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Original Research

The minimum distal resection margin in rectal cancer surgery and its impact on local recurrence - A retrospective cohort analysis

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ABSTRACT

Aim: The distal resection margin (DRM) plays a pivotal role in rectal cancer surgery. Colorectal surgeons are often torn between keeping an oncologically safe margin versus aiming at sphincter preserving surgery. This study was performed to assess the oncological safety of a minimal DRM of < 1 cm.

Methods: From a prospectively maintained database for rectal cancer 405 patients were identified. Out of 405 patients 88 patients were eligible for the study characterized by UICC tumor stage of II or III, cancer less than 12 cm from the anal verge and a complete course of preoperative chemoradiotherapy (CRT) before undergoing low anterior rectal resection between 2004 and 2012. Preoperative staging included rigid rectoscopy, endorectal ultrasound as well as pelvic MRI. Primary endpoints were overall survival (OS) and local recurrence-free survival (LRFS).

Results: The incidence of local recurrence was 5.7% (n = 5). In DRM < 1 cm (n = 33) local recurrence was seen in two patients (6.1%) and with DRM ≥ 1 cm (n = 55) in three patients (5.5%). The 5-year OS rate was 94.5% (93.2% DRM < 1 cm, 95.7% DRM ≥1 cm; P = 0.642). 5-year LRFS was 93.2% in DRM < 1 cm and 95.7% in DRM ≥1 cm (P = 0.936).

Conclusion: R0 resection of stage II and II rectal cancer of the mid and lower third after preoperative CRT yields excellent results even with DRM < 1 cm. Minimizing the distal resection margin may allow surgeons to offer sphincter sparing surgery without compromising local recurrence-free and overall survival in individual patients.

1. Introduction

The introduction of total mesorectal excision (TME) in rectal cancer surgery has led to a dramatic decrease in local recurrence of the disease [1]. The tumor distance from the intact mesorectal fascia has been defined as the critical circumferential resection margin (CRM) with prognostic significance for local recurrence-free survival [2]. The distal resection margin (DRM) is defined as the distance of the lowest intramural or mesorectal cancer spread and the distal dissection line of the specimen. Therefore, DRM is of major importance for the decision if sphincter preserving low rectal cancer surgery is feasible [3]. In the pre-TME era a DRM of at least 5 cm was mandatory. For that reason almost all patients with rectal cancer near the rectal sphincter had to undergo abdominal perineal resection [4,5]. Over the last decade the distal resection margin has been challenged in an effort to perform more sphincter-preserving surgery. With introduction of the TME surgery and preoperative chemoradiotherapy (CRT) the 5 cm-rule has been abandoned and a DRM of 2 cm was found to be oncological sufficient [6]. A non-inferior oncological outcome of a DRM of less than 1 cm has been described in patients receiving preoperative CRT for low rectal cancer [7]. In patients not receiving preoperative CRT a DRM of at least 2 cm seemed to be advisable [8,9] in the past. New data of single center experiences reported [7,10,11] a tumor free resection margin of less than 1 cm to be adequate to achieve excellent oncological results. The concept of a minimal distal resection margin is of increasing relevance for patients with partial or complete tumor regression after preoperative therapy aiming for sphincter saving rectal surgery.

Modern imaging techniques using high-resolution magnetic resonance imaging (MRI) of the rectum enable precise assessment of the CRM and extramural vascular invasion (EMVI). Both parameters have been found predictive for local recurrence and distant metastasis [12]. However, the assessment of the DRM remains still a challenge with significant variation on imaging techniques even for experienced radiologists [13,14]. Even more since histopathological studies on rectal cancers revealed intramural and extramural spread of cancer cells distal to the gross tumor mass [15]. Preoperative CRT induces regression in most rectal cancers and even complete tumor regression in 10%–30% of cases. However rectal cancer regression in response to CRT follows a

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scattered fashion, bearing the potential risk of small cancer deposits distant from the primary rectal cancer location even after good clinical response to CRT [16,17].

