Indian Journal of Surgical Oncology (June 2019) 10(2):335–341
https://doi.org/10.1007/s13193-019-00888-8

ORIGINAL ARTICLE

Impact of Length of Distal Margin on Outcomes Following Sphincter Preserving Surgery for Middle and Lower Third Rectal Cancers

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Received: 4 September 2018 / Accepted: 25 January 2019 / Published online: 9 February 2019

Abstract

Outcomes of sphincter preserving surgery for distal rectal cancers improve with clear circumferential resection and distal resection margin. However, the extent of distal resection margin after a complete mesorectal excision is often a cause for debate. We evaluated the outcome of middle and lower third rectal cancer patients undergoing sphincter preservation with variable distal resection margin at our center. Patients with biopsy-proven rectal adenocarcinoma within 10 cm from anal verge undergoing sphincter preserving resections were included. Patients with positive circumferential resection margin were excluded. Patients were divided into three groups based on the extent of distal resection margin (< 6 mm, 6–10 mm, > 10 mm) and oncological outcomes were compared. The median age of 242 patients was 50 years and 44 (18.2%) were high-grade tumors. Preoperative chemoradiation was used in 185 (75.2%) patients. Median distal resection margin was 20 mm. Patients in < 10 mm group had a significantly higher proportion of lower third (68.3% vs 39.8%, $p = 0.004$) and chemoradiation-treated tumors (85.4 vs 74.6%, $p = 0.001$). A significantly higher percentage required an intersphincteric resection in the < 10 mm group (53.7% vs 14.4%, $p = 0.0001$). Significantly higher percentage tumors were pT3 in > 10 mm group (45.3% vs. 31.7%) ($p = 0.05$). The median follow-up was 23 months. There was no difference in the overall, loco-regional, and distant recurrence rates between the three groups. A subcentimeter distal resection margin does not influence loco-regional or distant recurrence rates following sphincter preserving surgery for middle and lower third rectal adenocarcinoma.

Keywords Adenocarcinoma · Rectum · Margin · Survival

Introduction

The principle of rectal cancer surgery revolves around performing resection with clear margins (R0 resection). Total mesorectal excision (TME) with an adequate distal resection margin (DRM) is the standard of care for rectal cancer surgery [1–4]. An inability to obtain an adequate DRM for low rectal cancers necessitates an abdominoperineal resection (APR). The need for APR and the prospect of a permanent stoma is one of the reasons for patients defaulting treatment for rectal cancer. A Cochrane review and a recent randomized trial have shown APR to be associated with the worst quality of life as compared to sphincter saving resections (SSR) [5, 6]. Close DRM is associated with an increased risk of local as well as distant recurrence [7].

However, the length of distal resection margin considered to be oncologically adequate has been a subject of debate. The studies published in the 1980s recommended a margin of 2 cm or more to avoid local recurrence [8, 9]. The studies published thereafter proposed a 1-cm DRM for low rectal cancers [10, 11]. With the use of preoperative chemoradiation (NACRT), even a subcentimeter DRM has been shown to provide acceptable oncological outcomes [12–17]. This has encouraged an increasing use of sphincter preserving surgeries like intersphincteric resections for low rectal tumors and with as good an outcome as APR [18, 19]. However, there are studies which still question the credibility of subcentimeter DRM. This is because of a variable response to NACRT and the inferior results seen in the non-responders [20, 21].

In this study, we evaluate the oncological safety of subcentimeter DRM after sphincter preserving surgeries for

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middle and lower third rectal cancers from a tertiary referral cancer center in India.

Patients and Methods

This is a retrospective analysis of a prospectively maintained colorectal database with colorectal service at Tata Memorial Centre, India. Patients undergoing sphincter saving surgery for the middle (5 to 10 cm from anal verge) and lower third (0 to 5 cm from anal verge) rectal cancers from 1 July 2011 to 31 May 2015 were included in the study. The upper rectal cancers were excluded from the analysis.

