Original Research Article

Prognostic Impact of the Length of the Distal Resection Margin in Rectosigmoid Cancer: An Analysis of the JSCCR Database between 1995 and 2004

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Abstract
Objectives: The necessary and sufficient length of the distal resection margin (l-DRM) for rectosigmoid cancer remains controversial. This study evaluated the validity of the 3-cm l-DRM rule for rectosigmoid cancer in the Japanese classification of colorectal cancer.
Methods: We retrospectively reviewed 1,443 patients with cT3 and cT4 rectosigmoid cancer who underwent R0 resection in Japanese institutions between 1995 and 2004. We identified the optimal cutoff point of the l-DRM affecting overall survival (OS) rate using a multivariate Cox regression analysis model. Using this cutoff point, the patients were divided into two groups after balancing the potential confounding factors of the l-DRM using propensity score matching, and the OS rates of the two groups were compared.
Results: A multivariate Cox regression analysis model revealed that the l-DRM of 4 cm was the best cutoff point with the greatest impact on OS rate (hazard ratio [HR], 1.37; 95% confidence interval [CI], 1.00-1.84; P = 0.0452) and with the lowest Akaike information criterion value. In the matched cohort study, the OS rate of patients who had l-DRM of 4 cm or more was significantly higher than that of patients who had l-DRM < 4 cm (n = 402; 5-year OS rates, 87.6% vs. 80.3%, respectively; HR, 1.60; 95% CI, 1.09-2.31; P = 0.0136).
Conclusions: For cT3 and cT4 rectosigmoid cancer, l-DRM of 4 cm may be an appropriate landmark for a curative intent surgery, and we were unable to definitively confirm the validity of the Japanese 3-cm l-DRM rule.

Keywords
rectosigmoid cancer, length of the distal resection margin, propensity score matching analysis, retrospective study

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Introduction

The Japanese Classification of the Colorectal Cancer, which was published by the Japanese Society for Cancer of the Colon and Rectum (JSCCR), defines the rectosigmoid as a segment of the large intestine between the sacral promontory and lower border of the second sacral vertebra[1]. It is not identical to the rectosigmoid junction that is coded as C-19 by the International Classification of Diseases for Oncology, 3rd edition. The Cancer Staging Manual of the American Joint Committee on Cancer and most clinical studies performed in Western countries treat rectosigmoid cancer as

a colon cancer. On the other hand, the TNM classification of the Union for International Cancer Control defines the rectum as the distal large intestine commencing opposite the sacral promontory and ending at the upper border of the anal canal[2]. Thus, the transitional portion of the large intestine between the colon and the rectum is ill-defined worldwide, and the rectosigmoid may be said to have anatomical and oncological characteristics of both the colon and the rectum.

In recent years, the mortality of colorectal cancer (CRC) has decreased in economically developed countries due to increased CRC survival[3]. Steady improvement in CRC survival may be partly attributable to a standardization of surgical procedures. In rectal cancer surgery, total mesorectal excision has become a well-established standard procedure not only for local control but also for survival benefit[4-6]. However, one criticism of this procedure is that the total resection of the mesorectum is not always necessary for every rectal cancer, especially for those located in the upper rectum. In these cases, a major concern in surgery is the ideal length of the distal resection margin (l-DRM). The l-DRM is an important factor that regulates both the elimination of lymph node metastasis in the mesorectum and distal intramural spread (DIS) in the intestinal wall. Up to the prior version of the Japanese classification of CRC[1], the distal para-rectal regional nodes of the rectosigmoid were defined as those within 6 cm of the mesorectum from the distal tumor edge. This definition was changed to 3 cm in the latest revision without sufficient verification[7]. Under these circumstances, this present study was conducted to clarify the validity of the 3-cm l-DRM rule for rectosigmoid cancer surgery.

Methods

Patients

We obtained the data from the database of the JSCCR that maintains a hospital-based nationwide registration system of CRC in Japan. The registry has been prospectively collecting detailed clinical and pathological information on CRC and follow-up data each year in accordance with the Japanese classification of CRC since 1980. The database currently contains information on more than 180,000 CRC patients treated in academic institutes or community hospitals between 1974 and 2007. It accounted for approximately 8%-10% of the CRC incidence in Japan. However, the database does not contain information on the short-term surgical outcomes. Furthermore, the disease recurrence and the cause of death were not always documented. Therefore, we were unable to accurately evaluate cancer-specific, disease-free, or relapse-free survival.

