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Clinicopathological characteristics and prognostic factors of advanced colorectal mucinous adenocarcinoma

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Clinicopathological characteristics and prognostic factors of advanced colorectal mucinous adenocarcinoma

Aims: Mucinous adenocarcinoma (MUC) is a histological variant of colorectal adenocarcinoma. The aim of the present study was to characterize clinicopathological features and identify prognostic factors of MUCs.
Methods and results: A total of 181 patients with MUC who underwent surgery between 1975 and 2003 were reviewed. The clinicopathological features of these patients were compared with those of 4125 non-MUC patients. Univariate and multivariate analyses were conducted to identify significant prognostic factors in 102 patients with pT3 or pT4 tumour who underwent curative surgery. Patients with MUCs tended to present with more advanced clinical stages. The overall 5-year survival rate of MUC patients was lower than that of non-MUC patients; however, no prognostic difference was found when patients with the same clinical stages were compared. Multivariate analysis revealed male sex, bowel obstruction and infiltrating growth type as independent prognostic factors. Five-year cancer-specific survival rates for MUC patients with ≤1, 2 and 3 risk factors identified by multivariate analysis were 95.5%, 52.1% and 0.0%, respectively ($P < 0.001$).
Conclusions: Mucinous adenocarcinoma represents a distinct clinicopathological entity. Sex, bowel obstruction and growth patterns might be useful prognostic factors to identify patients with a high risk of recurrence after curative resection of advanced MUCs.

Keywords: growth pattern, mucinous adenocarcinoma, prognostic factor

Abbreviations: CI, confidence interval; MUC, mucinous adenocarcinoma

Introduction

Mucinous adenocarcinoma (MUC) is a histological subtype of colorectal adenocarcinoma characterized by abundant pools of extracellular mucin.[1] According to several estimates, MUCs account for 4.5–15% of all colorectal carcinomas.[1–4] The clinicopathological features of MUCs are distinct from those of non-MUCs. Namely, MUCs are more common among younger patients[5–7] and develop preferentially in the proximal colon.[1,6,8–10]

Unfortunately, research on the prognostic significance of mucinous histology has provided inconsistent results. Whereas some studies have suggested that MUCs have a worse prognosis compared with non-MUCs,[1,4,11–14] others reported no differences.[8,15–17] Although Wu *et al.*[12] and Umpleby *et al.*[13] reported worse overall survival of MUCs, they suggested that this was merely a reflection of MUCs presenting with a more advanced disease stage, rather than mucinous histology itself being an independent prognostic factor.

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However, Connelly *et al.*[11] performed a stage-matched analysis and showed that MUCs had a worse 5-year survival among stage B patients. Furthermore, Kanemitsu *et al.*[4] conducted a multivariate analysis and found mucinous histology to be an independent prognostic factor for poor overall survival. Currently, it remains unclear whether MUCs have a different prognosis from non-MUCs.

Because MUCs have distinct clinicopathological properties, MUC prognostic factors might also be different from those of non-MUCs. Previously reported prognostic factors for MUCs include age,[4,18] sex,[4] tumour location,[4] tumour spread beyond the bowel wall,[19] lymph node metastasis,[14] liver metastasis,[14,19] peritoneal dissemination,[14] absence of a Crohn-like infiltrate[18] and higher tumour stage.[4,12,18] Recently, certain histopathological characteristics of the tumour-invasive front, such as an invasive margin (expanding versus infiltrating)[20] and tumour budding,[21] have been reported as prognostic factors in rectal cancer. However, these emerging histological prognostic factors in colorectal cancers have not been tested extensively in MUCs.

In the present study, we reviewed a large consecutive series of colorectal adenocarcinoma cases to test whether mucinous histology is an independent prognostic factor in colorectal cancer. In addition, we examined other potential prognostic factors for 5-year cancer-specific survival, including histological characteristics of the invasive front.

Materials and methods

CASES

We investigated consecutive colorectal adenocarcinoma surgical cases treated between 1975 and 2003 at the National Cancer Center Hospital in Tokyo. Cases included 181 patients with MUCs and 4125 patients with non-MUCs, including well, moderately and poorly differentiated adenocarcinomas, as well as signet-ring cell carcinomas. In accordance with World Health Organization criteria,[22] a histological diagnosis of MUC was made when extracellular mucin accounted for >50% of tumour volume. Tumours were staged according to the International Union Against Cancer tumour–node–metastasis (TNM) system.[23] Median follow-up times in the MUC and non-MUC patients were 5.2 and 6.0 years, respectively.

PATHOLOGICAL ANALYSIS

All surgically resected specimens were first fixed in 10% (vol/vol) formalin, then embedded in paraffin, and finally stained with haematoxylin and eosin for pathological evaluation. Clinical and pathological characteristics (age, sex, tumour location, tumour size, stage, pathological T, pathological N, distant metastasis, liver metastasis and peritoneal dissemination) were recorded prospectively by the hospital pathologists.

Of the 181 cases with MUC, 102 pT3 or pT4 cases that underwent curative surgery were examined further for the purposes of identifying potential prognostic factors of MUCs. Three pathologists (T.Y., H.T. and T.S.) retrospectively reviewed haematoxylin and eosin-stained sections representing the maximum diameter of the tumours for detailed histological evaluation. Mucinous carcinoma was classified into two types: one composed of well or moderately differentiated carcinoma in a mucinous lake, and the other composed