The presented study focuses on whether minimal tumor-free DRM in the intraoperative specimen justifies sphincter saving surgery for rectal cancer. We examined data of patients who were treated between 2004 and 2012. We enrolled patients with rectal cancer UICC stages II and III located no further than 12 cm from the anal verge who had received preoperative CRT prior to low anterior rectal resection.

2. Methods

2.1. Patient selection

We retrospectively analysed a cohort of consecutively treated patients with locally advanced rectal cancer (UICC stage II and III). These patients had all received preoperative chemoradiotherapy (CRT) prior to low anterior rectal resection at our tertiary referral center for colorectal surgery.

Clinical data of patients who underwent surgery for rectal cancer were collected in a prospective database of the tertiary referral center. The period between 2004 and 2012 was analysed retrospectively to ensure a minimal follow up period of five years regarding the incidence of local disease recurrence and overall survival. Patients who underwent abdominal perineal excisions and all patients with synchronous distant metastasis (UICC stage IV) were excluded from the study as well as patients with chronic inflammatory bowel disease or familial cancer syndromes (FAP, HNPCC). 88 of 405 consecutive patients with rectal cancer and surgery fulfilled these criteria. These 88 patients had all received curative R-0 TME surgery following preoperative CRT of the mid and lower third of the rectum (Fig. 1).

Our rectal cancer database provided information regarding primary tumor stage, CRT, surgical procedures as well as surgical outcome and oncological follow-up. Overall survival data were matched with the local tumor registry.

2.2. Patient work up

All patients underwent a standardized clinical examination and staging procedure before any therapeutic intervention. Primary diagnosis of rectal cancer was histologically confirmed in all patients. The initial tumor stage and tumor location were assessed by rigid rectoscopy, endorectal ultrasonography (ERUS) and/or magnetic resonance imaging (MRI) of the rectum. The macroscopic distal tumor margin was measured from the anal verge by rigid rectoscopy. Computertomography (CT) of thorax and abdomen were performed to rule out distant metastasis. Tumor response to preoperative CRT was evaluated clinically by rigid rectoscopy and ERUS once again prior to surgery. MRI of the rectum was not routinely performed after CRT in all patients.

Preoperative CRT consisted of a median radiation dose of 50.4Gy and concurrent fluoropyrimidine-based chemotherapy [18].

Surgical procedures included (low) anterior resections of the rectum with TME with and without diversion by loop ileostomy (AR or LAR ± stoma). Abdominoperineal resection (APR) as well as local transanal excisions (TAE) were excluded from the study. All surgical procedures have been performed by or under supervision of senior colorectal surgeons to ensure consistency and quality of the procedures.

Pathologic assessment of tissue specimens was performed according to the guidelines of the German pathologists. The tissue specimens were first judged macroscopically. The specimens were opened anteriorly and pinned on a corkboard to assess the distal resection margin (DRM) of the unfixed fresh specimen. The DRM was defined as the distance between the lower verge of the primary rectal tumor to the resection margin of the bowel specimen. Subsequently the gross tumor area was entirely embedded, and serial sectioned for hematoxylin and eosin (H&E) staining and microscopic evaluation. The mesorectum was manually dissected and lymph nodes were examined microscopically after embedding. Pathological complete response to preoperative CRT was defined as absence of any viable tumor cells in the surgical specimen (ypT0ypN0).

2.3. Statistical analysis

Categorical variables were summarized as counts and percentages and compared with the use of Fisher's exact test. Overall survival (OS) and local recurrence-free survival (LRFS) were calculated by the Kaplan-Meier method. SPSS software 21.0 (IBM, USA) was used for statistical analysis. The level of significance was set at $P < 0.05$.

2.4. Ethical approval and study registration

The study has been approved by local institutional review board and has been registered within the clinical trial registry.

2.5. Manuscript preparation

The work has been reported in line with the STROCSS criteria [19].

3. Results

3.1. Study population

A total of 405 patients with histologically proven rectal cancer were enrolled into our database between 2004 and 2012 (Fig. 1).