This present study used the data of 1,443 patients with cT

3 and cT4 rectosigmoid cancer that were extracted from a total of 52,126 CRC patients who underwent R0 resection between 1995 and 2004. Patients were excluded from the analysis based on the following characteristics: cancer sites other than the rectosigmoid (n = 45,890), unknown age (n = 36), multiple primary cancers and/or multiple CRCs (n = 826), l-DRM greater than 20 cm or unknown l-DRM (n = 1,272), length of the proximal resection margin (l-PRM) greater than 100 cm or unknown l-PRM (n = 71), cTis or cT1 or cT2 or cTX (n = 624), cStage IV or cStage X (n = 649), histology other than adenocarcinoma or unknown histology (n = 26), resection other than R0 or positive circumferential resection margin (n = 287), tumor diameter of 50 cm or larger (n = 14), other than the anterior resection (n = 263), and unknown follow-up information (n = 725).

The following clinical and pathological variables other than the l-DRM were included in this study: year of surgery, sex, age, preoperative carcinoembryonic antigen (CEA) level, tumor size, histology, cN classification, number of harvested lymph node, and adjuvant chemotherapy. The cutoff point of age was determined by the median value, that of preoperative serum CEA level was determined by each institute, and that of tumor size and l-PRM were determined using receiver operating characteristic curve analysis based on their own cohorts. Measurements of the l-PRM and l-DRM were performed intracorporeally according to the method at each institution by surgeons. The number of harvested lymph nodes did not include lateral lymph nodes. The clinical and pathological stages were classified according to the 8th edition of the TNM classification system[8].

Statistical analysis

The effects of the clinical and pathological findings explored in this study on the overall survival (OS) rate were examined using the univariate logistic regression model. To identify the optimal cutoff point of the l-DRM affecting the OS rate, we used a multivariate Cox regression analysis model and an Akaike information criterion (AIC) value. Using this cutoff point, patients were divided into two groups after adjusting the potential biases affecting the OS rate using the propensity score of a 1:1 nearest neighbor matching with a caliper of 0.01. The actual OS rates of the propensity score-matched pairs were examined using the Kaplan-Meier method and the log-rank test. The statistical analysis was performed using JMP 13 software (SAS Institute, Inc., Cary, NC, USA). Statistical significance was established at P < 0.05 for all results.

Ethical statement

Ethics approval with the provisions of the Declaration of Helsinki was obtained from the JSCCR's Institutional Review Board (No.90-2).
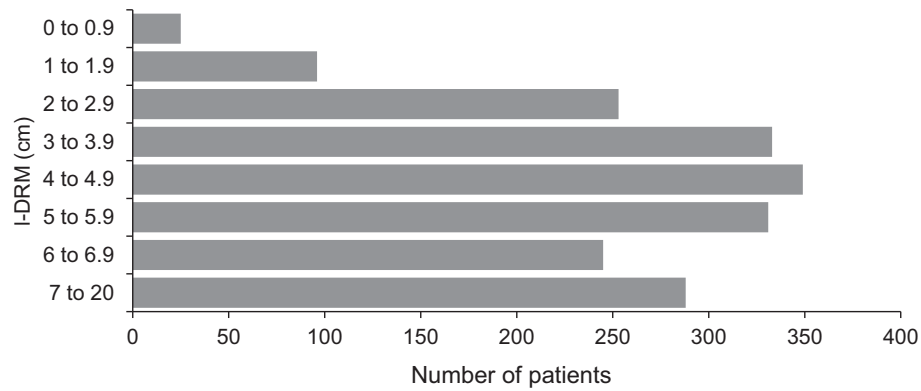
Figure 1. Distribution of the length of the distal resection margin among rectosigmoid cancer patients.

l-DRM length of the distal resection margin.

Results

The mean and median l-DRM were 4.8 ± 0.6 and 4.5 (range, 2.5-20.0) cm, respectively. The median follow-up time was 72 (range, 1 to 123) months. The distribution of the l-DRM is shown in Figure 1. Table 1 shows the characteristics and OS rates of patients with cT3 and cT4 rectosigmoid cancer according to their clinical and pathological findings. The patient population included 834 (57.8%) males and 609 (42.2%) females, with a mean age of 63.1 ± 11.1 years. The results of the univariate analysis of the variables expected to influence the OS rate are also presented in Table 1. Age group ≥ 63 years old (hazard ratio [HR], 1.37; 95% confidence interval [CI], 1.04-1.81; P = 0.0229), preoperative serum CEA level ≥ the cutoff point (HR, 1.64, 95% CI, 1.23-2.17; P = 0.0006), l-DRM < 2 cm (HR, 2.08; 95% CI, 1.30-3.16; P = 0.0031), l-DRM < 3 cm (HR, 1.40; 95% CI, 1.01-1.92; P = 0.0433), l-DRM < 4 cm (HR, 1.33; 95% CI, 1.01-1.76; P = 0.0407), moderately differentiated adenocarcinoma (tub 2), poorly differentiated adenocarcinoma (por), mucinous adenocarcinoma and signet-ring cell carcinoma (HR, 1.39; 95% CI, 1.05-1.85; P = 0.0200), positive cN (HR, 1.57; 95% CI, 1.18-2.12; P = 0.0018), and number of harvested lymph nodes < 12 (HR, 1.38; 95% CI, 1.03-1.84; P = 0.0304) were the factors that significantly influenced the OS rates of the patients with cT3 and cT4 rectosigmoid cancer.

