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ORIGINAL ARTICLE

Neoadjuvant chemoradiotherapy for rectal carcinoma: effects on anastomotic leak rate and postoperative bladder dysfunction after non-emergency sphincter-preserving anterior rectal resection

Results of the quality assurance in rectal cancer surgery multicenter observational trial

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Abstract
Introduction Randomized trials have demonstrated a reduction in local recurrence rate in rectal cancer patients treated with preoperative chemoradiotherapy and total mesorectal excision (TME) compared to patients undergoing TME alone. Accordingly, preoperative chemoradiotherapy in all UICC stages II and III rectal cancers has been recommended in the German treatment guidelines as of 2004. However, this policy has been questioned in recent years, partly due to concern regarding an increase in postoperative complications through preoperative therapy. Studies on this issue are sparse; most have been conducted in specialized centers, included relatively few patients, and yielded partly contradicting results. It was the aim of our analysis to investigate the influence of preoperative chemoradiotherapy on anastomotic leak rate and postoperative bladder dysfunction in rectal cancer patients using a representative data set from the Quality Assurance in Rectal Cancer Surgery multicenter observational trial.
Method This is a retrospective analysis of data from the Quality Assurance in Rectal Cancer Surgery prospective multicenter observational trial. Data of all patients undergoing curatively intended sphincter-preserving resection for UICC stage I through III rectal carcinoma between 01 Jan 2005 and 31 Dec 2007 with or without preoperative chemoradiotherapy (groups A and B, respectively) were included. Multivariate statistical analysis using propensity score analysis was carried out regarding outcome parameters total anastomotic leak rate, rate of anastomotic leaks requiring reoperation, and postoperative bladder dysfunction.
Results A total of 2,085 patients were included (group A, n=676, group B, n=1,409). Significant differences were present between groups regarding age, sex, distance of the tumor from the anal verge, pT-stage, UICC stage, hepatic risk factors, and use of protective enterostomy by univariate analysis. Multivariate logistic regression including these parameters was used to calculate the propensity score (likelihood to be assigned to group A or B as a consequence of the individual profile of these factors) for each patient. When outcome parameters were compared between groups A and B after stratification for propensity score, no significant differences regarding postoperative bladder dysfunction (p=0.12), total anastomotic leak rate (p=0.56), and anastomotic leaks requiring reoperation (p=0.56) could be demonstrated.
Conclusion Neoadjuvant chemoradiotherapy for rectal carcinoma does not increase the risk for anastomotic leakage

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or postoperative bladder dysfunction after curatively intended sphincter-preserving rectal resection.

Keywords Rectal cancer · Preoperative chemoradiotherapy · Short-term postoperative outcome · Anastomotic leakage · Bladder dysfunction

Introduction

Total mesorectal excision (TME) in rectal cancer surgery has lead to a massive reduction in local recurrence rate. Several randomized-controlled trials have shown that preoperative radiotherapy (RT) or chemoradiotherapy (CRT) is capable of further reducing local recurrences after TME, leading to its use being recommended by the German rectal cancer guidelines for all UICC stages II and III rectal cancers [1–9]. However, preoperative (chemo)radiotherapy does not improve overall survival after TME surgery [6, 7] and may constitute a significant overtreatment for many patients [10, 11]. Furthermore, concern has been raised about its possible long-term toxicities. Long-term follow-up of surviving individuals from the Stockholm-I- and Stockholm-II-trials has demonstrated a significantly elevated rate of fecal or urinary incontinence, sexual function disorders, and secondary cancers in the patients receiving radiotherapy [12–15]. As a consequence, the use of preoperative therapy in all stages II and III rectal cancer patients has been questioned in recent years.