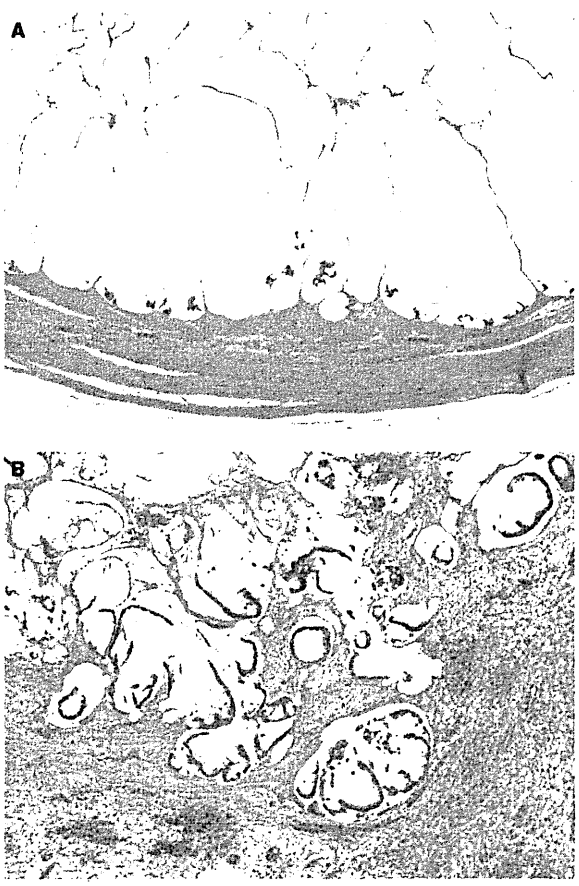

Figure 1. Tumour-invasive front of mucinous adenocarcinomas (haematoxylin and eosin staining). A, The invasive front of the tumour was classified as the expansive growth type when a distinct or reasonably well circumscribed border was evident. B, The invasive front was classified as the infiltrating growth type in the presence of irregular infiltration of small mucin pools which contained tumour cells.

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of poorly differentiated or signet-ring cell carcinoma. Histology of the invasive front was also classified into the expansive growth type or the infiltrating growth type. The expansive growth type lesions were characterized by a tumour growth pattern with a distinct circumscribed border at the invasive front (Figure 1A).

Table 1. Clinicopathological features of 181 patients with mucinous adenocarcinoma (MUC) and 4125 patients with non-MUC

	MUC	Non-MUC	
	(*n* = 181)	(*n* = 4125)	*P*-value
Median age (range) years	59 (28–88)	60 (19–93)	0.837
Sex			
Male	104 (57.5)	2435 (59.0)	0.674
Female	77 (42.5)	1690 (41.0)	
Tumour location			
Proximal colon	68 (37.6)	923 (22.4)	<0.001
Distal colon and rectum	113 (62.4)	3202 (77.6)	
Median tumour size (range) mm	65 (14–160)	42 (3–220)	<0.001
Stage			
I	8 (4.4)	888 (21.5)	<0.001
II	37 (20.4)	1072 (26.0)	
III	72 (39.8)	1433 (34.7)	
IV	64 (35.4)	732 (17.7)	
pT			
T1	0	521 (12.6)	<0.001
T2	14 (7.7)	631 (15.3)	
T3	100 (55.2)	2147 (52.0)	
T4	67 (37.0)	826 (20.0%)	
pN			
N0	49 (27.1)	2041 (49.5)	<0.001
N1	53 (29.3)	1207 (29.3)	
N2	79 (43.6)	877 (21.3)	
Distant metastasis			
M0	117 (64.6)	3393 (82.3)	<0.001
M1	64 (35.4)	732 (17.7)	
Liver metastasis			
Negative	159 (87.8)	3603 (87.4)	0.843
Positive	22 (12.2)	522 (12.7)	
Peritoneal dissemination			
Negative	148 (81.8)	3953 (95.8)	<0.001
Positive	33 (18.2)	172 (4.2)	

Values in parentheses are percentages unless noted otherwise.

The infiltrating growth type lesions were characterized by an irregular infiltration of small mucin pools which contained tumour cells (Figure 1B).

Tumour budding was defined as isolated cancer cells or those forming a cluster composed of fewer than five cells in the invasive frontal region.[21] Microscopic abscess formation was defined as the presence of debris and leucocytes (mainly neutrophils) at the invasive tumour margin.[24]

To test the reproducibility of the categorization of tumour growth pattern, four observers (T.Y., H.T., S.S. and R.K.) were asked to review independently 55 consecutive MUCs and to assess histology of the invasive front according the definition described above. The results were analysed to evaluate interobserver agreement, as described below.

STATISTICAL ANALYSIS

All statistical analyses were performed using computer software (JMP version 7.0; SAS Institute Inc., Cary, NC, USA, 1989–2007). The chi-square test or Mann–Whitney *U*-test was used for comparison of two groups. Survival rates were calculated by the Kaplan–Meier method and differences were compared statistically by the log-rank test. Cox's proportional hazards model was used for multivariate analysis. Data differences between groups were considered statistically significant at $P < 0.05$. Interobserver agreement (reproducibility) was tested by obtaining κ-scores[25] according to a widely used statistical chart that grades the strength of agreement into six categories (poor, κ-value <0.00; slight, 0.00–0.20; fair, 0.21–0.40; moderate, 0.41–0.60; substantial, 0.61–0.80; and almost perfect, 0.81–1.00).

Results

CLINICOPATHOLOGICAL ANALYSIS OF MUC AND NON-MUC

Table 1 summarizes the clinicopathological features of the 181 patients with MUC and the 4125 patients with non-MUC. MUCs were located more frequently in the proximal colon, and tended to be larger than non-MUCs. Patients with MUCs presented with more advanced disease, with significantly higher stage, pathological T and pathological N, and increased incidence of distant metastasis. Although the incidence of liver metastasis did not differ significantly between MUCs and non-MUCs, peritoneal dissemination was more frequent in MUCs. The overall survival rate of MUC patients was lower than that of non-MUC patients. However, when comparisons were made between stage-matched groups, the patient survival rates did not differ significantly between MUC and non-MUC (Table 2).

Table 2. Overall survival rates of patients with mucinous adenocarcinoma (MUC) and those with non-MUC

	MUC		Non-MUC		
	No. of patients	5-year survival rate (%)	No. of patients	5-year survival rate (%)	*P*-value
Stage					
I	8	100	888	95.7	0.768
II	37	89.2	1072	89.1	0.137
III	72	63.9	1433	73.7	0.097
IV	64	10.9	732	19.1	0.318
Total	181	51.9	4125	72.9	<0.001

PROGNOSTIC FACTORS AFFECTING THE OUTCOME OF MUC

In order to identify clinicopathological factors affecting cancer-specific survival, we further analysed 102 MUC patients with pT3 or pT4 tumour who underwent curative surgery. None of these patients died due to acute presentation or postoperative complications. The results of univariate analyses are summarized in Table 3. Among these, histology of the tumour-invasive front represents an increasingly recognized prognostic factor. We therefore assessed interobserver agreement in the assessment of the tumour-invasive front using four independent observers to review 55 MUCs. The results showed a κ-value of 0.79, indicating 'substantial' reproducibility.

