

Oncologic results in rectal cancer patients with a subcentimeter distal margin after laparoscopic-assisted sphincter-preserving surgery by stratified analysis

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Research article

Keywords: Rectal cancer, Sphincter-preserving surgery, Distal resection margin, Local recurrence, Overall survival

Posted Date: May 15th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-26917/v1>

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Abstract

Background

Distal resection margin (DRM) is closely associated with sphincter-preserving surgery and oncologic safety for patients with mid-low rectal cancers. However, the optimal DRM has not been determined. The purpose of this study to assess the impact of a DRM of ≤ 1 cm on oncologic safety.

Methods

Data of 378 patients who underwent laparoscopic-assisted sphincter-preserving surgery from 2009 to 2015 were retrospectively analyzed. Patients were divided into two groups based on DRM: ≤ 1 cm ($n = 74$) and > 1 cm ($n = 304$). Stratified analysis was performed according to neoadjuvant chemoradiotherapy.

Results

On the whole, no significant differences in 5-year disease-free survival (DFS) (92.8 vs. 81.3%; $P = 0.128$) and 5-year overall survival (OS) (83.7 vs. 82.2%; $p = 0.892$) were observed in patients with DRMs of ≤ 1 and > 1 cm, respectively. A total of 44 patients received preoperative chemoradiotherapy. In this cohort, the 5-year local recurrence (LR) rates ($p = 0.118$) and the 5-year DFS rates ($p = 0.298$) were not significantly different between the two groups. A total of 334 patients received surgery without neoadjuvant chemoradiotherapy. There were also no significant differences in the 5-year LR rates ($p = 0.150$) and 5-year DFS rates ($p = 0.172$) between the two groups.

Conclusions

No matter whether patients with rectal cancers received neoadjuvant therapy or not, sphincter-preserving surgery with a DRM ≤ 1 cm may be acceptable in low rectal cancer without jeopardizing oncologic safety.

Background

Circumferential resection margin (CRM) and distal resection margin (DRM) are strongly associated with LR and distant metastasis[1, 2]. The positive distal margins are associated with worse oncologic results and chemoradiotherapy cannot compensate them[3, 4]. Therefore, a DRM of at least 5 cm was suggested for patients with locally advanced rectal cancers in the past[5, 6]. In this case, almost all patients with mid-low rectal cancers had to receive abdominal perineal resection (APR) with a permanent sigmoid colostomy. However, with the advent of total mesorectal excision (TME) surgery[7], neoadjuvant chemoradiotherapy (NCRT)[8–10] and advances in laparoscopic surgery[11], the 5 cm-principle has been

gradually abandoned, and the shorter DRM was found to be oncologically adequate [12, 13]. Therefore, more patients with low-lying rectal cancers are increasingly offered sphincter-preserving resection.

However, the optimal DRM is still controversial in sphincter-saving surgery. Several studies showed that a DRM of less than 1 cm did not jeopardize the long-term survival and local recurrence of rectal cancer patients [13–15]. Nevertheless, Akihiro Kondo et al. revealed that a DRM of 2 cm was required (1 cm was insufficient) for patients with low-lying rectal cancer even if they were offered NCRT [16]. So, the optimal DRM and its oncological implications during sphincter-preserving surgery for rectal carcinoma patients with or without NCRT need further investigation. In addition, most previous studies on this issue did not perform stratified analyses based on NCRT and were limited by small sample size.

The purpose of the present study was to evaluate the impact of a DRM \leq 1 cm on long-term oncologic outcomes after sphincter-sparing resection for patients with mid-low rectal cancers by stratified analysis based on NCRT.

Methods

Patients

Clinicopathological data of 378 patients with rectal cancers who were treated by laparoscopy-assisted anterior resection with standard total mesorectal excision (TME) were collected from January 2009 through December 2015. Patients with a history of other malignant tumors, distant metastasis, emergency surgery, palliative surgery, Hartmann procedure, abdominoperineal resection, or a pathologically-proven positive circumferential resection margin (CRM) or DRM were excluded. Patients treated with and without NCRT were analyzed separately.

