0-2	225 (55.8)	198 (51.8)				
ypT3-4	176 (43.7)	183 (47.9)	0.008	1.87 (1.18-2.98)	0.024	1.89 (1.09-3.27)
Missing	2 (0.5)	1 (0.3)				
Number of examined lymph nodes						
< 8	188 (46.7)	167 (43.7)				
≥ 8	206 (51.1)	207 (54.2)	0.714	0.92 (0.59-1.44)	0.895	0.96 (0.56-1.66)
Missing	9 (2.2)	8 (2.1)				
Pathologic nodal status						
ypN0	278 (69.0)	281 (73.6)				
ypN+	119 (29.5)	97 (25.4)	0.818	1.06 (0.67-1.66)	0.903	1.04 (0.59-1.80)
Missing	6 (1.5)	4 (1.0)				
Venous, perineural or lymphatic invasion						
No	310 (76.9)	294 (77.0)	0.568	1.15 (0.71-1.88)	0.423	1.28 (0.70-2.32)
Yes	82 (20.3)	80 (20.9)				
Missing	11 (2.7)	8 (2.1)				

HR = hazard ratio; RT = radiotherapy; RT-CT = radiochemotherapy; AR= anterior resection; APR= abdominoperineal resection. *Not stratified for preoperative treatment.



OS	O	N	Number of patients at risk				
No adjuvant CT	119	403	332	208	108	41	9
Adjuvant CT	102	382	300	199	110	37	7
PFS							
No adjuvant CT	170	403	264	164	99	37	8
Adjuvant CT	145	382	244	173	101	33	5

Figure 1. Progression-free survival (PFS) and overall survival (OS) from the date of surgery by adjuvant treatment. O = number of events; N = number of patients; CT = chemotherapy.

was very similar with (HR = 0.94; 95% CI 0.73-1.20; *P* = 0.262) or without (HR = 0.92; 95% CI 0.73-1.14; *P* = 0.443) adjustment for the covariates; as was the adjuvant treatment HR for overall survival with (HR = 0.93; 95% CI 0.69-1.25; *P* = 0.623) or without adjustment for the covariates (HR = 0.92; 95% CI 0.70-1.19; *P* = 0.514).

The univariate interaction tests for DFS and overall survival are also presented in Table 1 with the HRs and the CIs. Only the downstaging (ypT0-2 versus ypT3-4) statistically significantly influenced the magnitude of the adjuvant treatment effect (*P* = 0.008, Figure 2), with an interaction HR of 1.87 (95% CI 1.18-2.98) indicating a significantly larger treatment benefit for the group with downstaging. In the group of patients with downstaging to ypT0-2 at the time of surgery, the treatment HR for DFS was 0.64 (95% CI 0.45-0.91) in favour of adjuvant CT (*P* = 0.013); the DFS rate was 65.6% (95% CI 58.3%-72.0%) without CT and 76.7% (95% CI 69.4%-82.5%) with CT (Figure 3). In patients without downstaging, there was no statistically significant benefit of adjuvant CT (HR = 1.18; 95% CI 0.89-1.57; *P* = 0.244). For that group, the 5-year DFS rate was 48.9% without CT (95% CI 40.8%- 56.5%) and 45.1% with adjuvant CT (95% CI 37.3%-52.5%; Figure 3).

For survival, the downstaging also significantly influenced the effect of the adjuvant treatment (heterogeneity test *P* = 0.024, Figure 4), with an interaction HR of 1.89 (95% CI 1.09-3.27; Table 1). In the group with downstaging, adjuvant CT significantly prolonged survival time after surgery (*P* = 0.030; HR=0.64; 95% CI 0.42-0.96), whereas the group without downstaging did not seem to benefit (*P* = 0.337; HR = 1.19; 95% CI 0.84-1.68).

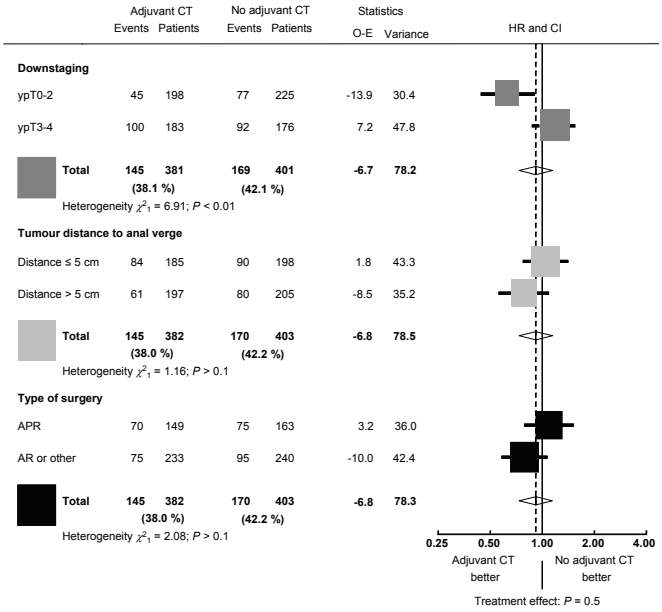
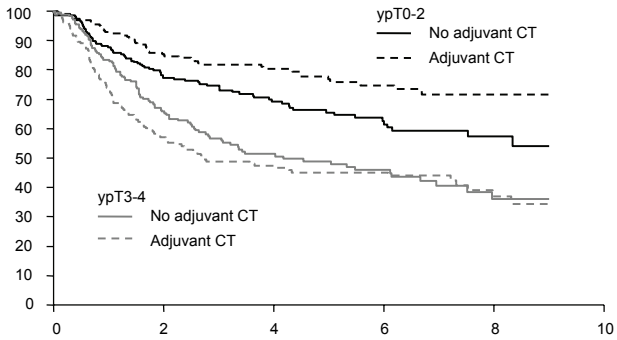


Figure 2. Forest plot of the univariate interactions between the effect of adjuvant chemotherapy (CT) on disease-free survival after surgery and downstaging by preoperative treatment, tumour localisation, and type of surgical procedure. Solid vertical line represents no effect. Dashed vertical line and diamond represent the overall hazard ratio (HR) and confidence interval (CI). Centre of squares indicates HR in each group with 95% CI (horizontal bars). Square size is proportionate to the amount of information in each group. O = number of events observed; E = number of events expected in the absence of treatment effect; APR = abdominoperineal resection; AR = anterior resection.



ypT0-2	O	N	Number of patients at risk			
No adjuvant CT	77	225	157	101	57	22
Adjuvant CT	45	196	150	111	59	16
ypT3-4						
No adjuvant CT	92	176	107	63	42	15
Adjuvant CT	100	183	94	62	42	17

Figure 3. Kaplan-Meier curve of disease-free survival after surgery by adjuvant treatment and pathological down staging to ypT0-2. O = number of events; N = number of patients; CT = chemotherapy.

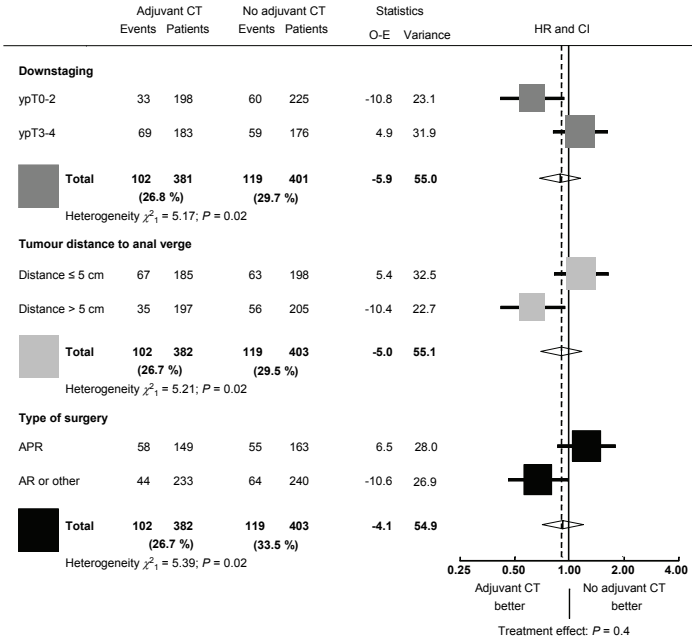


Figure 4. Forest plot of the univariate interactions between the effect of adjuvant chemotherapy (CT) on survival after surgery and downstaging by preoperative treatment, tumour localisation and type of surgical procedure. Solid vertical line represents no effect. Dashed vertical line and diamond represent the overall hazard ratio (HR) and confidence interval (CI). Centre of squares indicates HR in each group with 95% CI (horizontal bars). Square size is proportionate to the amount of information in each group. O = number of events observed; E = number of events expected in the absence of treatment effect; APR = abdominoperineal resection; AR = anterior resection.

Unlike for DFS, the benefit from adjuvant CT was significantly increased in patients with tumour located more than 5 cm from the anal verge compared to the benefit seen in patients with a tumour located at 5 cm from the anal verge (low rectum; heterogeneity test $P = 0.026$; interaction HR = 0.54; 95% CI 0.31-0.98; Figure 4). For tumours in the low rectum, adjuvant CT was not beneficial ($P = 0.353$; HR = 1.18; 95% CI 0.83-1.66), whereas it was beneficial in patients with tumours located higher up in the rectum ($P = 0.033$), with a treatment HR of 0.64 (95% CI 0.42-0.96) indicating prolonged survival with adjuvant treatment. Similarly, the type of surgical procedure also influenced the effect of adjuvant chemotherapy (interaction HR = 0.54; 95% CI 0.31-0.93; $P = 0.026$). Patients who had undergone an abdominoperineal resection (APR) did not seem to benefit from adjuvant CT (HR = 1.26; $P = 0.222$), whereas those with another type of surgical procedure did (HR = 0.68; $P = 0.046$; Figure 4). This is not surprising, because tumour localisation in the rectum is the major driver of choice of the surgical procedure, and 68% of the patients with a tumour in the low rectum underwent APR, compared with only 12% in those with tumours located higher in the rectum.

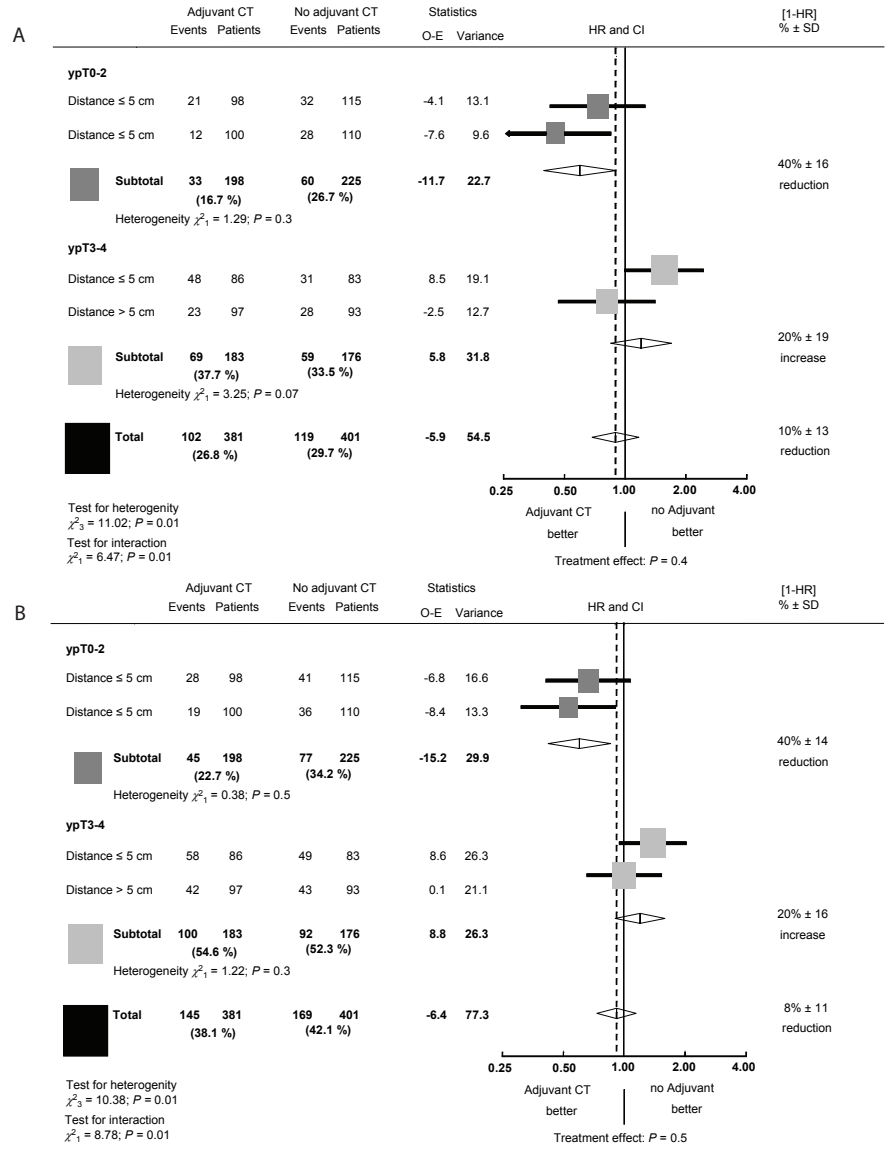


Figure 5. Forest plot of the effect of adjuvant chemotherapy (CT) by downstaging and tumour localisation on (A) overall survival and (B) disease-free survival after surgery. Solid vertical line represents no effect. Dashed vertical line and diamond represent the overall hazard ratio (HR) and confidence interval (CI). Centre of squares indicates HR in each group with 95% CI (horizontal bars). Square size is proportionate to the amount of information in each group. O = number of events observed; E = number of events expected in the absence of treatment effect; SD = standard deviation.

Because the type of surgical procedure and the tumour localisation in the rectum are strongly correlated,[8,9] only the tumour localisation was combined with tumour downstaging for a multivariate predictive factor analysis of overall survival. The four-group

classification combining tumour downstaging (ypT0-2 versus ypT3-4) and tumour localisation (≤ 5 cm versus > 5 cm from the anal verge) statistically significantly influenced the treatment effect (heterogeneity test $P = 0.012$; 3 *df*; Figure 5A). However, within the subgroup with ypT0-2, the treatment effect seemed not to significantly vary according to tumour localisation (heterogeneity $P = 0.255$) whereas it seemed to differ more within the subgroup with ypT3-4, although not statistically significantly (heterogeneity $P = 0.071$). Nevertheless, the three-way interaction amongst ypT, tumour localisation, and treatment was not statistically significant ($P = 0.731$). In the patients with ypT0-2, the HR favoured adjuvant CT (HR = 0.73; 95% CI 0.43-1.26; and HR = 0.45; 95% CI 0.24-0.85 for low and middle/high rectum, respectively). In the patients with ypT3-4 disease, the treatment HRs were not in favour of adjuvant CT: the treatment HR was 1.55, pointing against adjuvant CT for patients with a tumour in the low rectum (95% CI 0.99-2.44; $P = 0.053$), and it was 0.81 for patients with tumours located in the middle or high rectum (95% CI 0.47-1.41).

The impact of this classification on DFS after surgery is represented in Figure 5B and shows that only the classification by ypT influences the treatment effect on this endpoint. The study could not demonstrate a statistically significant behaviour according to the type of preoperative treatment administered, but the predictive effect remained significant even if patients had no preoperatively CT.

DISCUSSION

Overall, the EORTC trial 22921 could not demonstrate that delivering adjuvant CT to all patients with resectable T3-T4 rectal cancer would prolong progression-free or overall survival.[1] In the present analysis, we focused on those patients whose tumour could be resected completely and whose disease had not extended to metastatic sites by the time of the surgery. We then showed that, in the subgroup of patients whose disease had been downstaged to ypT0-2 by preoperative treatment, the delivery of adjuvant CT prolonged both the time to relapse and the survival time.

These findings should not, however, be misinterpreted: It is a common mistake to conclude causality when only associations have been demonstrated. We did not show that it is because tumour downstaging was achieved that these patients also benefited of further CT, but rather that those same patients who achieved downstaging have a disease that is responsive to both the preoperative and the adjuvant treatment. This suggests that the same good prognostic factors induce both an increased likelihood of downstaging from preoperative treatment and increased likelihood of a benefit from adjuvant CT. These findings are no proof of surrogacy of the downstaging for the long-term end-points,[10] but are in line with Valicenti et al.'s statement that heterogene-

ity of tumour behaviour exists, which identification may be promoted by preoperative treatment.[11]

One could then ask which factors drive the sensitivity to pre- and postoperative treatment. In this database, the factors predicting an increased likelihood of downstaging were preoperative treatment,[4] along with tumour length and the use of modern staging by endorectal ultrasonography (data not shown). The factors predicting for progression-free survival after surgery were type of surgical procedure, pN status, microscopic surgical margin status, and tumour downstaging by preoperative treatment.[9] We therefore focused on curatively resected patients. We believe, however, that other factors more closely related to sensitivity to RT and/or CT and to the biology of the disease are probably more relevant to the definition of the "good prognostic" patient group. However, these factors are not known from the data collected in the trial. We can therefore only identify this subgroup a posteriori, on the basis of the pathologic downstaging after preoperative treatment.

The other factors that seemed to influence the effect of the adjuvant treatment on overall survival (tumour localisation and type of surgery) were not confirmed to influence the effect of the treatment on progression-free survival. These factors are known prognostic factors of outcome,[8,9] but in our study, they were not confirmed to be predictive for a benefit from adjuvant treatment regarding progression-free survival.

This analysis is exploratory in nature: neither the end-point nor the hypotheses studied were planned in the study protocol. The hypothesis that a subgroup might benefit from adjuvant treatment emerged from the first trial results that were suggestive of mixture of patients in the sample, with varying sensitivity to and potential benefit from the tested adjuvant treatment. These findings must, therefore, be validated on an independent set of patients with cT3-4 rectal cancer who received preoperative treatment, were operated on, and were downstaged to pT0-2 and are then randomly assigned to receive or not receive fluorouracil-based adjuvant CT.