As for the influence of preoperative therapy on perioperative parameters (e.g., operating time, intraoperative blood loss) or early postoperative morbidity (especially anastomotic leak rate) existing studies are equivocal. While intraoperative and postoperative complications were not significantly different in both arms of the German CAO/ARO/AIO-94-study [7], early postoperative morbidity was moderately elevated in the patients receiving preoperative hypofractioned (5×5 Gy) radiotherapy in the Dutch rectal cancer trial. However, this was predominantly due to an elevated number of perineal wound complications after abdomino-perineal excision while preoperative radiation had no influence on the anastomotic leak rate after anterior resection [16]. Apart from these two multicenter RCTs, most studies dealing with the influence of preoperative therapy on anastomotic leak rate after rectal cancer surgery have been single-center trials including relatively few patients (n=39 through 425) [17–28]. Preoperative RT or CRT was not related to anastomotic leak rate in some of these trials while it was an independent risk factor for anastomotic leakage in others. Moreover, the influence of preoperative RT or CRT on postoperative bladder function and sexual function disorders is under debate. These functional problems are closely related to the preservation of the autonomic pelvic nerves [29, 30]. Ideally, TME surgery produces a specimen with an undamaged mesorectum while fully preserving the surrounding structures; however, this can only be achieved if the correct plane of dissection is precisely maintained. If this rule is observed, TME leads to a lesser degree of sexual function impairment in men compared to conventional rectal cancer surgery [31]. Data on the relationship between preoperative RT/CRT and postoperative autonomic pelvic nerve function are extraordinarily sparse; however, some studies have demonstrated additional impairment of sexual function in men receiving preoperative radiation plus TME compared to TME alone [32, 33]. It is unclear if this effect is a direct consequence of radiation, a result of compromised tolerance of the irradiated nerves to ischemia, or due to the higher level of difficulty of surgical dissection in irradiated tissue [32].

Due to the small number and contradictory results of the existing studies, the relationship between preoperative RT/CRT and early postoperative morbidity after TME surgery is not clear at the moment. When addressing this issue, anastomotic leakage, being the most severe surgical complication in rectal cancer surgery, is of particular interest. Also, the rate of postoperative bladder function impairment deserves special attention since it is a simple and reproducible parameter indicating autonomic pelvic nerve dysfunction. Using a representative data set from the Quality Assurance in Rectal Cancer Surgery observational trial which includes patients from more than 300 hospitals of all levels of care throughout Germany, it was the aim of the present study to investigate the effect of preoperative chemoradiotherapy on these two parameters in routine clinical care.

Methods

Study design

We retrospectively reviewed data from the Quality Assurance in Rectal Cancer Surgery multicenter observational trial. Since January 1st, 2005, this trial has been collecting epidemiologic and treatment-related parameters as well as data on the early postoperative course of rectal cancer patients from more than 300 hospitals of all levels of care throughout Germany. Data were collected by the institutions involved in patient care using a standardized questionnaire. Written informed consent was obtained from all patients whose data were collected.

Inclusion/exclusion criteria for retrospective data analysis

All UICC stages I through III rectal cancer patients documented in the Quality Assurance trial database undergoing non-emergency sphincter-preserving TME surgery between

01 Jan 2005 and 31 Dec 2007 whose cancers were located at maximum 12 cm from the anal verge were included in the present retrospective data analysis. Patients with metastatic disease (UICC stage IV), patients undergoing emergency surgery, local tumor excision without anastomosis, abdominoperineal resection, or reconstruction using a colon pouch were excluded. Also, patients undergoing preoperative short-course radiotherapy (5×5 Gy) were excluded.

Anastomotic leaks were divided into leaks treated conservatively and leaks requiring reoperation. Postoperative bladder dysfunction was documented for patients not capable of normal bladder emptying (i.e., those requiring a transurethral or suprapubic catheter) after hospital discharge. Data on the long-term bladder function are not documented in the Quality Assurance trial database and thus could not be analyzed.

For analysis, three categories were formed for each of the continuous variables age (years, <65/65–80/>80), body mass index (kg/m², <20/20–30/>30), and tumor location from the anal verge (cm, <4/4–8/8–12).