All variables considered as potential prognostic factors were included in a Cox's proportional hazards model to identify independent prognostic factors. Multivariate analysis identified male sex, presence of bowel obstruction and infiltrating growth type as independent prognostic factors (Table 4).

Based on this result, we defined three risk groups depending on the number of risk factors that were identified by multivariate analysis: a low-risk group (one risk factor or no risk factors), an intermediate-risk group (two risk factors) and a high-risk group (all three risk factors). Five-year cancer-specific survival rates for the low-, intermediate- and high-risk groups were 95.5%, 52.1% and 0.0%, respectively ($P < 0.001$; Figure 2).

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Table 3. Clinicopathological features and cancer-specific survival rates in 102 patients with pT3 or pT4 mucinous adenocarcinoma (MUC) who underwent curative surgery

	No. of patients	5-year cancer-specific survival rate (%)	*P*-value
Age			
<60 years	54	77.7	0.604
≥60 years	48	78.5	
Sex			
Male	58	68.2	0.021
Female	44	88.3	
Tumour location			
Proximal colon	48	80.7	0.433
Distal colon and rectum	54	73.3	
Tumour size			
<65 mm	43	82.7	0.247
≥65 mm	59	72.8	
Bowel obstruction			
Negative	79	85.6	<0.001
Positive	23	60.9	
pT			
T3	68	80.2	0.257
T4	34	70.2	
pN			
N0	37	97.1	<0.001
N1	37	78.3	
N2	28	48.4	
Lymphatic invasion			
Negative	52	92.0	<0.001
Positive	50	61.8	
Venous invasion			
Negative	84	79.2	0.331
Positive	18	66.7	
Perineural invasion			
Negative	89	83.7	<0.001
Positive	13	30.8	
Histopathological grading of the mucinous component			
Well/moderate	78	86.8	<0.001
Poor/sig	24	45.8	
Tumour budding			
Negative	74	87.5	<0.001
Positive	28	48.4	
Invasive tumour front			
Expansive growth type	60	94.8	<0.001
Infiltrating growth type	42	51.4	
Microscopic abscess formation			
Negative	84	71.9	0.017
Positive	18	100	

Discussion

Previous studies have yielded conflicting data regarding the clinical importance of distinguishing MUC from non-MUC. Some studies have suggested that MUCs have a worse prognosis compared with non-MUCs,[1,4,11–14] whereas others reported no significant differences.[8,15–17] There are several potential reasons for the inconsistent results regarding MUC prognosis. First, most of the studies were performed using a relatively limited number of cases. Additionally, the definition of MUC has not been consistent across studies. Depending on the study, MUCs have been defined as tumours with a mucinous component of at least 50%[4,8,14,15] or >60%.[1,11–13] Also, different non-MUC groups were used for comparison. While Kanemitsu *et al.*[4] included only well and moderately differentiated adenocarcinomas in the comparison group, Akino *et al.*[14] used only well-differentiated adenocarcinomas, and Xie *et al.*[16] analysed all colorectal carcinomas including tumours other than adenocarcinoma, such as undifferentiated carcinomas. Some studies did not even describe detailed histology of the non-MUC group.[11] These differences in study design might explain, at least in part, the inconsistent results.

Table 4. Multivariate analysis of clinicopathological factors affecting cancer-specific survival

	Hazard ratio	95% CI	*P*-value
Sex			
Female	1.00	1.39–12.81	0.011
Male	4.22		
Bowel obstruction			
Negative	1.00	1.83–12.49	0.001
Positive	4.78		
Invasive tumour front			
Expansive growth type	1.00	1.43–52.82	0.019
Infiltrating growth type	8.69		

CI, Confidence interval.

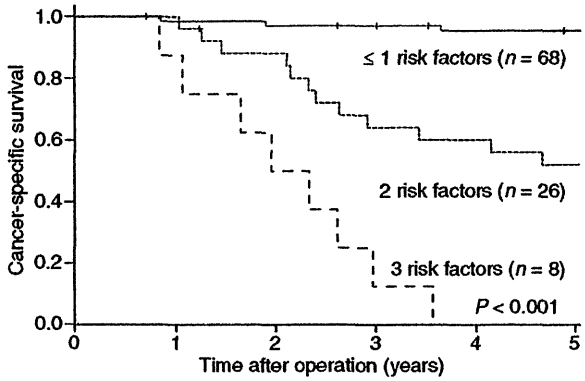

Figure 2. Cancer-specific survival based on the number of prognostic risk factors.

In the present study, we analysed a large consecutive series of colorectal adenocarcinoma cases, including 181 MUC patients and 4125 non-MUC patients. The diagnosis of MUC was made according to the World Health Organization criteria.[22] All other adenocarcinoma patients, irrespective of their histological subtypes, were included in the non-MUC group, as all these adenocarcinoma subtypes can be tumour components of MUCs. Conversely, non-adenocarcinoma cases, such as undifferentiated and squamous cell carcinomas, were excluded due to their distinct clinical behaviour.