Despite the lack of evidence to support the routine use of adjuvant CT for all patients with resectable T3-4 rectal cancer after preoperative treatment,[1] adjuvant chemotherapy is regarded by some as standard adjuvant treatment.[12-16] The present report, however, confirms that, at least in patients presenting with poorer risk features (i.e., without tumour downstaging after preoperative radiotherapy or radiochemotherapy), adjuvant chemotherapy with fluorouracil and leucovorin may be an ineffective treatment, causing extra burden and toxicity to the patients without evidence, so far, of any clinical benefit. Our findings contrast with the recommendations by Das et al.[14] who suggest, rather, that adjuvant chemotherapy might benefit more higher-risk patients but are in line with those of Janjan et al.,[17] who report higher rates of relapse despite adjuvant chemotherapy in patients showing no response to preoperative treatment. However, they suggest the use of FOLFOX for high-risk patients, which includes oxali-

platin in addition to the fluorouracil and leucovorin used in EORTC 22921 trial. In a study of 95 rectal cancer patients who all underwent preoperative radiochemotherapy and a microscopically complete resection, Frietkau et al.[13] concluded that postoperative chemotherapy may not be necessary in patients with ypN0. Their conclusions are based on the observation that ypN was the most important and sole independent prognostic factor for disease-free survival in their study and that there was no significant impact of the type, if any, of postoperative treatment on outcome. EORTC 22921 trial confirmed that ypN was a strong independent prognostic factor for overall survival and DFS;[9] however, we demonstrated in the present report that ypN status after preoperative treatment did not show an interaction with the benefit from postoperative CT. The findings reported by Frietkau may well have resulted from lack of power in their analyses, in relation to the limited number of patients in their study.

We can therefore conclude that newer agents are worth investigating either alone or in combination as (neo)adjuvant treatment of rectal cancer, but predictive factors such as tumour responsiveness to preoperative treatment must be taken into account in the design of future phase III trials. Separate treatment strategies may be devised for patients with differing sensitivity to classical chemotherapeutic agents. Finally, the analysis of gene expression profiles of the primary tumour may be relevant to identify patients who may benefit from preoperative radiochemotherapy[16] and adjuvant fluorouracil-based chemotherapy.[18,19]

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Chapter 9

The association between diverting stomas and symptomatic anastomotic leakage after low anterior resection for rectal cancer

Marcel den Dulk, Corrie A.M. Marijnen, Laurence Collette, Hein Putter, Lars Påhlman, Joakim Folkesson, Jean-Francois Bosset, Claus Rödel, Krzysztof Bujko, Cornelis J.H. van de Velde

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ABSTRACT

Purpose

The association between a diverting stoma and the rate of symptomatic anastomotic leakage following rectal cancer surgery was studied here. Furthermore, the impact of anastomotic leakage on the rate of local recurrence, distant metastases, disease-free survival, overall survival, and cancer-specific survival was investigated.

Patients and methods

The Swedish Rectal Cancer trial, TME trial, CAO/ARO/AIO-94 trial, EORTC 22921 trial, and Polish Rectal Cancer trial were pooled (n = 5187). All eligible patients treated with a low anterior resection and without distant metastases at the time of surgery were selected (n = 2726). In the Swedish Rectal Cancer trial no data on stomas were available. The patients from that trial were thus excluded from all analyses related to stomas (n = 430). Overall survival was studied in the selected patients aged ≤ 75 years (n = 2480). Multivariable models were used to study the association between a diverting stoma and anastomotic leakage and the association between anastomotic leakage and recurrence or survival.

Results

In total 264 of 2726 (9.7%) patients were diagnosed with a symptomatic anastomotic leak; a diverting stoma was negatively associated with leakage (11.7% for patients without and 7.9% for patients with a diverting stoma, P = 0.002). Anastomotic leakage was negatively associated with overall survival in the multivariable analysis even after excluding patients who died within 90 days of surgery (hazard ratio (HR) 1.29; 95% CI 1.02-1.63; P = 0.034), but not with cancer-specific survival (HR 1.12; 95% CI 0.83-1.52; P = 0.466).

Conclusion

Diverting stomas were associated with less symptomatic anastomotic leakage. Although oncological outcome was not significantly influenced by a leak, overall survival (both short- and long-term) was reduced.

INTRODUCTION

Surgery is the cornerstone in the treatment of rectal cancer. Widespread use of standardised total mesorectal excision (TME) improved overall survival.[1,2] However, TME surgery might be associated with an increased risk of developing anastomotic leakage[3] with attendant morbidity and mortality in the postoperative period.[4,5] Leaks might be associated with decreased local control[6-11] and survival[7,12,13]. Therefore, the rate of (symptomatic) anastomotic leakage has been considered as one of the quality indicators of surgical performance.[14]

Studies to identify risk factors for anastomotic problems and methods to reduce symptomatic leaks are clearly important.[15,16] At the end of last century, two small randomised trials tested the hypothesis that a diverting stoma reduces the incidence of anastomotic leakage.[17,18] Although both trials showed fewer anastomotic leaks with stoma use, the difference was not statistically significant. A larger randomised trial concluded that a diverting stoma significantly reduces the risk of symptomatic anastomotic leakage.[19]

In this study, 5 large European randomised clinical trials were pooled to study the association between the creation of a diverting stoma and the rate of symptomatic leakage after a (low) anterior resection for rectal cancer. In addition, the impact of anastomotic leakage on the rate of local recurrence, distant metastasis, disease-free survival, overall survival, and cancer-specific survival were investigated.

PATIENTS AND METHODS

Trials and patients

Patient and treatment variables of the following 5 trials were pooled: Swedish Rectal Cancer trial[20], Dutch TME trial[21], German CAO/ARO/AIO-94 trial[22], EORTC 22921 trial[23], and the Polish Rectal Cancer trial[24]. The period of inclusion, randomisation arms and number of included patients are shown in Table 1. Of this pooled database of treatment variables, all eligible patients treated with a low anterior resection and without distant metastases at the time of surgery were selected. In the Swedish Rectal Cancer trial no data on stomas were available, although stomas in that trial were rarely used as mostly high anastomoses were created. The patients from that trial were thus excluded from all analyses related to stomas. The 5th edition of TNM classification of malignant tumours was used to determine the TNM stage.[25] The analyses of overall survival, disease-free survival, and cancer-specific survival were restricted to patients aged 75 year or less, to control those analyses for different age limits allowed in the various trials.

Table 1. Period of inclusion, randomisation arms and number of patients per trial.

Trial	Period	Randomisation	*n*
Swedish Rectal Cancer trial	1987-1990	preoperative 5 x 5 Gy RT surgery alone	1180
Dutch TME trial	1996-1999	preoperative 5 x 5 Gy RT with TME surgery TME surgery alone	1861
German CAO/ARO/AIO-94 trial	1995-2002	preoperative CRT postoperative CRT	823
EORTC 22921 trial	1993-2003	preoperative 45 Gy RT preoperative CRT preoperative 45 Gy RT and postoperative CT preoperative CRT and postoperative CT	1011
Polish Rectal Cancer trial	1999-2002	preoperative 5 x 5 Gy RT with TME surgery preoperative CRT with TME surgery	312
Total			5187

RT = radiotherapy; CRT = chemoradiotherapy; CT = chemotherapy.

End-points, variables and statistics

In the included trials, only symptomatic anastomotic leakages were documented. Anastomotic leakage was defined as clinically apparent leakage such as faecal discharge from pelvic drain or abdominal wound, or radiologically, endoscopically or surgically proven anastomotic leakage in symptomatic patients such as those with peritonitis.

The χ^2 test was used for comparisons of categorical variables. Univariate and multivariable logistic regression analyses were performed with the following variables to study their association with anastomotic leakage: gender, age, distance of the tumour from the anal verge, TNM stage, and the presence of a stoma. The multivariable analysis was adjusted for trial and randomisation arm.

To study the effects of anastomotic leakage on local recurrence, distant metastasis, overall survival, disease-free survival, and cancer-specific survival, Cox regression analyses were used, stratified for trial and randomisation arm. The following confounders were first studied by univariate analyses: gender, age, distance of the tumour from the anal verge, TNM stage, and circumferential resection margin (CRM) involvement. Variables with a *P*-value of ≤ 0.10 were then entered in the multivariable Cox regression models. A positive CRM was defined as microscopic or macroscopic tumour in the resection margin (unavailable in the Swedish Rectal Cancer trial). Time to local recurrence, distant metastases, and overall survival were calculated as the time from surgery to respectively local recurrence, distant metastases, and death. For overall survival, the analyses were performed first for all selected patients. These analyses were then repeated with a landmark selection, excluding all patients who died within 90 days postoperatively to correct for short-term mortality associated with anastomotic leakage itself. Disease-free survival, defined as time from surgery to first event of local recurrence, distant metas-

tases or death, and cancer-specific survival, defined as the time from surgery to death due to rectal cancer, were studied only using the landmark selection excluding patients with 90-day postoperative mortality. The probability of local recurrence is reported as cumulative incidences with death as competing risk; cancer-specific survival is reported as one minus cumulative incidence with death due to other causes than rectal cancer as competing risk.[26]

Data were analysed with the SPSS package (SPSS 14.0 for Windows; SPSS Inc., Chicago, IL, USA). A two-sided *P*-value of ≤ 0.05 was considered to be statistically significant.

RESULTS

Patients

In total, 5187 patients were included in the Swedish Rectal Cancer trial, Dutch TME trial, German CAO/ARO/AIO-94 trial, EORTC 22921 trial, and the Polish Rectal Cancer trial. Reasons for exclusion and number of patients are shown in Figure 1. Of 1962 patients with another than a low anterior resection, 1749 were treated with an abdominoperineal resection. For the analyses, 2726 patients (52.6%) were included. Patient and disease characteristics of these patients are shown in Table 2. The median follow-up of patients alive was 5.9 years (range 0.2-14.9 years). Overall, disease-free and cancer-specific survival were studied in 2480 of these 2726 patients who were aged ≤ 75 years.

Anastomotic leakage

In total, 264 patients (9.7%) were diagnosed with anastomotic leakage. No information on stoma construction was available for the Swedish Rectal Cancer trial ($n = 430$). Therefore, these patients were excluded in the analyses related to stomas: 2296 patients were studied. In 1226 patients (53.5%) a stoma was constructed; in 1067 patients (46.5%) no stoma was created; for 3 patients (0.1%), the stoma status was unknown. Symptomatic anastomotic leakage occurred in 124 patients (11.7%) without a stoma, whereas it was diagnosed in 96 patients (7.9%) with a stoma ($P = 0.002$).

In Table 3, the results of the univariate and multivariable analysis for risk factors associated with anastomotic leakage are shown. From the univariate analyses, both gender and the presence of a diverting stoma were selected for entry in the multivariable analysis due to a *P*-value ≤ 0.10. Trial and treatment arm were entered in the analysis as adjustment. Female gender and the presence of a diverting stoma were both independently associated with a reduced chance to develop symptomatic anastomotic leakage.

The anastomotic leakage rates per trial and randomisation arm are shown in Table 4. None of the trials showed a significant difference between the randomised treatment arms.

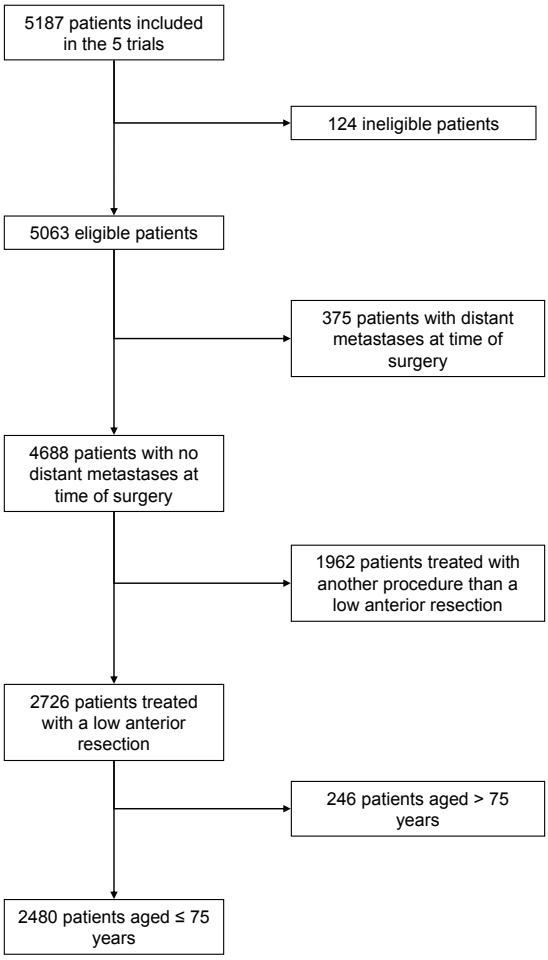


Figure 1. Flow diagram of selected and excluded patients.

1.3% of patients without anastomotic leakage (33 of 2446) died within 30 postoperative days, whereas the 30-day mortality rate after anastomotic leakage was 5.7% (15 of 263 patients; $P < 0.001$). For one patient with anastomotic leakage, no details on death status were available.

Anastomotic leakage and local recurrence

Anastomotic leakage was not associated with local recurrence in the univariate analysis and therefore not entered in the multivariable analysis: 5-year local recurrence rate 8.8% (95% confidence interval (CI) 7.6%-10.0%) for patients without anastomotic leakage and 12.0% (95% CI 7.4%-16.5%) for patients with anastomotic leakage ($P = 0.103$). The cumulative incidence of local recurrence with death as competing risk for patients with and without anastomotic leakage is depicted in Figure 2A.

Table 2. Patient and tumour characteristics of the patient population after selection of all eligible patients treated with a low anterior resection and without distant metastases at time of surgery.

Variable	*n* (%)
Sex	
Female	1018 (37.3)
Male	1708 (62.7)
Age	
≤ 60 years	1008 (37.0)
61-70 years	1007 (36.9)
> 70 years	711 (26.1)
Trial	
Swedish Rectal Cancer trial	430 (15.8)
Dutch TME trial	1132 (41.5)
German CAO/ARO/AIO-94 trial	495 (18.2)
EORTC 22921 trial	502 (18.4)
Polish Rectal Cancer trial	167 (6.1)
Distance of tumour to anal verge	
≥ 5.0 cm	2197 (80.6)
< 5.0 cm	500 (18.3)
Unknown	29 (1.1)
TNM stage	
TNM stage 0/I	951 (34.9)
TNM stage II	804 (29.5)
TNM stage III	954 (35.0)
Unknown	17 (0.6)
CRM involvement	
No	2070 (75.9)
Yes	87 (3.2)
Unknown	569 (20.9)
Stoma*	
No	1067 (46.5)
Yes	1226 (27.2)
Unknown	3 (0.1)
Anastomotic leakage	
No	2452 (89.9)
Yes	264 (9.7)
Unknown	10 (0.4)

CRM = circumferential resection margin. * Excluding 430 patients in the Swedish Rectal Cancer trial in which no data on stoma construction was available.

Table 3. Univariate and multivariable analyses of risk factors associated with anastomotic leakage.

Variable	Univariate analyses			Multivariable analysis		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Gender			0.002			0.002
Female	1.00			1.00		
Male	1.56	1.18-2.07		1.64	1.20-2.24	
Age			0.956			----
≤ 60 years	1.00					
61-70 years	1.00	0.74-1.34	0.975			
> 70 years	0.95	0.69-1.32	0.780			
Distance from tumour to anal verge			0.949			----
≥ 5.0 cm	1.00					
< 5.0 cm	0.99	0.71-1.38				
TNM stage			0.608			----
TNM stage 0/I	1.00					
TNM stage II	1.14	0.83-1.57	0.418			
TNM stage III	1.15	0.85-1.57	0.362			
Stoma			0.002			0.001
No	1.00			1.00		
Yes	0.65	0.49-0.85		0.62	0.47-0.82	

OR = odds ratio; CI = confidence interval.

Anastomotic leakage and distant metastases

The univariate analysis for the association between anastomotic leakage and distant metastases was not significant: rate of distant metastases at 5 years 25.6% (95% CI 23.7%-27.3%) and 27.5% (95% CI 21.4%-33.6%), respectively for patients without and with anastomotic leakage ($P = 0.480$). Therefore, no multivariable analysis with anastomotic leakage was performed for distant metastases.

Anastomotic leakage and overall survival

First, the analyses were performed with all selected patients. Anastomotic leakage was significantly associated with a worse overall survival rate (hazard ratio (HR) 1.49; 95% CI 1.20-1.84; $P < 0.001$ univariate analysis and HR=1.48; 95% CI 1.19-1.83; $P < 0.001$ multivariable analysis). Five-year overall survival rate was 74.4% (95% CI 72.4%-76.4%) within the group of patients without anastomotic leakage compared to 66.4% (95% CI 60.1%-72.7%) for patients with anastomotic leakage ($P < 0.001$).

In Table 5, the results of both the univariate and multivariable analyses for risk factors associated with overall survival are shown, excluding patients who died within 90 days after surgery ($n = 52$): 5-year overall survival rate 75.5% (95% CI 73.4%-77.4%) for patients without anastomotic leakage versus 71.5% (95% CI 62.2%-77.8%) for patients with

Table 4. Anastomotic leakage rate and univariate logistic regression analyses per trial and randomisation arm.

Variable	*n*	Anastomotic leakage (%)	Univariate analyses		
			OR	95% CI	*P*-value
Swedish Rectal Cancer trial					0.283
Surgery alone	209	18 (8.6)	1.00		
5 x 5 Gy RT + surgery	221	26 (11.8)	1.41	0.75-2.67	
TME trial[*]					0.418
TME surgery alone	578	65 (11.2)	1.00		
5 x 5 Gy RT + TME surgery	553	54 (9.8)	0.85	0.58-1.25	
CAO/ARO/AIO-94 trial[&]					0.609
Preoperative CRT	241	39 (16.2)	1.00		
Postoperative CRT	248	36 (14.5)	0.88	0.54-1.44	
EORTC 22921 trial					----
Preoperative RT	122	0 (0.0)	n.e.		
Preoperative CRT	125	0 (0.0)	n.e.		
Preoperative RT + postoperative CT	122	4 (3.3)	n.e.		
Preoperative CRT + postoperative CT	133	4 (3.0)	n.e.		
Polish Rectal Cancer trial[†]					0.657
Preoperative CRT	81	8 (9.9)	1.00		
Preoperative 5 x 5 Gy RT	83	10 (12.0)	1.25	0.47-3.35	

Due to differences in trial design and data collection, anastomotic leakage rates are not comparable between trials. Odds ratio (OR) not estimated (n.e.) for EORTC 22921 trial due to the small number of patients reported with anastomotic leakage. RT= radiotherapy; CRT=chemoradiotherapy. [*] Unknown for 1 patient; [&] unknown for 6 patients; [†] unknown for 3 patients.

anastomotic leakage ($P = 0.030$). Male gender, age above 70 years, advanced TNM stage, and postoperative anastomotic leakage were both in the univariate and multivariable analyses associated with diminished overall survival. The Kaplan-Meier curves for overall survival are presented in Figures 2B and 2C, respectively for all patients and excluding the patients who died in the first 90 postoperative days.

