Quality assurance in rectal cancer treatment

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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

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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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