Biopsy confirmed rectal adenocarcinomas with the lowest mucosal edge within 10 cm from anal verge on clinical and endoscopic examination were included. Patients were staged as per AJCC classification, 7th edition. Stage IV cases with distant metastases were included only if they were considered amenable to complete surgical resection. Patients with positive circumferential resection margin (CRM) and those requiring exenteration or palliative resection were excluded.

All patients were evaluated in colorectal disease management group meetings and their management decided in the same. Patients with T3/T4 and/or node positive (N+) tumors were administered either concurrent preoperative long-course chemoradiation with concurrent capecitabine (NACRT) or short course radiation. Patients treated with NACRT were administered a total of 50-Gy external beam radiation over a 5-week period. Selected stage IV patients with limited, potentially curable metastases were administered short course radiation (SCRT) (25 Gy in 5 fractions) followed by 3–4 cycles of preoperative chemotherapy. Resection of the rectal primary was performed 6 to 8 weeks after completion of NACRT.

Rectal surgeries were performed with open, laparoscopic, or robotic techniques. Standard principles of total mesorectal excision (TME), tumor-specific mesorectal excision (mesorectal excision 5 cm distal to the distal mucosal edge of the tumor) and high ligation of inferior mesenteric artery pedicle with the removal of lymph nodes at the root were followed irrespective of the approach. The decision to offer sphincter preservation was taken based on clinic-radiological (MRI based) evidence of uninvolved levator ani, intersphincteric space, and distal margin. Staplers were used for the transection and anastomosis of the rectum. The double stapling technique was used. Rectal stump was transected using Contour stapler during open and echelon 60 stapler during laparoscopic or robotic procedures respectively. A single cartridge was used for transection during open procedure, however, 1–3 cartridges were required during minimally invasive procedure. For patients requiring intersphincteric resection, hand-sewn coloanal anastomosis was performed. Whenever possible, a frozen section (FS) of the specimen for the status of the distal resection margin was performed. Protective stoma was performed in presence of at least two risk factors including male sex, low anastomosis, preoperative chemoradiation, advanced tumor stage, perioperative bleeding, and multiple firings of the linear stapler.

DRM was defined as the distance of distal resection edge of the specimen from the most distal macroscopically visible mucosal extent of the tumor. It was estimated in the fresh excised unpinned specimen by the pathologist. In case of stapled anastomosis, distal donut rings were not included in distal margin. The presence of tumor cells at the inked distal transaction edge of the specimen was classified as "positive" distal margin. Presence of tumor cells within 1 mm of mesorectal fascia was termed "positive" CRM. The patients were divided into three groups based on the extent of DRM as < 6 mm, 6–10 mm, and > 10 mm respectively. Tumor regression grade (TRG) was calculated based on the Mandard scoring system [22].

SPSS 21 (IBM Inc) software was used for analysis. Chi-square test was used for univariate comparison of categorical variables. Logistic regression was used for multivariate analysis of categorical variables. Kaplan Meir curves were used for survival analysis. P value < 0.05 was considered statistically significant.

Adjuvant chemotherapy was administered to all patients who underwent neoadjuvant chemoradiation irrespective of the pathological response. Postoperative follow-up was conducted as per NCCN guidelines. Follow-up investigations included regular clinical examination, colonoscopy, CT scan, and serum carcinoembryonic antigen (CEA) assay.

Relapse was documented on clinic-radiological and histopathological evaluation whenever possible. Local-regional recurrence was defined as recurrence involving the anastomotic site, peri-anastomotic soft tissue, and regional nodes. Visceral and non-regional nodal recurrences were defined as distant recurrence. Overall survival (OS) was defined as time duration from date of diagnosis to the date of death. Relapse-free survival (RFS) was defined as time duration from date of completion of treatment to date of diagnosis of relapse.

