Clinical Significance of the Mesorectal Extension of Rectal Cancer: A Japanese Multi-institutional Study

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Objective: The aim of this study was to emphasize the importance of a subclassification in the TNM staging system of rectal cancer.

Background: The clinical significance of the mesorectal extension of rectal cancer is unclear.

Patients and Methods: Data from 463 consecutive patients with stage IIa disease (T3N0) undergoing curative surgery at 28 institutes were analyzed. The measurement of the distance of the mesorectal extension (DME) was histologically evaluated. Risk factors for recurrence, for the optimal cutoff point of the DME, independent prognostic factors, and for survivals were studied using receiver operating characteristic curve and logistic and Cox regression analyses. Survivals were calculated using the Kaplan-Meier method.

Results: A value of 4 mm was determined as the optimal cutoff point. The patients were subdivided into 2 groups: DME $\leq$ 4 mm and DME $>$ 4 mm at the optimal cutoff point. DME $>$ 4 mm had the greatest impact on recurrence-free survival [$P = 0.00023$, hazard ratio (HR): 2.26, 95% confidence interval (95% CI): 1.465-3.492, L/U ratio: 0.420] and was an independent adverse prognostic factor ($P = 0.00323$, HR: 1.97, 95% CI: 1.254-3.091). The distant metastasis rate in DME $>$ 4 mm was higher 16.7% than that in DME $\leq$ 4 mm ($P = 0.00177$, OR: 2.61, 95% CI: 1.430-4.761). The incidence of local recurrence was not influenced by DME. The recurrence-free 5-year survival rate in DME $\leq$ 4 mm was significantly better than that in DME $>$ 4 mm (86.6% vs 71.3%, $P = 0.00015$, HR: 0.44, 95% CI: 0.286-0.683). The cancer-specific survival rate in DME $\leq$ 4 mm was also significantly better than that in DME $>$ 4 mm (91.3% vs 82.2%, $P = 0.000664$, HR: 0.52, 95% CI: 0.325-0.843).

Conclusions: A subclassification according to mesorectal extension based on a 4-mm cutoff point is needed for the TNM staging system. However, further prospective study is necessary to prove reproducibility and validity of the cutoff point.

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The current TNM staging system is now the standard for colorectal cancer staging and well reflects prognosis. However, the mesorectal extension in rectal cancer also seems to influence recurrence or prognosis, but the mesorectal extension is not mentioned in the TNM staging system. Although the UICC proposed optional subdivisions for T3 and T4 tumors in 1993,[1] the clinical significance of the mesorectal extension in rectal cancer has still not been recognized. Several reports from a single institute have shown the prognostic heterogeneity of T3 rectal cancers.[2–10] However, these reports have used different prognostic cutoff points for subdividing the mesorectal extension in T3 tumor, that is, microscopic invasion,[5] more or less than 2 mm,[3] 3 mm,[6,10] 4 mm,[2,8,9] 5 mm,[4] or 6 mm.[7] Those reports are still controversial because of the small number of patients, only a small amount of data, and being from a single institute, and insufficient statistical analyses. A Swiss Registry Study on Colorectal Cancer (SAKK) showed that the 30-month survival rate was better in N0 patients with mesorectal extension $\leq$ 5 mm (cited from reference 11). Based on multi-institutional large investigation, Merkel et al[4] analyzed the data of the Erlangen Registry for Colo-Rectal Carcinomas (ERCRC) and the German prospective multicenter study of the Study Group Colo-Rectal Carcinoma (SGCRC), and they reported that the prognosis was significantly better in patients with mesorectal extension $\leq$ 5 mm. We have now analyzed the multi-institutional large amounts of data from the Study Group of the Japanese Society for Cancer of the Colon and Rectum (JSCCR), and we report these findings here. The present study emphasizes the clinical importance of defining appropriate substages within the TNM staging system.