The overall survival rate of MUC patients was significantly lower than that of non-MUC patients. However, when comparisons were made between stage-matched groups, the patient survival rates did not differ between the two groups. These observations imply that the poor overall survival seen in MUC patients is not due to the aggressiveness of MUC *per se*, but instead reflects the fact that MUC patients present with disease in a more advanced stage than non-MUC patients. Our observation is in agreement with two previous studies that analysed a relatively large number of MUCs.[12,13]

Nine variables (sex, bowel obstruction, pathological N, lymphatic invasion, perineural invasion, histopathological grading of the mucinous component, tumour budding, invasive tumour front and microscopic abscess formation) were found to be associated significantly with cancer-specific survival for patients with curative resection of pT3 or pT4 MUC in univariate analysis. Among these, multivariate analysis revealed male sex, presence of bowel obstruction and infiltrating growth type as independent prognostic factors. Male sex has been reported to be a predictor of poor prognosis colorectal cancers in several studies.[26] Additionally, in agreement with the current study, Kanemitsu *et al.*[4] reported that sex was a prognostic factor in MUC. Nevertheless, the reason for the poorer prognosis among men remains unclear. Bowel obstruction has also been reported to represent a marker of poor prognosis in colorectal cancer.[27–29] Korenaga *et al.*[29] suggested that this might result from a greater likelihood for obstructing tumours to have metastasized through the lymphatics or spread to the visceral peritoneum by the time of diagnosis. The present study showed that bowel obstruction is also associated with poorer prognosis in MUC.

In colorectal adenocarcinomas, histological features of the invasive front have been proposed as important prognostic factors. Jass *et al.*[20] suggested that tumour classification based on the nature of the advancing tumour margin (divided into expanding and infiltrating types) was important for predicting survival in rectal cancer. Ueno *et al.*[21] reported that tumour budding is correlated with the aggressiveness of rectal cancer. For MUC, few studies have examined the prognostic significance of histological features at the tumour-invasive front. Okuyama *et al.*[30] reported the presence of budding as the only significant predictor of postoperative survival in both univariate and multivariate proportional hazard models. Kakar *et al.*[18] classified MUCs into those with pushing and infiltrative advancing fronts, and showed that infiltrative growth was not related significantly to a poorer prognosis.

The present study classified the invasive front of MUCs according to growth patterns and to the presence of budding. Univariate analysis showed that both an infiltrative growth pattern and the presence of budding were related significantly to poorer prognosis. Multi-

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variate analysis further identified infiltrative growth pattern as an independent prognostic factor. Of note, our study also showed 'substantial' reproducibility for the classification of the tumour-invasive front, superior to that seen with conventional histological prognostic factors, including lymphatic or vascular invasion.[31,32] Since evaluation of the tumour-invasive front can be performed on routine histological preparations and is reasonably reproducible, it represents a potential prognostic marker for use in regular diagnostic practice.

Risk group classification using three independent prognostic factors identified by multivariate analysis could be useful in predicting cancer-specific survival of patients who have undergone curative surgical resection of advanced MUCs. While confirmatory studies of independent cohorts are required, the identification of a high-risk group would contribute to appropriate selection of patients for adjuvant chemotherapy.

In conclusion, our study confirms that MUC is a distinct clinicopathological entity. The overall survival of MUCs is worse than that of non-MUCs; however, this is due probably to the fact that MUC patients present with advanced disease stages. Sex, bowel obstruction and histology of the tumour-invasive front are independent prognostic factors of advanced MUCs, which predict the behaviour of the tumour and aid classification into low, intermediate and high risk groups.

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Declarations of interest

None declared.

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Predicting oncologic outcomes by stratifying mesorectal extension in patients with pT3 rectal cancer: a Japanese multi-institutional study

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The goal of this study was to clarify the clinical significance of mesorectal extension in pT3 rectal cancer. This currently remains unclear. Data from 975 consecutive patients with pT3 rectal cancer that underwent curative surgery at 28 institutes were reviewed. The distance of the mesorectal extension (DME) was measured histologically. The optimal prognostic cut-off point of the DME for oncologic outcomes was determined using the receiver operating characteristic curve and Cox regression analysis. When patients were subdivided into two groups according to the optimal cut-off point, DME $\leq$ 4 mm and DME > 4 mm, DME was found to be a powerful independent risk factor for postoperative recurrence. A DME > 4 mm was significantly correlated with distant and local recurrences at Stage IIA and IIIB diseases. The recurrence-free 5-year-survival rate was significantly higher in patients with a DME $\leq$ 4 mm [86.6% at Stage IIA (p = 0.00015), and 68.7% at Stage IIIB (p < 0.0001)] than in patients with a DME > 4 mm (71.3% at Stage IIA and 49.1% at Stage IIIB). No significant difference was noted in the oncologic outcomes between the two groups at Stage IIIC. A value of 4 mm provides the best prognostic cut-off point for patient stratification and for the prediction of oncologic outcomes. A subclassification based on a 4-mm cut-off point may improve the utility of the TNM 7th staging system except for Stage IIIC. These findings warrant further prospective studies to determine the reliability and validity of this cut-off point.

Cancer Therapy

The influence of the distance of mesorectal extension (DME) on prognosis in patients with pT3 rectal cancer remains unclear. In 1990, Cawthorn *et al.*[1] advocated stratifying mesorectal extension (ME) using a cut-off point of 4 mm, and in 1993, the International Union Against Cancer (UICC) proposed optional cut-off points for ME in the context of pT3 and pT4 tumors.[2] Thereafter, several studies have described prognostic heterogeneity in patients with pT3 rectal cancers,[3–12] and they used different prognostic cut-off points to stratify the ME (*e.g.*, microscopic invasion,[5] 2 mm,[3] 3 mm,[9,12] 4 mm,[1,7,8] 5 mm[4,10,11] or 6 mm[6]). Furthermore, the clinical significance, statistical appropriateness and reliability of these cut-off points remain controversial, partly because these studies had small samples sizes with underpowered statistical analyses and included cohorts from only a single institution. The goal of this study was to retrospectively analyze a large multi-institutional database from the Study Group of the Japanese Society for Cancer of the Colon and Rectum (JSCCR) to determine the optimal cut-off point for stratification of DME to predict the clinical outcomes in patients with pT3 rectal cancer.