Neoadjuvant Chemoradiotherapy And Surgical Procedure

NCRT was recommended for participants with cT3 or T4 tumor and/or lymph nodes metastasis. However, not all eligible patients received neoadjuvant therapy due to various reasons. Three-dimensional conformal intensity-modulated radiotherapy was used. Neoadjuvant chemoradiotherapy protocol comprised a total irradiation dose of 50.4 Gy, delivered in 2-Gy fractions, 5 days per week for 5 weeks. Concurrent chemotherapy consisted of continuous infusion of 5-fluorouracil and leucovorin or oral capecitabine. Surgery occurred at least 6–8 weeks after completion of long-course preoperative radiotherapy.

Laparoscopy-assisted low anterior resection was performed by experienced surgeons. The TME principle was followed for patients with mid-low rectal lesions, and a partial mesorectal excision was conducted for patients with upper rectal tumors. 5 cm distal margin was recommended for upper rectal cancer, 1–2 cm for mid-low rectal tumor. For lesions close to the anorectal junction, a microscopically negative DRM was acceptable. The DRM of the fresh resected specimen was inspected by the surgeon. If it was

suspiciously positive or microscopically involved at a frozen-section examination, an additional part of the distal rectum was removed, or abdominoperineal resection (APR) was adopted. Digestive tract reconstruction was performed using double stapled anastomosis or hand-sewn. Whether to perform preventive ileostomy is determined by the surgeon based on the intraoperative situation.

Histopathology

All resected specimens were inspected by surgeons firstly and then sent to pathologists for further examination. The DRM was measured following the microscopic examination of the formalin-fixed specimen. It was defined as the closest distance from the lowest border of the lesion (or the scar tissue after NCRT) to the distal mucosal resection margin. The doughnut was examined microscopically, but not included in this measurement.

Adjuvant Therapy And Follow-up

Single-agent capecitabine was given to stage \geq patients with unfavorable prognostic factors. CAPOX (capecitabine plus oxaliplatin) was used to patients with positive lymph nodes. Traditionally, patients were followed-up every 3 months for the first two years after operation, every 6 months for the next 3 years, and every year thereafter. Examinations included physical examinations, carcinoembryonic antigen (CEA), X-ray/CT of chest, CT/ultrasonography of abdomen and pelvis, and endoscopy, but the adoption of each modality was at the discretion of physicians. PET/CT or bone scan was conducted when appropriate. Survival details were obtained from the follow-up office in our hospital or directly from patients or relatives by telephone or WeChat.

Definition Of Recurrence

Local recurrence (LR), including anastomotic and pelvic lymph nodes recurrence, was defined as any clinically or histopathologically confirmed carcinoma recurrence within the pelvis after primary operation. Local recurrence rate was regarded as the sum of all local recurrences, regardless of distant metastases. Distant metastasis is defined as the metastasis of cancer cells to distant organs (e.g., lung, liver, bone) or lymph nodes via lymphatic or blood pathways following primary surgery. The rates of distant metastases were regarded as the sum of metastases regardless of local recurrence.

Statistical analysis

Categorical variables are presented as frequencies and percentages. Continuous variables are described as mean (s.d.) values. The Student's *t*-test and χ^2 test and Mann-Whitney U test were used to analyze continuous and categorical variables, respectively. The Kaplan-Meier method with the log-rank test was

used for survival analysis. P -value ≤ 0.05 was considered statistically significant. All analyses were carried out with SPSS version 23.0 (SPSS, Inc., Chicago, IL, USA).

Results

Clinicopathological characteristics of patients with mid-low rectal cancer

Detailed clinicopathological data of the 378 rectal cancer patients who underwent anterior resection are shown in Table 1. In the present study, 74 cases with a DRM ≤ 1 cm were compared to 304 cases with a DRM > 1 cm. The mean DRM length was 0.8 ± 0.3 cm in the DRM ≤ 1 cm group and 2.6 ± 1.0 cm in the DRM > 1 cm group. The mean distance from the anal verge in the DRM ≤ 1 cm group was significantly different from that in the DRM > 1 cm group (8.3 ± 3.3 vs. 9.3 ± 2.8 cm, $p = 0.017$). The groups were comparable in gender, age, preoperative CRT, tumor differentiation, and lymphovascular invasion. There were more patients with pT1/T2 in the DRM ≤ 1 cm group (48.7 vs. 21.0%; $p < 0.001$), as well as more TNM p-stage ≥ 3 (62.2 vs. 53.9%, $p < 0.001$), respectively. There was a large proportion of the perineural invasion in the DRM ≤ 1 cm group compared with the DRM > 1 cm group (8.1 vs. 5.3%; $p = 0.037$). Preoperative chemoradiotherapy was administered to 16.2% (12/74) of the patients with a DRM ≤ 1 cm and 10.5% (32/304) of the patients with a DRM > 1 cm, respectively ($p = 0.171$).