PATIENTS AND METHODS

Approval from the Ethics Committee of both the JSCCR and the local institutional review board was obtained to allow review of the medical records and to permit follow-up patient contact. Data were reviewed on 1091 patients enrolled from 28 institutes that were members of the Study Group of the JSCCR on Extramural Mesorectal Extension of Rectal Cancer. All patients had a primary rectal adenocarcinoma that was located in the lower two-thirds of the rectum. Total mesorectal excision and histologically defined curative surgery were performed between 1995 and 1999. Neither preoperative radiotherapy nor neoadjuvant chemotherapy was performed in these enrolled patients. Of the 1091 patients, 1055 possessed available clinicopathological information and were eligible for analysis. Thirty-six patients were excluded because of insufficient clinical and follow-up information. Of the 1055 patients, the present study was focused on those 463 with stage IIa disease. The clinicopathological data and follow-up system were based on the Japanese rules defined by JSCCR.[12] They were restaged according to the pathological TNM classification (6th edition).[13] Most institutes established a postoperative follow-up examination period of 5 to 10 years. The follow-up system consisted of measurement of serum tumor marker, chest x-ray, and abdominal ultrasound examination every 3 months for the first 3 years and then every 6 months for the next 2 years. When the development of recurrence was suspected, the final diagnosis was made using CT and/or MRI and other diagnostic tools. Local recurrence

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was defined as the presence of radiologically confirmed or histologically proven tumor nonhematogenously occurring in the pelvis within the field of the initial surgery. Distant metastasis included hematogenous metastases to the liver, lung, bone, brain, kidney, and other organs. The other recurrences were defined as a recurrence except local recurrence and distant metastasis, that is, peritoneal dissemination, intra-abdominal, para-aortic, subclavicular, mediastinal, and inguinal lymph node metastases. The outcomes of all patients were investigated as carefully as possible. As of January 1995, the eligible surviving patients had been followed for a median of 86 months (range, 1–166). Of these patients, 89.2% were followed for at least 3 years, and 81.9% for at least 5 years.

Measurement of Mesorectal Extension

All surgically resected specimens were opened up along the antimesenteric side. The specimens were fixed in 20% formalin for at least 48 hours after being pinned to a wooden or corkboard. Then, 1 or more longitudinal sections of the tumor were sliced at the point of maximum extramural invasion. Those sections were embedded in paraffin after being divided into some blocks of suitable size, which were then routinely processed for hematoxylin-and-eosin and elastica-Van-Gieson staining. In those sections, the tumor category T3 was subdivided on the basis of the histological measurement of the maximum depth of invasion beyond the outer border of the muscular layer (in millimeters). Without any knowledge of clinical information, the histological measurement was assessed. Hematoxylin-and-eosin-stained sections are presented in Figure 1. When the outer border of the muscular layer was completely identifiable (sometimes identifiable as fragments of muscle), the distance from the outer border of the muscular layer to the deepest part of the invasion was measured (Fig. 1a). When the outer border of the muscular layer was not entirely identifiable because of destruction by the invasion or excessive inflammatory reaction, an estimate of the outer border was obtained by drawing a straight solid line between both break points in the muscular layer (Fig. 1b).

Statistical Methods

Statistical analysis was performed using computer software of StatView 5.0 and JMP 7.0 (SAS Institute, Inc, Cary, NC) for Windows. All clinicopathological independent variables (12 items) were encoded for analysis: sex (female: 0, male: 1), size of tumor ($\leq$ 5 cm: 0, $>$ 5 cm: 1), location of tumor (middle-third: 0, lower-third: 1), gross type (expansive: 0, infiltrative: 1), histology [well-differentiated adenocarcinoma: 0, others (moderately, poorly differentiated, and mucinous adenocarcinoma): 1], lymphatic invasion [negative-to-minimal invasion (ly0–1): 0, moderate-to-severe invasion (ly2–3): 1], venous invasion [negative-to-minimal invasion (v0–1): 0, moderate-to-severe invasion (v2–3): 1], operative methods [sphincter-saving operation (SSO): 0, abdominoperineal resection (APR): 1], lateral pelvic lymph node dissection (no: 0, yes: 1), autonomic-nerve-saving operation (yes: 0, no: 1), postoperative chemotherapy (no: 0, yes: 1), and mesorectal extension ($\leq X$ mm: 0, $> X$ mm: 1). Total recurrence (absent: 0, present: 1), distant metastasis (absent: 0, present: 1), local recurrence (absent: 0, present: 1), and survival (alive: 0, dead: 1) were coded as dependent variables. A receiver operating characteristic (ROC) curve was used to find an expected cutoff point. The continuous variable of distance of the mesorectal extension (DME) was applied to ROC analysis. Both univariate logistic regression analysis for recurrence and multivariate Cox regression analysis for recurrence-free survival were used to confirm the optimal cutoff point of mesorectal extension. The Cox regression analysis was also used to analyze the independent prognostic factors for recurrence-free survival. The Kaplan-Meier method and the logrank test were used for calculating survival rates. Some detailed P values were calculated using the chi-square calculator on the Web site of www.swogstat.org/statoolsout.html. The level for statistical significance was determined at $P < 0.05$ and the confidence interval (CI) was determined at the 95% level.