Anastomotic leakage, stomas and overall survival

If the analyses for overall survival were repeated with both the variables anastomotic leakage and stoma in the model, both were significantly associated with a worse overall survival (data not shown). However, no statistical significant interaction between anastomotic leakage and the presence of a stoma could be demonstrated ($P = 0.255$). Patients with a stoma had an increased risk of death (HR=1.24; 95% CI 1.04-1.48; $P = 0.015$; multivariable model). Figure 3A shows the Kaplan-Meier curves for overall survival separately for patients with/without anastomotic leakage and with/without stoma.

Table 5. Univariate and multivariable analyses for overall survival excluding patients with 90-day postoperative mortality.

Variable	*n*	Univariate analyses			Multivariable analysis		
		HR	95% CI	*P*-value	HR	95% CI	*P*-value
Gender				<0.001			<0.001
Female	902	1.00			1.00		
Male	1526	1.43	1.23-1.67		1.33	1.14-1.56	
Age				<0.001			<0.001
≤ 60 years	997	1.00			1.00		
61-70 years	984	1.16	0.98-1.38	0.084	1.23	1.04-1.46	0.016
> 70 years	447	1.86	1.54-2.25	<0.001	2.06	1.70-2.49	<0.001
Distance of tumour to anal verge*				0.466			----
≥ 5.0 cm	1939	1.00					
< 5.0 cm	464	1.08	0.88-1.32				
TNM stage&				<0.001			<0.001
TNM stage 0/I	845	1.00			1.00		
TNM stage II	712	2.11	1.70-2.63	<0.001	2.08	1.67-2.26	<0.001
TNM stage III	858	3.93	3.21-4.81	<0.001	4.02	3.28-4.92	<0.001
CRM involvement				0.045			0.704
No	1848	1.00			1.00		
Yes	81	1.63	1.11-2.39	0.013	1.17	0.79-1.72	0.442
Unknown	499	1.09	0.76-1.56	0.651	0.94	0.64-1.40	0.774
Anastomotic leakage†				0.030			0.034
No	2199	1.00			1.00		
Yes	220	1.29	1.02-1.63		1.29	1.02-1.63	

HR = hazard ratio; CI = confidence interval. * Unknown for 25 patients; & unknown for 13 patients; † unknown for 9 patients.

Figure 3B shows the Kaplan-Meier curves for overall survival excluding the patients who died within 90 postoperative days. The difference between Figures 3A and 3B is caused by early postoperative mortality. Patients without anastomotic leakage and without a stoma fared better than the other three groups in the long-term. For patients without anastomotic leakage and without a stoma, without anastomotic leakage and with a stoma, with anastomotic leakage and without a stoma, and with anastomotic leakage and with a stoma, the 90-day mortality was 1.3%, 1.9%, 8.9%, and 5.8%, respectively. The difference in 90-day postoperative mortality was significant only between patients with and those without anastomotic leakage ($P < 0.001$).

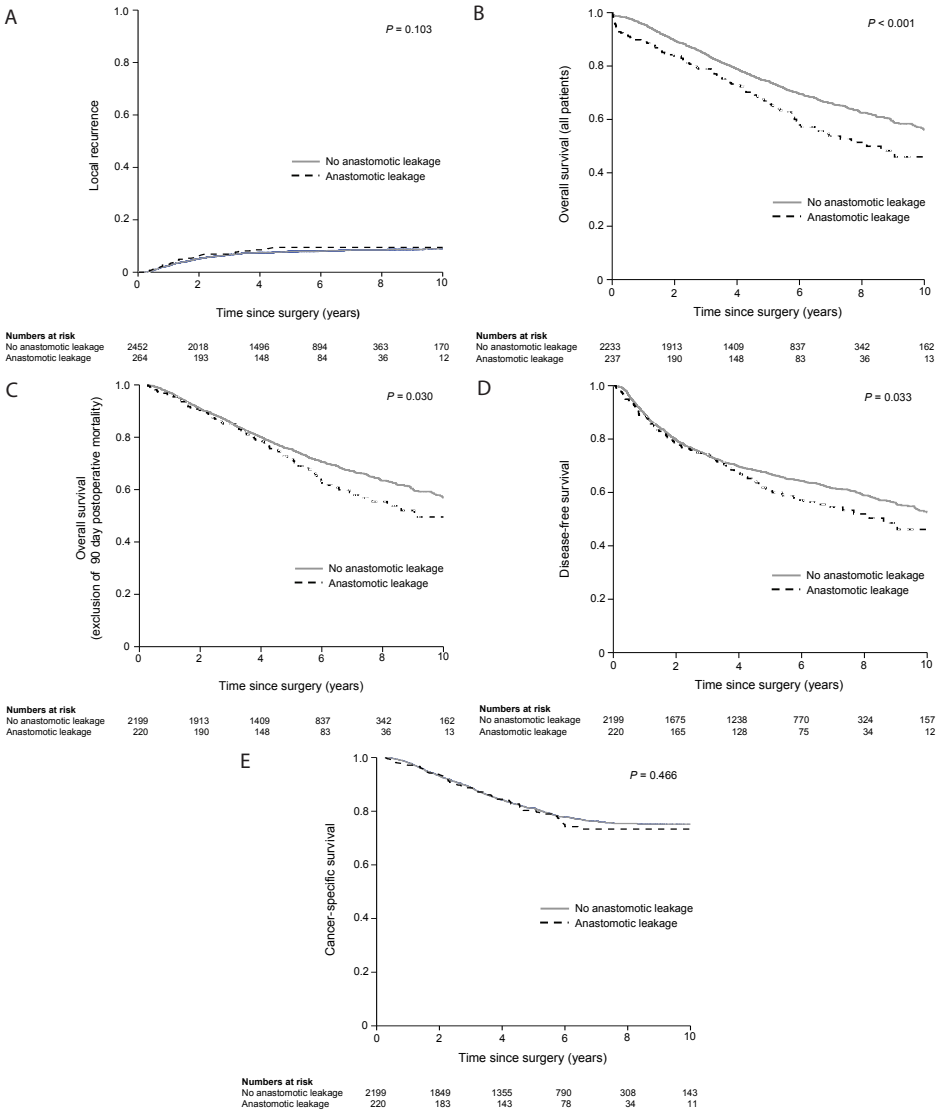
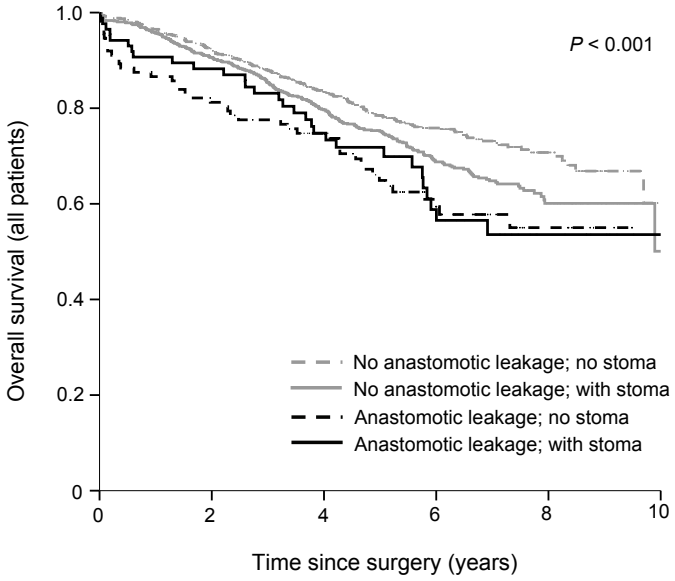


Figure 2. Local recurrence (A), overall survival for all patients (B) and after exclusion of patients with 90-day postoperative mortality (C), disease-free survival (D), and cancer-specific survival (E) shown as cumulative incidence (A), Kaplan-Meier survival (B, C, D), and one minus cumulative incidence (E) curves separately for patients with and without anastomotic leakage.

Anastomotic leakage and disease-free and cancer-specific survival

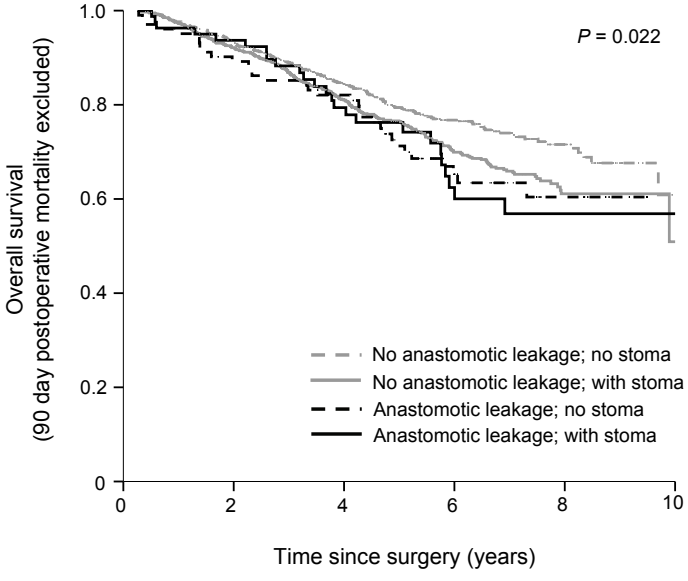
Anastomotic leakage was associated with a worse DFS rate: HR 1.26 (95% CI 1.02-1.56; P = 0.033) in the univariate analysis and HR 1.24 (95% CI 1.01-1.56; P = 0.040) when adjusted for gender, age, and TNM stage. The disease-free survival curve is shown in Figure 2D. The 5-year disease-free survival rate was 66.9% (95% CI 64.9%-68.9%) for

A



Numbers at risk						
No anastomotic leakage; no stoma	860	770	546	295	95	6
No anastomotic leakage; with stoma	1026	867	640	351	78	5
Anastomotic leakage; no stoma	112	89	72	37	12	0
Anastomotic leakage; with stoma	86	70	52	26	9	1

B



Numbers at risk						
No anastomotic leakage; no stoma	849	770	546	295	95	6
No anastomotic leakage; with stoma	1007	867	640	351	78	5
Anastomotic leakage; no stoma	102	89	72	37	12	0
Anastomotic leakage; with stoma	81	70	52	26	9	1

Figure 3. Kaplan-Meier curves for overall survival shown separately for patients with/without anastomotic leakage and with/without a stoma, for all patients (A) and after exclusion of patients who died within 90 postoperative days (B).

patients without anastomotic leakage and 60.6% (95% CI 53.7%-67.5%) for patients with anastomotic leakage (P = 0.033). The estimates of the cumulative incidence for cancer-related mortality with death due to causes other than rectal cancer as competing risk, are shown in Figure 2E. No significant association could be found between cancer-specific survival and anastomotic leakage (HR=1.12; 95% CI 0.83-1.52; P = 0.466); the 5-year cancer-specific survival rate was 80.6% (95% CI 78.8%-82.4%) for patients without and 79.5% (95% CI 73.6%-85.4%) for patients with anastomotic leakage (P = 0.466).

DISCUSSION

In the present study, patient data of 5 large randomised European trials for rectal cancer were pooled. Although the decision to create a stoma was left to the discretion of the surgeon, and each individual trial was not designed to study anastomotic leakage, the present results are interesting due to the large number of patients included from several European countries with a long and well documented follow-up. However, the results should be considered with caution. Patients with a diverting stoma had significantly less anastomotic leakage. Interestingly, leaks were associated with decreased disease-free and overall survival, but oncological outcome measures (local recurrence, distant metastases and cancer-specific survival) were not affected.

Apart from the early consequences after a leak, such as sepsis-related mortality, anastomotic failure has been reported to be associated with decreased local control[6-11] and survival[7,12,13]. However, the association between anastomotic leakage and local control cannot be confirmed in all studies: in a population-based cohort study in Norway (1958 patients), anastomotic leakage did not result in an increased local recurrence rate.[27] In the present study, anastomotic leakage was associated with both impaired disease-free survival and overall survival. When excluding early postoperative mortality, overall survival in the groups with and without anastomotic leakage is very similar in the first 4 years. After 4 years, however, overall survival in the group of patients who leaked, significantly decreased. In the present analysis, no association between anastomotic leakage and cancer-specific survival was found, although in other studies such an association was demonstrated.[7,12,13] Apparently, patients in the pooled database who developed anastomotic leakage had a higher chance of dying than those without anastomotic leakage, but mainly due to other causes rather than rectal cancer. The observed consequences of anastomotic leakage - early and late morbidity and mortality - stress the importance of decreasing the incidence of (symptomatic) anastomotic leakage. One of the options is to create a diverting stoma. Recently, Matthiessen et al. performed a randomised trial in 234 patients who underwent a low anterior resection.[19] Patients were randomised between a diverting loop stoma and no stoma. In this study it was found

that a diverting stoma decreased the rate of symptomatic anastomotic leakage. Hüser et al. did a systematic review and meta-analysis on the role of a diverting stoma in low rectal cancer surgery.[28] In total 27 relevant retrospective and 4 randomised clinical trials were studied. The authors concluded that a diverting stoma reduces the rate of clinically relevant anastomotic leakage and is thus recommended in surgery for low rectal cancer. Nevertheless, stoma closure is also associated with morbidity and mortality.[29,30] Besides, one out of five diverting stomas is never closed.[31]

In this analysis, patients without leakage and without a stoma had a better survival than those without leakage and with a stoma. As the pooled studies did not randomise between a stoma and no stoma (the decision to create a stoma was left at the discretion of the surgeon), there is likely a selection bias here. However, this reflects daily clinical practice and one can hypothesise that patients with a stoma had more comorbidity than those without a stoma. Even so, patients with a stoma had less symptomatic leakage. Besides, postoperative mortality after anastomotic leakage tends to be lower with a stoma (5.8% versus 8.9%), though this was not statistically significant. Due to the aforementioned bias, the question whether the presence of a stoma (as an isolated variable) might improve overall survival, cannot be answered by this study.

Many observational studies have examined the association between preoperative treatment and anastomotic leakage. In national population-based studies in both Sweden and Norway, preoperative radiotherapy was found to be associated with anastomotic leakage.[27,32] Similarly, in a case-control study using the Swedish Cancer Registry, preoperative radiotherapy was found to be a risk factor for anastomotic leakage.[15] However, there is no association between an anastomotic leak and short-course radiotherapy in randomised trials.[16,33] Due to different treatment protocols and other variance, anastomotic leakage rates cannot be fairly compared across trials, although comparison within each trial is valid. In none of the 5 randomised trials discussed here was a significant difference found in the anastomotic leak rate due to preoperative treatment, but trials are notorious for not necessarily reflecting real practice. Indeed, based on the real life observational studies,[15,27,32] other (confounding) factors that affect the selection of patients for preoperative radiotherapy contribute to the observed higher leak risk.

Anastomotic leakage cannot be avoided but their consequences can be limited by a diverting stoma.[28,34] Apart from a diverting stoma, some have found that the placement of a pelvic drain limited the consequences of anastomotic leakage,[16] although others could not find such an association.[35] Nevertheless, prompt diagnosis and treatment of anastomotic leakage are necessary to limit morbidity and mortality. Standardised postoperative surveillance results in early identification of and reduced mortality from symptomatic anastomotic leakage.[4]

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Chapter 10

Improved diagnosis and treatment of anastomotic leakage after colorectal surgery

Marcel den Dulk, Saidja L. Noter, Eduard R. Hendriks, Mark A.M. Brouwers, Cornelis H. van der Vlies, Rob J. Oostenbroek, Anand G. Menon, Willem-Hans Steup, Cornelis J.H. van de Velde

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ABSTRACT

Aim

This study aimed at testing feasibility of a standardised postoperative surveillance protocol to reduce delay in the diagnosis of anastomotic leakage (AL) and, subsequently, mortality.

Material and methods

Patient files of patients operated between 1996 and 1999 were reviewed and used as historical controls (n = 1066). As a result, a protocol for standardised postoperative surveillance was designed using easily accessible, clinical parameters. Between August 2004 and August 2006, all operated patients with a colorectal anastomosis (n = 223) were prospectively subjected to this standardised surveillance.

Results

AL was diagnosed in 7.0% of patients in the historical control group and 9.4% of patients in the standardised surveillance group. AL mortality decreased from 39% to 24% with standardised surveillance (n.s.). The delay in AL diagnosis was significantly reduced during standardised surveillance (4 versus 1.5 days, P = 0.01), which was confirmed in the multivariate analysis.

Conclusion

With non-standardised postoperative monitoring, AL was associated with a high mortality rate. Patients were subjected to several additional tests, which were not primarily useful to diagnose AL. Standardised postoperative surveillance for AL was introduced successfully and resulted in a shorter delay between the first signs and symptoms to the confirmation of AL.

INTRODUCTION

Anastomotic leakage (AL) is a feared complication after colorectal surgery causing morbidity and mortality.[1] Different percentages are published for the incidence of AL, varying between 1 and 25%, partly depending on the method of evaluation and the level of the anastomosis.[2-5] AL does not only result in increased and serious morbidity and mortality,[6-9] but has also been associated with a higher local recurrence rate after curative treatment of colorectal malignancies.[10,11]

In literature, different mortality rates after AL are reported.[8,12,13] In the evaluation of surgery, slowly, more attention is focussed on adverse events such as postoperative morbidity and mortality.[14] AL can never be reduced to zero and therefore it is of relevant importance to control the negative and sometimes fatal sequelae in case an AL occurs. Consequently, not only the occurrence but also the clinical outcome after AL might be considered as a performance indicator of surgical care. Firstly, this study aimed at investigating the occurrence of AL and associated mortality in several training hospitals in the Netherlands. Secondly, we hypothesised that the interval between first signs or symptoms and action on AL can influence the clinical outcome. As a result, a standardised postoperative surveillance protocol was designed which aimed at reducing the delay in the diagnosis of AL and subsequently at reducing the mortality rate. The feasibility of this surveillance protocol was studied prospectively.

PATIENTS AND METHODS

Retrospective analysis

Patient files from all patients of three training hospitals (Haga Hospital location Leyenburg (The Hague), Haga Hospital location Red Cross (The Hague) and Albert Schweitzer Hospital (Dordrecht)) in whom a colorectal anastomosis was created were reviewed (part of the data previously published[15] and presented at the Surgical Infection Society Meeting in 2003[16]). As AL is an issue after both resections for malignant and benign diseases, we included all resections in this period in the study. Malignancies were colon or rectal cancer, whereas benign diseases included resections for polyps, ulcerative colitis, diverticulosis, Crohn's disease, and continuity restoration after a stoma. Delay in the diagnosis of AL was calculated as the period from the first signs of clinical deterioration to confirmation of the diagnosis. These signs consisted of the presence of fever (temperature >38.0°C), ileus (absence of passage of faeces or air after the third postoperative day) or an elevated number of leukocytes in the blood count (>12.0 x 10^9/l).