Table 1
Features of the patients in the different subgroups.

Variables	DRM ≤ 1 cm (n = 74)	DRM > 1 cm (n = 304)	<i>p</i>
Distal margin (cm), median (mean ± sd)	0.8 ± 0.3	2.6 ± 1.0	
Age (mean ± sd)	63 ± 10.9	60 ± 10.3	0.055
Sex			
Male	40	166	0.932
Female	34	138	
Median distance from tumor to anal verge (mean ± sd)	8.3 ± 3.3	9.3 ± 2.8	0.017
Pathologic T stage			< 0.001
T1	12	18	
T2	24	46	
T3	36	188	
T4	2	52	
TNM stage			< 0.001
I	28	50	
II	18	114	
III	28	140	
Preoperative CRT			0.171
Yes	12	32	
No	62	272	
Tumor differentiation			0.745
Well	4	20	
Moderately	56	242	
Poorly	12	36	
Uncertainly	2	6	

Data are given as number of patients with percentage. DRM, distal resection margin; CRT, chemoradiotherapy.

Variables	DRM ≤ 1 cm (n = 74)	DRM > 1 cm (n = 304)	<i>p</i>
Perineural invasion, n (%)	4(5.4)	16 (5.3)	0.037
Lymphovascular invasion, n (%)	8 (10.8)	44 (14.5)	0.412
Data are given as number of patients with percentage. DRM, distal resection margin; CRT, chemoradiotherapy.			

Oncologic results in relation to the different distal margins regardless of NCRT

The median follow-up period was 78 months (range, 3–126 months) in patients with a DRM ≤ 1 cm and 70 months (range, 8–132 months) in patients with a DRM > 1 cm ($p = 0.646$, Table 2). During follow-up, 5 out of 74 (6.8%) patients with a DRM ≤ 1 cm developed local recurrence, and 18 out of 304 (5.9%) patients with a DRM > 1 cm had local recurrence ($p = 0.920$). The distant metastasis rate was similar between the two groups (8.1 vs. 13.2%, $p = 0.183$).

Table 2
Oncologic results in relation to the different distal margins.

Variable	DRM ≤ 1 cm (n = 74)	DRM > 1 cm (n = 304)	<i>p</i>
Median follow-up, mo (range)	78 (3–126)	70 (8–132)	0.646
local recurrence (%)	5/74 (6.8)	18/304 (5.9)	0.920
Metastasis (%)	6/74 (8.1)	40/304 (13.2)	0.183
5-y DFS (%)	92.8	81.3	0.128
5-y OS (%)	83.7	82.2	0.892
Data are given as number of patients with recurrence / total number of patients. DRM, distal resection margin; DFS, disease-free survival; OS, overall survival.			

The patterns of local recurrence and distant metastasis in the two groups are presented in Table 3. With regard to local recurrence, pelvic lymph nodes recurrence was more common than anastomotic recurrence in both groups. As for distant metastasis, the lung was the most common metastatic organ in two groups. Four patients had lung metastases, 2 patients had simultaneous lung and liver metastases, and another patient had paraaortic lymph nodes relapse in the DRM ≤ 1 cm group. Similarly, there were 16 lung metastases, 12 liver metastases, 8 simultaneous lung and liver metastases, 2 paraaortic lymph nodes relapse, and 2 ovary metastases in the DRM > 1 cm group.

Table 3
Patterns of local recurrence and distant metastasis in the subgroups.