Data analysis

Patients were divided into two groups (group A, preoperative chemoradiotherapy (50.4 Gy/5-FU based chemotherapy) plus TME surgery 6 weeks later; group B, TME surgery without preoperative therapy). Since patients were not randomly assigned to either treatment group due to the retrospective nature of the analysis, propensity score analysis (PSA) [34] was used to determine the influence of preoperative CRT independently of patient- or treatment-related parameters age, sex, ASA score, cardiovascular, pulmonary, renal, and hepatic risk factors, body mass index, histopathologically determined T-stage (pT-stage), UICC-stage, use of protective enterostomy, intraoperative urethral lesion, and tumor location from the anal verge. Distribution of these variables in groups A and B was analyzed using χ^2 test. Variables that were not equally distributed between groups were entered into a logistic regression analysis in order to calculate the propensity score (defined as the probability to be assigned to group A or B as a result of the individual profile of patient- and treatment-related parameters) for each patient. Patients were then stratified according to propensity score, yielding propensity score quintiles with a comparable profile of the aforementioned parameters within each quintile. Analysis of predefined outcome parameters (anastomotic leak—conservatively treated, anastomotic leak—requiring reoperation, and postoperative bladder dysfunction) in groups A and B was then carried out within each quintile.

Statistical analysis was done using the SAS 9.2 software package (SAS Institute Inc., 100 SAS Campus Drive, Cary, NC 27513-2414, USA). A two-sided p value <0.05 was considered significant.

Results

A total of 2,085 patients were included in the analysis (group A, 676 patients (32.4%), group B, 1,409 patients (67.6%)). Patient- and treatment-related baseline characteristics in groups A and B are shown in Table 1. χ^2 test yielded significant differences between groups for the following parameters: age, sex, cardiovascular risk factors, hepatic risk factors, tumor location from the anal verge, UICC stage, pT stage, and use of protective enterostomy. These parameters were entered into a logistic regression model. After logistic regression none of the parameters could be removed from the model, i.e., significant differences between groups A and B were present for each of these parameters independently.

Eighty-seven cases (4.2%) of postoperative bladder dysfunction were recorded; 263 patients (12.6%) developed anastomotic leakage; 141 of these (6.8%) required reoperation (Table 2). Univariate analysis demonstrated a significant increase in postoperative bladder dysfunction in the patients undergoing preoperative CRT compared to the patients undergoing surgery only (5.5% vs. 3.5%, respectively; p=0.046). Anastomotic leak rate was not significantly different between groups A and B by univariate analysis (12.4% and 12.7%, respectively; p=0.888).

Fourteen cases had to be excluded from further analysis due to incomplete data records. Thus propensity scores could be calculated for 2,071 patients. Patients were then stratified into quintiles according to their individual propensity scores (Table 3). Within each quintile none of the baseline parameters entered into the model was significantly different between groups A and B, demonstrating an equal distribution of all potential confounding variables between treatment groups within each quintile.

Outcome parameters postoperative bladder dysfunction, total anastomotic leak rate and rate of anastomotic leaks requiring reoperation in both treatment groups are shown in Table 4. Analysis of outcome parameters after propensity score stratification yielded no significant differences between treatment groups A and B (bladder dysfunction: p=0.13; total anastomotic leak rate: p=0.56; rate of anastomotic leaks requiring reoperation: p=0.56).

Discussion

It is still under debate if preoperative RT or CRT increases perioperative morbidity with sphincter-preserving TME surgery in rectal cancer patients. Being the most severe of surgical complications, anastomotic leakage is of particular interest in this context. Existing studies dealing with this issue are predominantly single-center trials from highly specialized institutions including relatively few patients. Moreover, their

Table 1 Baseline characteristics according to treatment group (A vs. B)