RESULTS

Histogram of Distance of Mesorectal Extension

The DME in the 463 rectal cancers was histologically measured. The mean DME was 4.2 ± 4.2 mm, and the median DME was 2.9 mm (range, 0.1–30) (Fig. 2).

Postoperative Recurrence Pattern

Postoperative total recurrence occurred in 89 (19.2%) of the 463 patients. Twenty-five patients (5.4%) had local recurrence only, and 49 patients (10.6%) had distant metastasis only. The remaining 15 patients had other recurrences, that is, peritoneal dissemination, intra-abdominal, para-aortic, subclavicular, mediastinal, and inguinal lymph node metastases (Table 1).

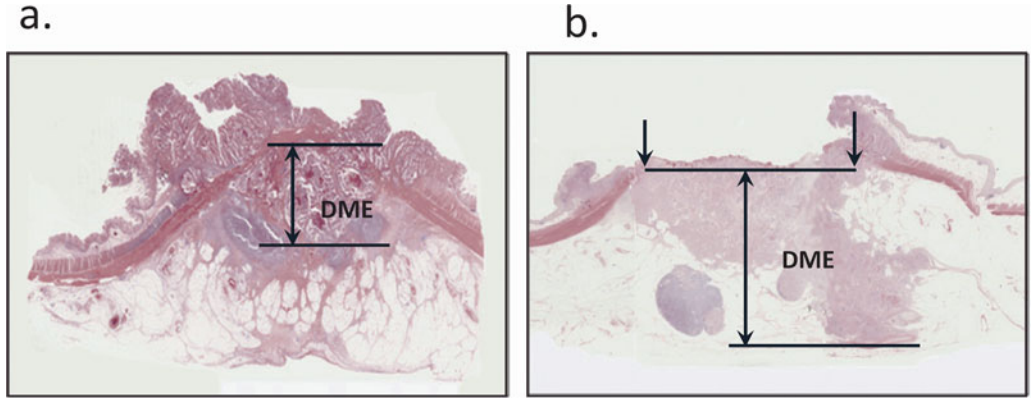

FIGURE 1. Measurement of DME. A, When the outer border of the muscular layer was completely identifiable, the distance from the outer border of the muscular layer to the deepest part of the invasion was measured (mm). B, When the outer border of the muscular layer was not entirely identifiable, an estimate of the outer border was obtained by drawing a straight solid line between the both break points of the muscular layer.

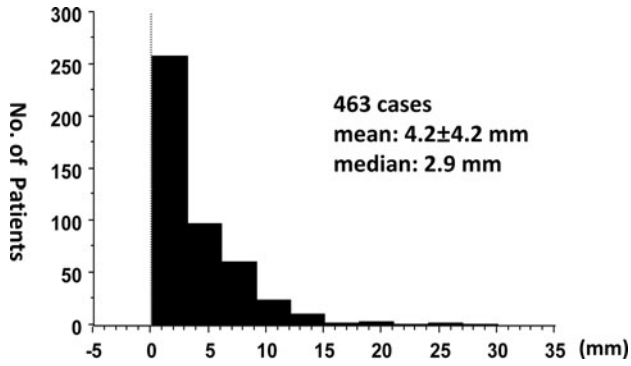

FIGURE 2. Histogram of DME. The mean DME is 4.2 ± 4.2 mm, and the median DME is 2.9 mm (range, 0.1–30).

TABLE 1. Postoperative Recurrence Pattern in Patients With Stage IIa (T3N0)

No. of Patients	Local only	Distant only	Local plus Distant	Others*	Total Recurrence
463	25 (5.4)	49 (10.6)	0	15	89 (19.2)

*Peritoneal dissemination, intra-abdominal, para-aortic, subclavicular, mediastinal, and inguinal lymph node metastases.

Risk Factors for Postoperative Recurrence

The risk factors for postoperative recurrence are listed in Table 2. The gross type (infiltrative type; odds ratio [OR]: 2.06, 95% CI: 1.100-3.840, $P = 0.0240$), histology (others: OR: 1.70, 95% CI: 1.010-2.852, $P = 0.0457$), lymphatic invasion (ly2–3; OR: 3.07, 95% CI: 1.777-5.303, $P = 0.000058$), venous invasion (v2–3; OR: 2.31, 95% CI: 1.426-3.726, $P = 0.000656$), and operative methods (APR; OR: 1.67, 95% CI: 1.050-2.660, $P = 0.0303$) were significant risk factors for postoperative recurrence.