Design of the protocol for standardised postoperative surveillance for AL

The results of the retrospective study led to the design of a protocol for standardised postoperative monitoring aiming to reduce the delay in the diagnosis of AL and subsequently to reduce AL related mortality. Literature was used to select postoperative variables which are prognostic for AL. Furthermore, the items had to be easily available during normal patient visits. The final selection process was done by MdD, MB and WS and are shown in Table 1. The items related to laboratory tests were checked at least every other day. For each item, points were given as shown in Table 1. If an item was scored as normal or if an item was not scored (such as items related to laboratory investigation), no points were given, whereas if the item was scored as abnormal, 1 or 2 points were given. The weight of an abnormal score was depending on the diagnostic importance of that specific item (determined by MdD, MB and WS). The sum of all items gave a score: the leakage-score. In case of more than one score determined within 24 h, the worst score was used.

Table 1. Items scored in the prospective study.

Item	Normal value	Score (points)	Abnormal value	Score (points)
General				
Fever	≤ 38.0°C	0	> 38.0°C	1
Heart rate	≤ 100/min	0	> 100/min	1
Respiratory rate	≤ 30/min	0	> 30/min	1
Urinary production	≥ 30 ml/h or 700 ml/day	0	< 30 ml/h or 700 ml/day	1
Mental status	Normal mental status	0	Agitation or lethargic	2
Clinical condition	Stable or improving condition	0	Deterioration	2
Local physical examination				
Signs of ileus	No ileus	0	Ileus	2
Gastric retention	No gastric retention	0	Gastric retention	2
Fascial dehiscence	No fascial dehiscence	0	Fascial dehiscence	2
Abdominal pain, other than wound pain	No pain other than wound pain	0	Pain other than wound pain	2
Laboratory investigation				
Signs of infection	No increase in leukocyte number or CRP	0	Increase of ≥ 5% in leukocyte number or CRP	1
Kidney function	No increase in urea and creatinine	0	Increase of ≥ 5% in urea or creatinine	1
Diet				
Nutritional status	Normal diet	0	Tube feeding/TPN	1/2

The leakage-score is the sum of all points. If a patient receives both tube feeding and total parental nutrition (TPN), only tube feeding is scored (1 point). CRP = C-reactive protein.

The prospective cohort study

All patients, in whom an intra-abdominal colorectal anastomosis was created in Haga Hospital location Leyenburg from 1 August 2004 to 1 August 2006, were monitored using the standardised postoperative surveillance protocol. Resections were performed both for malignant and benign diseases. Daily, all patients were scored by the treating surgical resident or surgeon (Table 1). The leakage-score was linked to a decision tree indicating the diagnostic and treatment actions that had to be taken (Figure 1). Patients with clinically proven AL (faecal leakage through drains or wounds) bypassed the diagnostic part of the decision tree. Patients were followed until one of the three end-points was reached: AL, postoperative mortality or discharge from the surgical ward. The first symptomatic day of AL was defined as the day after the last day with zero leakage-points before AL was diagnosed. The difference between the first symptomatic day and the day of confirmation of AL was considered to be the delay in the diagnosis of AL.

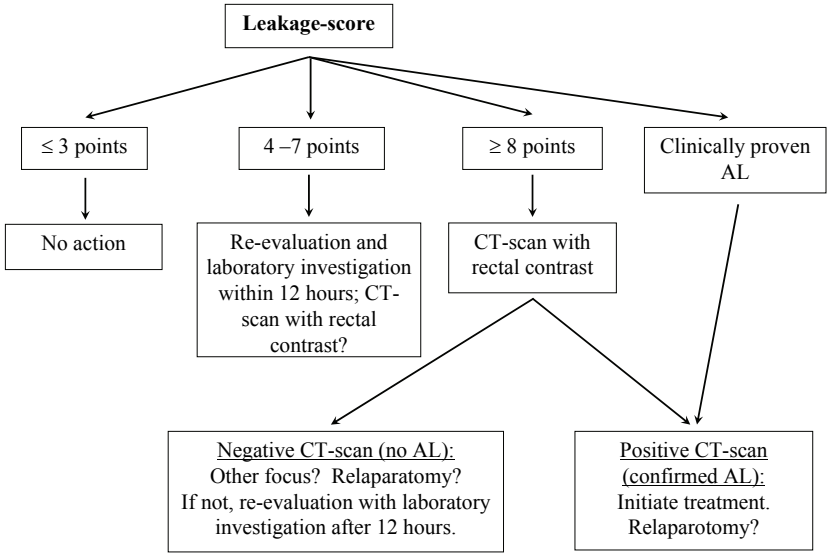

Figure 1. Decision tree of the leakage-score indicating which actions should be taken with each score. Clinically proven anastomotic leakage (AL; faeces in a drain or wound) was treated identically as a positive CT-scan.

Statistical analyses

Data were analysed with the SPSS package (SPSS 14.0 for Windows; SPSS Inc., Chicago, IL). In the analysis for delay, patients from the retrospective analysis were used as historical controls. Univariate analyses with categorical variables were performed with a χ^2 test. Delay and leakage-score were univariately studied using the non-parametric Mann-Whitney test. The multivariate analysis for delay was performed with a ranked ANOVA. A two-sided *P*-value of ≤ 0.05 was considered statistically significant.

RESULTS

Historical controls

In total 1066 resections were performed between 1996 and 1999. Demographic data are shown in Table 2. In this period, 29 patients were treated twice during separate admissions. As these patients were subjected to a risk of AL during each procedure, each admission was considered as a separate patient. AL was diagnosed in 75 patients. Overall mortality was 7.4%. Mortality after the diagnosis AL was 39%.

Before the diagnosis AL was made, several additional diagnostic investigations were performed to exclude other complications such as pneumonia or urosepsis. In 58 of AL patients the following imaging and laboratory studies were performed in the period before confirmation of AL: chest X-ray (*n* = 48), urine sediment test (*n* = 22), ultrasound

Table 2. Demographic data of patients.

Variable	Historical controls	Patients with standardised surveillance
	n = 1066	*n* = 223
Gender		
Male	509	115
Female	557	108
Age		
< 70 years	480	95
≥ 70 years	586	128
Primary disease*		
Malignancy	736	147
Benign disorder	314	76
Timing of procedure		
Elective	906	189
Emergency	160	34
Procedure+		
Right sided resection	391	101
Left sided resection	643	106
Other procedure	32	16
Hospital		
A	335	
B	290	
C	441	223

* Missing for 16 patients; + Right side resection includes ileocecal resection, right sided hemicolectomy, transversectomy, and removal of a stoma in ascending or transverse colon; left sided resection includes left sided hemicolectomy, sigmoid resection, low anterior resection, proctocolectomy, and removal of a stoma in descending colon or sigmoid; other procedure includes subtotal colectomy or unspecified procedures.

investigation (n = 25), CT-scan without contrast enhancement (n = 10), and plain X-ray of the abdomen without contrast (n = 8). In 21, 19 and 18 patients, respectively one, two and more than two of these additional diagnostic tests were used to exclude other complications before AL was diagnosed.

Prospective cohort study with standardised surveillance

In total 224 consecutive resections were performed in the period with standardised postoperative follow-up. During this period 6 patients underwent two resections during separate procedures. One patient was transferred to another hospital and was lost to follow-up and was excluded from all analyses. Demographic details of the remaining 223 patients are shown in Table 2. Twenty-one patients were diagnosed with AL. In total 14 patients died postoperatively. Nine patients died of causes not related to AL: respiratory complications (n = 3), cardio-vascular complications (n = 4), and progression of the malignant disease (n = 2). In all these cases AL was excluded as cause of death. Five patients died after AL was diagnosed.

Leakage-score

The leakage-score was determined daily for every patient. The median score for patients diagnosed with and without AL per day is shown in Figure 2. A significant higher score for patients with AL was found from day 5 to 9. When comparing the median of the highest leakage-score for patients with and without AL, this difference was significant: 7 points (range 0-13) versus 3 points (range 0-10), $P < 0.001$.

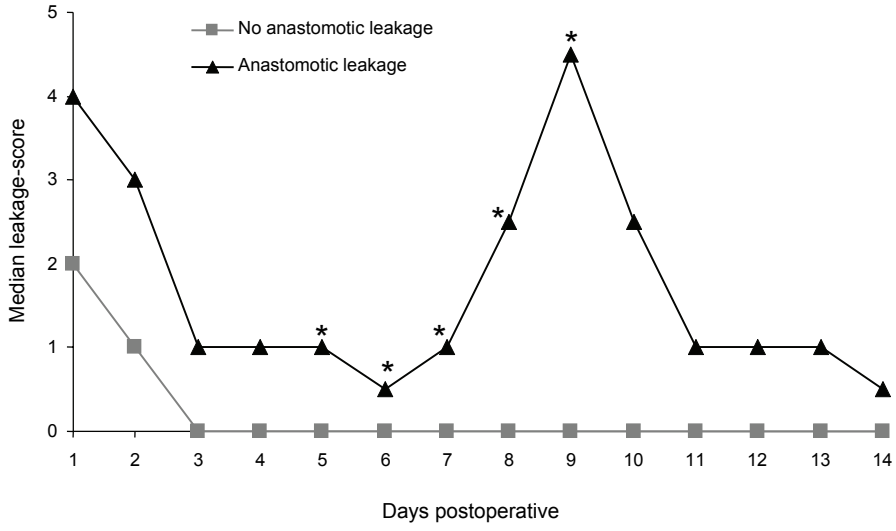

Figure 2. Median scores of patients with and without anastomotic leakage per day. * Indicates a significant difference between patients with and without anastomotic leakage (Mann-Whitney test).

The effects of standardised surveillance on the diagnosis of anastomotic leakage

In the period of standardised surveillance, three patients were dismissed from the hospital without any signs or symptoms on day 6, 7 and 17, respectively. These patients were later readmitted and AL was diagnosed, of whom one patient eventually died. As no information about delay is available for these patients, these patients could not be considered in the analysis for delay. However, these patients were included in all other analyses.

In Table 3 the univariate comparison is shown between patients subjected to standardised monitoring compared with patients without standardised postoperative surveillance. If the three patients who were discarded from the hospital and readmitted before AL was diagnosed were included in the analysis for the day of the diagnosis, no significant difference could be found (median 8 days in the historical control group versus median 6 days after standardised surveillance, $P = 0.22$). However, if these patients were excluded from the analysis, as these patients were not monitored after discharge, the difference was statistically significant (median 8 days versus 6 days, $P = 0.02$). Nevertheless, the delay in the diagnosis of AL was significantly shorter for patients monitored with standardised postoperative surveillance (median 4.0 versus 1.5 days, $P = 0.01$). If the analysis was performed using the same definition of delay in the standardised surveillance group as was used for the historical controls (temperature above 38.0°C, ileus after day 3 or leukocytes blood count >12.0 x 10^9/l), the delay was still significantly shorter (median delay 4.0 days (range 0-21) for historical controls and 3.0 days (range 0-14) after standardised surveillance, $P = 0.03$). In the multivariate analysis, in which patients from both periods are combined, the effects of gender, age, primary disease, timing, procedure, and hospital of treatment were not found to be significantly related to delay (data not shown). Treatment during the period with standardised postoperative surveillance was the only variable that was independently associated with an earlier diagnosis ($P = 0.03$). If for the calculation of delay in the prospective study a cut-off

Table 3. Univariate comparison between controls without standardised postoperative surveillance and patients with standardised surveillance.

	Historical controls	Standardised surveillance	*P*-value
Time to diagnosis since surgery (days)			0.22
Median	8.0	6.0	
Range	1–58	4-47	
Delay in the diagnosis of AL (days)			0.01
Median	4.0	1.5	
Range	0–21	0–21	
Mortality rate of AL diagnosed patients	29/75	5/21	0.21

AL = anastomotic leakage.

point of 4 leakage-points was used instead of 1 point or if the definition of delay as used for the historical controls was used for the group with standardised surveillance, the results were comparable (data not shown). The mortality rate decreased when patients were monitored with standardised surveillance, but this difference was not statistically significant (Table 3).

DISCUSSION

Delay in the diagnosis of anastomotic leakage

AL after colorectal surgery is a frequently occurring, important, postoperative complication, associated with a relatively high mortality rate.[8,9,12,13,17,18] Several studies indicated that delay was associated with increased mortality.[13,19] We studied AL in a retrospective study and developed a protocol for standardised postoperative surveillance, to reduce the delay in the diagnosis and treatment of AL and subsequently to reduce AL associated mortality. AL is found both after malign and benign diseases, although the majority of resections is performed for malignancies. Consequently, a complete cohort of patients was studied, which included both patients with benign and malign diseases, to prevent patient selection. In the present analysis, it is shown that it is feasible to introduce and perform postoperative standardised surveillance for AL after colorectal surgery. This standardised surveillance resulted in a shorter period of delay (median 1.5 day compared to 4 days), independent from gender, age, primary disease, timing of the procedure, type of resection, and hospital of treatment. It should be noted, that it cannot be excluded that the implementation of a standardised postoperative surveillance for AL also increased the awareness of AL, resulting in an earlier diagnosis. However, also in the period 1996-1999 surgeons were familiar with AL. Apparently, awareness of AL alone was insufficient to result in a earlier diagnosis of AL, as it was found not to be easy to notice clinical deterioration in an early stage without the standardised postoperative surveillance protocol.

Mortality after anastomotic leakage

Seven percent of patients treated in the period 1996-1999 were diagnosed with AL, which is in accordance with the percentage reported in literature.[2-5] The observed mortality rate after AL was 39%. Although differences exist in the diagnosis of AL (symptomatic AL versus radiologically proven AL) the highest mortality rate found in literature was reported by the West of Scotland and Highland Anastomosis Study Group.[12] In this study, 40 patients of 1004 had symptomatic AL, of whom 33% died. In general, a mortality rate below 22% is reported in literature.[8,9,13,17,18] In our historical control patients, the relatively large delay could have contributed to the high mortality rate, similar to

findings by others.[13,19] In all patients who died after AL, their death was considered to be related to the AL, which might have resulted in a higher mortality rate than reported in other studies. In the standardised surveillance group five patients died resulting in a decreased mortality rate of 24%, including one patient who died 19 days after the diagnosis of AL due to an aspiration pneumonia and myocardial infarction and one patient who died 125 days after AL due to a palliative treatment setting. Due to this small patient population (n = 5) and differences in the definition of AL mortality, a safe comparison of the mortality rate of the last period with literature can hardly be made.

Variability in diagnostic management

One of the possibilities that might explain the delay in diagnostic management, which was observed in patients treated between 1996 and 1999, is the finding that in 77% of patient various diagnostic procedures were performed to exclude other complications instead of an appropriate diagnostic test for AL, such as a CT-scan with rectal contrast.[20] These additional tests might have resulted in additional delay in the diagnosis of AL. According to the adage "treat first what kills first", exclusion or confirmation of the diagnosis AL (and subsequent treatment) have to take priority in patients with any suspicion of AL after colorectal surgery.

Development of the leakage-score

To reduce variability, a standardised postoperative surveillance protocol was developed which aimed at reducing delay in the diagnosis of AL and subsequently at reducing mortality. Literature was studied to select postoperative variables which have been associated with AL before. In 1991, the Surgical Infection Study Group described the clinical signs of AL which included fever, increased leukocyte count and increased CRP level.[21] Furthermore, Systemic Inflammatory Response Syndrome (SIRS) was indicated to be a sign of AL.[21,22] The following signs could also occur with SIRS: changed mental status, oliguria, increased levels of serum creatinine, and ileus.[23] Finally, the following other postoperative signs were associated with AL: pelvic pain[24], renal failure[13], and peritonitis[25]. Although various groups have described different postoperative parameters that were associated with AL, no scoring system was yet designed nor tested prospectively in a clinical setting. We designed a scoring list, in which most of the above mentioned parameters were included. As no literature was available on the weight of the variables, we determined the weight of the variable based on our opinion of clinical relevance. Most items used to determine the "leakage-score" could be easily obtained during history taking and physical examination, and should normally be recorded daily in the patient's file.

Limits of the analysis

A limit of the present analysis is that prospectively collected data from a single centre are compared with historical controls from three centres. Ideally, a randomised trial is performed, however this is not possible as the investigators will be biased by their knowledge of the protocol when treating a patient in the "conventional" arm. Performing a study in different centres raises the question whether observed differences could be explained just by differences between these centres. If in the present study the analyses were repeated with results from Haga Hospital location Leyenburg only, the results were similar (data not shown). Therefore, the present study using historical data is the best available evidence, although the results should be interpreted with caution.

A difference in the data collection existed between the two periods: retrospective versus prospective. In the historical controls the presence of fever, ileus or an elevated number of leukocytes were considered to be reliably recorded and used in the definition of delay. For comparison, in the prospective study any sign or symptom was considered in the calculation of delay. Therefore, it is likely that signs for anastomotic leakage were detected earlier in the prospective trial, which could have resulted in a relatively longer period of delay in the group followed with standardised surveillance. However, using the definition of delay of the retrospective analysis for the standardised surveillance group still resulted in a significant decrease in delay (median 4 days compared with median 3 days, $P = 0.03$). Apart from that, the period of delay in the historical control group could be underestimated. For this group, patient's files were reviewed, in which the first signs could have been underreported. During a prospective study, this problem is less likely. Due to these differences in data collection the delay could have been underestimated in the historical control group, resulting in an underestimation in the decrease in delay with standardised surveillance.

Further improvements of the leakage-score

In the leakage-score several items were considered. It could however be questioned whether the used cut-off values were chosen optimally. Besides, the present analysis did not study whether all items were weighted properly in the scoring system. Nevertheless, in Figure 2 is shown, that the leakage-score as currently defined, could be used to distinguish the group of patients with and without AL. In order to optimise the leakage-score, a registration project has been launched in several Dutch centres, in which various parameters are collected prospectively for a large number of patients with a colorectal anastomosis in order to come to a more validated scoring system. Eventually, this might result in a modified DUtch LeaKage (DULK) scoring list.

CONCLUSION

AL is a serious complication after colorectal surgery. With non-standardised postoperative monitoring, AL was associated with a high mortality rate. Patients were subjected to several additional tests, which were not useful to diagnose AL. Standardised postoperative surveillance for AL was introduced successfully and resulted in a shorter delay between the first signs and symptoms to the confirmation of AL. In the daily clinical practice, standardised postoperative surveillance after colorectal surgery could be a guide for surgical residents who are developing clinical experience. Its usage could result in improved postoperative care. To further validate the scoring list and decision model, a larger group of patients is necessary. Recently, we started a registration project in several Dutch hospitals. In this project patients are postoperative monitored as normal, without usage of the decision model. Of all patients, various parameters are scored to determine which set of parameters is an early predictor of AL. Eventually, this project will result in an improved and validated DUtch LeaKage scoring list and decision model.