Recurrence sites	DRM ≤ 1 cm (n = 74)	DRM > 1 cm (n = 304)
LR, n (%)		
Anastomotic	2 (2.7)	6 (2.0)
Pelvic LN	3 (4.1)	12 (3.9)
DM, n (%)		
Liver	0 (0.0)	12 (3.9)
Lung	4 (5.4)	16 (5.3)
Liver and lung	2 (2.7)	8 (2.6)
Paraaortic lymph nodes	1 (1.4)	2 (0.7)
Ovary	0 (0.0)	2 (0.7)
LR, Local recurrence; LN, lymph node; DM, Distant metastasis; DRM, distal resection margin.		

The 5-year disease-free survival (DFS) rate was 92.8% in patients with a DRM ≤ 1 cm group and 81.3% in patients with a DRM > 1 cm group ($p = 0.128$). No significant differences were observed between groups. The overall survival (OS) rate at 5 years was 83.7% in the DRM ≤ 1 cm group and 82.2% in the DRM > 1 cm group ($p = 0.892$, Fig. 1).

Subgroup analysis of overall survival stratified by DRM and the use of NCRT

Considering the influence of NCRT on the distance of tumor invasion, we analyzed the effect of DRM on overall survival of rectal cancer patients according to whether preoperative chemoradiotherapy was adopted.

A total of 44 patients received preoperative chemoradiotherapy. In this cohort, the 5-year local recurrence rates were similar between the DRM ≤ 1 cm group and the DRM > 1 cm group (8.3 vs. 1.9%, $p = 0.118$). The estimated 5-year DFS rate was not significantly different between the two groups (83.3 vs. 68.8%, $p = 0.298$, Table 4 and Fig. 2).

Table 4
Kaplan-Meier estimates of 5-y LR and 5-y DFS stratified by DRM and NCRT.

	Variable	Group (n)	No. of events (%)	<i>p</i> (Log-rank)
NCRT (n = 44)	LR	DRM ≤ 1 cm (12)	1 (8.3)	0.118
		DRM > 1 cm (32)	6 (1.9)	
	DFS	DRM ≤ 1 cm (12)	10 (83.3)	
		DRM > 1 cm (32)	22 (68.8)	
Surgery alone (n = 334)	LR	DRM ≤ 1 cm (62)	0 (0.0)	0.150
		DRM > 1 cm (272)	10 (3.7)	
	DFS	DRM ≤ 1 cm (62)	55 (93.5)	
		DRM > 1 cm (272)	226 (83.8)	

LR, local recurrence; DFS, disease-free survival; NCRT, neoadjuvant chemoradiotherapy; DRM, distal resection margin.

Three hundred thirty-four patients received surgery alone without NCRT. Nobody developed local recurrence in 62 patients with a DRM ≤ 1 cm, but 10 patients experienced local recurrence out of 272 patients with a DRM > 1 cm (0 vs. 3.7%, *p* = 0.150). Consistent with the neoadjuvant chemoradiation group, there was no significant difference between the two groups (93.5 vs. 83.8%, *p* = 0.172, Table 4 and Fig. 3).

Discussion

The optimal length of DRM has not been determined during sphincter-sparing surgery for patients with mid-low rectal cancers, due to the lack of evidence from high-level randomized controlled studies. In this situation, it is challenging to choose a reasonable surgical type (e.g., low anterior resection or APR) for both surgeons and patients. Therefore, the investigation of the effect of the DRM on the oncological results of the low-lying rectal cancer patients is necessary and of important clinical significance. In the current study, patients with positive CRM and/or DRM were excluded in order to avoid interference with the oncological results. Several studies[17, 18] have confirmed that positive CRM was significantly associated with worse clinical outcomes. Patients with microscopically positive DRMs were related to a significantly higher local recurrence rate[3, 19].

The length of the DRM is mainly depended on the tumor location in the rectum. In this study, the mean distance from the anal verge in the DRM ≤ 1 cm group was shorter than that in the DRM > 1 cm group, similar to previous studies[13, 20, 21]. Meanwhile, we found that the proportion of patients with T1 and T2 stages in the DRM ≤ 1 cm group was higher than that in the control group. Similarly, the proportion of the patients with stage I and II in the DRM ≤ 1 cm group was higher than that in the DRM > 1 cm group.