200 patients had primary rectal cancer and the UICC stage II or III. 27 patients had rectal cancer of the upper third (more than 12 cm from the anal verge), leaving 173 patients for further analysis. To avoid confounders, we only enrolled patients who had received preoperative CRT and complete tumor resection (R0) after LAR. Applying these restrictive criteria, 88 patients with metric details on the distal resection margin were analysed (Fig. 1).

Patient characteristics are depicted in Table 1. The study population consisted of 68 (77.3%) male and 20 (22.7%) female patients aged between 25 and 83 years (mean 60.0 years).

3.2. Preoperative chemoradiotherapy (CRT)

Preoperative CRT consisted of a median radiation dose of 50.4 Gy (range 37.8–50.4Gy) and concurrent fluoropyrimidine based chemotherapy (intravenous fluorouracil or oral capecitabine). Eight (9.1%) patients received a combination of fluoropyrimidine based chemotherapy and oxaliplatin (Table 1).

3.3. Surgery

Surgery was performed 7 weeks (range 3–13 weeks) after completion of CRT. Surgical procedures and perioperative morbidity are summarized in Table 1.

Prior to surgery tumor response to preoperative CRT was clinically assessed by digital examination, rigid rectoscopy and ERUS and MRI. All patients underwent TME surgery: 85 (96.5%) patients received a low anterior resection (LAR) with colorectal or coloanal anastomosis. In 81 (92%) patients diversion of the anastomosis was performed by means of a loop ileostomy. The remaining three (3.4%) patients underwent LAR with terminal colostomy and closure of the blind anal/rectal stump due to sphincter insufficiency and faecal incontinence before surgery.

