

ORIGINAL ARTICLE

# Multivisceral resection for locally advanced rectal cancer: adequate length of distal resection margin

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**Purpose:** Locally advanced rectal cancer may require an intraoperative decision regarding curative multivisceral resection (MVR) of adjacent organs. In bulky tumor cases, ensuring sufficient distal resection margin (DRM) for achievement of oncologic safety is very difficult. This study is designed to evaluate the adequate length of DRM in multiviscerally resected rectal cancer. **Methods:** A total of 324 patients who underwent curative low anterior resection for primary pT3-4 rectal cancer between 1995 and 2004 were identified from a prospectively collected colorectal database. **Results:** Short lengths of DRM ( $\leq 1$  cm) did not compromise essentially poor oncologic outcomes in locally advanced rectal cancer ( $P = 0.736$ ). However, especially in rectal cancers invading adjacent organs, DRM of less than 2 cm showed poor survival outcome. In 5-year and 10-year survival analysis of MVR, a shorter DRM ( $< 2$  cm) showed 41.9% and 30.5%, although a longer DRM ( $\geq 2$  cm) showed 72.4% and 60.2% ( $P = 0.03, 0.044$ ). In multivariate analysis of MVR, poorly differentiated histology, ulceroinfiltrative growth of tumor, and short DRM ( $< 2$  cm) were significant factors for prediction of poor survival outcome, although short DRM was not significantly related to local and systemic recurrence. **Conclusion:** In locally advanced rectal cancer of pT3-4, a short length of DRM ( $\leq 1$  cm) did not compromise essentially poor oncologic outcome. In rectal cancers invading adjacent organs and requiring MVR, a shorter DRM ( $< 2$  cm) was found to be related to poor survival outcome.

**Key Words:** Multivisceral resection, Distal resection margin, Locally advanced rectal cancer

## INTRODUCTION

Despite efforts to detect rectal cancer at an early stage, advanced rectal cancer invading adjacent organs is not uncommon. In up to 15% of cases, the primary tumor is adherent to adjacent organs as a result of direct malignant invasion or peritumoral inflammatory reaction. Intraoperative assessment of adhesions as malignant or benign has often been debated [1,2].

For patients' quality of life postoperatively, preserva-

tion of the sphincter was of significant importance and sphincter saving rectal surgery requires determination of the optimal length of the distal resection margin. In advanced primary tumors invading adjacent organs, curative *en bloc* resection and ensuring a sufficient length of distal resection margin are very difficult. The current National Comprehensive Cancer Network guidelines recommend a distal resection margin of 4 to 5 cm for partial mesorectal excision and 1 to 2 cm for total mesorectal excision, in patients with low rectal cancer [3]. However,

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careful pathologic studies have demonstrated that distal intramural spread (DIS) occurs in only 4% of patients with rectal cancer. DIS exceeds 1 cm in only 2 to 5% and 2 cm in 1 to 2% of cases, respectively [4,5]. Thus, distal resection margin of 1 to 2 cm or greater should theoretically be sufficient for the vast majority of patients. Recent reports have suggested that a distal margin of 1 cm may be sufficient [6]. In addition, some reports appear to demonstrate that the length of distal clearance has little importance in determination of local recurrences. While the focus has previously been concentrated on the distal mucosal margin, the clinical resection margin, or mesorectal margin has recently gained importance in rectal cancer surgery [7]. However, sufficient distal resection margin could be ensured by surgeons intraoperatively, instead the result of these margins could not be established during the operation and just could be gained by pathologists post-operatively.

In cases involving invasion of adjacent pelvic organs, achievement of both a curative resection and sphincter preservation is a challenge for colorectal surgeons. This study is designed to assess the adequate length of distal resection margin in locally advanced rectal cancer requiring treatment with curative multivisceral resection.

## METHODS

A total of 577 consecutive patients, who underwent a low anterior resection for treatment of rectal cancer at the department of surgery, between 1995 and 2004, were identified from a prospectively collected colorectal database. Palliative resection and positive distal resection margin were excluded. Excluding pT1-2 patients, a total of 324 pT3-4 patients were enrolled.