This condition is mainly caused by case selection. Compared to low-lying rectal cancer patients with advanced T/TNM stage, patients with earlier stage are more likely to be received sphincter-preserving resection rather than APR.

Overall, there were no significant differences in the 5-year LR rate, 5-year DFS, and 5-year OS between the two groups in this study. Similarly, A systemic review of 5574 rectal cancer patients conducted by Bujko et al. [22] was to evaluate whether a DRM of < 1 cm jeopardizes oncologic safety. They concluded that a DRM of < 1 cm did not compromise oncologic outcomes. Dong Woo Kang et al.[21] reported that the 5-year LR rate was 8.8% in the DRM \leq 1 cm group and 8.5% in the DRM > 1 cm group ($p = 0.630$). The 5-year DFS rate was 75.1 and 76.3% ($p = 0.895$), and the 5-year OS rate was 82.6 and 85.9% ($p = 0.401$), respectively. In the study, about 41.4% of enrolled patients were treated by NCRT according to risk factors, such as cT4, positive CRM.

Many previous studies[13–16, 19, 20, 23] attempted to define the narrowest sufficient DRM (5 mm, 8 mm, 1 cm, and 2 cm) in patients with sphincter-preserving surgery. However, most of these studies, the analysis of the impact of DRM on survival results was not well stratified by NCRT.

A subgroup analysis of this study showed that there were no significant differences in the 5-year LR and 5-year DFS between the two groups in 44 patients who received NCRT. In agreement with our result, Philipp et al. analyzed 88 patients with mid-low rectal cancer receiving NCRT. They found that the 5-year LR rate was 6.7% in patients with DRM < 1 cm and 5.5% in patients with DRM \geq 1cm[13]. Preoperative chemotherapy may increase the rate of sphincter-preserving surgery due to the regression of primary tumors[24, 25]. It was reported that neoadjuvant chemoradiation of tumors was associated with shorter distal spread compared to tumors without preoperative radiation[26, 27].

In addition, many previous studies showed that distal intramural spread greater than 1 cm was only in 0–5% of patients[26, 28, 29]. However, Akihiro Kondo et al.[16] analyzed 71 patients with low rectal carcinoma who received preoperative chemotherapy. They found that 42 (59%) patients had distal spread. Distal spreads of 10–19 mm, and \geq 2 cm were observed in 11 (15%), and 4 (6%) patients, respectively. Besides, they revealed that the presence of different therapeutic effect between the mucosal and deeper layers and poorly differentiated adenocarcinoma were independent risk factors for DRM \geq 1 cm after preoperative chemotherapy. Thus, these findings suggest that for carefully selected patients with neoadjuvant chemoradiotherapy, a subcentimeter DRM is acceptable and not associated with worse oncologic results. It should be noted that for patients with high-risk factors who underwent preoperative chemotherapy, a DRM of 1 cm may not be sufficient.

By subgroup analysis in the present study, a DRM of \leq 1 cm did not compromise the oncologic outcomes of patients who received TME surgery alone. The introduction and application of TME principle for advanced rectal cancer have significantly reduced local recurrence and improved a safe DRM[7, 30, 31]. A study including 152 mid-low rectal cancer patients with TME surgery alone reported that there were no significant differences in 10-year recurrence rates between the DRM \leq 1 cm group and the DRM > 1 cm group (0.0 vs. 3.6%, $p = 0.27$). The authors believed that sphincter-saving TME with a subcentimeter DRM

was a preferable option to preserve anal function without compromising oncological safety. Although patients were not treated by NCRT, postoperative adjuvant chemotherapy and/or radiotherapy may compensate for the negative impact of near margin on survival.

The present study has several drawbacks. First, some statistical bias is inevitable due to the retrospective nature of the research design. Prospective cohort studies will be conducted to reduce such errors. Second, although the total sample size is large, the number of patients with a DRM ≤ 1 cm group is small. Third, The proportion of patients receiving neoadjuvant therapy was low, and adjuvant therapy was not uniform, which may affect oncologic results. In addition, not all specimens in this study were pinned. So, the length of DRM may be affected by different measurement methods. Tissue shrinkage of about 30% in unpinned specimens was caused by formalin fixation, and no significant difference was observed in the DRM length of formalin-fixed specimens if they had been pinned[32, 33].

