Quality assurance in rectal cancer treatment

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Chapter 9

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

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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.

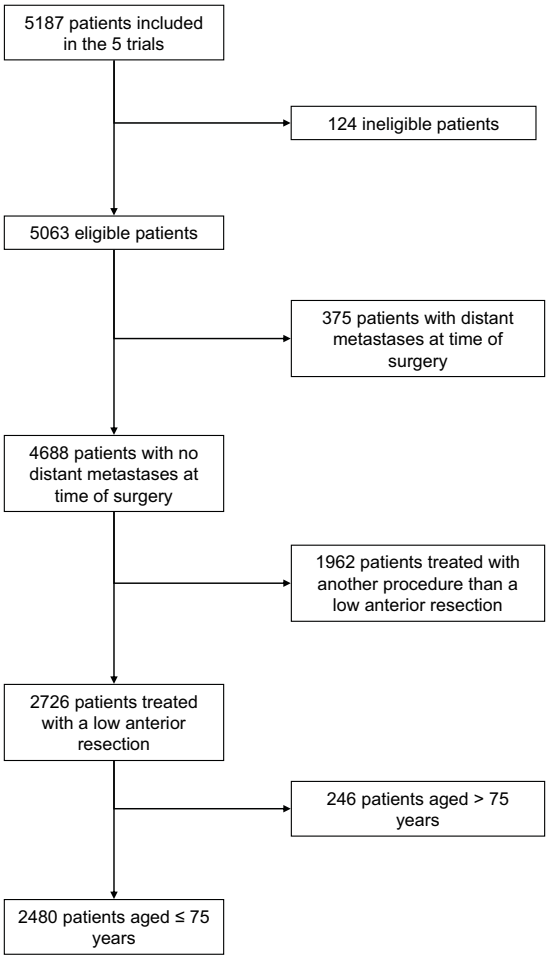


Figure 1. Flow diagram of selected and excluded patients.

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 ($P < 0.001$).

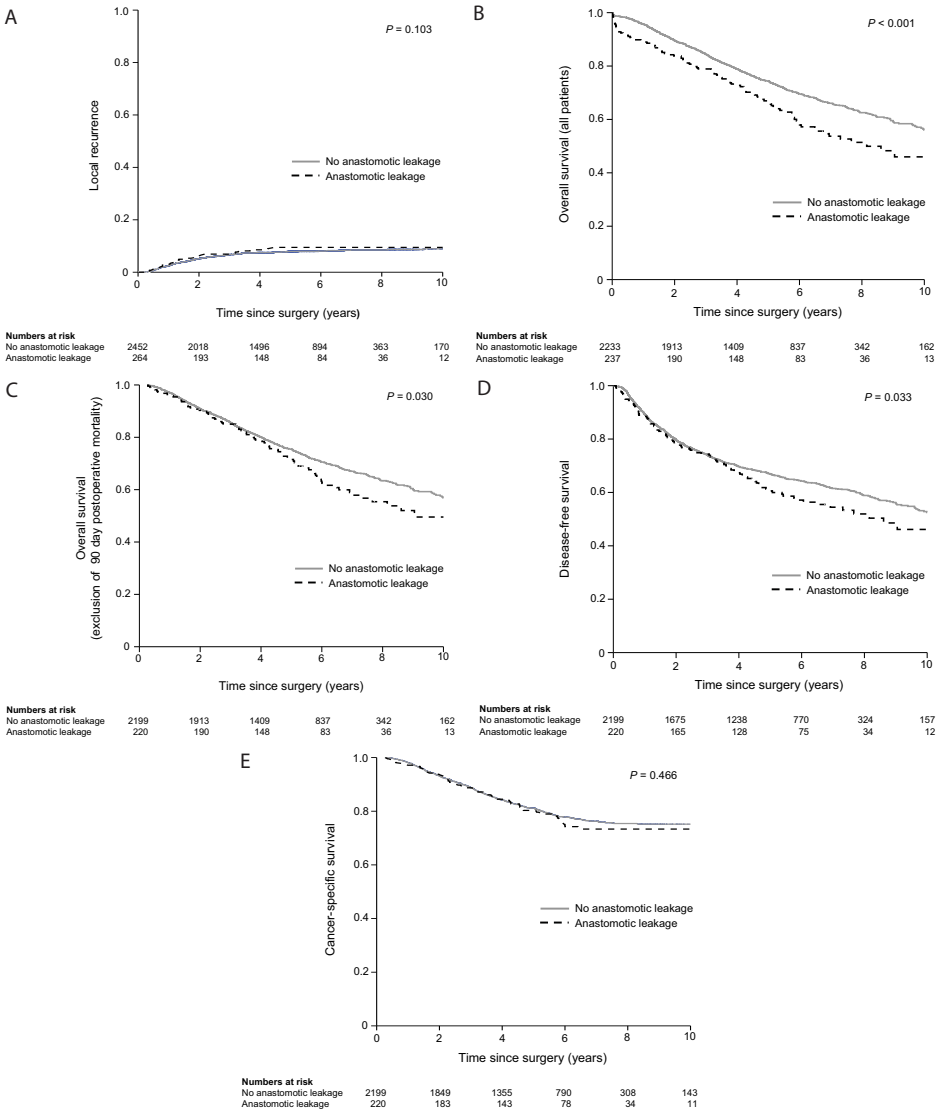
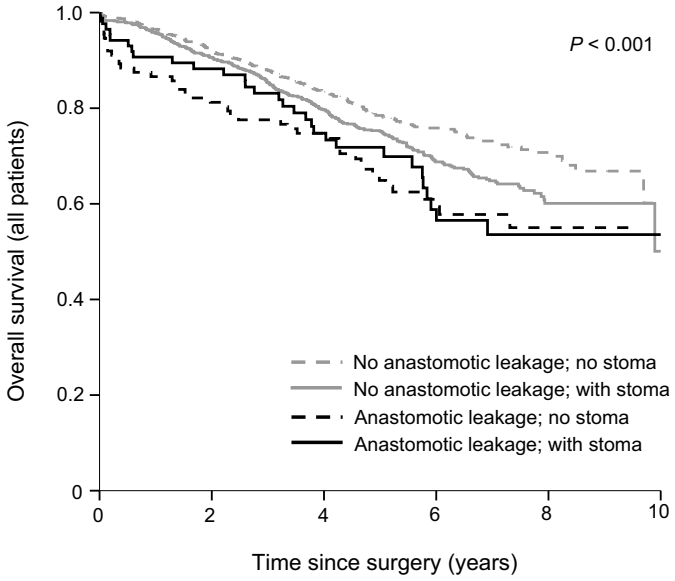