Results

Sphincter preserving surgeries were performed in 336 patients during this period. After excluding upper third rectal cancers, 242 patients were analyzed. The demographic details of the DRM groups are mentioned in Table 1. The median age of the cohort was 50 (18–83) years with a male preponderance (57.4%). Tumors of 134 (55.4%) patients were located in the middle third of the rectum (cf: 108 i.e., 44.6% in the lower third). Majority of the patients had stage III disease (145/242; 59.9%). Most of the tumors were clinico-radiological T3 stage (206/242; 85.1%). NACRT was administered in 185/242(75.2%) patients. Minimal access operative procedure

Table 1 Demographic profile of DRM groups

Parameters	< 6 mm	6–10 mm	> 10 mm	Significance
Total	16 (6.6%)	25 (10.3%)	201 (83.1%)	
Sex				
Male	8 (50%)	18 (72%)	113(56.2%)	0.26
Female	8 (50%)	7 (28%)	88 (43.8%)	
Location				
M3rd	5 (31.2%)	8 (32%)	121 (60.2%)	0.004*
L3rd	11 (68.8%)	17 (68%)	80 (39.8%)	
Stage (clinico-radiological)				
I	1 (6.3%)	3 (12%)	19(9.5%)	0.42
II	3 (18.8%)	5 (20%)	52(25.9%)	
III	9 (56.3%)	16 (64%)	120 (59.7%)	
IV	3 (18.8%)	1 (4%)	10 (5%)	
T stage (clinico-radiological)				
T1	0 (0%)	0 (0%)	1 (0.5%)	0.83
T2	3 (18.8%)	3 (12%)	20 (10%)	
T3	12 (75%)	22 (88%)	172 (85.6%)	
T4	1 (6.3%)	0 (0%)	8(4%)	
Neoadjuvant treatment				
NACRT	15 (93.8%)	20 (80%)	150(74.6%)	0.0001*
NACT	0 (0%)	0 (0%)	9 (4.5%)	
SCRT	0 (0%)	1 (4%)	13 (6.5%)	
None	1 (6.2%)	4 (16%)	29 (14.4%)	
Surgery				
LAR	8 (50%)	11 (44%)	172 (85.6%)	0.0001*
ISR	8 (50%)	14 (56%)	29 (14.4%)	
Sx approach				
Lap	5 (31.2%)	4 (16%)	41 (20.4%)	0.15
Robotic	2 (12.5%)	2 (8%)	4 (2%)	
Open	9 (56.2%)	19 (76%)	156 (77.6%)	
T stage (pathological)				
pT1	3 (18.8%)	4 (16%)	9 (4.5%)	0.05*
pT2	3 (18.8%)	4 (16%)	47 (23.4%)	
pT3	5 (31.2%)	8 (32%)	91 (45.3%)	
pT4	1 (6.2%)	0 (0%)	7 (3.5%)	
pCR	4 (25%)	7 (28%)	45 (22.4%)	
pTx	0 (0%)	1 (4%)	2 (1%)	
pN stage				
pN0	10 (62.5%)	17 (68%)	134 (66.7%)	0.99
pN1	4 (25%)	5 (20%)	43 (21.4%)	
pN2	2 (12.5%)	3 (12%)	24 (11.9%)	
Grade				
WD	0 (0%)	2 (8%)	2(0.9%)	
MD	11 (68.8%)	18 (72%)	141 (70.1%)	
PD	2 (12.5%)	4 (16%)	28 (13.9%)	
SRC	2 (12.5%)	0 (0%)	6 (2.9%)	
MC	0 (0%)	0 (0%)	2 (0.9%)	
NA	1 (6.3%)	1 (4%)	22 (10.9)	
TRG group				
≤ 3	10 (62.5%)	14 (56%)	126 (62.7%)	0.93
> 3	3 (18.8%)	7 (28%)	41 (20.4%)	
NA	3 (18.8%)	4 (16%)	34 (16.9%)	
Adjuvant treatment				
CT	14 (87.5%)	21 (84%)	172 (85.6%)	0.74
CTRT	0 (0%)	0	7 (3.5%)	
No	2 (12.5%)	4 (16%)	22 (10.9%)	