Cancer stage was determined with a surgical specimen by a pathologist according to the 6th edition of the American Joint Committee on Cancer TNM staging system. Follow-up was conducted every 3 months for 2 years after surgery, and every 6 months for 3 years after that. At the time of follow-up, a physical examination, including interview and digital rectal examination, was performed. Serum carcinoembryonal antigen level was

checked and a simple chest X-ray was taken at 2 to 3 month intervals. Abdominal computed tomography and colonoscopic examinations were performed at 1-year intervals. Recurrence and survival of patients were followed up based on outpatient medical records. The recurrence pattern was classified based on the area where the recurrence was detected for the first time, and local recurrence was defined as tumors that recurred in the pelvic cavity and the anastomotic area. When both of local and systemic re-

**Table 1.** Patient demographics of T3 and T4 rectal cancer

Variable	Standard resection (n = 270)	Multivisceral resection (n = 54)	P-value
Gender			<0.001
Male	162 (60.0)	13 (24.1)	
Female	108 (40.0)	41 (75.9)	
Age (yr)	60.3 ± 0.7	59.5 ± 1.3	0.61
Tumor size, n (%)			
<5.0 cm	187 (69.3)	41 (75.9)	
≥5.0 cm	83 (30.7)	13 (24.1)	0.415
Distance from AV			
<7.0 cm	126 (46.7)	23 (42.6)	
≥7.0 cm	144 (53.3)	31 (57.4)	0.654
Tumor growth pattern			0.005
Fungating	177 (65.6)	26 (48.1)	
Ulceroinfiltrative	93 (34.4)	28 (51.9)	
Histologic grade			0.539
Grade I, II	250 (92.6)	48 (88.9)	
Grade III & mucinous, signet	19 (7.0)	6 (11.1)	
Others	1 (0.4)	0 (0.0)	
Stage			0.293
II	141 (52.2)	23 (44.4)	
III	129 (47.8)	30 (55.6)	
Perioperative CRT			
No	218 (80.7)	42 (77.8)	
Yes	52 (19.3)	12 (22.2)	0.580
PNI/LVI			
No	171 (86.4)	31 (83.8)	
Yes	27 (13.6)	6 (16.2)	0.615
Recurrence			0.002
No	190 (73.7)	28 (51.9)	
Local	28 (10.4)	7 (13.0)	
Systemic	43 (15.9)	19 (35.2)	
Leakage			
No	259 (95.9)	50 (92.6)	
Yes	11 (4.1)	4 (7.4)	0.228

Values are presented as number (%) or mean ± SD.

AV, anal verge; CRT, chemoradiation therapy; PNI/LVI, perineural invasion/lymphovascular invasion.

currence were detected simultaneously, cases were classified into systemic recurrence group.

In general, operative reports did not reliably contain information on adequacy of resection, therefore, distal margins were measured and recorded by the pathologist prior to tissue fixation in the unpinned specimen. The "donuts" created by circular intraluminal staplers were not included in measurement of distal margin length, however, they were examined and found to be negative for tumor in all cases.

Survival rate analysis was performed using a Kaplan-Meier survival curve, and for risk factors affecting survival rate, a Cox regression model was used. A multivariate logistic regression test was performed for analysis of risk factors for recurrence.

## RESULTS

Of 324 patients, 270 (83.3%) patients with pT3-4 rectal cancer were treated with standard low anterior resection (standard resection, SR) and 54 (16.7%) patients under-

went multivisceral resection (MVR). Mean follow-up period was  $49.3 \pm 1.4$  months. Mean age of patients was  $60.1 \pm 0.7$  years. In SR, male gender was dominant, 162 (60%), while in MVR female was dominant, 41 (75.9%) ( $P < 0.001$ ). Table 1 showed that ulceroinfiltrative pattern of tumor growth (UI) was shown more frequently in the MVR group ( $P = 0.005$ ). Also, recurrence rate was higher in the MVR group. However, there were no differences in relation to age, tumor size, distance from anal verge, radiation therapy, perineural invasion / lymphovascular invasion, anastomotic leakage, and histologic grade between the two (Table 1). Multivariate analysis using Cox regression model showed that UI and anastomotic leakage were related significantly to poor overall survival outcome. Additionally, mutivisceral resection affected to shorter disease free survival (Table 2).