Using the multivariate Cox regression analysis model and the AIC value, l-DRM of 4 cm was selected as the most appropriate cutoff point (HR, 1.37; 95% CI, 1.00-1.84; P = 0.0452; AIC 2404.62, Table 2). In the entire cohort, distribution of the patient's characteristics between the l-DRM < 4 cm and l-DRM ≥ 4 cm groups did not differ in terms of years of surgery, sex, age group, preoperative serum CEA level, tumor size, histology, and adjuvant chemotherapy (Table 3 left column). On the other hand, distribution of l-PRM, cN classification, and number of harvested lymph nodes differed between the two groups. To eliminate these biases, the two groups were compared using a propensity score matching method. Even after the matching, however, the number of harvested lymph nodes was still larger in the l-DRM ≥ 4 cm group (P = 0.0037) (Table 3 right column). In the matched cohort, the 5-year OS rate of the patients who had l-DRM < 4 cm was significantly lower than that of the patients who had l-DRM ≥ 4 cm (5-year OS, 80.3 vs. 87.6%; P = 0.0136; HR, 1.60; 95% CI, 1.09-2.31) (Figure 2).

Discussion

The results of this present study using a Japanese large-scale multi-institutional CRC database reveal that the 5-year OS rate of patients who had l-DRM ≥ 4 cm was significantly higher than that of patients who had l-DRM < 4 cm. This result indicates that l-DRM < 4 cm might be insufficient in cT3 and cT4 rectosigmoid cancer for curative intent surgery.

In 1951, Goligher et al. proposed that l-DRM of 5 cm was necessary to secure cancer-free margins in rectal cancer[9]. In 1954, Grinnell supported this 5-cm l-DRM rule based on pathological proof, including the presence of DIS in the intestinal wall 4 cm from the tumor distal edge. He examined 18 rectal cancers located 5-18 cm from the dentate line and reported the presence of DIS up to 4 cm from the tumor distal edge[10]. Thereafter, several studies supporting this 5-cm l-DRM rule were reported[11,12]. However, subsequent studies showed that the survival rate of patients with rectal cancer with DIS did not improve even if a longer l-DRM was secured. DIS is usually accompanied by poorly differentiated cancer; in such patients, the disease cannot be treated by surgery. These cancers often rapidly spread to distant organs[13-15]. Therefore, in order to determine the appropriate l-DRM, it is essential to consider not only DIS in the intestinal wall but also the extent of lymph

Table 1. Overall Survival Rate of Patients Who Underwent Curative Surgery for cT3 or cT4 Rectosigmoid Cancer According to Clinical and Pathological Findings in the Entire Cohort.

Prognostic factors	N (%)	OS	HR	95% CI	P
Year of surgery					
1995-1999/2000-2004	593 (41.1)/850 (58.9)	82.3/85.5	1.23/ref	0.94-1.62	0.12
Sex					
Male/Female	834 (57.8)/609 (42.2)	82.9/85.9	1.23/ref	0.93-1.64	0.13
Age group (years)					
<63/≥63	677 (46.9)/766 (53.1)	86.5/82.0	ref/1.37	1.04-1.81	0.0229
Preoperative serum CEA level					
<cutoff value/≥cutoff value/Missing	812 (56.3)/503 (34.9)/128 (8.8)	86.6/78.9	ref/1.64	1.23-2.17	0.0006
Tumor size (cm)					
<3.6/≥3.6/Missing	300 (20.8)/1031 (71.4)/112 (7.8)	85.8/83.8	ref/1.16	0.82-1.67	0.38
l-PRM (cm)					
<10/≥10	506 (35.0)/937 (65.0)	84.5/84.0	ref/1.06	0.80-1.42	0.64
l-DRM (cm)					
<2/≥2	82 (5.7)/1361 (94.3)	71.4/84.9	2.08/ref	1.30-3.16	0.0031
<3/≥3	255 (17.7)/1188 (82.3)	79.4/85.2	1.40/ref	1.01-1.92	0.0433
<4/≥4	497 (34.4)/946 (65.6)	81.1/85.8	1.33/ref	1.01-1.76	0.0407
<5/≥5	761 (52.7)/682 (47.3)	84.0/84.4	1.01/ref	0.77-1.33	0.91
<6/≥6	1021 (70.8)/422 (29.2)	83.9/84.9	1.06/ref	0.79-1.45	0.66
<7/≥7	1218 (84.4)/225 (15.6)	84.6/81.6	ref/1.20	0.83-1.69	0.29
Histology					
tub1/tub2,por,muc,sig	620 (43.0)/823 (57.0)	86.7/82.3	ref/1.39	1.05-1.85	0.0200
cN-classification					
negative/positive	592 (41.0)/851 (59.0)	87.9/81.6	ref/1.57	1.18-2.12	0.0018
Number of harvested lymph nodes					
<12/≥12/Missing	459 (31.8)/850 (58.9)/134 (9.3)	81.2/86.4	1.38/ref	1.03-1.84	0.0304
Adjuvant chemotherapy					
absent/present/Missing	692 (48.0)/587 (40.7)/164 (11.3)	85.4/82.8	ref/1.16	0.87-1.54	0.30