Statistical Analysis of Cut-off Points

The mean value of 4.2 mm was considered as a cutoff point from the DME histogram (Fig. 2). The ROC curve showed 4.2 mm as the cutoff value expecting postoperative recurrence at a high true positive rate (sensitivity: 0.5169), low false positive rate (1 − specificity: 0.3262), high accuracy rate (0.6436), high positive likelihood ratio (1.5846), high positive predictive value (0.2738), high OR (2.2097), and low chi-square P value (0.0012) among other cutoff points (Fig. 3). The ROC curve analysis was reasonable as a statistical model [AUC (area under curve): 0.617, OR: 1.05, 95% CI: 0.9991-1.1050, $P = 0.0541$]. A value of 4 mm was then considered as an appropriate cutoff point. Univariate logistic regression analysis showed that the value of 4 mm was a good cutoff point that had significant influence on postoperative recurrence ($\chi^2 = 10.997$, OR: 2.21, 95% CI: 1.383-3.531, $P = 0.00091$). The L/U ratio (lower/upper limits of CI) showed high reliability (0.392), among other cutoff points (Table 3a). Multivariate Cox regression analysis confirmed that the value of 4 mm was an optimal cutoff point that had the greatest impact on recurrence-free 5-year survival, among all other cutoff points (highest $\chi^2 = 13.567$, higher hazard ratio [HR]: 2.26, 95% CI: 1.465-3.492, highest LU ratio: 0.420, and lowest $P = 0.00023$) (Table 3b). Therefore, the patients were subdivided into 2 groups: DME ≤ 4 mm and DME > 4 mm.

Independent Prognostic Factor for Recurrence-free Survival

The significant variables extracted in Table 2 and the cutoff point of 4 mm determined in Table 3 were analyzed to determine the independent prognostic factors for recurrence-free survival using Cox regression analysis. The variables are listed in Table 4. Lymphatic invasion (ly2–3; $\chi^2 = 9.873$, HR: 2.22, 95% CI: 1.351-3.659, L/U ratio: 0.369, $P = 0.00168$), venous invasion (v2–3; $\chi^2 = 5.446$, HR: 1.73, 95% CI: 1.091-2.727, L/U ratio: 0.400, $P = 0.01961$), and DME (> 4 mm; $\chi^2 = 8.674$, HR: 1.97, 95% CI: 1.254-3.091, L/U ratio: 0.406, $P = 0.00323$) were extremely higher independent adverse prognostic factors for recurrence-free survival. Especially, DME > 4 mm was the most reliable adverse predictor with the highest value of L/U ratio.

Distant Metastasis and Local Recurrence

The distant metastasis rate was significantly higher in DME > 4 mm (16.7%, $\chi^2 = 9.774$, OR: 2.61, 95% CI: 1.430-4.761, $P = 0.00177$). The local recurrence showed no significant difference at the cutoff point ($\chi^2 = 2.733$, $P = 0.09829$) (Table 5).

Recurrence-free and Cancer-specific Survivals

The 5- and 10-year recurrence-free survival rates of DME ≤ 4 mm in patients were 86.6% and 85.3%, respectively. They were significantly better than those of DME > 4 mm (HR: 0.44, 95% CI: 0.286-0.683, $P = 0.00015$) (Table 6, Fig. 4a). The 5- and 10-year cancer-specific survival rates of DME ≤ 4 mm were 91.3% and 82.2%, respectively. They were significantly better than those of DME > 4 mm (HR: 0.52, 95% CI: 0.325-0.843, $P = 0.00664$) (Table 6, Fig. 4b).