### Multivisceral resection

Of MVR, 17 patients showed tumor infiltration to adjacent organs and 37 patients showed inflammatory cellular response. Female was the dominant gender, and the uterus was the most common organ involved by rectal

**Table 2.** Univariate and multivariate analysis using a Cox regression test adherent to disease free and overall survival

	Univariate analysis				Multivariate analysis			
	DFS		OS		DFS		OS	
	P-value	P-value	P-value	Odds	95% CI	P-value	Odds	95% CI
Age	0.466	0.120						
( $<60$ vs. $\geq 60$ )	66.8 vs. 72.5	69.9 vs. 63.3						
Sex	0.665	0.947						
(male vs. female)	68.7 vs. 77.5	66.0 vs. 66.7						
Multivisceral resection	$<0.001$	0.070	0.002	2.05	1.29-3.23			
(yes vs. no)	71.3 vs. 51.4	69.0 vs. 53.4						
Tumor size	0.703	0.284						
( $<5$ cm vs. $\geq 5$ cm)	69.3 vs. 70.3	65.0 vs. 70.0						
Growth pattern	0.009	0.003	0.017	1.63	1.09-2.44	0.001	1.76	1.24-2.49
(fungating vs. infiltrative)	75.3 vs. 59.4	70.9 vs. 58.7						
Distal resection margin	0.280	0.140						
( $<2$ cm vs. $\geq 2$ cm)	65.7 vs. 76.0	63.3 vs. 70.8						
Histologic grade	0.168	0.105						
(G1, 2 vs. G3)	70.2 vs. 61.3	67.1 vs. 71.2						
Radiotherapy	0.039	0.105						
(yes vs. no)	72.2 vs. 59.2	56.1 vs. 69.1						
Anastomotic leakage	0.003	$<0.001$	0.009	2.66	1.28-5.54	$<0.001$	3.28	1.75-6.14
(yes vs. no)	70.9 vs. 43.3	39.8 vs. 62.1						

DFS, disease free survival; OS, overall survival; CI, confidence interval.

**Table 3.** Characteristics of locally advanced rectal cancer with multivisceral resection

Variable	Recurrence			P-value
	Absence (n = 28)	Local (n = 7)	Systemic (n = 19)	
Sex				0.911
Male	7 (25.0)	2 (28.6)	4 (21.1)	
Female	21 (75.0)	5 (71.4)	15 (78.9)	
Age (yr)	61.7 ± 1.8	60.0 ± 5.1	56.1 ± 1.8	0.148
Tumor size				0.369
<5.0 cm	23 (82.1)	4 (57.1)	14 (73.7)	
≥5.0 cm	5 (17.9)	3 (42.9)	5 (26.3)	
Tumor growth pattern				0.003
Fungating	16 (57.1)	3 (42.9)	7 (36.8)	
Ulceroinfiltrative	12 (42.9)	4 (57.1)	12 (63.2)	
Distal resection margin				0.743
<2.0 cm	20 (57.1)	5 (14.3)	10 (28.6)	
≥2.0 cm	9 (47.4)	4 (21.1)	6 (31.6)	
Histologic grade				0.244
Grade I, II	25 (89.3)	5 (71.4)	18 (94.7)	
Grade III & mucinous, signet	3 (10.7)	2 (28.6)	1 (5.3)	
Stage				0.019
II	16 (57.1)	4 (57.1)	3 (16.7)	
III	12 (42.9)	3 (42.9)	15 (83.3)	
PVI/LVI				0.637
No	19 (82.6)	4 (100.0)	8 (80.0)	
Yes	4 (17.4)	0 (0.0)	2 (20.0)	
Perioperative RTx				0.335
No	22 (78.6)	4 (57.1)	16 (84.2)	
Yes	6 (21.4)	3 (42.9)	3 (15.8)	
Resction organs				0.563
Bladder	4 (14.3)	1 (14.3)	5 (26.3)	
Small bowel	3 (10.7)	0 (0.0)	1 (5.3)	
Seminal vesicle	1 (3.6)	1 (14.3)	0 (0.0)	
Uterus	20 (71.4)	5 (71.4)	13 (68.4)	

Values are presented as number (%) or mean ± SD.