N, number; *OS*, overall survival; *HR*, hazard ratio; *CI*, confidence interval; *CEA*, carcinoembryonic antigen; *l-PRM*, length-proximal resection margin; *l-DRM*, length-distal resection margin; *tub1*, well-differentiated adenocarcinoma; *tub2*, moderately differentiated adenocarcinoma; *por*, poorly differentiated adenocarcinoma; *muc*, mucinous adenocarcinoma; *sig*, signet-ring cell carcinoma; *cN*, clinical lymph node

Table 2. Statistical Analysis of Cutoff Points for Overall Survival Rate after Adjusting Multivariate Cox Proportional Hazard Analysis for Multiple Cofounders.

l-DRM (cm)	Adjusted HR	95%C.I.	P	AIC
<2/≥2	1.64/ref	0.92-2.70	0.08	2405.72
<3/≥3	1.31/ref	0.90-1.86	0.15	2406.58
<4/≥4	1.37/ref	1.00-1.84	0.0452	2404.62
<5/≥5	1.06/ref	0.78-1.43	0.68	2408.47
<6/≥6	1.21/ref	0.86-1.71	0.27	2407.43
<7/≥7	ref/1.14	0.75-1.67	0.52	2408.23

l-DRM, length-distal resection margin; *HR*, hazard ratio; *CI*, confidence interval; *AIC*, Akaike's information criterion

node metastasis and lymphovascular invasion in the mesorectum. While DIS almost never proceeded beyond 1 cm from the tumor edge, lymphovascular spread and/or lymph node metastasis in the mesorectum was not uncommon at a distance of 2 to 5 cm[4,12,16-20]. To improve the local control rate of patients with rectal cancer, the National Comprehensive Cancer Network (NCCN) guidelines recommend removing the mesorectum by 4-5 cm from the distal edge of the tumors. In distal rectal cancer, however, the NCCN guidelines admitted that a negative bowel margin of 1-2 cm, which must be confirmed to be tumor-free by frozen section, may be acceptable[21].

Several previous retrospective observational studies have reported that an extended l-DRM for CRC did not improve the rates of local recurrence or the OS rates[14,22-36]. However, these studies assessed the entire study cohort without matching patient characteristics. Bernstein (2011) and colleagues reported that the survival and local recurrence rates of patients with longer l-DRM were equivalent to that of patients with shorter l-DRM. They concluded that this observation was due to a bias in patient selection; that is, patients with long l-DRM had more advanced T classification[37]. To eliminate these biases, we used propensity score matching. Nevertheless, in both entire cohort and matched

Table 3. Characteristics of Patients Who Underwent Curative Surgery for cT3 or cT4 Rectosigmoid Cancer According to Surgical Distal Resection Margin in the Propensity Score-Matched Cohort.