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Chapter 11

A multivariate analysis of limiting factors for stoma reversal in patients with rectal cancer entered into the total mesorectal excision (TME) trail: a retrospective study

Marcel den Dulk, Marije Smit, Koen C.M.J. Peeters, Elma Meershoek-Klein Kranenbarg, Harm J.T. Rutten, Theo Wiggers, Hein Putter, Cornelis J.H. van de Velde

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ABSTRACT

Background

In many patients with rectal cancer, defunctioning stomas are created to limit the consequences of anastomotic leakage. Although intended to be temporary, a substantial proportion of these stomas might never be reversed for various reasons. We aimed to describe stoma policy by use of data from the total mesorectal excision (TME) trial in patients with rectal cancer and to identify factors that limit stoma reversal.

Methods

924 Dutch patients with rectal cancer who underwent a low anterior resection were selected from the TME trial, a prospective, randomised multicentre trial studying the effects of short-term preoperative radiotherapy in 1861 patients who underwent TME. Creation of stomas and time to stoma reversal were analysed retrospectively by use of multivariate analysis.

Findings

In 523 of 924 (57%) patients, a primary stoma (defined as a stoma created at the time of TME) was constructed after a low anterior resection. Geographical differences in the number of primary stomas constructed were reported throughout the Netherlands. 19% of stomas that were created were never reversed. Postoperative complications and secondary constructed stomas (defined as a stoma created during a second or subsequent procedure after TME) were associated with a high likelihood of a permanent stoma. However, perioperative complications were not a limiting factor for stoma closure.

Interpretation

Postoperative complications are an important limiting factor for stoma reversal because, after occurrence of these complications, patients and surgeons might be reluctant to reverse the stoma, so a substantial proportion of these stomas are never closed. Future guidelines for stoma creation and closure should consider these factors.

INTRODUCTION

Stomas are created frequently in patients undergoing surgery for rectal cancer to limit the consequences of anastomotic leakage. Colostomies created after abdominoperineal resections are permanent. However, after a low anterior resection, a defunctioning stoma -such as a diverting colostomy- is constructed to protect the healing anastomosis, and these stomas are intended to be temporary. Although studies have not shown a substantial difference in the incidence of anastomotic leakage when comparing patients with and without a diverting stoma,[1,2] we have previously reported a substantial decrease in clinically evident anastomotic leakage in patients with stomas.[3] Furthermore, defunctioning stomas might mitigate the consequences of symptomatic anastomotic leakage, a notion that is supported by the decreased proportion of patients with a leak needing secondary surgery.[1-3]

The decision to create a stoma is affected by factors such as availability of high-quality stoma care, capability of stoma handling, and risk of stoma-related complications. Stoma complications occur in up to 30% of patients with a stoma.[4] These complications affect patients' daily activities and a relation between the number of stoma-care problems and the amount of restriction in social activities has been reported.[5] These stoma-related difficulties might be permanent because some of these stomas will never be closed.[6] The quality of life of a patient with a stoma is decided by multiple factors, such as patients' preferences and sociodemographical characteristics. Engel and coworkers found that patients undergoing a low anterior resection without creation of a stoma had better quality of life than did patients treated with an abdominoperineal resection and given a stoma.[7] By contrast, we previously reported that overall perceived health in patients who had undergone an abdominoperineal resection was not lower than that in patients who had been treated with a low anterior resection.[8] A recent Cochrane review[9] suggested that published studies challenged the assumption that patients who had undergone anterior resection fare better, but that data from larger, better designed and executed prospective trials are needed to answer the question of whether anterior resected patients had a better quality of life.

We aimed to describe the policy of stoma formation in patients entered into the TME trial for rectal cancer and to identify factors that limit reversal of these stomas.

METHODS

Patients and procedures

The TME trial included 1861 patients between 1 January 1996 and 31 December 1999.[10] This randomised multicentre trial asessed TME surgery with or without preoperative 5

x 5 Gy radiotherapy. Patients aged 18 years or over with clinically resectable adenocarcinoma of the rectum were randomly assigned to either radiotherapy followed by TME, or TME alone. The trial had no age limit. Radiotherapy, surgery, and pathology were standardised and strictly quality controlled, as described previously.[11] Both the decision to construct a stoma and the type of stoma were at the discretion of the surgeon, as defined in the protocol. A stoma created at the time of the TME procedure was defined as a primary stoma, and a secondary stoma was defined as a stoma created during a second (or following) procedure after the TME procedure. Follow-up of all patients was done according to trial protocol. The study was approved by all participating institutes and central and local ethics committees. All patients gave informed consent.

For the current analysis, all relevant data were collected at the time of trial. Only patients undergoing low anterior resection who were eligible for trial participation were studied in this analysis. Inclusion criteria have been reported previously.[10] Only Dutch patients were included because detailed and reliable information on patient and treatment characteristics was available for these patients, and data checking with hospital reports was done for these patients. Stomas created after a local recurrence were not included in the analysis. Exclusion criteria have been reported previously.[10]

Statistical analysis

Data were analysed with the SPSS package (version 12.0 for Windows; SPSS Inc., Chicago, IL, USA). Time to stoma reversal was analysed by use of the Kaplan-Meier method. Univariate log-rank and multivariate Cox regression analyses were used to study limiting factors for stoma reversal. The initial list of prognostic factors was based on clinical importance decided by the investigators (MdD, TW, CvdV). Each of these variables was retained for the multivariate analysis if either the univariate effect of that variable was significant or if the interaction with timing of stoma (primary versus secondary) was significant. In this selection process of variables, a *P*-value of ≤ 0.100 was deemed to be significant. For significant interactions, the results are presented separately for primary and secondary stomas, and the interaction was included in the multivariate Cox regression analysis. For non-significant interactions, the overall hazard ratio is shown. Except in the above mentioned selection process, a two-sided *P*-value of ≤ 0.050 was deemed to be statistically significant.

The following variables were studied as limiting factors for stoma closure: preoperative radiotherapy; sex; age; body-mass index; timing of stoma (primary versus secondary); type of stoma (ileostomy versus colostomy for primary stomas; end colostomy or ileostomy versus diverting stoma for secondary stomas); tumour-node-metastasis (TNM) stage; distance of the tumour to the anal verge; perioperative complications (including bleeding, organ injury, and tumour spill); postoperative infective complications (including wound infection, urinary tract infection, abscess, sepsis, and fever without

known cause); postoperative general complications (including thrombosis, embolism, cholecystitis, pulmonary, renal, neurological, and cardiac problems); postoperative surgical complications (for primary stomas only, including wound dehiscence, anastomotic leakage, ileus, postoperative bleeding, fistula, and perforation); and recurrence (either local recurrence defined as evidence of a tumour within the lesser pelvis or perineal wound, or distant recurrence defined as evidence of a tumour in any other area) after stoma creation as identified by: clinical assessment every 3 months in the first year and annually thereafter for at least 2 years; also, annual liver imaging and endoscopy. Overall recurrence status was entered as a time-dependent covariate.

RESULTS

Median follow-up of patients who were alive at the time of analysis was 7.1 years (range 2.5 to 9.8 years). Primary stomas were created in 523 of 924 (57%) patients who underwent low anterior resections (Figure 1). 329 (63%) of these stomas were ileostomies, and the remaining 194 patients (37%) received a colostomy. Characteristics of the patients

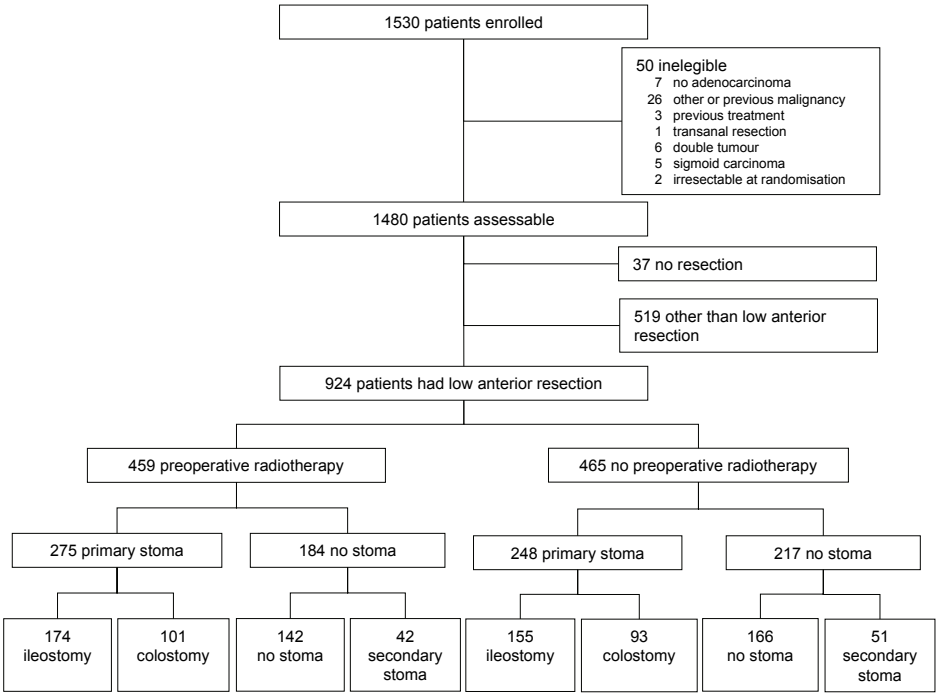


Figure 1. TME trial profile. Patients were randomised to TME surgery alone and TME surgery with preoperative radiotherapy at the time of inclusion.

Table 1. Characteristics of patients included in the analysis.

Variable	No primary stoma (%)	Primary stoma (%)
Preoperative radiotherapy		
No	217 (54)	248 (47)
Yes	184 (46)	275 (53)
Sex		
Male	234 (58)	336 (64)
Female	167 (42)	187 (36)
Age at randomisation (years)		
Mean	63.3	63.7
Standard deviation	11.2	10.6
TNM stage		
TNM Stage 0	11 (3)	9 (2)
TNM Stage I	120 (30)	165 (32)
TNM Stage II	106 (26)	124 (24)
TNM Stage III	141 (35)	204 (39)
TNM Stage IV	23 (6)	21 (4)
Distance tumour to anal verge		
< 5.0 cm	18 (4)	49 (9)
5.0-9.9 cm	174 (43)	288 (55)
≥ 10.0 cm	209 (52)	186 (36)
Type of anastomosis*		
End-to-side	257 (64)	293 (56)
End-to-end	55 (14)	52 (10)
Pouch	87 (22)	174 (33)

* Data missing for six patients. Percentages might not add up to 100% due to rounding.

and tumours are shown in Table 1. The Netherlands comprises nine comprehensive cancer centre regions, each serving a different part of the country. The geographical differences in primary stoma construction within the rectal cancer TME trial are shown in Figure 2.

Stomas were created at a secondary surgical procedure in 93 of 401 (23%) patients for reasons other than a recurrence. Stomas were created after a recurrence in four patients (0.4%), which were not included in this analysis. In one patient, a secondary stoma was created in conjunction with an abdominoperineal resection, which was done because of a positive resection margin. This patient was deemed to have had a permanent stoma and was, therefore, discarded from all further analyses. Of the 93 patients who had temporary stomas created at a secondary surgical procedure, 58 of 93 (62%) had diverting stomas, whereas 29 of 93 (31%) had end ileostomies or colostomies. The type of secondary stoma was unknown in six (6%) patients. The reasons for formation of secondary stomas are shown in Table 2. These secondary procedures were undertaken because of clinical anastomotic leakage in 61 of 93 (66%) patients. Taken together, 616 of 924 (67%) patients initially treated with a low anterior resection received a temporary stoma, either at initial or at secondary surgery.

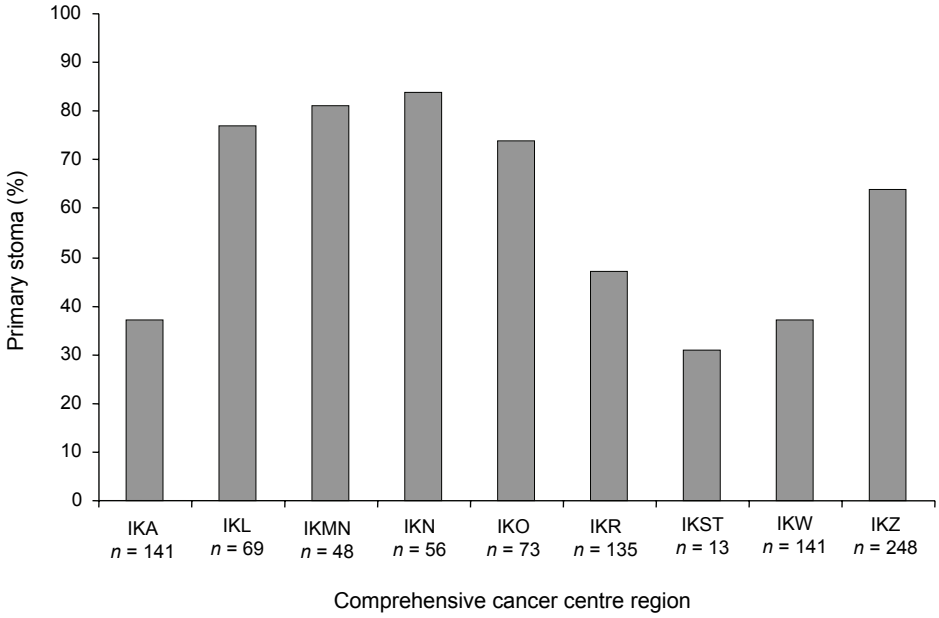


Figure 2. Primary stomas per comprehensive cancer centre region in the TME trial. IKA = comprehensive cancer centre Amsterdam; IKL = comprehensive cancer centre Limburg; IKMN = comprehensive cancer centre Middle Netherlands; IKN = comprehensive cancer centre North Netherlands; IKO = comprehensive cancer centre East; IKR = comprehensive cancer centre Rotterdam; IKST = comprehensive cancer centre Stedendriehoek Twente; IKW = comprehensive cancer centre West; IKZ = comprehensive cancer centre South.

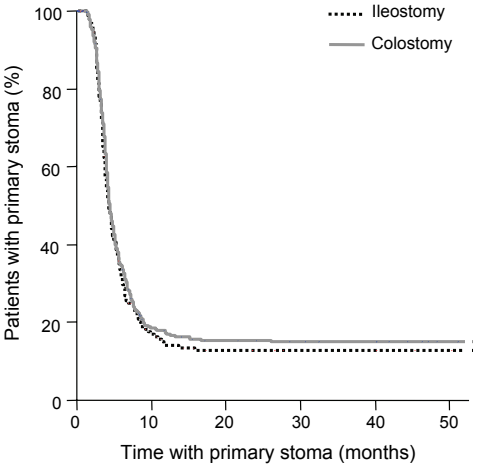
Table 2. Reasons for secondary-stoma creation.

Reason for secondary-stoma formation	n (%)
Anastomotic leakage	61 (66)
Abscess, sepsis or peritonitis	18 (19)
Fistula	6 (6)
Bleeding	1 (1)
Stenosis or ileus	2 (2)
Other	3 (3)
Unknown	2 (2)

Percentages might not add up to 100% due to rounding.

97% (95% CI 95%-98%) of stomas that were reversed were closed within the first year after surgery. The median time to stoma reversal was 4.1 months (range 1.3-33.1 months). 19.0% (16%-22%) of all stomas were not removed during follow-up. No significant difference was found between closure rate of ileostomies (15% not reversed [11%-19%]) and colostomies (13% not reversed [7%-18%]; $P = 0.474$; Figure 3).

Table 3 shows the univariate and multivariate analyses on limiting factors for stoma closure. In the univariate analysis, a relation between timing of the stoma, preopera-



Numbers at risk						
Ileostomy	329	48	36	32	30	24
Colostomy	194	26	15	12	12	10

Figure 3. Kaplan-Meier curve for stoma reversal of primary ileostomies and colostomies.

tive radiotherapy, and TNM stage was found. The results for these variables are shown separately for primary and secondary stomas in Table 3. Figure 4 shows the rate of stoma closure per age group ($P = 0.046$), and the rate of stoma closure for primary and secondary stomas. During follow-up, the closure rate was 86% (83%-89%) for primary stomas and 49% (37%-61%) for secondary stomas ($P < 0.0001$).

In the multivariate analysis, preoperative radiotherapy was significantly associated with a decreased likelihood of stoma reversal for secondary stomas, but not for primary stomas. Older age, secondary stoma construction, an end colostomy or ileostomy, any postoperative complication, and a recurrence were identified as limiting factors for stoma reversal. By contrast, no significant difference was reported for perioperative complications.

DISCUSSION

This study describes the policy on stoma construction used in the TME trial. As 84 of 102 hospitals in the Netherlands participated in this trial, the present study indicates common practise in the Netherlands. However, all extrapolations should be made carefully, because no information on treatment policy in the nontrial setting was studied and only Dutch patients entered into the TME trial are included in this analysis. We can assume that surgeons did not want to increase the risk of symptomatic anastomotic leakage, and so created more stomas in patients treated with preoperative radiotherapy

Table 3. Univariate log-rank and multivariate Cox regression analyses for factors limiting stoma reversal.