	Missing cases (*n*)		Group A—*n*=676		Group B—*n*=1,409		*p* (χ^2 test)
			n	% of total group A	*n*	% of total group B	
Age group	0	<65 years	306	45.3	413	29.3	<0.001
		65–80 years	353	52.2	830	58.9	
		>85 years	17	2.5	166	11.8	
Sex	0	Male	443	65.5	759	53.9	<0.001
		Female	233	34.5	650	46.1	
ASA status	0	1	72	10.7	125	8.9	0.062
		2	395	58.4	769	54.6	
		3	203	30.0	495	35.1	
		4	6	0.9	20	1.4	
Cardiovascular risk factors	0	No	306	45.3	490	34.8	<0.001
		Yes	370	54.7	919	65.2	
Pulmonary risk factors	0	No	613	90.7	1,256	89.1	0.318
		Yes	63	9.3	153	10.9	
Renal risk factors	0	No	646	95.6	1,327	94.2	0.213
		Yes	30	4.4	82	5.8	
Hepatic risk factors	0	No	670	99.1	1,378	97.8	0.034
		Yes	6	0.9	31	2.2	
Body mass index	86	<20	31	4.8	45	3.3	0.255
		20–30	506	78.8	1,088	80.2	
		>30	105	16.4	224	16.5	
Tumor localization (distance from anal verge)	0	<4 cm	19	2.8	13	0.9	<0.001
		4–8 cm	323	47.8	402	28.5	
		8–12 cm	334	49.4	994	70.5	
UICC stage	0	I	248	36.7	581	41.2	<0.001
		II	226	33.4	357	25.3	
		III	202	29.9	471	33.4	
pT stage	8	1	57	8.5	223	15.9	<0.001
		2	237	35.3	490	34.9	
		3	360	53.6	661	47.0	
		4	18	2.7	31	2.2	
Intraoperative urethral lesion	0	No	675	99.9	1,408	99.9	0.543
		Yes	1	0.1	1	0.1	
Use of protective enterostomy	6	No	137	20.3	564	40.2	<0.001
		Yes	538	79.7	840	59.8	

Table 2 Distribution of outcome parameters according to treatment group (A vs. B) by univariate analysis

		Group A—*n*=676		Group B—*n*=1,409		*p* (χ^2 test)
		n	% of total group A	*n*	% of total group B	
Postoperative bladder dysfunction	No	639	94.5	1,359	96.5	
	Yes	37	5.5	50	3.5	0.046
Anastomotic leakage—Total	No	592	87.6	1,230	87.3	
	Yes	84	12.4	179	12.7	0.888
Anastomotic leakage—requiring reoperation	No	639	94.5	1,303	92.5	0.083
	Yes	37	5.5	106	7.5	

Table 3 Distribution of patients according to propensity score quintile

Propensity score quintile	Group A		Group B		All patients	
	n	% of total group A	*n*	% of total group A	*n*	% of total all patients
1	44	6.56	370	26.43	414	19.99
2	86	12.82	329	23.50	415	20.04
3	128	19.08	283	20.21	411	19.84
4	172	25.63	249	17.79	421	20.33
5	241	35.92	169	12.07	410	19.80
Total	671	100.00	1,400	100.00	2,071	100.00