NACRT = preoperative chemoradiation; NACT = preoperative chemotherapy; SCRT = short course radiotherapy; LAR = low anterior resection; ISR = intersphincteric resection; Lap = laparoscopic; WD = well differentiated; MD = moderately differentiated; PD = poorly differentiated; SRC = signet ring cell; MC = mucinous adenocarcinoma; NA = not available; CT = chemotherapy; CTRT = chemoradiation

*Indicates significant *p* value

was conducted in 58 (22%) patients. The mean lymph node yield of the entire cohort was 12.1 (0–34). The DRM groups were comparable with respect to gender distribution, clinico-radiological tumor (T) stage, clinico-radiological stage, tumor grade, surgical approach, pathological nodal stage, tumor regression grades, and adjuvant treatment.

Median DRM achieved for the entire cohort was 20 mm. Median DRM achieved for middle third cancers was significantly longer than lower third cancers (27.5 mm vs 17.5 mm, $p < 0.0001$). Patients with subcentimeter DRM were significantly more likely to have lower third rectal tumors (68.3% vs 68% vs 39.8%, $p = 0.004$). Significantly higher number of patients in subcentimeter DRM group were treated with NACRT (93.8% vs 80% vs 74.6%, $p = 0.0001$). The percentage of ISR performed in the subcentimeter group was significantly higher (50% vs 56% vs 14.4%, $p = 0.0001$). Conversely, > 10 mm group had a significantly higher percentage of pT3/T4 tumors (48.8% vs 32% vs 37.4%, $p = 0.05$).

Intra-operative frozen section (FS) for DRM was performed in 200 cases and DRM was concluded to be free of tumor. Among them, 4 patients had DRM involvement on final histopathology (false negative rate for FS = 2%). These patients were included in the final analysis. One of these belonged to < 6 mm group and 3 to > 10 mm group. Three of these patients were treated with adjuvant chemotherapy and 1 with adjuvant chemoradiation. One of these 4 patients had a solitary synchronous liver metastases and was treated with adjuvant chemotherapy after synchronous resection.

Median follow-up of the cohort was 23 months after surgery (1–62 months). Five (2.1%) patients were lost to follow-up. There were 58 (23.9%) recurrences at the time of analysis. Of these, 4/58 (6.9%) were loco-regional (1 was anastomotic site), 50/58 (86.2%) systemic, and 4/58 (6.9%) were both loco-regional and systemic recurrences. The 4 patients with combined loco-regional and systemic recurrences were included in the systemic recurrence group. The loco-regional

Table 2 Recurrence profile of DRM groups

Recurrence	< 6 mm ($n = 16$)	6–10 mm ($n = 25$)	>10 mm ($n = 201$)	Significance
Overall	5 (31.3%)	7 (28%)	46 (22.9%)	0.66
Loco-regional	0 (0%)	1 (4%)	3 (1.5%)	0.74
Systemic	5 (31.3%)	6 (24%)	43 (21.4%)	

recurrence rate for the entire cohort was 1.7% (4/242). There was no significant difference in overall, loco-regional and systemic recurrences among the DRM groups (Table 2).

Median relapse-free survival (RFS) of the entire cohort was 13 months. Median RFS for lower third rectal tumors was lesser than that of middle third rectal tumors but did not reach significance (12 months vs 14 months, $p = 0.058$). None of the other factors including T stage, N stage, neoadjuvant chemoradiation, or length of DRM were found to be significantly associated with RFS. Median overall survival (OS) of the cohort was not reached as there were only two deaths at the time of analysis.

Discussion

Rectal cancer surgery is challenging due to narrow confines of the pelvic cavity. All efforts should be directed towards obtaining negative circumferential and distal margins. The outcome for rectal cancer has improved with the use of magnetic resonance imaging (MRI) of the pelvis, preoperative chemoradiation, and TME [23–25].