3.4. Postoperative morbidity and mortality

Anastomotic leakage occurred in nine (10.5%) out of 85 patients

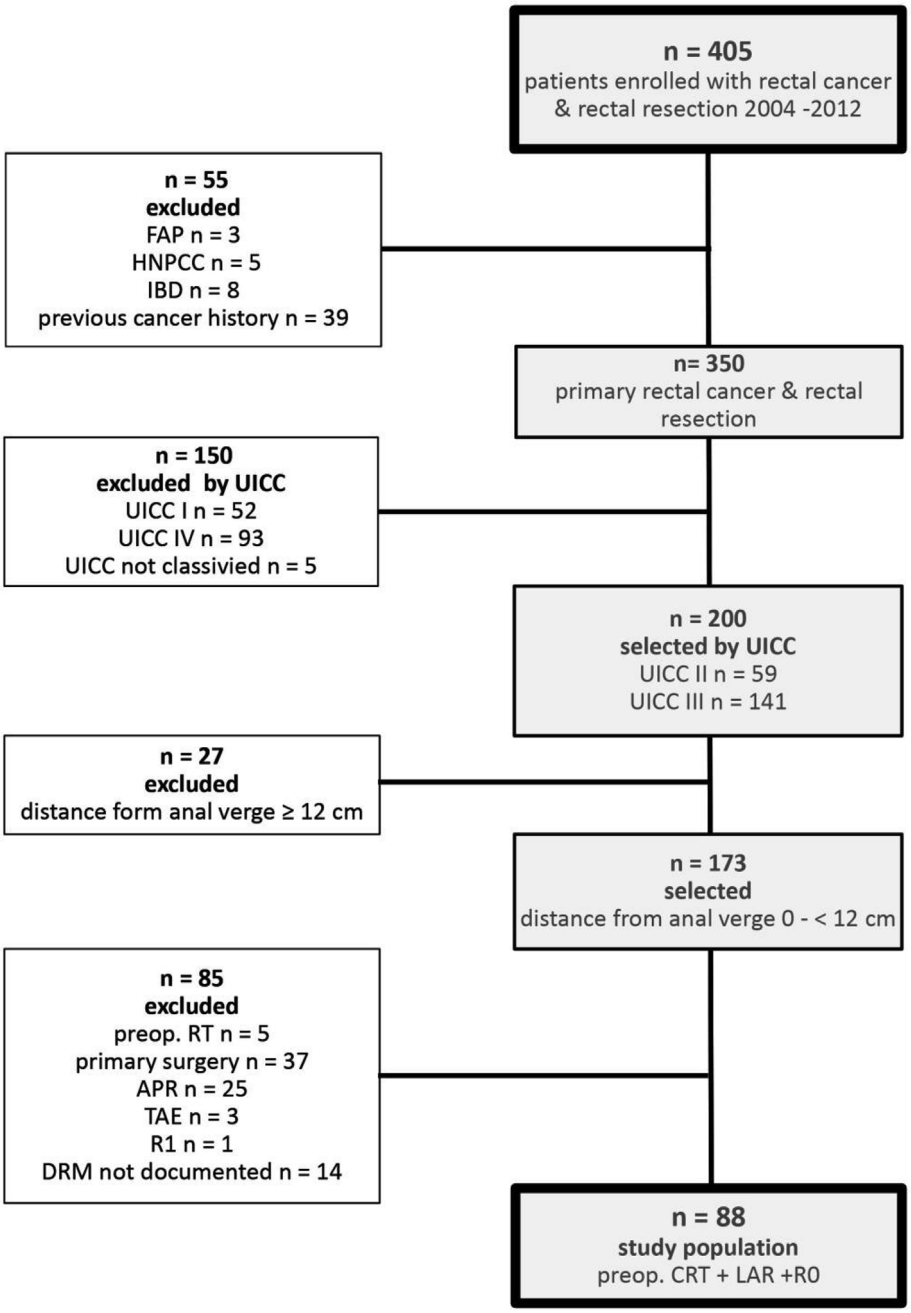


Fig. 1. Patient selection.

who received coloanal or colorectal anastomosis. Six (66.6%) grade B anastomotic leaks were definitively treated using transanal lavage and endosponge therapy. Three (33.3%) anastomotic leaks were grade C [20]. These patients required surgical revision. One of the patients required secondary Hartmann-procedure.

TME-surgery was prone to minor adverse events: Wound infections developed in 26 (29.5%) patients. Perioperative bladder dysfunction that required placement of a Foley catheter or suprapubic urinary catheter occurred in twelve (13.6%) cases. Bladder function recovered and urinary catheters were removed in all cases before discharge or during short follow-up. None of the patients died within the first thirty days after surgery (Table 1).

3.5. Tumor characteristics

31 (35.2%) tumors were located within the lower third (0–6 cm) and 57 (64.8%) tumors within the mid third (> 6–12 cm) of the rectum. Initial staging diagnostics by ERUS and MRI revealed 21 (23.8%) clinical UICC stage II cases and 67 (76.2%) clinical UICC stage III cases. The majority of the tumors were advanced. Thus, 77 patients had cT3 (87.5%) and 4 patients had cT4 tumors (4.5%). Lymph node metastases (cN+) were described in 65 (73.8%) cases at first clinical assessment (Table 2).

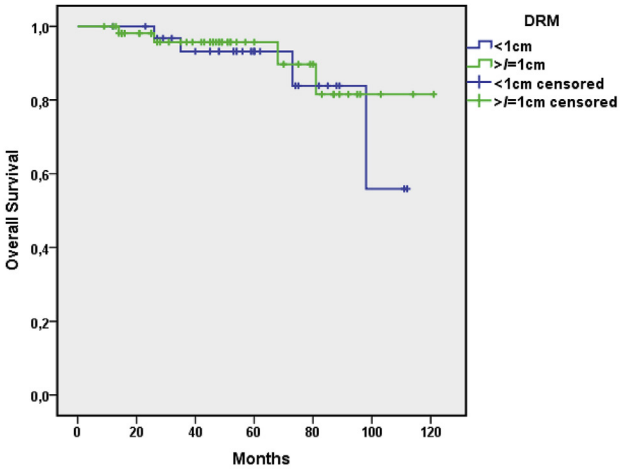
The pathological assessment of the resected specimens revealed significant effects of preoperative CRT on initial tumor stages. Neither vital tumor cells within the rectal wall nor lymph node metastasis were found in 9 patients representing a pathological complete response rate of 10.2% in this selected cohort of rectal cancer patients. Down-staging was observed in the remaining patients. After final pathological assessment 38 (43.2%) were classified stage I, 20 (22.7%) stage II and 21 (23.8%) stage III. In comparison to the pre-therapeutic clinical tumor stage, there was reduction of approximately 50% in pT3 (n = 31,

Table 1
Study population.