PNI/LVI, perineural invasion/lymphovascular invasion; RTx, radiation therapy.

cancer. Patients with systemic recurrence were significantly younger comparing to patients without recurrence (61.7 ± 1.8 vs. 56.1 ± 1.8,  $P = 0.038$ ) among the MVR group. Within the MVR group, predictive factor for systemic recurrence were younger age, UI and advanced stage (Table 3). In multivariate analysis using Cox regression model for poor survival outcome, poorly differentiated histology (PD), UI and shorter DRM were significantly predictive factors (Table 4).

**Table 4.** Multivariate analysis of MVR regarding survival outcome

Variable	P-value	Odds (95% CI)
Univariate analysis		
Tumor size (<5.0 cm vs. ≥5.0 cm)	0.771	1.21 (0.33-4.38)
Histologic grade (G1, 2 vs. G3)	0.020	4.77 (1.28-17.75)
Growth pattern (infiltrating vs. fungating)	0.024	3.19 (1.10-9.18)
Perineural / Lymphovascular invasion (yes vs. no)	0.621	1.53 (0.28-8.32)
Distal resection margin (<2.0 cm vs. ≥2.0 cm)	0.033	3.38 (1.11-10.42)
Multivariate analysis		
Histologic grade (G1, 2 vs. G3)	0.006	5.57 (1.65-18.79)
Growth pattern (infiltrating vs. fungating)	0.037	3.13 (1.07-9.19)
Distal resection margin (<2.0 cm vs. ≥2.0 cm)	0.042	2.89 (1.03-8.62)

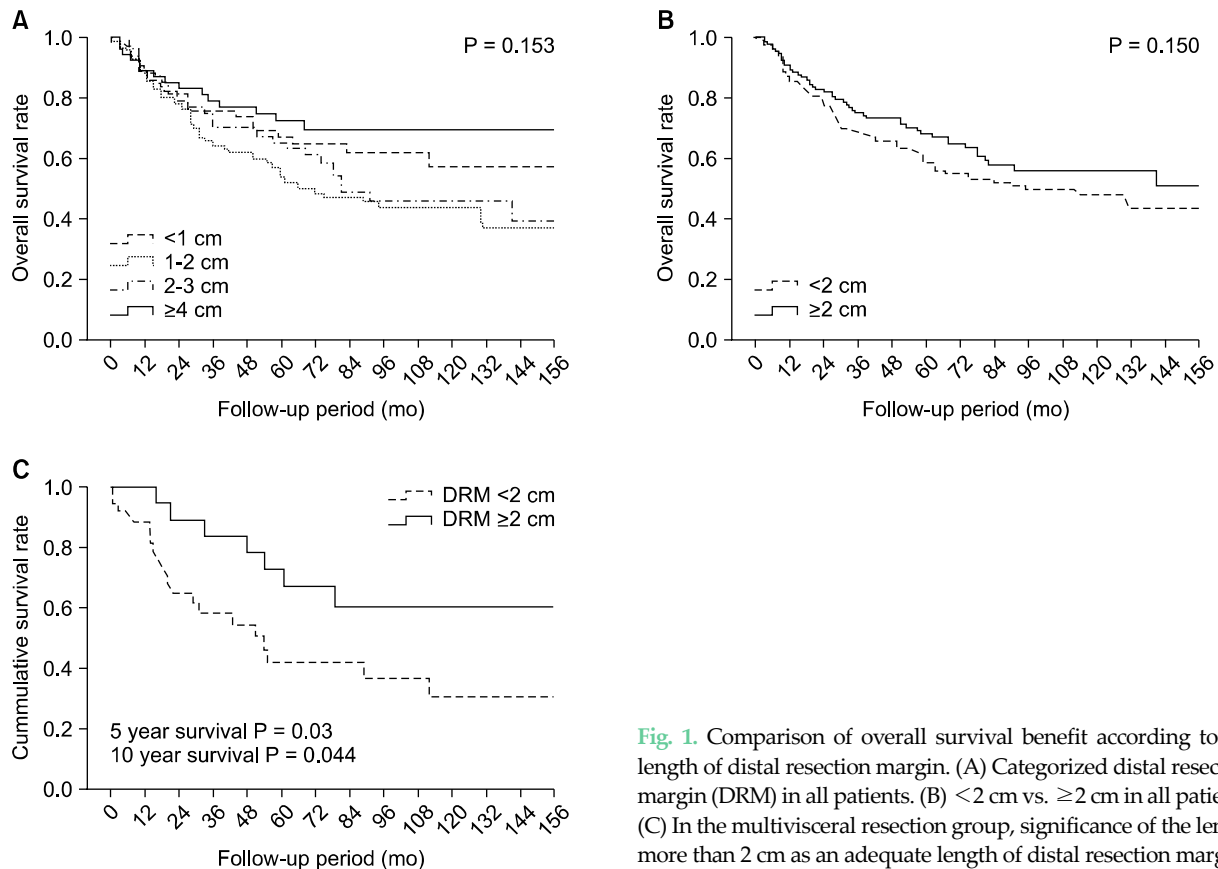
MVR, multivisceral resection; CI, confidence interval.