	Entire cohort			Matched cohort		
	l-DRM < 4 cm N = 497	l-DRM ≥ 4 cm N = 946	P	l-DRM < 4 cm N = 402	l-DRM ≥ 4 cm N = 402	P
Year of surgery						
1995-1999	198 (39.8)	395 (41.7)	0.48	175 (43.5)	155 (38.6)	0.15
2000-2004	299 (60.2)	551 (58.3)		227 (56.5)	247 (61.4)	
Sex						
Male	284 (57.1)	550 (58.1)	0.71	226 (56.2)	244 (60.7)	0.20
Female	213 (42.9)	396 (41.9)		176 (43.8)	158 (39.3)	
Age group (years)						
<63	235 (47.3)	442 (46.7)	0.83	187 (46.5)	180 (44.8)	0.62
≥63	262 (52.7)	504 (53.3)		215 (53.5)	222 (55.2)	
Preoperative serum CEA level						
<cutoff value	293 (59.0)	519 (54.9)	0.09	257 (63.9)	257 (63.9)	1.0
≥cutoff value	155 (31.2)	348 (36.8)		145 (36.1)	145 (36.1)	
Missing	49 (9.8)	79 (8.3)				
Tumor size (cm)						
<3.6	103 (20.7)	197 (20.8)	0.15	91 (22.6)	91 (22.6)	1.0
≥3.6	346 (69.6)	685 (72.4)		311 (77.4)	311 (77.4)	
Missing	48 (9.7)	64 (6.8)				
l-PRM (cm)						
<10	214 (43.1)	292 (30.9)	<0.0001	161 (40.0)	161 (40.0)	1.0
≥10	283 (56.9)	654 (69.1)		241 (60.0)	241 (60.0)	
Histology						
tub1	209 (42.1)	411 (43.4)	0.61	172 (42.8)	184 (45.8)	0.39
tub2, por, muc, sig	288 (57.9)	535 (56.6)		230 (57.2)	218 (54.2)	
cN-classification						
negative	226 (45.5)	366 (38.7)	0.013	178 (44.3)	178 (44.3)	1.0
positive	271 (54.5)	580 (61.3)		224 (55.7)	224 (55.7)	
Number of harvested lymph nodes						
<12	197 (39.6)	262 (27.7)	<0.0001	157 (39.1)	120 (29.9)	0.0037
≥12	261 (52.5)	589 (62.3)		216 (53.7)	232 (57.7)	
Missing	39 (7.9)	95 (10.0)		29 (7.2)	50 (12.4)	
Adjuvant chemotherapy						
absent	244 (49.1)	448 (47.4)	0.72	210 (52.2)	203 (50.5)	0.34
present	195 (39.2)	392 (41.4)		161 (40.1)	156 (38.8)	
missing	58 (11.7)	106 (11.2)		31 (7.7)	43 (10.7)	

N, number; *OS*, overall survival; *HR*, hazard ratio; *CI*, confidence interval; *CEA*, carcinoembryonic antigen; *l-PRM*, length-proximal resection margin; *l-DRM*, length-distal resection margin; *tub1*, well-differentiated adenocarcinoma; *tub2*, moderately differentiated adenocarcinoma; *por*, poorly differentiated adenocarcinoma; *muc*, mucinous adenocarcinoma; *sig*, signet-ring cell carcinoma; *cN*, clinical lymph node

cohort, the 5-year OS rate of patients who had l-DRM < 4 cm was significantly lower than that of patients with l-DRM ≥ 4 cm (Figure 2).

It is possible that the l-DRM measurement method influenced the results. Shrinkage occurs in the first 10 to 20 minutes after the specimen is resected, and the specimens further shrink in formalin fixation[16,17,38-40]. The l-DRM measurement of formalin-fixed specimens may affect the outcomes of this kind of retrospective observational study. This may be one of the reasons why in the previous reports, the OS rate did not differ between the patients who had

longer and shorter l-DRM. Park and Kim suggested that fixed specimens may not be useful to determine the l-DRM for CRC surgery[40]. The JSCCR database records the l-DRM both during surgery and after formalin fixation. Since this present study used the l-DRM measured during surgery, the timing of measuring of the l-DRM was appropriate.