	DRM < 1 cm	DRM ≥ 1 cm	total
Patients [n]	33	55	88
Distal resection margin (DRM) [cm]			
Median	0.5	2.0	1.15
Range	0.04–0.9	1.0–12.0	0.04–12.0
Tumor distance from anal verge [n (%)]			
0–6 cm	19 (57.6)	12 (21.8)	31 (35.2%)
> 6–12 cm	14 (42.4)	43 (78.2)	57 (64.8%)
Age [years]			
Mean	62	59.25	60.0
Range	33–78	25–83	25–82
Sex [n (%)]			
Male/Female	28/5 (84.8/15.2)	40/15 (72.7/27.3)	68/20 (77.3/22.7)
Preoperative Radiation [Gy]			
Median	50.4	50.4	50.4
Range	37.8–50.4	39.0–50.4	37.8–50.4
Chemotherapy [n (%)]			
5-FU	30 (90.9)	50 (90.0)	80 (90.9)
5-FU + Oxaliplatin	3 (9.1)	5 (10.0)	8 (9.1)
Interval between CRT and surgery [weeks]			
Median	7	7	7
Range	3–11	3–13	3–13
Surgical procedure [n (%)]			
Low anterior resection (LAR)	33 (100)	52 (94.5)	85 (96.6)
Hartmann procedure	0	3 (5.5)	3 (3.4)
Postoperative Complications [n (%)]			
Mortality within 30 days	0	0	0
Anastomotic leakage (LAR only)	4 (12.1)	5 (9.6)	9 (10.2)
Urinary retention	2 (6.1)	10 (18.2)	12 (13.6)
Wound infection	9 (27.3)	17 (30.9)	26 (29.5)

35.2%) and pT4 (n = 2; 2.3%) disease in response to preoperative CRT. The pathological assessment of the lymph node status was negative in the majority of the patients (pN0, n = 67, 76.1%) (Table 2).

All resection margins were tumor-free (R0, 100%). A subgroup analysis was performed by dividing patients into a DRM < 1 cm (n = 33, 37.5%) and DRM ≥1 cm (n = 55, 62.5%) group. Population-based and tumor-specific characteristics of both groups are depicted in Table 1 and Table 2. There was no significant difference regarding age, sex and ASA score (data not shown). DRM < 1 cm was more frequently associated with lower third rectal cancers (57.6% vs 21.8%). On initial clinical assessment, UICC stage III cancers were more often found in patients with DRM ≥1 cm (n = 44, 80%) compared to patients with DRM < 1 cm (n = 23, 69.7%).



DRM		Months						
		0	12	24	36	48	60	70
<1cm	Events	0	0	0	2	2	2	2
	Remaining cases	33	33	31	26	23	14	10
≥1cm	Events	0	0	1	2	2	2	3
	Remaining cases	55	53	44	36	25	16	14

DRM	N	5y-OS	Cumulative events	Remaining cases
<1cm	33	93.2	2	11
≥1cm	55	95.7	2	16

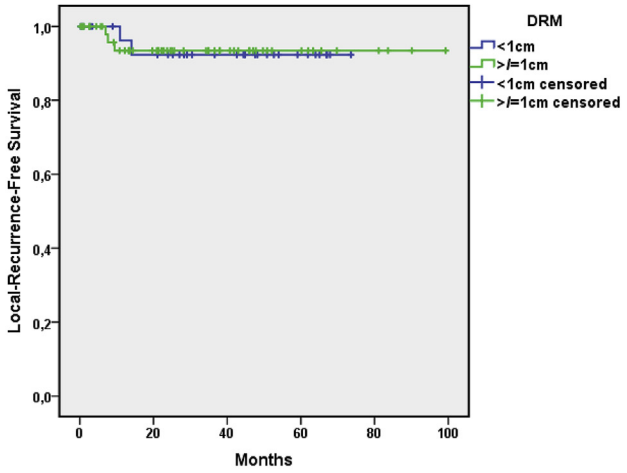
Log-Rank p = 0.642

Fig. 2. Overall survival.