Key words: rectal cancer, mesorectal extension, depth of invasion, TNM staging system, prognosis
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Material and Methods

All protocols contained within this study were approved by the Ethics Committee of the JSCCR and by the local Institutional Review Board. Data were derived from 1,009 patients with pT3 rectal cancer from 28 member institutions of the Study Group of the JSCCR on Extramural ME of Rectal Cancer. All patients had primary rectal adenocarcinoma that was located in the lower two-thirds of the rectum. Patients with rectosigmoid colon cancer were not included in this study. None of the patients received radiotherapy or neoadjuvant

chemotherapy before operative management in this study. Total mesorectal excision (TME) and histologically defined curative surgery were performed in each patient by well-trained colorectal surgeons strictly according to the standard technique[13] between 1995 and 1999. Thirty-two colorectal surgeons took part in this study and all were trained in TME. The TME quality including longitudinal and circumferential resection margins (CRM) was independently evaluated by expert surgeons and local pathologists according to the rules defined by the JSCCR.[14] The CRM positive case was not included in this study. Pelvic lymph node dissection was performed in 593 patients (60.8%). Of the 1,009 patients, clinicopathological information was available for 975 patients, which were eligible for analysis. Thirty-four patients were excluded because of insufficient clinical and follow-up information. Four hundred twenty-five patients (43.6%) received abdominoperineal resection and 550 patients (56.4%) received sphincter-saving operation. The median number of retrieved lymph nodes was 28 (range: 2–129).

The clinicopathological data and follow-up system were based on the rules defined by the JSCCR.[14] Patients were restaged according to the pathological TNM classification (7th edition)[15,16] identifying 463 patients at Stage IIA, 422 patients at Stage IIIB and 90 patients at Stage IIIC. According to the postoperative adjuvant treatment protocol of each institution, peroral 5-fluorouracil (5-Fu)-based chemotherapy, such as doxifluridine (5′DFUR), 1-hexylcarbamoyl-5-fluorouracil (HCFU) or uracil-tegafur (UFT), were most frequently administered. One hundred and seventy-seven patients with Stage II (38.2%) and 270 patients with Stage III (52.7%) diseases received postoperative chemotherapy.

Follow-up studies were also conducted in patients and 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 following 2 years. When recurrence was suspected based on the serum tumor marker, digital examination and/or ultrasonography, the final diagnosis was made using rectoscopy, computerized tomography (CT) and/or magnetic resonance imaging (MRI) and other diagnostic tools. Local recurrence was defined as the presence of radiologically confirmed or histologically proven tumor occurring *via* nonhematogenous mechanisms within the pelvis and within the field of the initial surgery. Distant metastasis included hematogenous metastases to the liver, lung, bone, brain, kidney or other organs. Peritoneal dissemination, intra-abdominal, paraaortic, subclavicular, mediastinal and inguinal lymph node metastases also qualified as other recurrences. The outcomes of all patients were precisely investigated. As of January 1995, the eligible surviving patients had been followed for a median period of 86 months (range: 1–166 months).

Measurement of DME

All surgically resected specimens were opened along the antimesenteric side. They were fixed in 20% formalin for at least 48 hr after pinning to a wooden or cork board. Next, one or more longitudinal sections of the tumor were sliced at the point of maximum extramural invasion. They were embedded in paraffin after division into blocks of suitable size and were then routinely processed for staining with hematoxylin and eosin and elastica Van Gieson. Using these sections, tumors in the pT3 category were subdivided based on the histological measurement of the maximum depth (mm) of invasion beyond the outer border of the muscular layer (*i.e.*, DME). Pathological workshops were held by six specialized pathologists before this study to standardize the measurement of DME. Histological tumor depth measurements were carried out without prior knowledge of patient clinical information according to our methods previously reported.[17] 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. When the outer border of the muscular layer was not entirely identifiable due to destruction by 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.

Statistical analysis

Statistical analysis was performed using StatView 5.0 and JMP 8.0 (SAS Institute Inc, Cary, NC, USA) for Windows. All clinicopathological independent variables (15 items) were coded for analysis. These were: gender (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 [well]: 0, others :1); lymphatic invasion (negative-to-minimal [ly0-1]: 0, moderate-to-severe [ly2-3]: 1); venous invasion (negative-to-minimal [v0-1]: 0, moderate-to-severe [v2-3]: 1); circumferential resection margin (CRM) ($>$ 1 mm: 0, $\leq$ 1 mm: 1); lymph node (LN) metastasis (negative: 0, positive: 1); number of retrieved LN ($\geq$12: 0, $<$ 12: 1); operative methods (sphincter-saving operation (SSO): 0, abdominoperineal resection (APR): 1); pelvic LN dissection (no: 0, yes: 1); autonomic-nerve-saving operation (no: 0, yes: 1); postoperative chemotherapy (no: 0, yes: 1) and DME ($\leq$ X mm: 0, $>$ X mm: 1). Overall 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. Univariate logistic regression analysis and multivariate Cox regression analysis were used to estimate the independent risk factors for overall postoperative recurrence. The receiver operating characteristic (ROC) curve and multivariate Cox regression analysis were used to determine the optimal cut-off point of the DME for recurrence-free survival. The Kaplan-Meier method and the log-rank test were used for calculating survival rates. The level for statistical significance was determined at $p < 0.05$, and the confidence interval (CI) was determined at the 95% level.

Results

Measurement of the DME

The mean DME for the 975 cases of pT3 rectal cancer was 4.8 ± 4.4 mm (median: 3.7 mm; range: 0.1–30 mm).

Postoperative recurrence after curative surgery

Postoperative recurrence occurred in 336 patients (34.5%), including 89 patients (19.2%) at Stage IIA, 183 patients (43.4%) at Stage IIIB and 64 patients (71.1%) at Stage IIIC. Eighty patients (8.2%) had local recurrence only, whereas 171 patients (17.5%) had distant metastasis only, and 24 patients (2.5%) had both local recurrence and distant metastases. The remaining 61 patients had other recurrence including peritoneal dissemination, intra-abdominal, para-aortic, subclavicular, mediastinal or inguinal lymph node metastases. The stage-specific local recurrence rate was 5.4% at Stage IIA, 8.8% at Stage IIIB and 20% at Stage IIIC. The recurrence rate of distant metastasis was 10.6% at Stage IIA, 22.2% at Stage IIIB and 31.1% at Stage IIIC.