An increasing acceptance for lesser lengths of DRM has been seen, over the last two decades. Encouraging results from most of the studies has led to an increase in the use of SSR like low anterior resections with stapled coloanal anastomosis and ISR for low rectal cancers. Kuvshinoff et al. and Huh et al. have compared the outcomes of NACRT treated distal rectal cancers undergoing SSR with negative distal margin to those undergoing APR [14, 19]. The survival in these studies was not influenced by the type of surgical procedure but by the radial margin and node positivity respectively [14, 19].

In our study, significantly higher percentage of patients in the subcentimeter group were lower third cancers, received preoperative chemoradiation, and underwent intersphincteric resection, whereas the > 10 mm group has a significantly higher proportion of pT3/T4 tumors. The tumors in the < 6 mm DRM group were most likely to receive NACTRT and undergo ISR procedure. The overall, local, and systemic recurrence rates were found to be similar in all the DRM groups and RFS was not associated with T and N stages, NACRT, and DRM.

There have been several studies which have shown that sphincter preserving resections with subcentimeter DRM result in acceptable oncological outcomes for distal rectal cancers. However, there are studies which question the safety of a subcentimeter DRM. Table 3 shows studies which have evaluated the impact of DRM in patients undergoing sphincter preserving resections for distal rectal cancers.

The median age of patients undergoing sphincter preservation in our study was 50 years. This is lower than the median age of patients included in other studies (range 58–64 years). In a previous publication from our center, the younger patients were found to have a significantly higher nodal positivity and lower disease-free survival as compared to their older counterparts [30].

Most of the studies which have evaluated the significance of subcentimeter DRM have included tumors with the distal edge within 8–12 cm from anal verge. The median DRM achieved in these studies ranges from 1 to 2 cm. Similarly, tumors in our study were within 10 cm from anal verge and median DRM for our cohort was 2 cm. However, Andreola et al. were able to performed SSR for tumors within 5 cm from anal verge with a median DRM of 0.5 cm [15]. Patients in this study were not treated with NACRT and were all node-negative [15]. According to authors of this study, negative nodal, as well as radial and distal margin status and not the extent of DRM, were determinants of local recurrence [15].

The use of NACRT has varied among the various studies. Some studies have included only NACRT treated patients [17, 21, 26], others have included patients treated with upfront surgery and postoperative chemoradiation only [15, 27, 28]. In our study, majority of the patients (75%) were treated with NACRT given that almost a similar percentage of patients were clinicoradiologically stage II and III. DRM extent has not shown to impact oncological outcomes in most of the studies, whether NACRT was used or not. Studies which have found close DRM to be associated with an unfavorable outcome have also utilized NACRT (63.3%; 100%) [7, 21]. Mezhir et al. showed that NACRT treated rectal cancers rarely have distal intramural spread (DIS) beyond 1 cm and DIS did not correlate with survival [31]. Shirouzu et al. in an earlier study showed that proportion of distal microscopic spread increased with stage and was > 1 cm in only 0.9% patients [10]. The distal spread was however associated with a significantly poor survival [10]. These clinic-pathological studies reiterate the safety of a subcentimeter DRM as well as the prognostic implication of distal microscopic tumor spread.

Most of the studies except Kiran et al. (19.3%) [13] and ours (18.2%) had poorly differentiated rectal cancers ranging from 3.7–7.1%. A recent multi-institutional study showed that high-grade rectal cancers had a significantly lower 5-year RFS and OS but was not associated with increased loco-regional recurrence [32].

Table 3 Studies evaluating impact of distal resection margin on oncological outcomes