DISCUSSION

The TNM staging system of the International Union Against Cancer[13] and American Joint committee on Cancer[14] are now the standards for colorectal cancer staging. The current sixth edition of the *AJCC Cancer Staging Manual* includes refinements in colorectal cancer staging that are based on large data sets from the National Cancer Data Bases.[15] The stage is the strongest predictor of survival, and the TNM staging system definitively reflects prognosis. Although subclassification of T3 was not essential, measurement of the depth of extramural soft tissue invasion has been previously proposed by some authors.[11,16] Several reports from a single institute showed the prognostic heterogeneity of T3 rectal cancers.[2–10] However, those authors reported a variety of prognostic cutoff points for subdividing mesorectal extension of T3/T4 tumors. Willett et al[3] constructed 3 subgroups of the depth of invasion: < 2 mm, 2 to 8 mm, and ≥ 8 mm. The recurrence-free survival in patients with T3N0 was significantly different: 87% vs 57% vs 36%, respectively. They recommended selecting patients with rectal cancer for postoperative adjuvant therapy by the depth of invasion into the perirectal fat. Harewood et al[17] assessed the mesorectal extension from a different approach, using preoperative endoscopic ultrasound. They reported that all T3 rectal tumors were not equal, and recurrence-free survival was significantly better in patients with minimally invasive T3 disease (≤ 2 mm). Tokoro et al[10] selected the cutoff point of 3 mm although the number of investigated patients was very small (26 patients). They reported that T3N0 patients with a mesorectal extension ≥ 3 mm had worse recurrence-free 5-year survival, and that ≥3 mm was an adverse independent prognostic factor for recurrence-free survival. However, Picon et al[6] showed no prognostic significance of mesorectal extension at a cutoff point of 3 mm. At the cutoff point of 4 mm, mesorectal extension more than 4 mm was confirmed as an independent adverse prognostic factor for survival by some multivariate

TABLE 2. Risk Factors for Postoperative Recurrence in Patients With Stage IIa (T3N0) Using Univariate Logistic Regression Analysis

Variable	No. of Patients	Rate of Recurrence	χ^2	OR (95% CI)	*P*
Sex					
Male vs female	331 vs 132	19% vs 19%	0.010	1.03 (0.614-1.715)	0.9222
Size of tumor					
> 5 cm vs ≤ 5 cm	231 vs 225	19% vs 20%	0.019	0.97 (0.608-1.541)	0.8907
Location of tumor					
Lower third vs middle third	300 vs 163	21% vs 15%	2.425	1.50 (0.901-2.487)	0.1194
Gross type					
Infiltrative vs expansive	56 vs 400	30% vs 18%	5.097	2.06 (1.100-3.840)	0.0240
Histology					
Others vs well	301 vs 162	22% vs 14%	3.994	1.70 (1.010-2.852)	0.0457
Lymphatic invasion					
ly2–3 vs ly0–1	74 vs 387	36% vs 16%	16.178	3.07 (1.777-5.303)	0.000058
Venous invasion					
v2–3 vs v0–1	135 vs 327	29% vs 15%	11.609	2.31 (1.426-3.726)	0.000656
Operative methods					
APR vs SSO	197 vs 266	24% vs 16%	4.690	1.67 (1.050-2.660)	0.0303
Lateral pelvic LN dissection					
Yes vs no	261 vs 202	18% vs 21%	0.981	0.79 (0.498-1.258)	0.3219
Autonomic nerve saving					
No vs yes	14 vs 421	21% vs 19%	0.042	1.15 (0.312-4.199)	0.8384
Postoperative chemotherapy					
Yes vs no	168 vs 286	17% vs 20%	0.621	0.82 (0.501-1.343)	0.4307

well: well differentiated adenocarcinoma, others: moderately, poorly differentiated, and mucinous adenocarcinomaly 0–1, v0–1: negative to minimal invasion, ly2–3, v2–3: moderate to severe invasion, LN: lymph node APR: abdominoperineal resection, SSO: sphincter saving operation, OR: odds ratio, CI: confidence interval

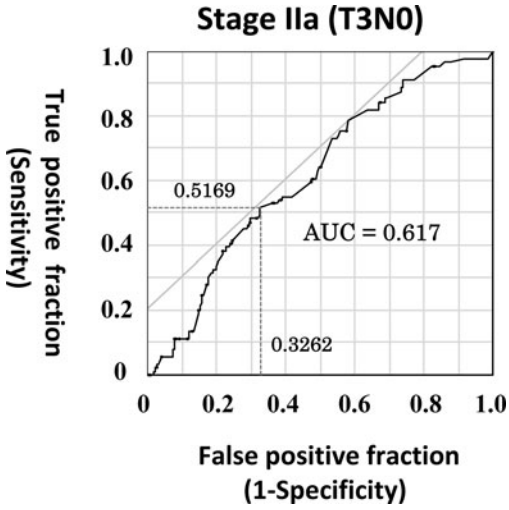

FIGURE 3. Cutoff point of DME using ROC curve analysis. The ROC curve analysis showed high sensitivity (0.5169), specificity (0.6737), positive likelihood ratio (1.5846), positive predictive value (0.2738), accuracy (0.6436), OR (2.2097), and smaller chi-square *P* (0.0012) at the cutoff point of 4.2 mm.