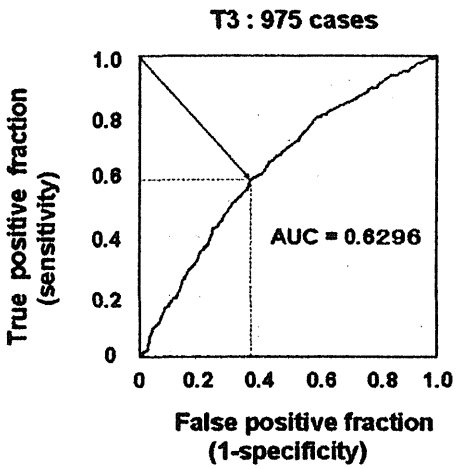

Figure 1. Cut-off point of the distance of mesorectal extension using ROC curve analysis. A cut-off value of 4 mm showed the best point with higher true-positive (sensitivity) recurrence rate (0.5863), lower false-positive (1-specificity) recurrence rate (0.3709) and highest accuracy rate (0.6144) among all cut-off points (odds ratio: 2.4, 95% CI (1.835–3.149), $p < 0.00001$). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Cut-off point for DME

To find an optimal prognostic cut-off point, continuous variable analysis of the DME was applied to the ROC curve. As shown in Figure 1, a cut-off value of 4 mm had the best point with higher true-positive (sensitivity) recurrence rate (0.5863), lower false-positive (1-specificity) recurrence rate (0.3709) and highest accuracy rate (0.6144) among all cut-off points (odds ratio [OR]: 2.4, 95% CI: 1.835–3.149, p <0.00001). The ROC curve analysis was valid as a statistical model (area under curve (AUC): 0.6296, OR: 1.08, 95% CI: 1.052–1.119, p <0.0001). Results from the log-rank and multivariate Cox regression analyses for recurrence-free survival are summarized in Table 1. A cut-off value of 4 mm was associated with the highest chi-square value (43.320), lowest p-value (p = 0.00000) and high hazard ratio (HR) of 2.11. The lower/upper limits of CI (*L/U* ratio) had higher reliability (0.6414) when this cut-off point was compared with other cut-off points. A cut-off value of 4 mm had the greatest influence on recurrence-free survival. Thus, the best prognostic cut-off point for DME was determined as 4 mm, and patients were stratified into two groups according to this value (≤ 4 mm and > 4 mm).

Independent risk factors for postoperative overall recurrence

Univariate and multivariate regression analyses showed that lymph node metastasis was the most powerful independent risk factor for overall postoperative recurrence. The DME was also validated as a powerful independent risk factor by multivariate Cox regression analysis (chi-square: 26.147, HR (95% CI): 1.80 (1.438–2.257), p <0.00001) (Table 2).

Table 1. Cut-off points of distance of mesorectal extension (DME) for recurrence-free (RF) survival using log-rank and multivariate Cox regression analyses

DME (mm)	No. of patients	RF survival at 5-years	Chi-square	HR (95% CI:*L–U*)	*L/U* ratio	Log-rank *p*-value
>1 *vs.* ≤1	814 *vs.* 161	64% *vs.* 80%	15.111	2.06 (1.432–2.973)	0.4817	0.00010
>2 *vs.* ≤2	679 *vs.* 296	61% *vs.* 80%	30.401	2.19 (1.658–2.896)	0.5725	<0.00001
>3 *vs.* ≤3	535 *vs.* 440	59% *vs.* 77%	34.162	2.02 (1.598–2.548)	0.6272	<0.00001
>4 *vs.* ≤4	435 *vs.* 540	55% *vs.* 76%	43.320	2.11 (1.687–2.630)	0.6414	0.00000
>5 *vs.* ≤5	334 *vs.* 641	54% *vs.* 73%	38.657	2.00 (1.609–2.495)	0.6449	<0.00001
>6 *vs.* ≤6	274 *vs.* 701	55% *vs.* 71%	29.611	1.87 (1.493–2.344)	0.6369	<0.00001
>7 *vs.* ≤7	225 *vs.* 784	54% *vs.* 70%	23.936	1.81 (1.426–2.293)	0.6219	<0.00001
>8 *vs.* ≤8	160 *vs.* 815	54% *vs.* 69%	17.803	1.76 (1.353–2.285)	0.5921	0.00003
>9 *vs.* ≤9	125 *vs.* 850	52% *vs.* 69%	17.110	1.82 (1.368–2.407)	0.5683	0.00004
>10 *vs.* ≤10	95 *vs.* 880	53% *vs.* 68%	13.361	1.80 (1.313–2.466)	0.5324	0.00026

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

Table 2. Independent risk factors for postoperative overall recurrence

Variable	Rate of recurrence	Univariate logistic regression analysis			Multivariate Cox regression analysis		
		Chi-square	OR (95% CI)	*p*-value	Chi-square	HR (95% CI)	*p*-value
Gender							
Male *vs.* female	34% *vs.* 35%	0.082	0.96 (0.721–1.276)	0.7745			
Size of tumor							
>5 cm *vs.* ≥5 cm	34% *vs.* 36%	0.497	0.91 (0.697–1.85)	0.4807			
Location of tumor							
Lower-third *vs.* middle-third	38% *vs.* 27%	12.548	1.68 (1.261–2.243)	0.0004	2.082	1.24 (0.926–1.654)	0.1491
Gross type							
Infiltrative *vs.* Expansive	46% *vs.* 33%	7.966	1.77 (1.191–2.640)	0.0048	7.756	1.56 (1.141–2.138)	0.0054
Histology							
Others *vs.* well	38% *vs.* 27%	10.634	1.65 (1.221–2.229)	0.0011	6.551	1.41 (1.084–1.833)	0.0105
Lymphatic invasion							
ly2-3 *vs.* ly0-1	49% *vs.* 28%	43.032	2.56 (1.932–3.386)	0.00000	8.945	1.44 (1.135–1.838)	0.0028
Venous invasion							
V2-3 *vs.* v0-1	40% *vs.* 32%	5.738	1.40 (1.063–1.843)	0.0166	0.014	0.99 (0.778–1.249)	0.9054
DME							
>4 mm *vs.* ≤4 mm	45% *vs.* 26%	39.947	2.39 (1.823–3.128)	0.00000	26.147	1.80 (1.438–2.257)	<0.00001
CRM							
≥1 mm *vs.* >1 mm	37% *vs.* 34%	0.559	1.16 (0.791–1.686)	0.4547			
Lymph node metastasis							
Positive *vs.* negative	48% *vs.* 19%	85.772	3.92 (2.934–5.229)	0.00000	53.554	2.70 (2.070–3.525)	0.00000
Number of retrieved LN							
<12 *vs.* ≥12	39% *vs.* 34%	1.101	1.25 (0.822–1.910)	0.2940			
Operative methods							
APR *vs.* SSO	43% *vs.* 28%	21.794	1.89 (1.447–2.470)	<0.00001	8.899	1.49 (1.147–1.937)	0.0029
Pelvic LN dissection							
Yes *vs.* no	36% *vs.* 31%	2.579	1.25 (0.952–1.644)	0.1083			
Autonomic nerve saving							
Yes *vs.* no	34% *vs.* 35%	0.003	0.99 (0.638–1.533)	0.9593			
Postoperative chemotherapy							
Yes *vs.* no	36% *vs.* 33%	1.466	1.18 (0.904–1.535)	0.2259			