The final pathological report described lower overall tumor stages in the DRM < 1 cm group. There were significantly more pT2 tumors in the DRM < 1 cm group compared to the DRM ≥1 cm group (60.6% vs. 27.3%, P = 0.038). Accordingly, there was a significantly reduced number of pT3 rectal cancers in the DRM < 1 cm group compared to DRM ≥1 cm group (24% vs. 41.8%, P = 0.038). Incidences of lymph node metastases however were not significantly different in both groups.

Table 2
Tumor characteristics.

	Clinical staging				Pathological staging			
DRM	**total**	**< 1 cm**	**≥ 1 cm**	**P**	**total**	**< 1 cm**	**≥ 1 cm**	**P**
UICC Stage [n (%)]								
No carcinoma	–	–	–	0.308	9 (10.2)	2 (6.1)	7 (12.7)	0.526
I	–	–	–		38 (43.2)	17 (51.5)	21 (38.2)	
II	21 (23.8)	10 (30.3)	11 (20.0)		20 (22.7)	6 (18.2)	14 (25.5)	
III	67 (76.2)	23 (69.7)	44 (80.0)		21 (23.8)	8 (24.2)	13 (23.6)	
T-stage [n (%)]								
0	–	–	–	0.103	9 (10.2)	2 (6.1)	7 (12.7)	0.038
1	0	0	0		11 (12.5)	3 (9.1)	8 (14.5)	
2	7 (8.0)	1 (3.0)	6 (10.9)		35 (39.7)	20 (60.6)	15 (27.3)	
3	77 (87.5)	32 (97.0)	45 (81.8)		31 (35.2)	8 (24.2)	23 (41.8)	
4	4 (4.5)	0 (0)	4 (7.3)		2 (2.3)	0 (0)	2 (3.6)	
N-stage [n (%)]								
0	20 (22.7)	8 (24.2)	12 (21.8)	0.953	67 (76.1)	25 (75.8)	42 (76.4)	0.872
1	56 (63.6)	20 (60.6)	36 (65.5)		12 (13.6)	4 (12.1)	8 (14.5)	
2	9 (10.2)	4 (12.1)	5 (9.1)		9 (10.2)	4 (12.1)	5 (9.1)	
x	3 (3.4)	1 (3.0)	2 (3.6)		–	–	–	



DRM		Months						
		0	12	24	36	48	60	70
<1cm	Events	0	1	2	2	2	2	2
	Remaining cases	33	25	22	17	12	7	1
≥1cm	Events	0	3	3	3	3	3	3
	Remaining cases	55	41	32	25	12	9	4

DRM	N	5y-LRFS	Cumulative events	Remaining cases
<1cm	33	92.3%	2	7
≥1cm	55	93.4%	3	8

Log-Rank p = 0.936

Fig. 3. Local recurrence-free survival.

3.6. Local recurrence rate and overall survival

The incidence of local rectal cancer recurrence was 5.7% (n = 5) during the complete study period. DRM did not affect the incidence of local recurrence. Local recurrence rates were 6.1% (n = 2) for DRM < 1 cm and 5.5% (n = 3) for DRM ≥1 cm (Fig. 2).

Survival analysis of the study cohort demonstrated a 94.5% overall survival (OS) after 5-years. The median 5-year OS were comparable for DRM < 1 cm with 93.2% and DRM ≥1 cm with 95.7% (Fig. 3).