This study had several limitations. First, this was a retrospective observational study. While confounding factors related to l-DRM were excluded using the Cox regression analysis models and propensity score matching method, the effect of factors other than the confounding factors on the l-
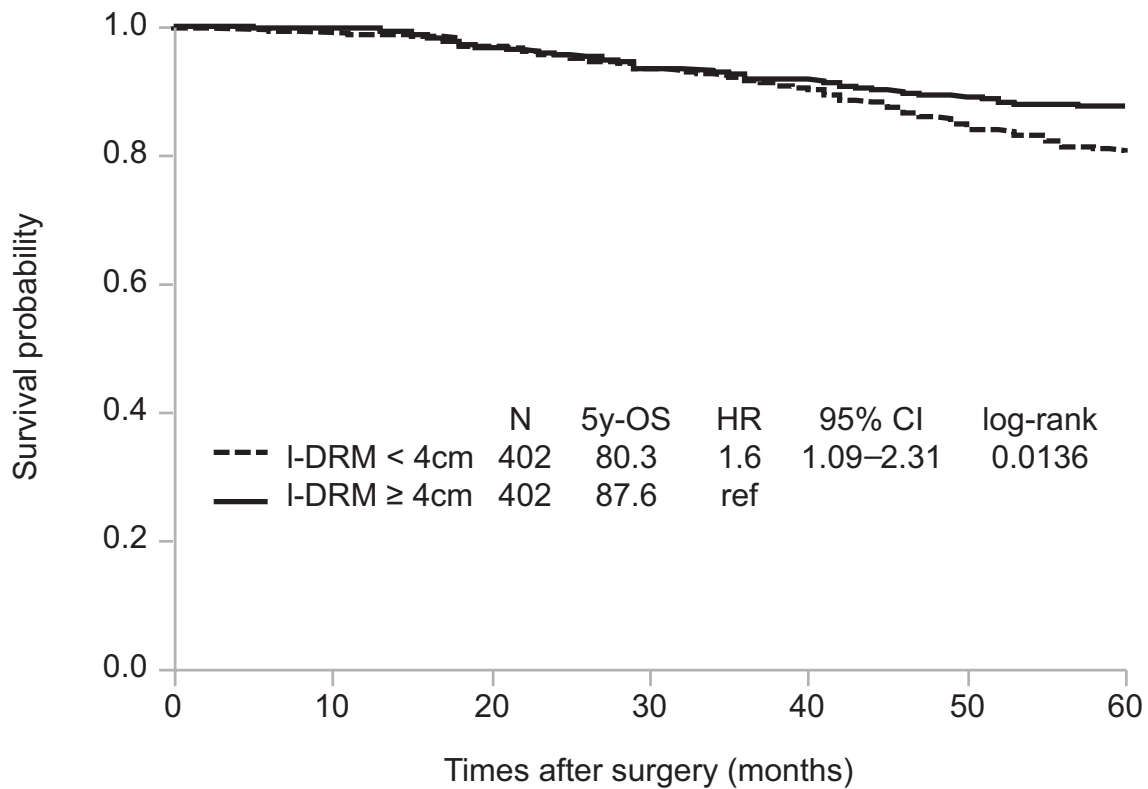
Figure 2. Overall survival for patients with cT3 or cT4 rectosigmoid cancer according to the length of the distal resection margin in the propensity score-matched cohort.

N number of patients, *HR* hazard ratio, *CI* confidence interval, *l-DRM* length of the distal resection margin, *ref* reference

DRM could not be completely excluded. Despite eliminating the influence of confounding factors using the propensity score method, the number of dissected lymph nodes was still larger in patients who had l-DRM ≥ 4 cm than that of patients who had l-DRM < 4 cm. This difference could have affected the OS rate. Additionally, because the l-DRM in this database represented that of the resected rectal wall, it did not always match the length of the resected mesorectum. However, since mesorectal resection was performed based on the blood supply to the remnant rectal stump, we believe the difference in lengths between the resected rectal wall and the mesorectum was minimal and hence they were almost the same. Additionally, a detailed method to measure bowel resection from the tumor edge in surgery was uncertain in this retrospective study. In addition, it was difficult for us to completely rule out the possibility of including only a small number of patients with sigmoid colon cancer in this study. Second, the study period was rather old. The adjuvant chemotherapy and chemotherapy for advanced CRC performed during the study period differ from those that are currently performed. In the present era, those advances in cancer treatment might affect the results of this study. Third, the database used in this study has poor information on recurrence; therefore, we were unable to consider local recurrence. Four, the strict data cleaning and matching resulted in a decreased number of cases used for the analysis. However, due to its severity, a highly accurate analysis was possible in this retrospective observational study.

In recent years, the recommended l-DRM in case of rectal cancer has been gradually shortened[21-36], while that for colon cancer remains 5 to 10 cm for the dissection of regional lymph nodes[11,17,40-44]. Our study of the l-DRM for rectosigmoid cancer using the JSCCR database suggested that an l-DRM < 4 cm may be insufficient, although we were unable to definitely confirm the validity of the Japanese 3-cm l-DRM rule. To overcome the limitations of this study, further prospective studies with a unified measuring method of a resection margin and accurate information on recurrence are necessary to determine an ideal l-DRM for rectosigmoid cancer surgery.

Conflicts of Interest

There are no conflicts of interest.

Author Contributions

All authors contributed significantly to the conception and design of the study, acquisition, analysis and interpretation of data, drafting of the manuscript, and revision and approval of the final version.

Approval by Institutional Review Board (IRB)

Approval code was 90-2 from the JSCCR's Institutional Review Board.

References

1. Japanese Society for Cancer of the Colon and Rectum. Japanese Classification of Colorectal Carcinoma, 1st English ed. 1997. Kanehara & Co, Ltd, Tokyo.