Abbreviations: OR, odds ratio; HR, hazard ratio; CI, confidence interval; well, well differentiated adenocarcinoma; others, moderately differentiated, poorly differentiated and mucinous adenocarcinoma, ly0-1, v0-1, negative to minimal invasion; ly2-3, v2-3: moderate to severe invasion; DME, distance of mesorectal extension; CRM, circumferential resection margin; LN, lymph node; APR, abdominoperineal resection; SSO, sphincter saving operation.

Distant metastasis and local recurrence

The distant metastasis rate was significantly higher in patients with DME > 4 mm at Stage IIA (16.7%, HR: 2.72, 95% CI: 1.529–4.820, $p = 0.0006$) and Stage IIIB (26.6%, HR: 1.87, 95% CI: 1.275–2.749, $p = 0.0014$) (Table 3). The local recurrence rate was higher in patients with DME > 4 mm at Stage IIA (7.7%, HR: 2.11, 95% CI: 0.960–4.614, $p = 0.0632$) and at Stage IIIB (10.6%, HR: 1.75, 95% CI: 1.007–3.036, $p = 0.0471$). No significant difference was noted in distant metastasis or in local recurrence when stratifying Stage IIIC according to the cut-off point of 4 mm ($p = 0.4716$ and $p = 0.5003$, respectively). In all Stage III, however, significant difference was noted in either distant or local recurrence at the cut-off point of 4 mm.

Recurrence-free and cancer-specific survival rates

The recurrence-free 5-year-survival rate was significantly higher in patients with a DME ≤ 4 mm than in patients with a DME > 4 mm: 86.6% *versus* 71.3% ($p = 0.00015$; HR: 0.44; 95% CI: 0.286–0.683) at Stage IIA and 68.7% *versus*

Table 3. Distant Metastasis and Local Recurrence at the Cut-off Value of 4 mm Using Cox Regression Analysis

	Distant metastasis			Local recurrence		
TNM Stage (7th ed)	No. of patients (%)	HR (95% CI)	*p*-value	No. of patients (%)	HR (95% CI)	*p*-value
Stage IIA (n = 463)						
≤4 mm (n = 295)	21 (7.1)	1		12 (4.1)	1	
>4 mm (n = 168)	28 (16.7)	2.72 (1.529–4.820)	0.0006	13 (7.7)	2.11 (0.960–4.614)	0.0632
Stage IIIB (n = 422)						
≤4 mm (n = 204)	36 (17.6)	1		14 (6.9)	1	
>4 mm (n = 218)	58 (26.6)	1.87 (1.275–2.749)	0.0014	23 (10.6)	1.75 (1.007–3.036)	0.0471
Stage IIIC (n = 90)						
≤4 mm (n = 41)	11 (26.8)	1		7 (17.1)	1	
>4 mm (n = 49)	17 (34.7)	1.28 (0.654–2.504)	0.4716	11 (22.4)	1.31 (0.594–2.904)	0.5003
All Stage III (n = 512)						
≤4 mm (n = 245)	47 (19.2)	1		21 (8.6)	1	
>4 mm (n = 267)	75 (28.1)	1.73 (1.238–2.411)	0.0013	34 (12.7)	1.61 (1.025–2.532)	0.0386

Abbreviations: HR, hazard ratio; CI, confidence interval.

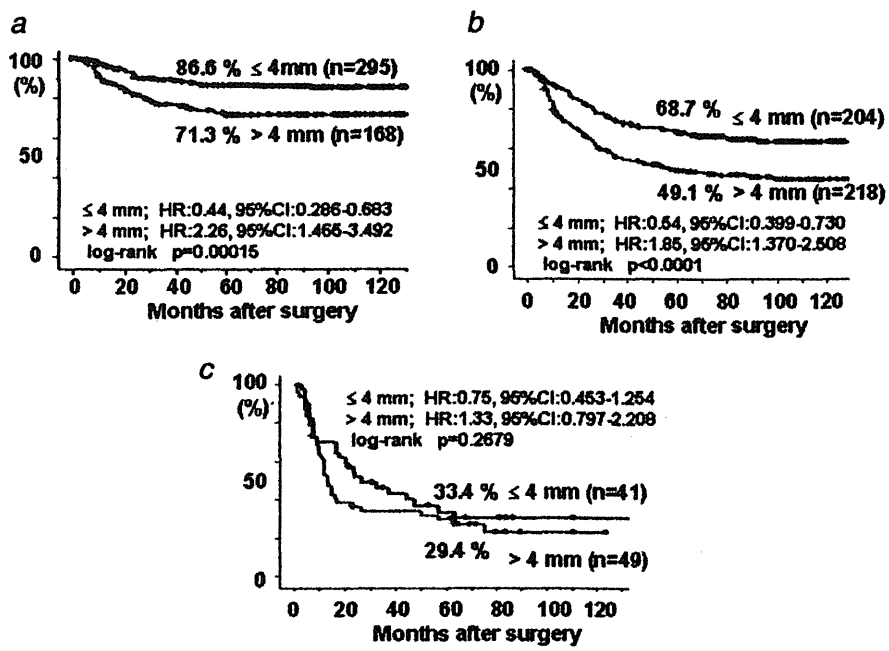

Figure 2. Recurrence-free survival. The recurrence-free 5-year-survival rate was significantly higher with a distance of the mesorectal extension (DME) ≤ 4 mm [86.6% (p=0.00015) at Stage IIA (*a*) and 68.7% (p<0.0001) at Stage IIIB (*b*)] than with DME > 4 mm. No significant difference was noted between the two groups at Stage IIIC [p = 0.2679, (*c*)].

