Quality assurance in rectal cancer treatment

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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

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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.

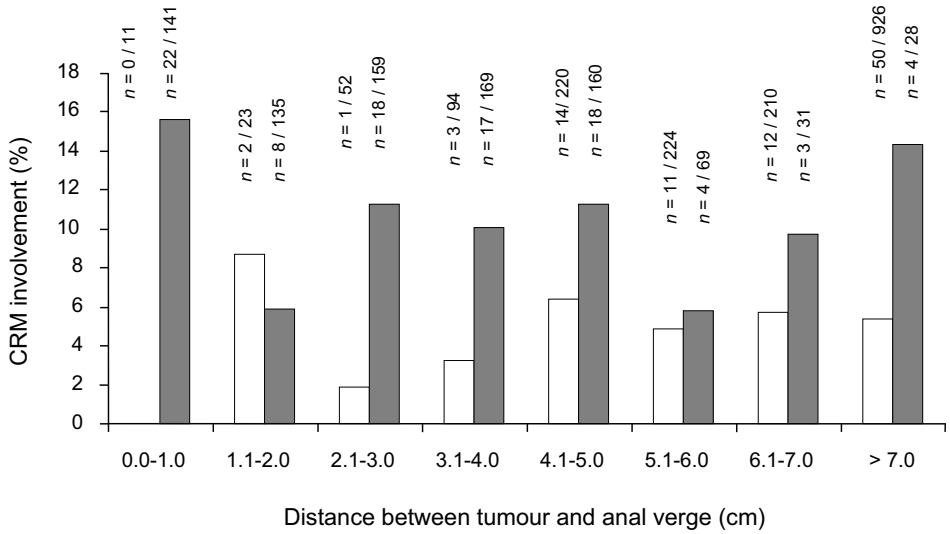

Figure 1. CRM involvement in relation to distance of the tumour to the anal verge, shown separately for patients treated with an abdominoperineal resection (grey bar) and low anterior resection, including Hartmann's procedure (white bar).

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

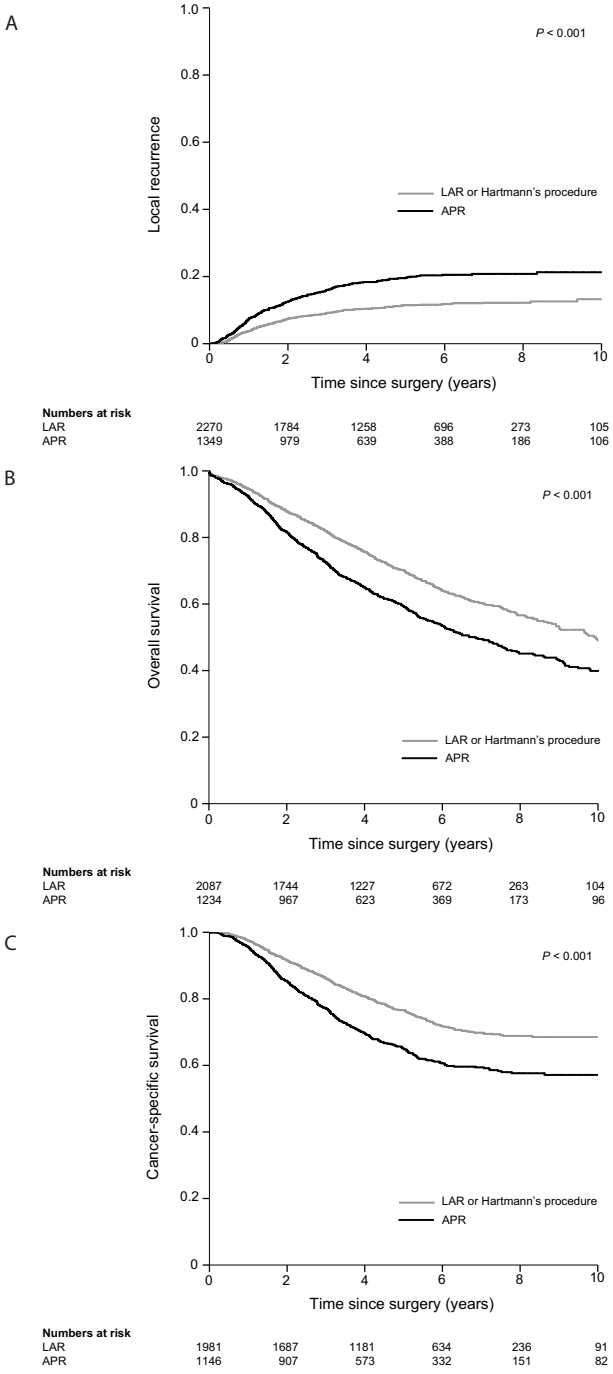

Figure 2. Local recurrence (A), overall survival (B), and cancer-specific survival (C) shown as cumulative incidence (A), Kaplan-Meier survival (B), and one minus cumulative incidence (C) curves separately for patients treated with a LAR (including Hartmann's procedure) and an APR.

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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