analyses.[2,8,9] Miyoshi et al[7] analyzed 2 different patient databases and decided the cutoff point at 6 mm. They reported that patients with mesorectal extension ≥ 6 mm had worse 5-year survival in stage II disease. Merkel et al[4] prospectively analyzed the different patient data from the multicenter institutes (ERCRC and SGCRC). They used 5 mm for the cutoff point of mesorectal extension of T3 tumor and subdivided T3 tumors into T3a (≤ 5 mm) and T3b (> 5 mm). They reported that in the ERCRC series the T3b patients with N0 had worse cancer-related 5-year survival. An extended T3 classification (T3a, T3b) was proposed. Thus, many authors have emphasized the prognostic heterogeneity of the mesorectal extension. Although it seems to be very difficult how to theoretically set an optimal cutoff value, it must be essential to subdivide the TNM staging system. Statistical analysis based on a large data set from multicenter institutes is required to clarify whether mesorectal extension is independent as a risk factor and how to reflect this in the TNM staging system. Based on our statistical analyses, DME > 4 mm was strongly associated with postoperative recurrence and recurrence-free survival, compared with DME ≤ 4 mm. It may be said that DME is one of the risk factors for postoperative recurrence. So, the optimal cutoff point was theoretically set to a value of 4 mm. Then, the mesorectal extension was divided into 2 groups: DME ≤ 4 mm and DME > 4 mm.

As a popular independent prognostic factor, lymphovascular invasion has been often reported. The DME was also reported as an independent prognostic factor for disease-free survival or cancer-specific survival.[2,3,7,9,10] In our multivariate analysis, lymphatic and venous invasion were also extracted each as a powerful indicator with high reliability and DME.

The local recurrence at stage II after total mesorectal excision for rectal cancer has varied from 4% to 21%.[18–22] A multicenter prospective randomized trial organized by the Dutch Colorectal Cancer Group[23] reported that the 2-year local recurrence rate after

TABLE 3. Statistical Analysis of Cutoff Points for Postoperative Recurrence and for Recurrence-free 5-year Survival

a. Univariate Logistic Regression Analysis

DME (mm)	No. of Patients	Rate of Recurrence	χ^2	Logistic OR (95% CI: L-U)	L/U ratio	*P*
>1 vs ≤ 1	369 vs 94	22% vs 9%	8.030	3.02 (1.406-6.499)	0.216	0.00460
>2 vs ≤ 2	288 vs 175	24% vs 11%	12.062	2.64 (1.525-4.557)	0.335	0.00052
>3 vs ≤ 3	205 vs 258	24% vs 16%	5.523	1.71 (1.075-2.727)	0.394	0.02361
>4 vs ≤ 4	168 vs 295	27% vs 15%	10.997	2.21 (1.383-3.531)	0.392	0.00091
>5 vs ≤ 5	130 vs 333	29% vs 16%	9.673	2.15 (1.327-3.483)	0.381	0.00187
>6 vs ≤ 6	107 vs 356	29% vs 16%	8.293	2.10 (1.267-3.468)	0.365	0.00398
>7 vs ≤ 7	83 vs 380	27% vs 18%	3.403	1.69 (0.968-2.933)	—	0.06508
>8 vs ≤ 8	62 vs 401	19% vs 19%	0.001	1.01 (0.513-1.988)	—	0.9773
>9 vs ≤ 9	46 vs 417	22% vs 19%	0.208	1.19 (0.566-2.497)	—	0.6484
>10 vs ≤ 10	36 vs 427	19% vs 19%	0.001	1.02 (0.430-2.400)	—	0.9719