results are varied and sometimes contradictory. Akiyoshi et al. [17] report moderately increased intraoperative blood loss in 20 patients receiving neoadjuvant RCT in a cohort of 125 patients undergoing laparoscopically assisted TME surgery; however, postoperative morbidity including anastomotic leak rate was not increased in the preoperative RCT patients. Similar results were reported by Rosati et al. [19] who retrospectively compared 20 patients receiving RCT before TME surgery with 39 individuals undergoing TME alone. Several risk factors for postoperative anastomotic leakage were identified by Valenti et al. [21] and Martel et al. [25] in their studies of 273 (170 receiving preoperative RCT) and 220 (54 receiving preoperative RCT) patients, respectively. These included comorbidity, extended operating time, low anastomosis, tobacco smoking, and technically "difficult" anastomosis; however, preoperative RCT was not associated with an elevated risk for anastomotic leakage. In contrast, anastomotic leaks occurred twice as frequently in patients receiving neoadjuvant therapy compared to patients undergoing TME surgery alone in the study by Buie et al. [22]. Moreover, preoperative RCT was identified as the sole idependent predictive risk factor for anastomotic leakage or pelvic abscess in this trial. Matthiessen et al. [35] also reported preoperative radiation to be idependently associated with anastomotic leakage after rectal resection. In two trials by Horisberger et al. [18] and Lyall et al. [20], a significant correlation between the degree of histopathologically confirmed tumor regression after neoadjuvant therapy and anastomotic leak rate was demonstrated. In a meta-analysis of 14 randomized-controlled trials comparing 2,264 patients undergoing resection alone with 2,246 patients receiving preoperative radiation [5] postoperative morbidity (mainly sepsis and anastomotic leakage) was significantly increased in the patients irradiated preoperatively; however, some of the trials included were published more than 30 years ago. Very few studies exist as to the issue of sexual and bladder function disorders after preoperative radio- or chemoradiotherapy and TME surgery; however, some studies suggest that preoperative therapy might indeed cause some degree of additional damage to the pelvic autonomic nerves compared to TME surgery alone [32, 33]. In addition to the unresolved question of the influence on immediate postoperative morbidity, studies have demonstrated an increased rate of secondary cancers [12], intestinal passage disorders [36], and anorectal functional disorders [15] in patients receiving preoperative RT or CRT. Since an extended follow-up period is required for studies on late postoperative morbidity, most of these studies report data recorded more than 10 years (sometimes as many as 30 years) ago. Since radiation technique has greatly evolved in recent years, results of these trials may not be applicable to present-day practice. When modern radiation techniques are used, late toxicity of

Table 4 Comparison of outcome parameters after stratification for propensity score

Propensity score quintile	Bladder dysfunction		Anastomotic leak—total		Anastomotic leak—requiring reoperation	
	Group A (*n* (%))	Group B (*n* (%))	Group A (*n* (%))	Group B (*n* (%))	Group A (*n* (%))	Group B (*n* (%))
1	3 (6.82)	11 (2.97)	3 (6.82)	40 (10.81)	3 (6.82)	32 (8.65)
2	4 (4.65)	9 (2.74)	11 (12.79)	52 (15.81)	9 (10.47)	31 (9.42)
3	7 (5.47)	10 (3.53)	17 (13.28)	34 (12.01)	9 (7.03)	19 (6.71)
4	6 (3.49)	11 (4.42)	22 (12.79)	30 (12.05	10 (5.81)	13 (5.22)
5	3 (6.82)	32 (8.65)	31 (12.86)	22 (13.02)	6 (2.49)	11 (6.51)
	p=0.13		p=0.56		p=0.56	

neoadjuvant RT or CRT in rectal cancer appears to be low [36, 37].

Current practice in rectal cancer therapy includes neoadjuvant therapy in all UICC stage II or higher patients; however, this recommendation has been questioned and a more selective use of preoperative radiation has been advocated in recent years [10, 11]. Indeed, none of the randomized-controlled rectal cancer trials has been able to demonstrate a survival benefit in patients undergoing neoadjuvant therapy compared to TME surgery alone. Moreover, preoperative diagnostic overstaging frequently occurs and may result in overtreatment in a significant proportion of patients. In the German CAO/ARO/AIO-94 trial [7] almost 20% of patients preoperatively diagnosed to be UICC stage II or III and randomized into the postoperative RCT treatment arm actually had UICC stage I tumors on histopathological examination. If neoadjuvant therapy was proven to increase perioperative morbidity this would constitute another powerful argument in favor of its more selective use in contrast to current practice. However, our study clearly demonstrates that this does not seem to be the case for the most severe of postoperative complications (anastomotic leakage) and for damage to the pelvic autonomic nerves as indicated by postoperative bladder dysfunction. The anastomotic leak rate was not found to be significantly different between groups A and B at univariate analysis nor at analysis after propensity score stratification. Bladder function disorders were marginally more frequent in the patients undergoing preoperative CRT ($p=0.046$); after stratification for propensity scores, however, this difference could no longer be demonstrated. Based on a cohort of more than 2,000 patients, our analysis is the largest of all studies investigating these issues. Included patients were treated in more than 300 institutions of all levels of care throughout Germany which guarantees a precise image of routine clinical care conditions. This also resulted in the observed total anastomotic leak rate of 12.6% (Table 2) which is substantially higher than the rates reported in specialized single-center trials but still lies in the expected range for routine care in non-specialized institutions [38].