Variable	*n*	Univariate analyses			Multivariate analysis		
		HR	95% CI	*P*-value	HR	95% CI	*P*-value
Radiotherapy, primary stoma				0.960			0.244
No	248	1.00			1.00		
Yes	275	1.00	0.82 – 1.21		1.13	0.92 – 1.38	
Radiotherapy, secondary stoma				0.021			0.010
No	51	1.00			1.00		
Yes	42	0.41	0.19 – 0.87		0.34	0.15 – 0.77	
Sex*				0.923			----
Female	220	1.00					
Male	396	1.01	0.83 – 1.23				
Age				0.046			0.029
< 60 years	204	1.00			1.00		
60-69 years	226	1.03	0.82 – 1.28	0.815	1.10	0.88 – 1.38	0.394
≥ 70 years	186	0.77	0.61 – 0.99	0.038	0.79	0.62 – 1.02	0.071
Body mass index*†				0.369			----
< 25.0 kg/m^2	240	1.00					
25.0-29.9 kg/m^2	213	1.17	0.94 – 1.47	0.158			
≥ 30.0 kg/m^2	50	1.08	0.75 – 1.55	0.681			
Distance*				0.608			----
< 5.0 cm	57	1.00					
5.0 – 9.9 cm	330	1.01	0.72 – 1.42	0.939			
≥ 10 cm	229	1.12	0.79 – 1.59	0.536			
TNM stage, primary stoma				0.226			0.309
0-II	298	1.00			1.00		
III-IV	225	0.88	0.72 – 1.08		0.90	0.73 – 1.10	
TNM stage, secondary stoma				0.090			0.134
0-II	57	1.00			1.00		
III-IV	36	1.79	0.91 – 3.52		1.71	0.85 – 3.45	
Type of primary stoma*				0.474			----
Colostomy	194	1.00					
Ileostomy	329	0.93	0.76 – 1.14				
Type of secondary stoma‡				0.006			0.008
Diverting stoma	58	1.00			1.00		
End ileostomy or colostomy	29	0.13	0.03 – 0.55		0.14	0.03 – 0.59	
Perioperative complication				0.089			0.103
No	422	1.00			1.00		
Yes	194	0.84	0.68 – 1.03		0.84	0.68 – 1.04	
Infectious postoperative complication				<0.0001			0.0005
No	439	1.00			1.00		
Yes	177	0.50	0.39 – 0.63		0.65	0.51 – 0.83	
General postoperative complication				<0.0001			0.012
No	429	1.00			1.00		
Yes	187	0.61	0.49 – 0.77		0.73	0.57 – 0.93	
Surgical postoperative complication, primary stoma only				<0.0001			0.0001
No	350	1.00			1.00		
Yes	173	0.58	0.46 – 0.72		0.62	0.49 – 0.79	
Local or distant recurrence§				0.002			0.0001
No	431	1.00			1.00		
Yes	156	0.46	0.28 – 0.75		0.36	0.22 – 0.59	
Timing of stoma				<0.0001			0.0001
Primary	523	1.00			1.00		
Secondary	93	0.30	0.21 – 0.43		0.06	0.01 – 0.24	

HR = hazard ratio. HR < 1 indicates decreased likelihood of stoma reversal, whereas HR > 1 indicates increased likelihood of stoma reversal. *Multivariate analysis not done. †Data on height or weight were missing for 113 patients. ‡Unspecified for six patients. §Entered as time-dependent covariate, data missing for 29 patients (recurrence status unknown for one; recurrence status not applicable because of M1 disease in 28 at the time of surgery).

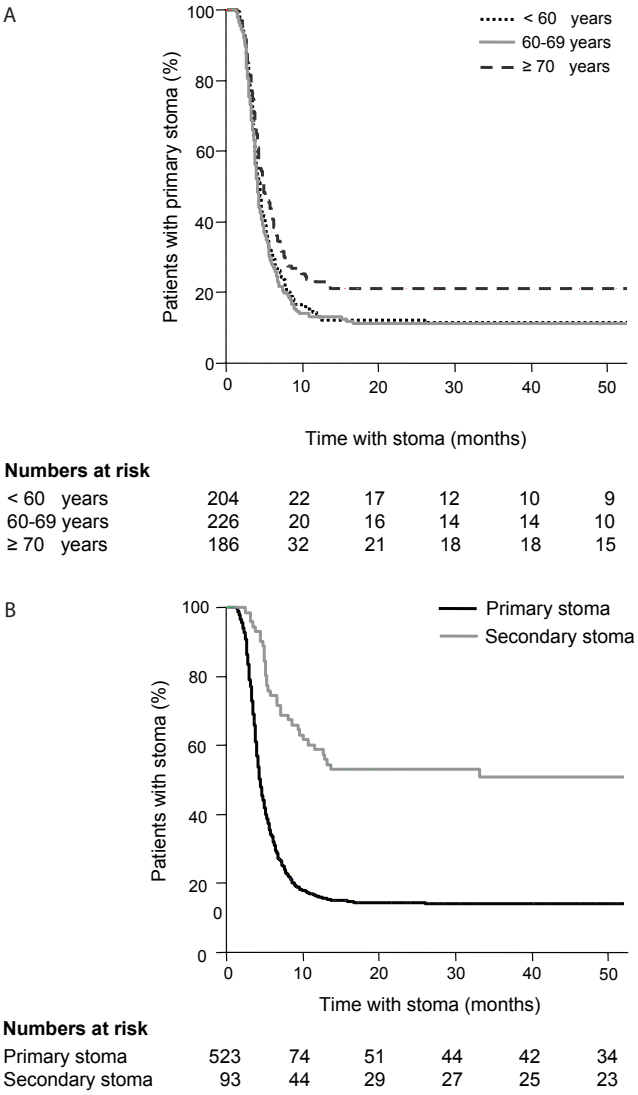


Figure 4. Kaplan-Meier curves for stoma reversal per age group (A) and for primary and secondary stomas (B).

and for distally located tumours with, consequently, distally located anastomoses. Large geographical differences in primary stoma policy were detected -and similar findings have been reported in the UK[12]- but that such large differences exist is remarkable.

We report that 19% of temporary created stomas were not closed during follow-up. Of the stomas that were closed during follow-up, 97% were closed in the first year after construction. Therefore, if a stoma was not closed in the first year, it would probably become permanent. Although the outcome of temporary stomas in terms of the numbers closed has been studied before,[13,14] little is known about risk factors associated with

stoma closure. To our knowledge, this study is the first to analyse systematically factors that limit stoma reversal in a large population with a long follow-up.

Age was found to be a significant risk factor associated with a decreased likelihood of stoma reversal. In the TME trial, an upper age limit was not set, whereas most other randomised trials studying neoadjuvant treatment restricted the age of older participants.[15,16] Consequently, only few researchers report on older age as a limiting factor for stoma reversal. However, Kairaluoma and co-workers[13] also reported that age above 70 years was associated with fewer stoma closures due to fear of increased morbidity in older patients. Age has also been associated with increased morbidity and mortality after stoma closure,[17] although such an association could not be found in another study.[18] Fear of increased comorbidity in the elderly and patients' refusals to undergo more surgery might have resulted in the decreased frequency of stoma reversal in these patients. Additionally, patients with stomas who have had postoperative complications, such as infection, had their stomas reversed less frequently. By contrast, perioperative complications, such as bleeding, which were not perceived directly by the patient, could not be identified as a risk factor. Generally secondary stomas, which were created after complications, were less frequently removed. A reason for this could be that older patients and patients who have had postoperative complications after initial (curative) treatment of rectal cancer are more willing to accept a stoma than other patients. We have previously reported a similar finding for faecal incontinence:[19] a substantial proportion of patients treated with a low anterior resection had faecal incontinence. In our opinion, few secondary stomas are constructed in such patients, suggesting that patients accept faecal incontinence.

Other risk factors for not having stomas reversed might not be related directly to patients' or surgeons' motivation, but more related to surgical problems. The decision to create an end ileostomy or colostomy instead of a diverting stoma also highlights expected technical difficulties in creating a primary anastomosis. Accordingly, reversal of an end ileostomy or colostomy is less probable, and so these stomas are often permanent. Obviously, the development of a recurrence shifted treatment focus to a palliative setting in which the aim was to optimise quality of life and to prevent unnecessary surgery. Remarkably, other factors that might be associated with technical difficulties in reversing stomas, such as distance and TNM stage, were not identified as limiting factors in this study.

Although a side-to-end or colonic pouch anastomosis is recommended as an attempt to minimise the risk of anastomotic dehiscence,[20] an end-to-end anastomosis was created in only 107 of 924 patients. We previously showed that anastomosis type was not an independent factor for anastomotic dehiscence in the TME trial.[3] Similarly, in this study, the type of anastomosis was not associated with the necessity to create a secondary stoma (data not shown). However, the type of anastomosis and the decision

to create a stoma were left to the surgeons' discretion, which might have resulted in biased data. Preoperative radiotherapy was a risk factor for secondary stomas becoming permanent, but not for primary stomas -suggesting that the combination of preoperative radiotherapy and serious complications after primary surgery that necessitated a secondary stoma resulted in fewer stoma reversals.

The large difference in stoma reversal in patients having primary and secondary stomas might raise the question of whether all patients should have a stoma in the first operation. However, based on the findings in this study, we would not support this idea. Almost one-third of all patients treated with a low anterior resection in the rectal cancer TME trial never had a stoma. Also, only about 81% of stomas were reversed. Furthermore, the stomas themselves and second procedures to reverse stomas are associated with morbidity and mortality. Patients' preferences, morbidity -which sometimes even results in a new stoma- and mortality were not included in this analysis. Moreover, the costs associated with the stoma and its reversal are a burden for health-care systems.

A temporary diverting stoma is often created in an attempt to decrease the risk of clinical anastomotic leakage. However, data in published studies are inconsistent about the relation between defunctioning stoma usage and prevention of anastomotic leakage after surgical treatment of rectal cancer. Some studies have reported no significant difference in the frequency of anastomotic leakage if a diverting stoma is created,[1,2] whereas we and others have found a decreased incidence of clinically evident leakage.[3,21,22] More consistent evidence is available that suggests a diverting stoma reduces the clinical consequences of anastomotic leakage, for example, the finding that fewer patients with diverting stomas than those without such stomas need surgery when anastomotic leakage occurs.[1-3]

Other factors might support the argument for stoma construction. In the TME trial, patients with a stoma were more satisfied with their bowel function than those without a stoma (174 of 235 [74%] versus 199 of 362 [55%], $P < 0.001$).[19] Others, however, reported lower quality of life with a stoma.[7] Obviously, patients' preferences and sociodemographical characteristics, such as the availability of good stoma care and cultural acceptance of stomas, will decide the individual patient's quality of life to a certain extent. Eventually, the loss of quality of life due to a stoma needs to be counterbalanced with the patient's comorbidity, which might limit successful stoma reversal. Only in this way can an individualised decision be made on stoma reversal.

Our results do not suggest that the unreversed stomas should not have been made, but show that temporary stomas should be created as if they are permanent stomas; correct placement that helps life-long handling is of utmost importance. In an attempt to lower clinical anastomotic leakage and variability in surgical management of patients with rectal cancer, a working party has been developed in the Netherlands. This party will document prospectively surgical procedures in colorectal surgery in the Netherlands,

including the incidence of stoma formation and anastomotic leakage. This prospective audit should provide data that will guide surgeons towards a more standardised and evidence-based approach in stoma formation. Only then can treatment be further tailored to the individual patient with rectal cancer.

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Chapter 12

General discussion

Summary

Nederlandse samenvatting

GENERAL DISCUSSION

Colorectal cancer is the cancer with the second highest cancer incidence in Europe.[1] Roughly, one out of three patients with a colorectal malignancy has a rectal carcinoma. Surgery is the cornerstone in the curative treatment of rectal cancer. In the 1980s with conventional surgery, the 5-year local recurrence rate was over 20% and the 5-year overall survival rate around 50%.[2,3] In the Swedish Rectal Cancer trial in which 1168 patients were included, preoperative radiotherapy in addition to conventional surgery resulted in a reduction of more than 50% in the 5-year local recurrence rate in comparison to conventional surgery alone (11% versus 27%; $P < 0.001$).[2] Besides, the 5-year overall survival rate improved from 48% to 58% if patients were treated with preoperative radiotherapy in addition to conventional surgery ($P = 0.004$).[2] With the total mesorectal excision (TME), by which the rectum with its mesorectum and visceral fascia are dissected sharply and under direct vision,[4] local recurrence rates dropped and overall survival improved.[5,6] In the Dutch TME trial, 5 x 5 Gy preoperative radiotherapy in combination with TME surgery was compared to TME surgery alone (1861 patients). In this trial, the 5-year local recurrence rate for patients treated with TME surgery alone was similar to patients treated in the Swedish Rectal Cancer trial with blunt dissection in combination with preoperative 5 x 5 Gy radiotherapy (11%)[2,7] If preoperative radiotherapy was added to TME surgery, 5-year local recurrence rate was reduced to 5.6%[7] The overall survival rate at 5 year was 64% for both patients treated with TME surgery alone and patients treated with preoperative radiotherapy followed by TME surgery,[7] compared to 48% for patients treated with blunt dissection alone in the previously mentioned Swedish trial.[2] TME surgery is now considered the standard surgical procedure for rectal cancer.[4] However, even if TME surgery is performed, surgical quality varies.[8,9] First, these results indicate that improvements in the surgical procedure itself can result in major progress regarding long-term oncological outcome such as decreased local recurrence rates and improved overall survival. Second, it illustrates that variation in surgical quality could lead to large differences in outcome. Recently, it was shown that surgical variation is not only important for patients with rectal cancer, but also plays an important role for the outcome of patients with colon cancer.[10,11]

SURGICAL QUALITY ASSURANCE

In 1991, McArdle and Hole wrote that "some surgeons perform less than optimal surgery… If by meticulous attention to detail the results of surgery could be improved, and our results suggest that this would not be difficult, the impact on survival might be greater than that of any of the adjuvant treatment therapies currently under study".[12]

Quality assurance aims at reducing variability and can be defined as the systematic measures required to achieve a treatment result that meets a certain standard. These measures include training of all participating surgeons to reduce the variation in skill level, presence of an instructor surgeon during the first procedures of each surgeon, and pathological quality control of the resected specimen on, for example, the number of resected lymph nodes or circumferential resection margin involvement.

Several studies showed that circumferential resection margin involvement is a risk factor for increased local recurrence and reduced overall survival.[13-15] Some even consider circumferential resection margin involvement as an early (surrogate) end-point.[16,17] Furthermore, it has been shown that preoperative radiotherapy could not compensate for circumferential resection margin involvement.[18] The predictive value of the circumferential resection margin for local recurrence is significantly higher if preoperative therapy has been applied compared to no preoperative treatment (hazard ratio 6.3 versus 2.0, respectively; $P < 0.05$).[19] Consequently, circumferential resection margin involvement is not only prognostic for oncological outcome, but also influences the studied effects of the (neo)adjuvant treatment. This illustrates the necessity to document circumferential resection margin involvement in randomised trials. Feedback from the pathologist to the surgeon on, for example, circumferential resection margin involvement could eventually improve the number of radical resections. In the MRC CR07 trial, which compared short course preoperative radiotherapy with selective postoperative chemoradiotherapy in case of involvement of the circumferential resection margin, quality of the resection specimen was prospectively assessed and reported to the surgeons.[8] During this trial, the frequency of involved circumferential resection margins decreased. Furthermore, both this trial and the Dutch TME trial showed that poor quality of surgery, defined as resection in the muscularis plane, was associated with poor local control and disease-free survival.[8,9] This feedback could also improve the surgical resection quality in the daily clinical practice: distance of the tumour to the circumferential resection margin should be a standard parameter in the pathology report of a rectal resection specimen.

Considerations after the introduction of TME surgery

Although in general the outcome for patients improved since the introduction of the TME procedure,[5,20] outcome for some groups of patients improved less than for others.[9,21,22] In the Netherlands, TME surgery was nationwide introduced during the TME trial (1996-1999).[23] For patients under 75 years, the population-based 5-year overall survival rate in the Netherlands was 60% in the period before the TME trial, 67% in the period of the trial and 70% in the period after the TME trial.[21] However, in the same study, patients aged ≥ 75 years had a 5-year overall survival rate of respectively 41%, 40% and 43% in these periods.[21] In the elderly patients, the 1-month and 6-month postoperative mortality rates are much higher compared to the rates of younger patients.[21,22] Treatment

related mortality is probably an important competitive risk factor, which obscures the positive effects of TME surgery in patients aged ≥ 75 years.[21,22]

Another group of patients who used to have a worse outcome, is the group of patients treated with an abdominoperineal resection compared with the group of patients treated with a low anterior resection. These patients have higher rates of circumferential resection margin involvement, worse local control, and a reduced overall survival rate.[24] At the beginning of the 1990s, it became clear that the distal margin of 5 cm from the tumour could be safely reduced to 2 cm or less.[25] Simultaneous, the TME technique was introduced as standard treatment.[4,26] Consequently, the frequency of abdominoperineal resections decreased, whereas more low anterior resections were performed.[27] Marr and collegues studied the abdominoperineal resection before and after the introduction of the TME procedure in Leeds.[24] They found that patients treated with an abdominoperineal resection had more involved circumferential resection margins, an increased local recurrence rate, and a reduced overall survival rate.[24] Interestingly, since the introduction of the TME technique the frequency of involved circumferential resection margins after an abdominoperineal resection did not change: 43% involved margins between 1997 and 2000 compared to 36% in the period 1986 to 1997.[24] Over time less patients were treated with an abdominopereneal resection compared to an low anterior resection.[24] This difference in patient selection could have influenced the results, as nowadays only the more difficult, distal tumours are treated with an abdominoperineal resection. Nevertheless, also in the Dutch TME trial, high rates of circumferential resection margin involvement were found after an abdominoperineal resection.[9] In general, with TME surgery overall survival is still 10% worse for patients treated with an abdominoperineal resection in comparison to patients treated with a low anterior resection.[9,28,29]

The above mentioned examples are indicating the importance of performing continuous research and quality monitoring to identify the areas where treatment results are not as expected. The findings for the elderly patients question the benefit of the "standard" TME procedure for some frail elderly patients with a limited tumour: neoadjuvant treatment in combination with a smaller surgical procedure might be a good alternative for these patients.[22] The results of the abdominoperineal resection did also lead to a change in practice in several institutes, where a wider, cylindrical resection is performed instead of the traditional conic excision.[30,31]

National cancer plans

In several countries, the importance of continuous research and quality assurance for improving oncological care has been recognised. In the United Kingdom, the National Health Service (NHS) Cancer Plan was formulated in 2000, which gave cancer services high priority. The plan aimed to reduce death rates and improve prospects of survival and quality of life for patients with cancer and to guarantee high quality treatment and

care throughout the country. Also in France, a national cancer plan was introduced (2003). As a result the French National Cancer Institute was founded in 2004. Its mission is to direct the course of cancer care policy, to provide a network hub for research, and to act as a catalyst for European and international cooperation.[32] In several other countries, including Australia, New Zealand and Canada, similar national cancer plans have been formulated. These plans emphasize the improvement of quality of care for the patient with cancer. Nevertheless, to structurally gain insight in the nationwide improvements of cancer care, and more importantly in the short and long-term results of the provided care, an audit is necessary.