Conclusions

No matter whether patients with mid-low rectal cancers received neoadjuvant therapy or not, there are no significant differences in 5-year LR rate, 5-year DFS, and 5-year OS between the DRM ≤ 1 cm group and the DRM > 1 cm group. Sphincter-preserving TME with a DRM ≤ 1 cm may be acceptable in low rectal cancer without jeopardizing oncologic safety. However, low anterior resection with a minimum DRM should be based on individual patient conditions and tumor features.

Abbreviations

DRM: Distal resection margin; DFS: disease-free survival; OS: overall survival; LR: local recurrence; CRM: circumferential resection margin; APR: abdominal perineal resection; TME: total mesorectal excision; NCRT: neoadjuvant chemoradiotherapy; CAPOX: capecitabine plus oxaliplatin; CEA: carcinoembryonic antigen; CT: computed tomography; PET/CT: positron emission tomography/ computed tomography.

Declarations

Ethics approval and consent to participate This study was approved by the Ethics Committee of Peking University Cancer Hospital & Institute and in accordance with the 1964 Helsinki declaration. Written informed consent was obtained from each patient included in the study.

Consent for publication

Not applicable.

Availability of data and material

The datasets used in the present study are available from the corresponding author on reasonable request.

Competing interest

The authors declare that they have no conflict of interest.

Funding

This study was supported by the National Natural Science Foundation of China (No.81872022, 81672439), Beijing Natural Science Foundation (No.7162039), Capital's Funds for Health Improvement and Research (CFH 2018-2-2153). The funders were not involved in designing the study, collecting or analyzing the data, or preparing the manuscript.

Authors contribution

CZ, HY, and XS designed the research; CZ, MC, and JX analyzed the data and wrote the paper; HY, ZY, FT, NZ, LC, ML, KX contributed to patient follow-up and data collection; CZ and HY contributed equally to this work. All authors have read and approved the manuscript.

Acknowledgments

We thank the staff members at the database office at Peking University Cancer Hospital and Institute for assistance with the data search.