There are a number of limitations to our study that need to be considered. Firstly, it is a general problem of retrospective data analyses that patients are not randomly assigned to the groups studied. Assignment to the treatment modalities studied in our analysis (neoadjuvant RCT plus TME surgery vs. TME surgery alone) was decided upon by the treating physician based on individual patient- and tumor-related factors that could in turn have, by themselves, influenced the outcome parameters. Moreover, the decision to use specific measures of treatment in the course of therapy (e.g. protective enterostomy) was also not made randomly. PSA is a statistical tool that is used to create a pseudo-randomized assignment to the groups studied in non-randomized observational trials. The propensity score for a given individual is defined as that individual's likelihood to be assigned to either treatment group as a result of his or her profile of predefined confounding variables [34]. Comparison between treatment groups is then done between individuals with a similar propensity score. In our study, no significant difference was found for any of the predefined confounding variables within each propensity score quintile. This demonstrates that PSA worked well for our patient cohort and results are valid independently of the confounders tested.

Definition of the outcome parameters "anastomotic leak" and "anastomotic leak requiring reoperation" is another relevant issue. The questionnaire used for documentation in the quality assurance study does not contain any data on diagnostics used to verify if anastomotic leak was present nor on the reasons leading to reoperation. It can be assumed, though, that anastomotic leaks in this trial were mostly clinically apparent leaks that were secondarily confirmed by imaging studies or endoscopy since patients were treated under routine clinical conditions and inclusion into the observational quality assurance study had no influence on treatment decisions. Through the inclusion of a large patient cohort from a wide spectrum of healthcare institutions a systematic error due to specific institutional procedures in diagnostics and treatment can be excluded. Furthermore, the observed total anastomotic leak rate of 12.6% lies in the range of what is expected in multicenter observational studies.

Finally, postoperative bladder dysfunction was used as a surrogate for postoperative dysfunction of the autonomic pelvic nerves since it is an easily reproducible parameter that was documented for all patients included in the quality assurance trial. Studies have shown that avoidance of postoperative bladder dysfunction is closely related to intraoperative identification and preservation of the pelvic autonomic nerves [30]. However, it is important to know that disorders of sexual function which is also dependent on pelvic nerve function may occur postoperatively even in patients with an unimpaired bladder function [32]. Thus, normal postoperative bladder function does not necessarily exclude damage to the pelvic autonomic nerves. However, it was not possible to include sexual function in our retrospective analysis since no such data are recorded in the observational quality assurance trial.

Conclusion

Data of the Quality Assurance in Rectal Cancer Surgery multicenter observational trial provide a valid image of treatment for rectal carcinoma in Germany under routine clinical conditions. Data of more than 2,000 patients

presented in our retrospective analysis do not support an increase in anastomotic leak rate or postoperative bladder dysfunction through preoperative chemoradiotherapy with sphincter-preserving TME surgery. Thus, limiting the use of preoperative radiochemotherapy in order to avoid these complications does not seem justified. Nonetheless, preoperative radiochemotherapy may have influenced parameters that were not included in our analysis (e.g., sexual function disorders, intestinal passage disorders, secondary cancer development). Therefore, avoidance of significant overtreatment is still desirable. Using an MRI-based indication for preoperative RT or CRT use depending on the distance between the tumor and the mesorectal fascia as suggested by Junginger et al. and Ulrich et al. [10, 11, 39] may be a reasonable approach; however, this requires standardized high-resolution MR imaging and needs to be further evaluated.

Conflicts of interest None.

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