### Distal resection margin in MVR

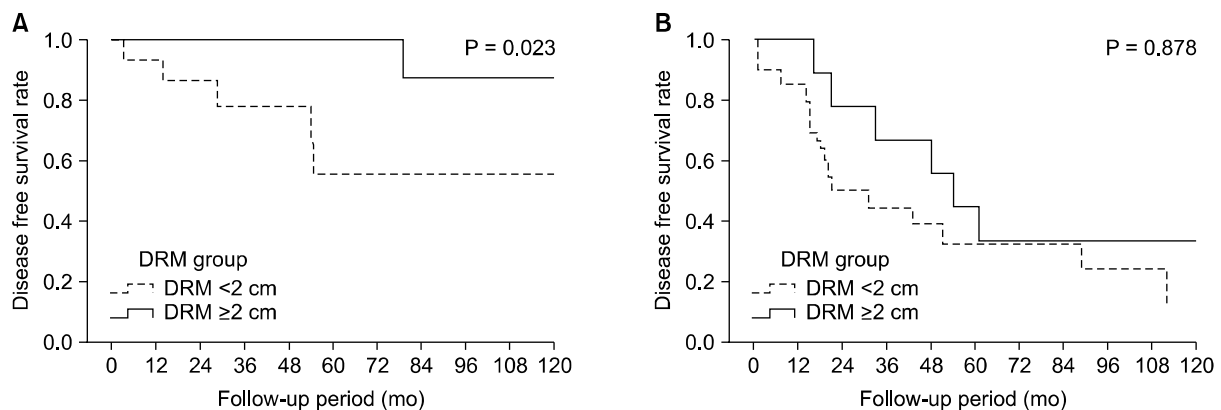
In a total of 324 patients, short DRM of less than 1 cm did not compromise essentially oncologic poor outcome (Fig. 1A, B) and recurrence. However, a length of less than 2 cm was significantly related to poor survival outcome in the MVR group (Fig. 1C). As commented in Table 4, PD, UI and shorter DRM were significantly predictive factors for poor survival outcome. Among the MVR group, in cases without unfavorable factor (PD and / or UI) there were not significantly different results in survival outcome, although it had shorter DRM (<2 cm) (Fig. 2B). However, In cases with unfavorable factors there was significant differences between shorter and longer DRM group for survival outcome (Fig. 2A).

## DISCUSSION

Multivisceral resection is planned before surgery in only a few patients. The decision to extend the resection to include adjacent organs or structures is made during surgery in most cases. Whether infiltration to adjacent organs was caused by true tumor infiltration or as a result of inflammatory cellular response could not be determined based on histopathological findings after surgery [3]. Adherence of the tumor to adjacent structures demonstrated



**Fig. 1.** Comparison of overall survival benefit according to the length of distal resection margin. (A) Categorized distal resection margin (DRM) in all patients. (B) <2 cm vs. ≥2 cm in all patients. (C) In the multivisceral resection group, significance of the length more than 2 cm as an adequate length of distal resection margin.