2. Wittekind Ch, Compton CC, Brierley J, et al. Union for International Cancer Control TNM Supplement: a commentary on uniform use, 4th ed. 2012.

3. Global Cancer Observatory. International Agency for Research on Cancer. World Health Organization. Available from: http://www.iarc.fr/.

4. Heald RJ, Husband EM, Ryall RD. The mesorectum in rectal cancer surgery--the clue to pelvic recurrence? Br J Surg. 1982 Oct; 69 (10): 613-6.

5. Heald RJ, Ryall RD. Recurrence and survival after total mesorectal excision for rectal cancer. Lancet. 1986 Jun; 28(8496): 1479-82.

6. Quirke P, Durdey P, Dixon MF, et al. Local recurrence of rectal adenocarcinoma due to inadequate surgical resection: histopathological study of lateral tumour spread and surgical excision. Lancet. 1986 Nov 1; 2(8514): 996-9.

7. Japanese Society for Cancer of the Colon and Rectum. Japanese Classification of Colorectal Carcinoma, 2nd English ed. Kanehara & Co, Ltd, Tokyo. 2009. 43 p.

8. Brierly JD, Gospodarowicz MK, Wittekind C, et al. UICC International Union Against Cancer: TNM classification of malignant tumors, 8th ed. Wiley-Blackwell. 2017. 73-6 p.

9. Goligher JC, Dukes CE, Bussey HJ. Local recurrences after sphincter saving excisions for carcinoma of the rectum and rectosigmoid. Br J Surg. 1951 Nov; 39(155): 199-211.

10. Grinnell RS. Distal intramural spread of carcinoma of the rectum and rectosigmoid. Surg Gynecol Obstet. 1954 Oct; 99(4): 421-30.

11. Enker WE, Laffer UT, Block GE. Enhanced survival of patients with colon and rectal cancer is based upon wide anatomic resection. Ann Surg. 1979 Sep; 190(3): 350-60.

12. Hida J, Yasutomi M, Maruyama T, et al. Lymph node metastases detected in the mesorectum distal to carcinoma of the rectum by the clearing method: justification of total mesorectal excision. J Am Coll Surg. 1997 Jun; 184(6): 584-8.

13. Williams NS, Dixon MF, Johnston D. Reappraisal of the 5 centimetre rule of distal excision for carcinoma of the rectum: a study of distal intramural spread and of patients' survival. Br J Surg. 1983 Mar; 70(3): 150-4.

14. Madsen PM, Christiansen J. Distal intramural spread of rectal carcinomas. Dis Colon Rectum. 1986 Apr; 29(4): 279-82.

15. Shirouzu K, Isomoto H, Kakegawa T. Distal spread of rectal cancer and optimal distal margin of resection for sphincter-preserving surgery. Cancer. 1995 Aug 1; 76(3): 388-92.

16. Ono C, Yoshinaga K, Enomoto M, et al. Discontinuous rectal cancer spread in the mesorectum and the optimal distal clearance margin in situ. Dis Colon Rectum. 2002 Jun; 45(6): 744-9.

17. Nelson H, Petrelli N, Carlin A, et al. National Cancer Institute Expert Panel Guidelines 2000 for colon and rectal cancer surgery. J Natl Cancer Inst. 2001 Apr 18; 93(8): 583-96.

18. Morikawa E, Yasutomi M, Shindou K, et al. Distribution of metastatic lymph nodes in colorectal cancer by the modified clearing method. Dis Colon Rectum. 1994 Mar; 37(3): 219-23.

19. Reynolds JV, Joyce WP, Dolan J, et al. Pathological evidence in support of total mesorectal excision in the management of rectal cancer. Br J Surg. 1996 Aug; 83(8): 1112-5.

20. Zhao GP, Zhou ZG, Lei WZ, et al. Pathological study of distal mesorectal cancer spread to determine a proper distal resection margin. World J Gastroenterol. 2005 Jan; 11(3): 319-22.

21. National Comprehensive Cancer Network. 2017. Available from: https://www.nccn.org/.

22. Wilson SM, Beahrs OH. The curative treatment of carcinoma of the sigmoid, rectosigmoid, and rectum. Ann Surg. 1976 May; 183 (5): 556-65.

23. Pollett WG, Nicholls RJ. The relationship between the extent of distal clearance and survival and local recurrence rates after curative anterior resection for carcinoma of the rectum. Ann Surg. 1983 Aug; 198(2): 159-63.

24. Williams NS. The rationale for preservation of the anal sphincter in patients with low rectal cancer. Br J Surg. 1984 Aug; 71(8): 575-81.