AUDITS ON RECTAL CANCER

Several countries have organised a national audit, such as Norway and Sweden. Recently, a national colorectal audit was also implemented in the Netherlands. In Norway, a national audit for the period 1986-1988 was performed. It was found that the 5-year local recurrence rate was 28% with a 5-year overall survival rate of 55% for patients aged younger than 75 years.[33] The Norwegian Rectal Cancer Group was founded and established a national rectal cancer registry. Each department regularly received its own results together with the national average for comparison and quality control.[33] From November 1993 until December 1999, 5382 patients with rectal cancer were included. TME surgery was rapidly implemented: 96% of patients were treated with this surgical technique in 1998.[33] For patients younger than 75 years, the local recurrence rate was 8% after a mean follow-up of 39 months, and the 5-year overall survival was 71%.[33] Wibe and colleagues conclude the following: "The Rectal Cancer Registry has provided the opportunity for monitoring treatment standard in each department, and the routine reports of results to the departments are also believed to encourage every surgeon and pathologist to do his or her best. Moreover, it provides data which allow comparison of the results of individual units to the national average."[33]

In Sweden, an audit for all patients with rectal cancer was launched in 1995: the Swedish Rectal Cancer Registry. According to the Swedish healthcare system it is obligatory for pathologists and surgeons to report cancer diagnoses to the Swedish Cancer Registry. All departments of surgery agreed to provide clinical data to the registry. Feedback is given to all centres on treatment outcome. Between 1995 and 2003, 13434 patients were documented in the Swedish Rectal Cancer Registry.[28] The 5-year survival rate for rectal cancer improved significantly from 36.1% in the period 1960-1964 to 57.6% in the period 1995-1999.[34] The survival rates for colon cancer were not included in the national audit and improved from 39.6% to 57.2% in these periods.[34] These results indicate that in Sweden, survival for both rectal cancer and colon cancer have improved. Similar to the

Swedish results, in the regional database of the Dutch Comprehensive Cancer Centre West was found that, historically, patients with colon cancer had a better survival rate than patients with rectal cancer: hazard ratio 0.84; $P = 0.001$ for patients with colon cancer compared to patients with rectal cancer in the period 1990-1995, adjusted for age, gender, and TNM stage (unpublished data). However, due to the focus on rectal cancer in the last decade, the survival rate for patients with rectal cancer is now similar to patients with colon cancer. The concentration of patients with rectal cancer to a specialised hospital, the nationwide introduction of TME surgery, and the implementation of preoperative radiotherapy have probably contributed to these improvements.

The EUROCARE collaboration is an example of a collaboration between more than 83 cancer registries across 23 countries.[35] The data are obtained from some national registries, which cover 100% of the cases, and also from many regional registries. For colorectal cancer, the 5-year relative survival in the EUROCARE-4 study was 56.2% for patients diagnosed in the period 2000-2002.[36] In general, the countries in Northern and Central Europe had the best survival rates, whereas countries in Eastern Europe, such as Poland and Czech Republic, had a 10% lower overall survival rate compared to the average.[36] Furthermore, also the survival rate of the United Kingdom, a country with a Cancer Plan since 2000, was below the average survival rate in the EUROCARE study.[36] A limitation of the EUROCARE study is that for some nations only regional registries were available and only a proportion of all cases was included in the database: for example in Poland and the Czeck Republic respectively only 9% and 8% of the national population is covered by the used registries.[35] Nevertheless, the results indicate that large differences exists in survival rates of rectal cancer between nations. It is important to realise that not only survival differences between nations are present, but also within a nation due to different outcome in different centres.[37,38] An audit such as the EUROCARE study helps to identify where the quality of care should and could be improved. However, interesting questions, such as why these differences exist and how the survival rate can be improved, cannot be answered by the EUROCARE database.

An European audit on colorectal cancer treatment outcome

In Europe, international initiatives for collaboration to improve cancer care outcome are limited. In the early 1980s, the Federation of European Cancer Societies (FECS) was founded, based on the vision that treating cancer is an effort of a multidisciplinary team. The European Society of Surgical Oncology (ESSO) took with support of the European Society for Therapeutic Radiology and Oncology (ESTRO) the initiative to officially disband and replace the FECS in 2007 by the European CanCer Organisation (ECCO), which aims at taking an even wider approach to oncology. One of the goals of the ECCO is to uphold the right of all European cancer patients to the best possible treatment and care. The ECCO supported a recently initiated, European audit on colorectal cancer, which is

an outcome-based quality improvement project. The following outcomes will be considered: morbidity, mortality, loco-regional control, and survival. The aims of the audit are first to improve outcome for patients with cancer in Europe by quality assurance measures, and second to decrease the use of unproven treatments, which might cause side-effects without improving outcome. Regularly, collected data will be analysed to identify areas where further improvements in the quality of care are possible or necessary. Additional data, such as TNM stage and other confounders, are collected so the analyses can be adjusted for confounders such as patient case-mix.

Furthermore, the audit could be used to identify centres which have the best (adjusted) outcome for colorectal cancer treatment: the "centres of excellence". Studies why these centres have better results will contribute to the understanding of factors that influence colorectal cancer outcome. Apart from that, the audit could give insight in the actual number of procedures that are performed within each centre and by an individual surgeon each year. This could be important as Birkmeyer and colleagues showed that hospital volume was associated with operative mortality for colectomy in the United States (6.5% in hospitals with less than 33 resections per year compared to 4.5% for hospitals with more than 124 resections per year, $P < 0.001$).[39] Besides, several groups showed that surgical caseload was associated with oncological outcome for rectal cancer.[38,40] Surprisingly, in the Swedish Uppsula trial was found that 50% of patients were operated by surgeons who performed less than one rectal cancer operation per year.[28,41] As a consequence of above mentioned findings rectal cancer care in Sweden was eventually concentrated to centres with specialised surgeons. In the future, the outcome-based European audit for colorectal cancer could also result in reorganisation of colorectal cancer care in other countries in Europe: concentration of colorectal cancer care in the centres with the best outcome. It could be that these centres are high volume centres, but the decision should be based on outcome parameters and not solely on caseload.

Costs of quality improvement

Every treatment costs money. Chemotherapeutic agents are relatively expensive, and the effects on outcome in the treatment of rectal cancer are currently limited. An example in which systemic treatment is used is metastatic colorectal disease. Due to the chemotherapeutic agents, the prognosis has improved from a median survival of eight months to more than 21 months (regimen including bevacizumab or cetuximab).[42] Although the progress is commendable, we should remember that these treatments costs over US$ 21,000 for the initial 8 weeks.

In the last decade, the largest improvements in survival of patients with rectal cancer resulted from a change in surgical technique: due to a change from blunt dissection to TME surgery the survival rates in several countries have improved.[5,20,43] Professor Wibe showed during the Colorectal Conference 2007 in St. Gallen that the National Rectal

Cancer Audit in Norway, which started in 1993, costed € 120,000 per year including the costs of two secretaries and one statistician (50%). Until 2007, more than 14000 patients were included in a country with 4.6 million inhabitants. During the audit each department was monitored. Feedback and, if necessary, counselling was given. The local recurrence rate decreased and the overall survival rate improved from 55% in the period 1986-1988 to 71% in the period 1993-1999.[33,44] Wibe estimated that since the introduction of the audit 2500 patients have been saved due to improved treatment. As the audit has cost around 1.6 million euros since 1993, the costs per saved life were around 700 euros. This does not implicate that radiotherapy or chemotherapy should not be used. Rather, it indicates that quality assurance projects such as an audit have been shown to be very cost effective.

Although the costs of an audit are relatively low, it still has to be financed. One of the parties who could contribute towards the costs is the government: an audit fits within the national cancer plans as its helps to improve cancer care outcome. Consequently, an European audit might be supported by both the national government and the European Union. Moreover, an audit could result in reduction of the incidence of (expensive) complications and a decreased use of unproven treatments, which could eventually result in a reduction of total expenses. Therefore, it is also interesting for medical insurance companies to invest in an outcome based audit. Finally, independent, grant-giving institutes such as cancer foundations might be willing to contribute to quality improving initiatives.

Considerations for the audit

A registration project in which only data is collected for documentation purposes, will not lead to an improved quality of care. First of all, an audit should be an interactive system in which regularly feedback is given on performance, mirrored to the regional, national and European average. Besides, recommendations where further improvements can be made should be given at least annually to the participants. Second, if only dedicated treatment teams register their data, a bias of the results will exist, eventually resulting in a failure to improve overall treatment outcome. Therefore, participation to the audit should be mandatory.

CONCLUSIONS

Variability results in differences in outcome. Surgical variability can be minimised by extensive quality assurance. In several surgical randomised trials, the importance of quality assurance measurements are shown. However, the majority of patients is treated outside the framework of a trial. For patients treated in the daily clinical practice, quality

assurance by means of auditing is necessary. Registration of outcome-based quality measurements is cost effective and provides transparency, benchmarking, and internal feedback which will rapidly lead to improvements in cancer care.

SUMMARY

In the last decade the surgical procedure for rectal cancer has been changed. At the end of the 1980s, a blunt dissection was performed. Several studies have shown that a total mesorectal excision (TME), which is a sharp removal under direct vision of the complete rectum with its intact mesorectum and visceral fascia with preservation of the autonomic nerves, resulted in better local control and overall survival.[26,45] In the same period as the introduction of TME surgery, it became clear that the distal margin of 5 cm from the tumour could be safely reduced to 2 cm or less.[25] Consequently, fewer abdominoperineal resections were performed.[27]

In the Netherlands, the TME trial introduced the TME technique nationwide.[23] In this trial, radiotherapy, surgery, and pathology were extensively quality controlled. For the surgical procedure, several workshops were organised, videotapes with the procedure produced, trainings at the dissection table were given, and the first procedures of each participating surgeon were supervised by an instructor surgeon. This thesis focuses on quality assurance of rectal cancer treatment, in particular on the surgical treatment.

In **chapter 1** the general introduction and outline of the thesis are described.

The effect of the introduction of TME surgery on population-based overall survival in the Netherlands is studied in **chapter 2**. In this study the cancer registries of the Comprehensive Cancer Centres South and West are used. In total 3179 patients were included. Three periods were studied: before, during and after the TME trial. Overall survival was respectively 56%, 62% and 65% in the pre-trial, trial and post-trial period ($P < 0.001$). Overall survival, adjusted for the confounders gender, age, pT-stage, lymph node involvement, and (neo)adjuvant treatment, improved in the trial period ($P < 0.001$), suggesting that the introduction of TME surgery was successful. Preoperative radiotherapy was increasingly used over time. In the period of the TME trial, overall survival was similar for patients treated with preoperative radiotherapy and without (neo)adjuvant treatment ($P = 0.315$). In the post-trial period, preoperative radiotherapy was significantly related to improved overall survival compared with no (neo)adjuvant treatment ($P = 0.002$). The results indicate that population-based overall survival improved since the nationwide introduction of TME surgery. Besides, with standardised TME surgery, preoperative radiotherapy resulted in an improved overall survival rate, whereas withholding preoperative radiotherapy was associated with a poorer prognosis.

Although chapter 2 showed that in general overall survival increased since the introduction of TME surgery, in chapter 3 and 4 it was studied whether the outcome for the elderly patients with rectal cancer also improved. In most rectal cancer trials patients

aged over 75 years are underrepresented due to exclusion based on age or comorbidity. However, rectal cancer is a disease predominately occurring in the elderly patient. For both chapters 3 and 4, the Dutch TME trial and the cancer registries of Comprehensive Cancer Centres South and West were used. In **chapter 3** it was shown that the 5-year overall survival was 60% before the introduction of TME surgery, 67% during the TME trial, and 70% after the TME trial in patients aged younger than 75 years ($P < 0.0001$). The survival for older patients did not improve and remained at 41%, 40% and 43% at 5 years in the respective periods. Furthermore, mortality during the first 6-month period after treatment is significantly raised compared to younger patients: 14% in the elderly patients, compared to 3.9% in the younger TME study patient ($P < 0.0001$). In the database of the Comprehensive Cancer Centres these figures were confirmed at 16% and 3.9% ($P < 0.0001$). In **chapter 4**, the association between age, morbidity and 6-months mortality is shown. Treatment related mortality is probably an important competitive risk factor which obscures the positive effects of TME surgery in patients aged ≥ 75 years. It is discussed that for elderly patients who retain a good physical and mental condition, treatment that is given to younger patients is regarded to be appropriate, whereas for those with diminished physiological reserves and comorbid conditions, alternative treatments that keep surgical trauma to a minimum and optimise the use of radiotherapy might be more suitable.

Another group of patients who had a worse outcome is the group of patients treated with an abdominoperineal resection compared with those treated with a low anterior resection. In **chapter 5** it is studied which of the following is associated with circumferential resection margin involvement, local recurrence, overall survival, and cancer-specific survival: the abdominoperineal resection itself or the factors resulting in the decision to perform an abdominoperineal resection. Patient and treatment related variables of the Swedish Rectal Cancer trial, Dutch TME trial, CAO/ARO/AIO-94 trial, EORTC 22921 trial and Polish Rectal Cancer trial were combined (5187 patients). A propensity score was calculated, which indicated the predicted probability of undergoing an APR given gender, age, and distance of the tumour to the anal verge. The results showed that an abdominoperineal resection was associated with an increased risk of circumferential resection margin involvement (odds ratio 2.52; $P < 0.001$), increased local recurrence rate (hazard ratio 1.53; $P = 0.001$), and a decreased cancer-specific survival rate (hazard ratio 1.31; $P = 0.002$), whereas the propensity score was not. The results suggest that the abdominoperineal resection itself is a significant predictor for nonradical resections and is associated with an increased risk of local recurrence and death due to cancer for patients with advanced rectal cancer.

Chapter 6 focuses on patients treated with an abdominoperineal resection in the TME trial, to identify tumour and patient related risk factors associated with positive

circumferential resection margins, local recurrence, and overall survival. A positive circumferential resection margin was found in 29.6% of all patients: 44% for anterior, 21% for lateral, 23% for posterior, and 17% for (semi)circular tumour location ($P < 0.001$). In a multivariate analysis, T-stage, N-stage, and tumour location were independent risk factors for circumferential resection margin involvement. If a (partial) resection of the vaginal wall was performed in women, 47.8% of patients still had a positive circumferential resection margin. T-stage, N-stage, and circumferential resection margin were risk factors for local recurrence and age, T-stage, N-stage, circumferential resection margin, and distance of the tumour to the anal verge for overall survival. The results indicate that the surgical treatment should primarily be aimed at adequate resection margins. To further improve the outcome of patients treated with an abdominoperineal resection, tumours should be properly preoperatively staged, including an assessment of the circumferential resection margin (mesorectal fascia). For patients with a threatened circumferential resection margin preoperatively, 5 x 5 Gy radiotherapy alone is insufficient and treatment should preferentially consist of chemoradiotherapy and/or extended resection.

The EORTC 22921 trial studied the addition of pre- and/or postoperative chemotherapy to preoperative radiotherapy followed by surgery in T3 or resectable T4 rectal cancer. The trial ran from April 1993 to March 2003. In 1999, an addition to the trial protocol was made in which it was recommended to perform a TME procedure. Circumferential resection margin involvement, local recurrence, overall survival, and disease-free survival in patients treated with a long schedule of (chemo)radiotherapy are studied in **chapter 7**. Circumferential resection margin involvement was associated with the period of treatment: less circumferential margin involvement was found after 1999. Although preoperative chemoradiotherapy resulted in more downstaging and downsizing in comparison to preoperative radiotherapy alone in a previous analysis,[46] the preoperative treatment did not significantly affect circumferential resection margin involvement. A positive circumferential resection margin was associated with a higher risk of a local recurrence and a decreased disease-free and overall survival rate. Although downstaging might be helpful in the treatment of these advanced tumours, the results suggest that the ultimate aim of the treatment should be to perform a radical operation.

In **chapter 8**, the data of EORTC 22921 trial are further explored, to study which patients might benefit from the addition of postoperative chemotherapy to a preoperative schedule of long (chemo)radiotherapy. Although there was no statistically significant impact of postoperative chemotherapy on disease-free survival for the whole group ($P > 0.05$),[47] the treatment effect differed significantly between the patients showing downstaging (ypT0-2) and the patients that did not show downstaging after preoperative therapy (ypT3-4): only the ypT0-2 patients seemed to benefit from postoperative

chemotherapy (P = 0.013). The same pattern was observed for overall survival. These results indicate that predictive factors such as tumour responsiveness to preoperative treatment must be taken into account in the design of future trials studying postoperative treatments. Besides, tumour sensitivity for the primary treatment might be considered to tailor postoperative therapy and prevent ineffective treatments, which might cause addition burden and toxicity.

One of the feared complications after a low anterior resection is anastomotic leakage. In **chapter 9**, the data of the Swedish Rectal Cancer trial, Dutch TME trial, CAO/ARO/AIO-94 trial, EORTC 22921 trial, and Polish Rectal Cancer trial were used to study the association between anastomotic leakage and long-term outcome. In total 2726 patients with a low anterior resection were selected. Anastomotic leakage occurred in 9.7% of patients. The presence of a diverting stoma was negatively associated with anastomotic leakage (P = 0.002). After exclusion of patients with early postoperative mortality, anastomotic leakage was independently associated with overall survival (HR 1.29; 95% CI 1.02-1.63; P = 0.034), but not with cancer-specific survival (HR 1.12; 95% CI 0.83-1.52; P = 0.466). These data indicate that patients who survived their anastomotic leakage still have a decreased long-term overall survival rate.

In the early postoperative period, anastomotic leakage is feared for its associated morbidity and mortality. In **chapter 10** is focused on this period. First, historical data of 3 regional hospitals were collected (1066 patients). These data revealed that 7.0% of patients developed a symptomatic anastomotic leakage. The mortality rate of patients diagnosed with anastomotic leakage was 39%. It was considered that delay in the diagnosis of anastomotic leakage might have contributed to these findings: the diagnosis was made with a median delay of 4 days after the first symptoms were observed. As a result a protocol for standardised postoperative surveillance was made, using easily accessible clinical parameters such as temperature, heart rate, and physical examination of the abdomen. This protocol was then prospectively tested between August 2004 and August 2006 (223 patients). The anastomotic leakage rate was 9.4% in this period. Compared to the historical controls, the delay between the first symptoms and the diagnosis of anastomotic leakage decreased significantly from a median of 4 days to 1.5 days (P = 0.01). The mortality rate dropped, but this difference was not statistically significant. The results indicate that standardised postoperative surveillance for anastomotic leakage could result in a shorter delay between the first signs and symptoms to the confirmation of anastomotic leakage. At present a multicentre registration project is performed, to further improve and validate the scoring list and decision model (DUtch LeaKage score).

In chapter 9 and in other studies it was shown that the presence of a diverting stoma is associated with a lower rate of anastomotic leakage.[48] However, part of the stomas constructed with temporary intent are never removed. In **chapter 11**, the data of the

Dutch TME trial were used to study the rate of stoma reversal and to identify factors that limit stoma closure. In 19% of patients, the stoma was never reversed. Postoperative complications and secondary constructed stomas, for example after anastomotic leakage, were associated with a higher likelihood of a permanent stoma. The results show that temporary stomas should be created as if they are permanent stomas; correct placement that helps life-long handling is of utmost importance.

In **Chapter 12** this thesis is placed in a wider context. The importance of quality assurance is illustrated, using the results of the TME trial. To continuously improve the outcome of the oncological care it is necessary to monitor structurally. Quality assurance should not only be used within randomised clinical trials, but be a part of the daily clinical practice. In several countries the efficiency of audits has been shown before. Recently, an European outcome-based audit was initiated, supported by the European CanCer Organisation (ECCO). Eventually, feedback of the audit will result in an improved outcome of the oncological treatment.