The local-recurrence-free survival (LRFS) was similar for both groups: 5-year Local recurrence-free survival was 92.3% for DRM < 1 cm and 93.4% for DRM ≥1 cm (Fig. 2). In both study groups local recurrences occurred only in tumors with an advanced ypT-stage (DRM < 1 cm: n = 2, ypT2, ypT3; DRM ≥1 cm: n = 3, ypT3).

No correlation was detected between the onset of distant metastasis and lymph node status within our study population. Tumor response to preoperative CRT did not predict risk for distant metastasis, either.

4. Discussion

The presented single center retrospective database analysis of low rectal cancer (UICC stage II and III) provides additional evidence that a DRM of less than 1 cm is not associated with an increased risk of local tumor recurrence. All patients in this analysis received preoperative CRT and TME surgery.

Our study cohort includes 88 patients who were divided into two groups depending on the DRM of < 1 cm (n = 33) and DRM ≥1 cm (n = 55). The incidence for local recurrence was 6.7% in patients with a DRM < 1 cm and 5.5% in patients with a DRM ≥1 cm.

Current recommendations regarding DRM are based on retrospective studies. In the early 1950s, a distal resection margin of not less than 5 cm below the palpable rectal tumor mass was recommended for state of the art rectal cancer resection [5,21]. In 1983 Pollett et al. [3] advocated that a DRM of < 2 cm is sufficient to achieve low rates of local rectal cancer recurrence. This statement was supported by the results of Madsen et al. [22], who demonstrated that distal intramural spread of the primary cancer was not observed beyond 1.5 cm. Therefore, the authors concluded curative resection can be achieved with a DRM of 1.5 cm.

The introduction of TME by Heald et al. [23] had a significant impact on the incidence of local recurrence and the definition of a safe DRM. In fact, precise TME surgery reduces the overall risk for local recurrence by about 50% compared to surgery using less radical techniques [1]. Karanjia et al. [24] analysed 152 early curative TME resections of rectal cancers located within the lower two thirds of the rectum. During the 10-year follow-up, 42 patients with a DRM of less than 1 cm had a local recurrence rate of 0%. However, rectal cancer recurred in 3.6% of the remaining 110 patients with a DRM of more than 1 cm. The authors concluded that sphincter preserving TME with a minimal cancer free resection margin is a viable option to preserve quality of life without compromising patients' survival prospects.

Multimodal oncologic treatment concepts like radiotherapy (RT) and chemoradiotherapy (CRT) further improved local control of rectal cancer. It is well accepted that preoperative 5-FU based CRT reduces the risk for local recurrence of locally advanced rectal cancer [25]. However, the incidence of distant metastasis and overall patient survival remain unaffected [25].

It is assumed that preoperative CRT may increase the rate of sphincter saving rectal cancer surgery due to shrinkage and regression of the primary tumor. However, this hypothesis has not been proven yet. Generally, extent of rectal cancer surgery is still based on the initial measured distance between the distal edge of the rectal cancer and the upper edge of the rectal sphincter before initiation of CRT. Only in cases of complete or near-complete tumor regression which is associated with a preferable oncological outcome can alternative surgical strategies be discussed [26–28]. Retrospective studies described a significantly higher risk for local recurrence of locally advanced ypT3/4 rectal cancer not responsive to CRT [29]. Postoperative CRT has been advocated for patients without preoperative CRT, poorly differentiated rectal cancer and a DRM of less than 1 cm [30]. However, uncertainty remains because rectal cancer shows scattered regression pattern in response to CRT with islands of viable tumor cells distant to the main tumor mass or residual scar [16,17]. Furthermore, no association has been found between the DRM and the incidence of local recurrences and overall survival [31,32].

The attempt to define the narrowest sufficient DRM in rectal cancer was the focus of many studies. In several of these studies, the enrolled study population was not well defined.