25. Phillips RK, Hittinger R, Blesovsky L, et al. Local recurrence following 'curative' surgery for large bowel cancer: II. The rectum and rectosigmoid. Br J Surg. 1984 Jan; 71(1): 17-20.

26. Kirwan WO, Drumm J, Hogan JM, et al. Determining safe margin of resection in low anterior resection for rectal cancer. Br J Surg. 1988 Jul; 75(7): 720.

27. McDermott FT, Hughes ES, Pihl E, et al. Local recurrence after potentially curative resection for rectal cancer in a series of 1008 patients. Br J Surg. 1985 Jan; 72(1): 34-7.

28. Wolmark N, Fisher B. An analysis of survival and treatment failure following abdominoperineal and sphincter-saving resection in Dukes' B and C rectal carcinoma. A report of the NSABP clinical trials. National Surgical Adjuvant Breast and Bowel Project. Ann Surg. 1986 Oct; 204(4): 480-9.

29. Phillips RK. Adequate distal margin of resection for adenocarcinoma of the rectum. World J Surg. 1992 May-Jun; 16(3): 463-6.

30. Andreola S, Leo E, Belli F, et al. Distal intramural spread in adenocarcinoma of the lower third of the rectum treated with total rectal resection and coloanal anastomosis. Dis Colon Rectum. 1997 Jan; 40(1): 25-9.

31. Moore HG, Riedel E, Minsky BD, et al. Adequacy of 1-cm distal margin after restorative rectal cancer resection with sharp mesorectal excision and preoperative combined-modality therapy. Ann Surg Oncol. 2003 Jan-Feb; 10(1): 80-5.

32. Leo E, Belli F, Miceli R, et al. Distal clearance margin of 1 cm or less: a safe distance in lower rectum cancer surgery. Int J Colorectal Dis. 2009 Mar; 24(3): 317-22.

33. Kiran RP, Lian L, Lavery IC. Does a subcentimeter distal resection margin adversely influence oncologic outcomes in patients with rectal cancer undergoing restorative proctectomy? Dis Colon Rectum. 2011 Feb; 54(2): 157-63.

34. Bujko K, Rutkowski A, Chang GJ, et al. Is the 1-cm rule of distal bowel resection margin in rectal cancer based on clinical evi-

dence? A systematic review. Indian J Surg Oncol. 2012 Jun; 3(2): 139-46.

35. Kwak JY, Kim CW, Lim SB, et al. Oncologically safe distal resection margins in rectal cancer patients treated with chemoradiotherapy. J Gastrointest Surg. 2012 Oct; 16(10): 1947-54.

36. Kang DW, Kwak HD, Sung NS, et al. Oncologic outcomes in rectal cancer patients with a ≤1-cm distal resection margin. Int J Colorectal Dis. 2017 Mar; 32(3): 325-32.

37. Bernstein TE, Endreseth BH, Romundstad P, et al. Norwegian Colorectal Cancer Registry: what is a safe distal resection margin in rectal cancer patients treated by low anterior resection without preoperative radiotherapy? Colorectal Dis. 2011 Feb; 14(2): e48-55.

38. Weese JL, O'Grady MG, Ottery FD. How long is the five centimeter margin? Surg Gynecol Obstet. 1986 Aug; 163(2): 101-3.

39. Søndenaa K, Kjellevold KH. A prospective study of the length of the distal margin after low anterior resection for rectal cancer. Int J Colorectal Dis. 1990 May; 5(2): 103-5.

40. Park IJ, Kim JC. Adequate length of the distal resection margin in rectal cancer: from the oncological point of view. J Gastrointest Surg. 2010 Aug; 14(8): 1331-7.

41. Toyota S, Ohta H, Anazawa S. Rationale for extent of lymph node dissection for right colon cancer. Dis Colon Rectum. 1995 Jul; 38 (7): 705-11.

42. Hida J, Okuno K, Yasutomi M, et al. Optimal ligation level of the primary feeding artery and bowel resection margin in colon cancer surgery: the influence of the site of the primary feeding artery. Dis Colon Rectum. 2005 Dec; 48(12): 2232-7.

43. Labianca R, Nordlinger B, Beretta GD, et al. ESMO Guidelines Working Group Early colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013 Oct; 24: Suppl 6: vi64-72.

44. Xynos E, Gouvas N, Triantopoulou C, et al. Clinical practice guidelines for the surgical management of colon cancer: a consensus statement of the Hellenic and Cypriot Colorectal Cancer Study Group by the HeSMO. Ann Gastroenterol. 2016 Mar; 29(1): 3-17.