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NEDERLANDSE SAMENVATTING

In het laatste decennium is de chirurgische behandeling van het rectumcarcinoom veranderd. Aan het einde van de jaren 80 van de vorige eeuw werd er een stompe dissectie verricht. Verschillende studies hebben aangetoond dat een operatie waarbij het complete rectum met een intact mesorectum en viscerale fascie onder zicht en middels een scherp resectie werd verwijderd, resulteert in betere lokale controle en algehele overleving: de totale mesorectale excisie (TME).[1,2] In dezelfde periode als de introductie van de TME procedure werd duidelijk dat de distale marge van 5 centimeter van de tumor gereduceerd kon worden tot (minder dan) 2 centimeter.[3] Dit leidde ertoe dat er minder abdominoperineale resecties werden verricht.[4]

In Nederland werd met de TME studie de TME techniek landelijk geïntroduceerd.[5] In deze studie naar rectumcarcinoom werd de kwaliteit van radiotherapie, chirurgie en pathologie uitgebreid gecontroleerd: kwaliteitsborging of "quality assurance". Het doel van deze kwaliteitscontrole was te garanderen dat radiotherapie, chirurgie en pathologie aan een bepaalde standaard voldeden. Voor de chirurgische kwaliteitsborging werden onder andere verschillende workshops georganiseerd, videobanden van de procedure verspreid, trainingen in de snijzaal gegeven en de eerste operaties van iedere deelnemende chirurg gesuperviseerd door een instructeur. Dit proefschrift richt zich op de kwaliteitsborging van de behandeling van het rectumcarcinoom, waarbij met name de chirurgische behandeling wordt bestudeerd.

Hoofdstuk 1 is de inleiding van dit proefschrift. Daarnaast wordt in dit hoofdstuk de inhoud van het proefschrift op hoofdlijnen weergegeven.

Het effect van de introductie van TME chirurgie in Nederland op de algehele overleving is onderwerp van studie in **hoofdstuk 2**. In deze studie met 3179 patiënten werd gebruik gemaakt van de kankerregistratie van de Integrale Kankercentra West (IKW) en Zuid (IKZ). Er werden drie perioden onderscheiden: voor, tijdens en na de TME studie. De algehele overleving was 56%, 62% en 65%, respectievelijk voor, tijdens en na de TME studie ($P < 0{,}001$). De algehele overleving, gecorrigeerd voor geslacht, leeftijd, pathologisch T-stadium, lymfklier status en (neo)adjuvante therapie was significant verbeterd in de periode tijdens de TME studie in vergelijking met voor de TME studie ($P < 0{,}001$). Dit suggereert een succesvolle introductie van de TME procedure. Preoperatieve radiotherapie werd in de opeenvolgende perioden steeds meer toegepast. In de periode van de TME studie was de algehele overleving van patiënten behandeld met preoperatieve radiotherapie gelijk aan de algehele overleving van patiënten die zonder (neo)adjuvante therapie werden behandeld ($P = 0{,}315$). In de periode na de TME studie had de groep patiënten die preoperatief behandeld werd met radiotherapie een significant betere

algehele overleving dan de groep die zonder (neo)adjuvante therapie werd behandeld (P = 0,002). De resultaten geven aan dat de algehele overleving is verbeterd sinds de introductie van TME chirurgie in Nederland. Daarnaast resulteert gestandaardiseerde TME chirurgie in combinatie met preoperatieve radiotherapie in een verbetering van de algehele overleving, terwijl de groep die niet wordt behandeld met preoperatieve radiotherapie een slechtere prognose heeft.

Alhoewel in hoofdstuk 2 is aangetoond dat voor de totale populatie van patiënten met een rectumcarcinoom de algehele overleving verbeterd is sinds de introductie van de TME procedure, werd in hoofdstuk 3 en 4 bestudeerd of de uitkomst ook voor de oudere patiënt is verbeterd. In de meeste studies die de behandeling van het rectumcarcinoom onderzoeken zijn patiënten ouder dan 75 jaar ondervertegenwoordigd door exclusie op basis van leeftijd of co-morbiditeit. Het rectumcarcinoom komt echter hoofdzakelijk voor bij oudere patiënten. Voor de hoofdstukken 3 en 4 werd gebruik gemaakt van de gegevens van zowel de TME studie als de Integrale Kankercentra West en Zuid. In **hoofdstuk 3** werd aangetoond dat de 5-jaars overleving voor patiënten jonger dan 75 jaar 60% was voor de introductie van de TME procedure in Nederland, 67% tijdens de TME studie en 70% na de TME studie (P < 0,0001). Voor patiënten van 75 jaar en ouder werd geen verbetering in de 5-jaars overleving gevonden: 41%, 40% en 43%, respectievelijk voor, tijdens en na de TME studie. Bovendien was de mortaliteit in de eerste 6 maanden postoperatief significant hoger voor de oudere patiënten in vergelijking met patiënten jonger dan 75 jaar: 14% voor oudere patiënten versus 3,9% voor jongere patiënten in de TME studie (P < 0,0001). In de database van het IKW en IKZ werden soortgelijke resultaten gevonden (16% versus 3.9%; P < 0,0001). In **hoofdstuk 4** werd de associatie tussen leeftijd, morbiditeit en 6-maanden mortaliteit aangegeven. Sterfte gerelateerd aan de behandeling is waarschijnlijk een belangrijke competitieve risicofactor, die de positieve effecten van TME chirurgie voor patiënten ouder dan 75 jaar doet vervagen. Voor oudere patiënten die een goede lichamelijke en geestelijke gezondheid hebben, lijkt de huidige therapie een goede behandeling. Echter, voor diegene met een verminderde fysiologische reserve door bijvoorbeeld co-morbiditeit, lijkt een alternatieve behandeling met gebruik van radiotherapie en minder uitgebreide chirurgie een meer geschikte optie.

Een andere groep met een relatief slechte uitkomst is de groep patiënten behandeld met een abdominoperineale resectie. In **hoofdstuk 5** wordt een studie omschreven die onderzoekt of de abdominoperineale resectie zelf of de combinatie van patiënt- en tumorgerelateerde factoren die resulteerde in de keuze voor een abdominoperineale resectie resulteert in deze slechte uitkomst. De volgende eindpunten worden bestudeerd: radicaliteit (gedefinieerd als een tumor positief circumferentieel snijvlak), lokaal recidiefpercentage, algehele en kanker-specifieke overleving. Voor deze studie werden

de gegevens van de Swedish Rectal Cancer trial, de TME studie, de CAO/ARO/AIO-94 studie, de EORTC 22921 studie en de Polish Rectal Cancer trial gecombineerd (5187 patiënten). Er werd een "propensity score" berekend: de voorspelde kans om een abdominoperineale resectie te ondergaan gegeven geslacht, leeftijd en afstand van de tumor tot de anus. De abdominoperineale resectie was geassocieerd met een toegenomen risico op een positief circumferentieel snijvlak (odds ratio 2,52; $P < 0,001$), een toegenomen kans op een lokaal recidief (hazard ratio 1,53; $P = 0,001$) en een afname van de kanker-specifieke overleving (hazard ratio 1,31; $P = 0,002$); een associatie tussen de "propensity score" en deze eindpunten werd niet gevonden. De resultaten suggereren dat de abdominoperineale resectie zelf een belangrijke voorspeller is voor een niet-radicale operatie met een toegenomen risico op een lokaal recidief en sterfte door kanker voor patiënten met een gevorderd rectumcarcinoom.

In **hoofdstuk 6** werd de groep patiënten behandeld met een abdominoperineale resectie in de TME studie onderzocht om tumor- en patiëntgerelateerde risicofactoren te vinden voor irradicale resecties, lokaal recidief en algehele overleving. Een positief circumferentieel snijvlak werd gevonden bij 29,6% van alle patiënten: 44% bij een anterieur gelegen tumor, 21% bij een lateraal gelegen tumor, 23% bij een dorsaal gelegen tumor en 17% bij een (semi)circumferentiële tumor ($P < 0,001$). In de multivariate analyse waren T-stadium, N-stadium en tumorlocatie onafhankelijke risicofactoren voor een positief circumferentieel snijvlak. Van de vrouwen die een (partiële) resectie van de vagina-achterwand ondergingen, hadden 47,8% nog steeds een positief snijvlak. T-stadium, N-stadium en status van het circumferentiële snijvlak waren onafhankelijke risicofactoren voor een lokaal recidief. De volgende risicofactoren werden gevonden voor algehele overleving: leeftijd, T-stadium, N-stadium, status van het circumferentiële snijvlak en afstand van de tumor tot de anus. De resultaten geven aan dat de chirurgische behandeling erop gericht moet zijn om een adequate afstand tussen tumor en snijvlak te verkrijgen. Om de uitkomsten van patiënten behandeld met een abdominoperineale resectie te verbeteren, moet een adequate preoperatieve stadiëring worden verricht, inclusief een inschatting van de betrokkenheid van het circumferentiële snijvlak (mesorectale fascie). Voor patiënten bij wie de tumor tot in of vlakbij het circumferentiële TME snijvlak komt, is preoperatief 5 x 5 Gy radiotherapie alleen onvoldoende. De behandeling bestaat dan bij voorkeur uit preoperatieve behandeling met chemoradiotherapie en/of een uitgebreidere resectie.

In de EORTC 22921 studie werd de toevoeging van pre- en/of postoperatieve chemotherapie aan een schema van 6 weken preoperatieve radiotherapie bestudeerd voor patiënten met T3 of resectabele T4 rectumcarcinomen.[6] De studie was open voor inclusie van april 1993 tot maart 2003. Vanaf 1999 werd in het studieprotocol geadviseerd een TME procedure te verrichten. De betrokkenheid van het circumferentiële snijvlak,

het lokaal recidiefpercentage, de algehele en ziektevrije overleving voor patiënten met een lang preoperatief schema met (chemo)radiotherapie waren onderwerp van studie in **hoofdstuk 7**. Het percentage positieve snijvlakken was gerelateerd aan de periode van behandeling: er werden minder positieve snijvlakken gevonden na 1999. Alhoewel preoperatieve chemoradiotherapie in vergelijking met preoperatieve radiotherapie resulteerde in een lager TNM-stadium en kleinere tumoren,[7] werd geen significant effect van het type preoperatieve behandeling op het percentage positieve circumferentiële snijvlakken gevonden. Een positief circumferentieel snijvlak gaf een hoger risico op een lokaal recidief en een afgenomen ziektevrije en algehele overleving. Alhoewel het nuttig kan zijn om een gevorderd rectumcarcinoom te "downstagen", suggereren de resultaten dat het ultieme doel een radicale operatie is.

In **hoofdstuk 8** werden de gegevens van de EORTC 22921 studie gebruikt om te bestuderen welke groep patiënten met een gevorderd rectumcarcinoom behandeld met een schema van 6 weken preoperatieve (chemo)radiotherpie voordeel kunnen hebben van de toevoeging van postoperatieve chemotherapie. In de totale groep patiënten werd geen significant voordeel gevonden voor postoperatieve therapie op de ziektevrije overleving ($P > 0,05$).[6] Het effect van postoperatieve chemotherapie op ziektevrije overleving verschilde echter significant tussen patiënten met een ypT0-2 stadium ("downstaging") na preoperatieve therapie en patiënten zonder "downstaging" (ypT3-4): alleen de patiënten met ypT0-2 leken een voordeel te hebben van postoperatieve chemotherapie ($P = 0,013$). Soortgelijke resultaten werden gevonden voor de algehele overleving. De resultaten tonen aan dat er onder andere rekening gehouden moet worden met de reactie van tumoren op preoperatieve therapie bij het ontwerpen en interpreteren van studies over postoperatieve therapie. Bovendien zou de tumorgevoeligheid voor de preoperatieve behandeling gebruikt kunnen worden om een eventuele postoperatieve behandeling aan te passen. Dit kan het gebruik van ineffectieve behandelingen, met de bijbehorende bijwerkingen, verminderen.

Eén van de gevreesde complicaties na een lage anterieure resectie is naadlekkage. In **hoofdstuk 9** werden de databases van de Swedish Rectal Cancer trial, de TME studie, de CAO/ARO/AIO-94 studie, de EORTC 22921 studie en de Polish Rectal Cancer trial gecombineerd om de associatie tussen naadlekkage en de gevolgen op lange termijn te bepalen. In totaal werden 2726 patiënten met een lage anterieure resectie geselecteerd. Naadlekkage trad op bij 9,7% van de patiënten. In de groep patiënten met een ontlastend stoma werd minder naadlekkage gevonden ($P = 0,002$). Na exclusie van patiënten die binnen 90 dagen na de operatie stierven, was naadlekkage een onafhankelijke risicofactor voor verminderde algehele overleving (hazard ratio 1,29; 95% betrouwbaarheidsinterval 1,02-1,63; $P = 0,034$), maar niet voor kanker-specifieke overleving (hazard ratio 1,12; 95%

betrouwbaarheidsinterval 0,83-1,52; $P = 0,466$). Patiënten die naadlekkage overleefden, hadden na enkele jaren nog steeds een afgenomen algehele overleving.

In de vroege postoperatieve periode wordt naadlekkage gevreesd door de geassocieerde morbiditeit en mortaliteit. Het onderzoek in **hoofdstuk 10** richtte zich op deze periode. Patiëntgegevens uit drie ziekenhuizen werden retrospectief verzameld (1066 patiënten). Van deze groep patiënten werd bij 7,0% een symptomatische naadlekkage gediagnosticeerd. Het sterftecijfer voor patiënten met een naadlekkage was 39%. Vertraging in het stellen van de diagnose naadlekkage zou een bijdrage geleverd kunnen hebben aan dit hoge sterftecijfer: 4 dagen (mediaan) nadat de eerste symptomen aanwezig waren, werd de diagnose gesteld. Dientengevolge werd een protocol gemaakt waarin de postoperatieve zorg gestandaardiseerd werd en waarin gebruik werd gemaakt van gemakkelijk beschikbare klinische parameters, zoals temperatuur, hartfrequentie en lichamelijk onderzoek van het abdomen. Vervolgens werd dit protocol prospectief getest tussen augustus 2004 en augustus 2006 (223 patiënten). Naadlekkage werd bij 9,4% van de patiënten in deze periode gediagnosticeerd. Vergeleken met de historische controles was de vertraging in het stellen van de diagnose naadlekkage na het optreden van de eerste symptomen significant korter in de periode waarin gebruik werd gemaakt van de gestandaardiseerde postoperatieve follow-up: de diagnose werd met een vertraging van 1,5 dag in plaats van 4 dagen (mediaan) gesteld ($P = 0.01$). Bovendien daalde de mortaliteit na het optreden van naadlekkage naar 24%, maar dit verschil was niet significant. Concluderend lijkt gestandaardiseerde follow-up voor naadlekkage te resulteren in een kortere periode tussen de eerste symptomen en het stellen van de diagnose naadlekkage. Op dit moment wordt er in meerdere centra in Nederland een registratieproject uitgevoerd om de scoringslijst en beslisboom verder te verbeteren en te valideren (de "DUtch LeaKage score").

Zowel in hoofdstuk 9 als in andere studies werden bij ontlastend stoma's minder naadlekkages gevonden.[8] Een deel van deze tijdelijke stoma's wordt echter nooit opgeheven. In **hoofdstuk 11** werden de gegevens van de TME studie gebruikt om het beleid ten aanzien van stoma's te bestuderen en om factoren te identificeren die gerelateerd zijn aan het niet opheffen van stoma's. Tijdens de eerste operatie werd bij 523 van de 924 patiënten met een lage anterieure resectie (57%) een stoma aangelegd. Bij 19% van deze patiënten werd het stoma nooit opgeheven. Risicofactoren voor een permanent stoma waren onder andere postoperatieve complicaties en een stoma aangelegd tijdens een tweede of opeenvolgende operatie (bijvoorbeeld na het optreden van naadlekkage). De resultaten tonen aan dat ieder tijdelijk stoma aangelegd moet worden alsof het een permanent stoma is: een juiste plaatsing is dan vooral van belang.

In **hoofdstuk 12** wordt dit proefschrift in een bredere context geplaatst. Het belang van kwaliteitsborgingprojecten wordt geïllustreerd, onder andere met de resultaten van de

TME studie. Om een continue kwaliteitsverbetering van de oncologische behandeling te bewerkstelligen, is monitoring nodig. Niet alleen binnen gerandomiseerde studies, maar ook als onderdeel van de dagelijkse praktijk. In diverse landen is de effectiviteit van een audit aangetoond. Recent is een Europese audit geïnitieerd, ondersteund door de European CanCer Organisation (ECCO). Door terugkoppeling van de resultaten van deze audit kan de zorg voor patiënten met kanker uiteindelijk verder worden verbeterd.

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Chapter 13

Acknowledgements

Curriculum Vitae

List of publications

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Jasper and Eveline, quality time is now assured!

CURRICULUM VITAE

Marcel den Dulk was born in Leidschendam on 31 December 1976. He graduated from the Alfrink College (VWO) in Zoetermeer in 1995. In the same year he started with the study Biomedical Science at the Leiden University and passed his propaedeutics *cum laude*. In 1996 he started his study Medicine at the Leiden University and received in 1997 his propaedeutics in medicine *cum laude* and in 2000 his medical Masters degree (*cum laude*). He performed his graduation project on interstitial kidney fibrosis at the Nephrology department of the Leiden University Medical Center under supervision of professor dr. L.A. van Es. In 2000 he was awarded with the Leiden University Medical Center Research Fellowship. In December 2001 Marcel was qualified as a Medical Practitioner (*cum laude*).

The author performed research on transplant immunology at the Centenary Institute/ Royal Prince Alfred Hospital, Sydney, Australia from January 2002 until January 2003. From March 2003, he worked as an AGNIO (surgical resident not in training) at the Leyenburg Hospital in The Hague and in January 2005, he started in the same hospital with his surgical residency (dr. C.M.A. Bruijninckx). In December 2005 Marcel began with his research for his thesis on Quality Assurance of Surgical Oncology at the Department of Surgical Oncology at the Leiden University Medical Center under supervision of professor dr. C.J.H. van de Velde. He received a Fellowship of the European Society of Surgical Oncology (ESSO) for one and a half year for this project. In June 2007 he continued with his surgical residency at the Haga Hospital in the Hague (dr. J.W. Merkus; merger between Leyenburg Hospital, Red Cross Hospital and Juliana Children's Hospital, all in the Hague). During his residency he initiated a multicentre project on anastomotic leakage, of which he is, at present, the coordinator and principal investigator. From July 2010 he will continue his residency at the Department of Surgery at Leiden University Medical Center (professor dr. J.F. Hamming).

Marcel and his wife Marjolein den Dulk-Burgers have two children: a son Jasper and a daughter Eveline.

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