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Figures

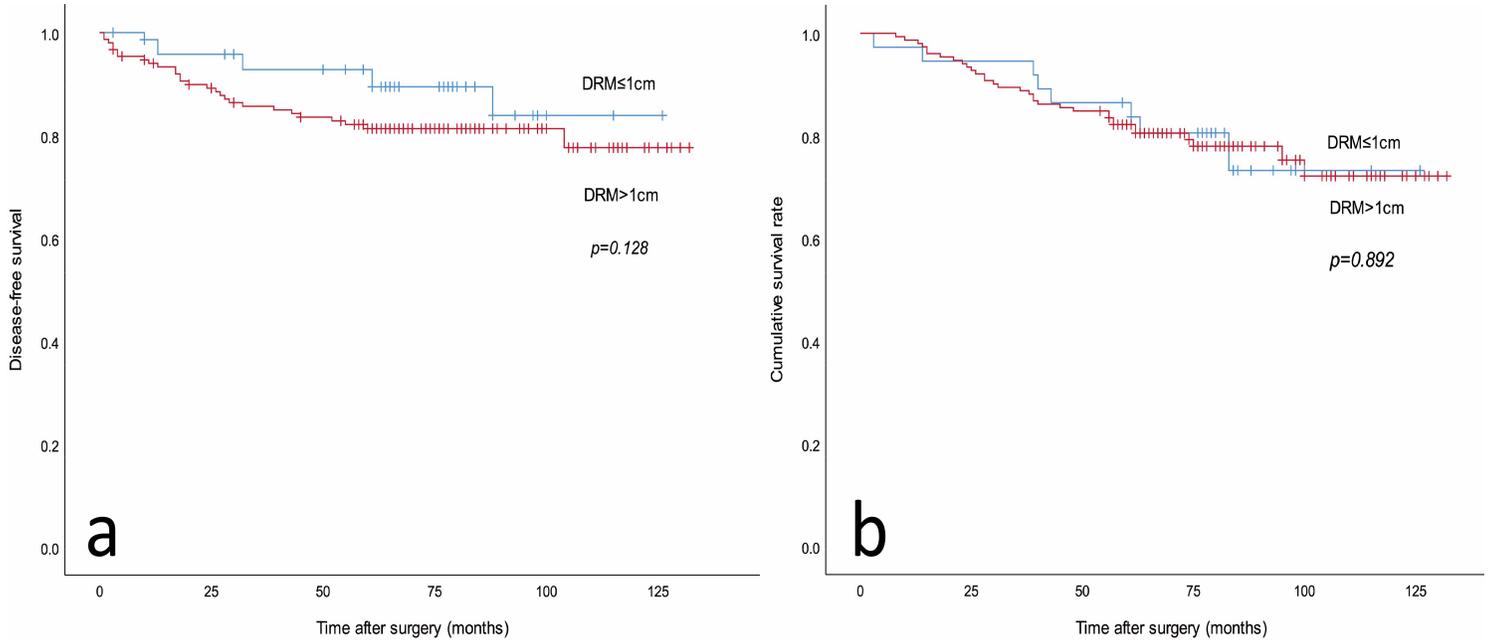


Figure 1

Overall survival (OS) and disease-free survival (DFS) related to the length of the DRM. No significant difference of 5-year DFS and 5-year OS was observed in the DRM ≤ 1 cm group (a) and >1 cm group (b). DRM, distal resection margin.

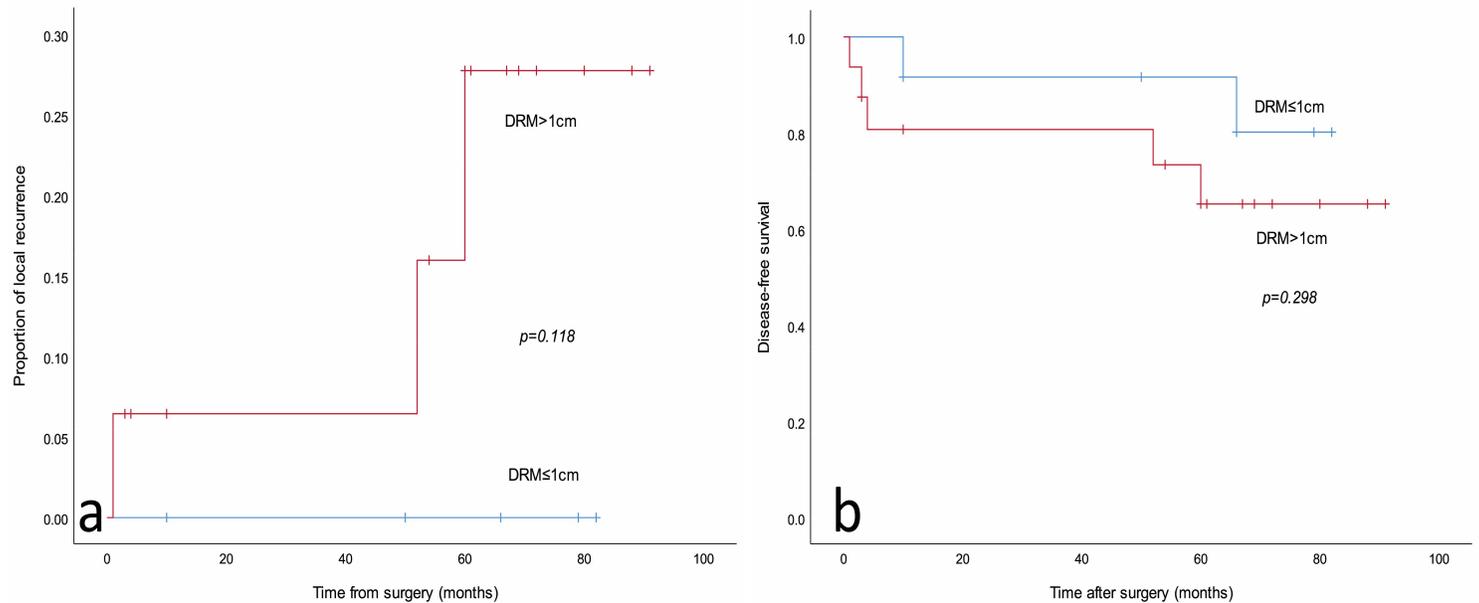


Figure 2

Local recurrence (LR) and disease-free survival (DFS) of patients with neoadjuvant chemoradiation (stratified by distal margin ≤ 1 cm). No significant differences of LR and 5-year DFS were observed in the

DRM ≤ 1 cm group (a) and >1 cm group (b). DRM, distal resection margin.