b. Multivariate Cox Regression Analysis

DME (mm)	No. of Patients	Recurrence-free 5-year Survival	χ^2	Logistic OR (95% CI: L-U)	L/U ratio	*P*
>1 vs ≤ 1	369 vs 94	78.1% vs 92.9%	7.519	2.96 (1.362-6.415)	0.212	0.00611
>2 vs ≤ 2	288 vs 175	75.3% vs 90.6%	11.702	2.54 (1.489-4.333)	0.344	0.00062
>3 vs ≤ 3	205 vs 258	75.8% vs 85.2%	5.450	1.68 (1.087-2.594)	0.419	0.01957
>4 vs ≤ 4	168 vs 295	71.3% vs 86.6%	13.567	2.26 (1.465-3.492)	0.420	0.00023
>5 vs ≤ 5	130 vs 333	69.9% vs 85.3%	12.842	2.23 (1.437-3.451)	0.416	0.00034
>6 vs ≤ 6	107 vs 356	69.3% vs 84.5%	11.390	2.18 (1.387-3.433)	0.404	0.00074
>7 vs ≤ 7	83 vs 380	72.9% vs 82.8%	3.909	1.66 (1.004-2.753)	0.365	0.04813
>8 vs ≤ 8	62 vs 401	78.5% vs 81.5%	0.347	1.20 (0.652-2.218)	—	0.55582
>9 vs ≤ 9	46 vs 417	76.3% vs 81.6%	0.882	1.37 (0.708-2.660)	—	0.34767
>10 vs ≤ 10	36 vs 427	78.3% vs 81.4%	0.211	1.20 (0.553-2.602)	—	0.64599

CI indicates confidence interval; DME, distance of mesorectal extension; HR, hazard ratio; L, lower limit; U, upper limit.

TABLE 4. Independent Prognostic Factor for Recurrence-free Survival in Patients With Stage IIa (T3N0) Using Multivariate Cox Regression Analysis

Variable	Recurrence-free 5-year Survival	χ^2	HR (95% CI: L-U)	L/U ratio	*P*
Gross type					
inf vs. exp	69.8% vs. 82.7%	1.861	1.49 (0.840-2.639)	—	0.17251
Histology					
others vs. well	78.5% vs. 85.9%	3.098	1.59 (0.949-2.658)	—	0.07839
Lymphatic invasion					
ly2–3 vs. ly0–1	61.8% vs. 85.0%	9.873	2.22 (1.351-3.659)	0.369	0.00168
Venous invasion					
v2–3 vs. v0–1	71.7% vs. 85.5%	5.446	1.73 (1.091-2.727)	0.400	0.01961
Operative methods					
APR vs. SSO	77.1% vs. 84.0%	2.352	1.42 (0.907-2.222)	—	0.12512
DME					
> 4 mm vs. ≤ 4 mm	71.3% vs. 86.6%	8.674	1.97 (1.254-3.091)	0.406	0.00323

APR indicates abdominoperineal resection; CI, confidence interval; DME, distance of mesorectal extension; exp, expansive; HR, hazard ratio; inf, infiltrative; L, lower limit, LN, lymph node; SSO, sphincter saving operation; U, upper limit.

surgery alone with total mesorectal excision in stage II patients was 5.7%. Those data were comparable with the results of our study on local recurrence after total mesorectal excision (Table 1). However, there have been only a few reports on the relevance between DME and local recurrence or distant metastasis. Willett et al[3] reported a statistically significant increase in local-free survival (93%) in T3N0 patients with DME < 2 mm. Merkel et al[4] reported that the local recurrence rate was significantly higher in T3b tumor more than 5 mm (N0; 15.4%), compared with T3a tumor up to 5 mm (N0; 5.5%) in the ERCRC data, but was not significant in the SGCRC data. Miyoshi et al[7] did not recognize the relevance concerning local recurrence between DME > 6 mm and ≤ 6 mm. Many authors also did not recognize the relevance between DME and local recurrence. The circumferential resection margin (CRM) of rectal cancer is strongly

TABLE 5. Distant and Local Recurrence in Patients With Stage IIa (T3N0) at the Cutoff Point of 4 mm

Recurrence Pattern	DME	No. of Recurrence (%)	χ^2	OR (95% CI: L-U)	L/U ratio	*P*
Distant	≤ 4 mm (n = 295)	21 (7.1)		1		
	> 4 mm (n = 168)	28 (16.7)	9.774	2.61 (1.430-4.761)	0.300	0.00177
Local	≤ 4 mm (n = 295)	12 (4.1)		1		
	> 4 mm (n = 168)	13 (7.7)	2.733	1.98 (0.881-4.441)	0.198	0.09829

CI indicates confidence interval; DME, distance of mesorectal extension; L, lower limit; OR, odds ratio; U, upper limit.