**Fig. 2.** Analysis of predictive factor for poor survival outcome in the multivisceral resection group. (A) In cases with poorly differentiated histology and/or ulceroinfiltrative pattern of tumor growth, shorter distal resection margin (DRM) (<2 cm) was related to poor survival outcome. (B) In cases without unfavorable factors, shorter DRM did not essentially compromise poor outcome.

histological tumor invasion in approximately 50 to 85% of cases [1,8-11]. Among our cases, 28 of 54 (51.9%) had adhesion due to direct tumor infiltration. This finding has led some to suggest dissection of the rectum free from structures that appear to be macroscopically infiltrated, extend-

ing the operation, only if separation is not feasible [12]. Goals of treatment of rectal cancer are to cure and to maintain good quality of life, including urinary and sexual function. For achievement of these goals, ensuring an adequate length of distal resection margin for preservation of

the anal sphincter was an essential challenge to colorectal surgeons.

Traditionally, the shortest curative distal clearance (DC) has been said to be 2 cm from the outer edge of the tumor [13], while some reports have suggested that a DC of 1 cm may be sufficient [4]. In addition, recent reports appear to demonstrate that length of the distal clearance has little importance in determination of local recurrence, while the clinical resection (CRM), lateral resection margin, has recently gained importance in rectal cancer surgery [7,14]. In this study, this finding led to some limitations of absence of CRM, because CRM was a relatively recent concept and has only been recently applied. Regarding an explanation for CRM, in our institute there has been no case of a cancer positive doughnut as a resection margin and insufficient margin of a cancer positive doughnut was included as an incomplete resection of palliative surgery and was excluded in this study.

Recently, it has been postulated that down-staging of low rectal cancer after preoperative radiation might reduce distal intramural spread to less than 1 cm [4,15]. Two studies have reported distal intramural spread after chemoradiotherapy of greater than 0.5 cm in 9% and 40% of patients, while spread of 1 cm was present in only 0% and 5% [6,16]. However, in this study, preoperative chemoradiation therapy was performed in only a small number of patients. This was a second limitation of our study, because patients with a locally advanced cancer and with a higher risk of distal intramural spread, like infiltrative growing pattern, were generally selected for preoperative radiation in other studies [17,18]. This might result in reduction of the number of patients with significant intramural spread and its actual extent.

Nevertheless, in intraoperative decision making to include the extent of resection, the length of DRM is important in deciding on preservation or scarification of the anal sphincter.

As commented in Fig. 2, poorly differentiated histology and ulceroinfiltrative pattern of tumor growth was important factor for prediction of poor survival outcome. And surgeons can make a decision for these two factor preoperatively using colonoscopy, pathologic report of colonoscopic biopsy, and abdominal imaging. So, especially

in cases of T4 rectal cancer with unfavorable factors, above mentioned, surgeons should make a every effort to ensure a sufficient resection margin.

In conclusion, our data suggests that a distal margin of 2 cm or more could ensure oncologic safety in cases of locally advanced rectal cancer invading to adjacent organs and early conversion to abdominoperineal resection could provide an opportunity to compensate for an initial inappropriate decision regarding low anterior resection with insufficient resection margin. In addition, further evaluation should be needed in order to assess the adequate length of DRM and CRM in cases of locally advanced rectal cancer treated with multivisceral curative resection.

Generally, a short length of distal resection margin in locally advanced rectal cancer did not compromise essentially poor oncologic outcome. However, the length of less than 2 cm in the MVR may compromise inadequate resection. Tumors which involved adjacent organs has a character of infiltrative growth and poorly differentiated histology. And these factor are related to a poor survival course. Therefore, in treating locally advanced rectal cancer invading to adjacent organs, every effort should be made for ensuring sufficient length of distal resection margin.

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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