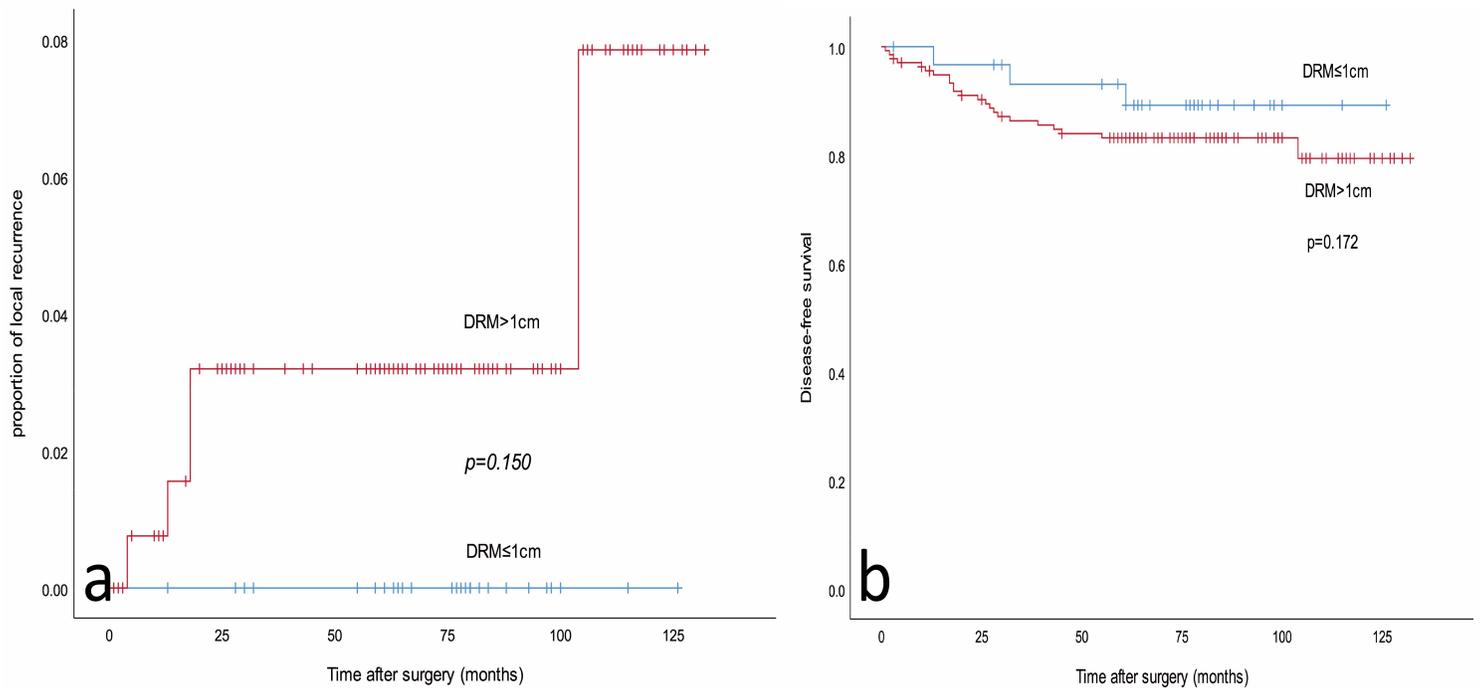


Figure 3

Local recurrence (LR) and disease-free survival (DFS) of patients with surgery alone (stratified by distal margin ≤ 1 cm). No significant differences of LR and 5-year DFS were observed in the DRM ≤ 1 cm group (a) and >1 cm group (b). DRM, distal resection margin.