Author, year	Number	Median age (in years)	NACRT (%)	Distance from anal verge (in cm)	Median DRM (in cm)	PD grade (%)	Median FU (in months)	Impact of DRM
Andreola et al., 2001 [15]*	77	NA	0**	≤ 5	0.5	NA	51	< 10 mm vs. ≥ 10 mm: no difference in LR
Kuvshinoff et al., 2001 [14]	28***	60	97.3	≤ 8	1	NA	33	< 10 mm vs. ≥ 10 mm: no difference in RFS
Moore et al., 2003 [26]	94	58****	100	≤ 12	2	6.4	44	≤ 10 mm vs. > 10 mm: no difference in LR and RFS
Leo et al., 2009 [27]	203	58/57#	0**	≤ 5##	–	–	61	< 10 mm vs ≥ 10 mm: no difference in LR and OS
Pricolo et al., 2010 [17]	33***	60.4****	100	≤ 10	1.8****	–	48.8****	< 10 mm vs ≥ 10 mm: no LR in either group
Nash et al., 2010 [7]	627	> 60 (52%)	63.6/71.7###	≤ 12	–	3.7	69.6	DRM associated with increased mucosal and overall recurrence
Kiran et al., 2011 [13]	784	60.7****	40	≤ 10	2	19.3	49	≤ 10 mm vs. > 10 mm; ≤ 5 mm vs. > 5 mm: no difference in LR and RFS
Lim et al., 2012 [28]	320	64	0**	≤ 12	1.5	4	45	< 10 mm vs. 10–19 mm vs. ≥ 20 mm: no difference on overall and LR
Kim et al., 2014 [21]	368	53/55###	100	≤ 8	1.5	7.1	48	≤ 3 vs > 3 mm shorter DRM not favorable in ypT3/T4 and those not responding to NACRT
Kang et al., 2017 [29]	415	61.3/62.3#,****	20.2%	≤ 12	0.7/2.7#,****	4.8	47.2	≤ 10 mm vs. > 10 mm; ≤ 5 mm vs. > 5 mm: no difference in LR, RFS and OS
Our study	242	50	75.2%	≤ 10	2	18.2	23	< 6 mm vs 6–10 mm vs > 10 mm: no difference in LR, SR and overall recurrence

*Included only node negative patients

**Received postoperative chemoradiation

***28/37 and 33/53 underwent sphincter preserving surgery

****Value in mean

≤ 1 cm/> 1 cm distal margin groups

88% within 5 cm

Percent treated with neoadjuvant therapy/radiotherapy overall

≤ 3 mm/> 3 mm distal margin groups

NACRT = preoperative chemoradiation; DRM = distal resection margin; PD = poorly differentiated; FU = follow-up; LR = local recurrence; SR = systemic recurrence; RFS = relapse-free survival; OS = overall survival

Pathological assessment of distal margin was done in most of the studies on the pinned specimen after formalin fixation. However, this assessment was done on unpinned specimen before fixation in studies by Nash et al. [7], Kiran et al. [13], and Moore et al. [26] (all from the same center) including our study. Søndenaa et al. have shown that the DRM was significantly less in unpinned vs pinned specimens and fixation does not cause a significant decrease in DRM if the specimen is pinned [33].

The median follow-up for the existing studies ranges from 24 to 70 months as against median of 23 months in our study. As per a multi-institutional Japanese study, cumulative recurrences for stage II and III colorectal cancers appeared most rapidly in the first 3 years following curative resection [34]. Although a longer follow-up is desirable, a median survival of 23 months, as in our study, provides a fair idea of oncological outcomes.

The local and distant recurrence rates in the various studies have ranged from 0 to 9.3% and 6–22.8%. The local and distant recurrence rates in our study were 1.7% and 22.3% respectively. The distant recurrence rate in our study was on a higher side despite a shorter follow-up. This could probably be due to a higher number of younger and higher grade patients seen in our study. These results should therefore be interpreted in light of a different demographic profile, which is specific to this part of the world.

Kiran et al. and Kang et al. excluded patients with positive CRM, DRM, and stage IV patients. We also excluded patients with positive CRM, as this has been shown to be associated with poorer survival and increased recurrence and would have confounded the real effect of DRM. In studies where subcentimeter DRM was found to be acceptable, the factors that have been associated with increased local recurrence and poorer survival included positive DRM, positive CRM stage, node positive, T3/T4 disease, perineural invasion, grade, and chemoradiation use.

Conclusion

Subcentimeter (< 1 cm) distal resection margin was oncologically safe for patients undergoing sphincter preservation for middle and lower third rectal adenocarcinoma, despite younger age and a higher proportion of high-grade tumors in our study.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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