Figure 2. Local recurrence (A), overall survival for all patients (B) and after exclusion of patients with 90-day postoperative mortality (C), disease-free survival (D), and cancer-specific survival (E) shown as cumulative incidence (A), Kaplan-Meier survival (B, C, D), and one minus cumulative incidence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

Anastomotic leakage and disease-free and cancer-specific survival

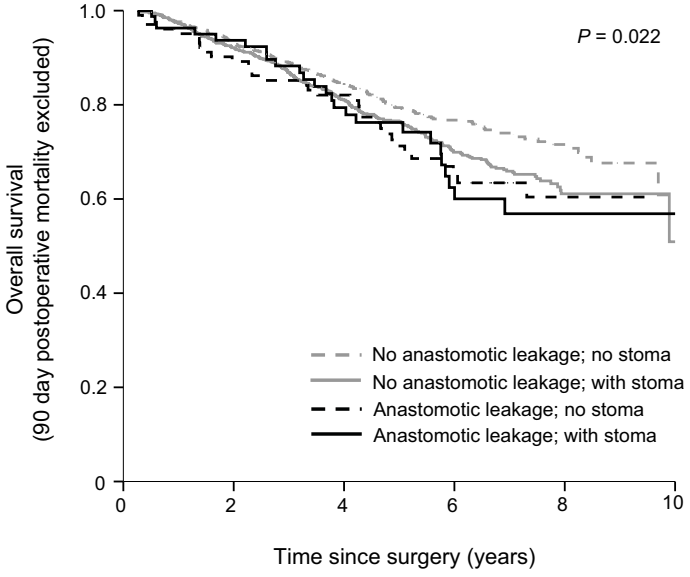
Anastomotic leakage was associated with a worse DFS rate: HR 1.26 (95% CI 1.02-1.56; $P = 0.033$) in the univariate analysis and HR 1.24 (95% CI 1.01-1.56; $P = 0.040$) when adjusted for gender, age, and TNM stage. The disease-free survival curve is shown in Figure 2D. The 5-year disease-free survival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