TABLE 6. Cumulative Recurrence-free and Cancer-specific Survivals in Patients with Stage IIa (T3N0) at the Cutoff Point of 4 mm

a. Recurrence-free survival

TNM Stage	DME	at 5-years (%)	at 10-years (%)	HR (95% CI) for Recurrence	Logrank *P*
IIa (T3N0)	≤ 4 mm (n = 295)	86.6%	85.3%	0.44 (0.286-0.683)	
	> 4 mm (n = 168)	71.3%	71.3%	2.26 (1.465-3.492)	0.00015
	Total	81.1%	80.2%		

b. Cancer-specific survival

TNM Stage	DME	at 5-years (%)	at 10-years (%)	HR (95% CI) for Recurrence	Logrank *P*
IIa (T3N0)	≤ 4 mm (n = 295)	91.3%	83.2%	0.52 (0.325-0.843)	
	> 4 mm (n = 168)	82.2%	73.9%	1.91 (1.187-3.073)	0.00664
	Total	88.4%	79.2%		

CI indicates confidence interval; DME, distance of mesorectal extension; HR, hazard ratio.

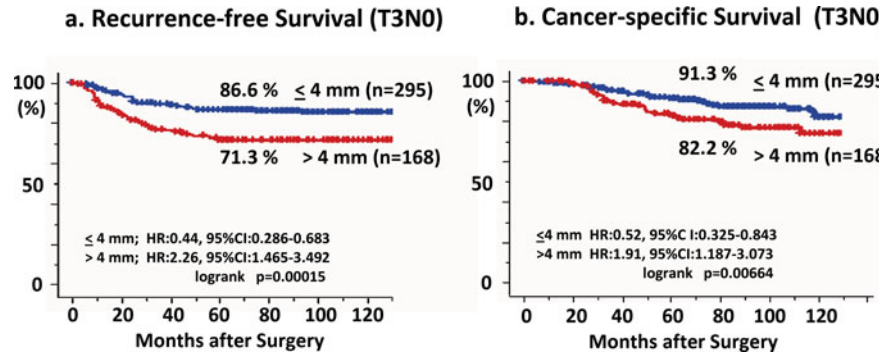

FIGURE 4. (A) Recurrence-free survival. The 5-year recurrence-free survival rate of DME ≤ 4 mm was 86.6%, which is significantly better than that of DME > 4 mm ($P = 0.00015$). (B) Cancer-specific survival. The 5-year cancer-specific survival rate of DME ≤ 4 mm was 91.3%, which is significantly better than that of DME > 4 mm ($P = 0.00664$).

associated with local recurrence.[24] In the present series, measurement of the CRM was not available because of too many missing values. A positive CRM (0 mm; tumor involvement directly at CRM) defined as noncurative resection by JSCCR was excluded from this analysis. Our data showed no significant difference concerning local recurrence at the cutoff point (Table 5). One reason for this difference may be the small number of patients developing local recurrence. Although the numbers may be too small to draw any definitive conclusions, the numbers did not seem to have an impact on local recurrence.

There have been only a few reports concerning distant metastasis and DME. Willett et al[3] reported statistically significant increase in distant-free survival (90%) in T3N0 patients with DME < 2 mm. Tokoro et al[10] also reported that distant metastasis differed significantly (< 3 mm; 0% vs ≥ 3 mm; 46.7%, $P = 0.01$), although the numbers of patients were very small. Based on our data, the DME was strongly associated with distant metastasis more so than local recurrence. As the DME becomes deeper, it is considered that many undetectable lymphovascular invasions exist in the mesorectal adipose tissues.

Many authors also have reported that the DME was an important predictor associated with recurrence-free and cancer-specific survivals. Merkel et al[4] reported that cancer-related 5-year survival of T3a tumors was significantly better than that of T3b (91.2% vs 77.2% at stage II). Similar outcomes in Dukes B (66% vs. 37%) at the cutoff value of 4 mm and in stage II (73% vs 52%) at the cut-off value of 6 mm have been reported.[2,7] Our statistical analysis also demonstrated that the DME was a powerful predictor for recurrence-free and cancer-specific survivals (Table 6). So, the DME has an extremely great impact on clinical significance in patients at stage IIa (T3N0). The subclassification in the TNM staging system consisting of a combination of T3 and DME is strongly proposed. Our statistical retrospective analysis was relevant to Merkel et al's[4] prospective

results and strongly supports their proposal of T3 classification. The reproducibility and applicability of this proposed staging system to other situations should be evaluated in further prospective studies.

CONCLUSIONS

A value of 4 mm provided the best cutoff point to dichotomize mesorectal extension for predicting prognosis. The distance of mesorectal extension more than 4 mm is an important predictor for postoperative recurrence and an independent prognostic factor for recurrence-free survival. A subclassification based on a 4-mm cutoff point is needed for improving the TNM staging system. However, further prospective study is necessary to prove reproducibility and validity of the cutoff point.

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