Kiran et al. [33] analysed 784 patients with mid and lower third rectal cancer receiving preoperative CRT or primary surgery. They found a 5-year local recurrence (LR) rate of 4.4% for patients with DRM ≤1 cm compared to 4.3% for a DRM > 1 cm. The risk for LR increased with further reduction of the DRM. Thus, a DRM ≤5 mm was associated with a 5-year LR of 6.4% compared to 4.1% for a DRM > 5 mm. The smaller DRM was correlated with more frequent hand-sewn anastomosis and less advanced tumor stages. Kiran et al. concluded that a DRM of < 1 cm might not compromise oncological outcome. In agreement with these results, Rutkowski et al. [32] evaluated the safety of a 5 mm DRM in 412 rectal cancer patients. In this study, 63% of patients received preoperative radiotherapy. The risk for local cancer recurrence was only slightly increased with a DRM of ≤5 mm (5.4%) compared to a DRM of > 5 mm (4.1%). But again, there were less locally advanced tumors within the first group.

Larger DRMs have been advocated patients without preoperative CRT who receive sphincter-saving rectal cancer surgery. Data of the Norwegian Rectal Cancer Register [30] provide insight into a large series of locally advanced rectal cancers treated by low anterior rectal

resection without preoperative CRT. These data reveal an increased risk for local recurrence by a factor of 2.2, if DRM was < 1 cm. The study results of Lim et al. corroborate these data of the Norwegian register [10]. They analysed an Asian population of 320 primary rectal cancer patients who received primary surgery without preoperative CRT. A DRM < 1 cm was associated with an increasing risk for local recurrence. Furthermore, a DRM < 1 cm was associated with a higher risk of a positive CRM in this study.

The presented study has several shortcomings. The presented study design is retrospective and not randomized. Due to very strict inclusion criteria, the study is statistically underpowered for a valid statistical analysis. Nevertheless, the presentation of 88 consecutive patients with a well-defined cancer stages and treatment algorithm provides valuable data. Furthermore, prospective randomized studies to clarify this question are not feasible due to the delicate randomization between sphincter saving rectal cancer surgery and abdominal perineal resection.

Finally, our study lacks pathological assessment of CRM and the quality assessment of mesorectal fascia preparation. These were routinely documented at our institution not until 2011. Therefore, we were not able to analyse these risk factors in our study cohort.

5. Conclusion

Preoperative CRT decreases the likelihood for distal cancer spread and lymph node metastasis. TME surgery preserving the rectal sphincter with a minimal DRM of < 1 cm seems to be acceptable in respect of local recurrence-free survival and overall survival in low rectal cancer. However, the minimum DRM should be based on individual patient and tumor characteristics. One has to consider initial tumor stage, response to preoperative CRT, tumor differentiation and last but not least the quality of rectal sphincter function. Larger prospective clinical trials will clarify the significance of these individual patient and tumor characteristics. High-quality TME with R0-resection is the essential goal in rectal cancer surgery.

Ethical approval

The study was approved by the Ethics Committee of the University of Freiburg (Vote No. 217/16, “Clinical registry for patients with primary and recurrent rectal cancer”).

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Author contribution

PM and OT wrote the manuscript, designed the research and analyzed the data.

JT and PM collected and analyzed the data.

HN and SFF contributed substantially by critical revision. The manuscript has been approved by all authors.

Conflicts of interest

The authors have no conflict of interest to declare. None of the authors received financial support or had any institutional or other relationships that might lead to bias.

Research registration unique identifying number (UIN)

DRKS (German Clinical Trial Register), DRKS00015005.

https://www.drks.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS00015005.

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Research registry

German Clinical Trial Register: DRKS00015005, http://apps.who.int/trialsearch.

Data statement

Due to local IRB regulation raw data have to remain confidential and would not be shared.

Provenance and peer review

Not commissioned, externally peer-reviewed.

CRediT authorship contribution statement

Philipp Manegold: Writing - original draft, Formal analysis. **Johannes Taukert:** Formal analysis. **Hannes Neeff:** Writing - review & editing. **Stefan Fichtner-Feigl:** Writing - review & editing. **Oliver Thomusch:** Writing - original draft.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijsu.2019.07.029.

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