49.1% (p < 0.0001; HR: 0.54; 95% CI: 0.399–0.730) at Stage IIIB (Fig. 2). In addition, the cancer-specific 5-year-survival rate of patients with a DME ≤ 4 mm was significantly higher when compared with patients with a DME > 4 mm: 91.3% *versus* 83.2% (HR: 0.52, 95% CI: 0.325–0.843, p = 0.0066) at Stage IIA and 79.2% *versus* 60.4% (HR: 0.54, 95%CI: 0.390–0.751, p = 0.0002) at Stage IIIB. However, no significant difference was noted in the recurrence-free and in the cancer-specific survival rates at Stage IIIC (p = 0.2679 and p = 0.0791, respectively).

Discussion

The 7th edition of TNM staging systems[15,16] is strong prognostic predictors in patients with colorectal cancer. Several

reports each from a single institution have also shown that there was prognostic heterogeneity among patients with pT3 rectal cancers[1,3,5–11] leading investigators to advocate subdivision of category pT3. In 1993, the UICC proposed optional subdivisions for pT3 and pT4 tumors.[2] Unfortunately, proposed cut-off points for the DME as a prognostic measurement have varied from 3 to 6 mm among these different studies. A cut-off point of 3 mm for the DME had no prognostic significance,[12] whereas a recent multi-institutional study carried out by our group demonstrated that a cut-off point of 4 mm could independently delineate adverse prognosis of pT3N0 rectal cancers (TNM 6th edition).[17] This study was focused on pT3N0-2 rectal cancers based on the new TNM 7th staging system.[15,16] Another large multi-institutional study analyzed patient data from the Erlangen Registry for Colo-Rectal Carcinomas (ERCRC) and the Study Group Colo-Rectal Carcinoma (SGCRC) registries.[4] The pT3 tumors were subdivided into pT3a (DME $\leq$ 5 mm) and pT3b (DME $>$ 5 mm), and the prognostic heterogeneity was reported. Another author examined two different patient databases and reported the oncologic outcomes that varied, based on a cut-off point of 6 mm.[6] In combination, data from these studies confirm the prognostic heterogeneity associated with different DMEs. However, the clinical significance and validity of the various proposed cut-off points remain unclear. This study utilized ROC curve and Cox regression analyses and demonstrated that a cut-off point of 4 mm produced the most useful predictor of oncologic outcomes in patients with pT3 rectal cancer.

Important risk factors for postoperative overall recurrence are summarized in Table 2. Although lymph node metastasis was the most powerful independent risk factor, DME was also a powerful independent risk factor. However, the circumferential resection margin, number of retrieved lymph nodes, venous invasion and postoperative chemotherapy were not extracted as independent risk factors for predicting outcomes. Therefore, the combination of lymph node status and DME was analyzed to predict prognosis and stratify the TNM 7th staging system.[15,16]

Previous studies have reported that local recurrence at Stage II and III following TME for rectal cancer can vary from 4 to 21%[18–22] and from 8 to 36%,[18,20,22] respectively. A multicenter prospective randomized trial organized by the Dutch Colorectal Cancer Group[23] reported that the 2-year local recurrence rate after surgery alone with TME was 5.7% in Stage II patients and 15.0% in Stage III patients, which is consistent with findings from this study. Some studies have investigated the relationship between DME stratification and local recurrence. The local recurrence rate was significantly higher in patients with pT3b tumors with a DME $>$ 5 mm (Stage II: 15.4%, Stage III: 34.0%) than in patients with pT3a tumors with a DME $\leq$ 5 mm (Stage II: 5.5%, Stage III: 17.1%) in the ERCRC cohort.[4] However, there was no significant difference when making the same comparison in the SGCRC cohort.[4] No significant correlation was found between local recurrence and DME stratification around a cut-off value of 6 mm,[6] and this finding is consistent with observations by other investigators.[9,12] However, in patients with overall Stage III rectal cancer, local recurrence seems to be associated with a DME $>$ 4 mm ($p = 0.0386$, Table 3).

It has been reported that distant metastasis was significantly different when patients were stratified by a cut-off value of 3 mm ($<$ 3 mm, 0% *vs.* $\geq$ 3 mm, 46.7%, $p = 0.01$), although the number of patients in that analysis was relatively small.[9] In this study, DME was strongly associated with distant metastasis, even more so than local recurrence. An increased DME is presumably associated with undetectable lymphovascular invasion and microtumor deposits in the mesorectal adipose tissues that increase the risk of local recurrence and/or distant metastases. In the Stage IIIC based on the TNM 7th edition,[15,16] however, distant metastasis and/or local recurrence may occur regardless of the grade of ME because the malignant behavior is more aggressive.

Other authors have also reported that DME was an important predictor of recurrence-free and cancer-specific survival.[1,3,4,6] For example, the ERCRC reported that the cancer-related 5-year-survival rate was significantly higher for pT3a tumors than for pT3b tumors (91.2% *vs.* 77.2% at Stage II and 77.8% *vs.* 40.3% at Stage III), which was similar to our findings. Other similar outcomes were noted for Dukes B tumors (66% *vs.* 37%) and Dukes C tumors (30% *vs.* 18%) at a cut-off value of 4 mm, and for Stage II tumors (73% *vs.* 52%) and Stage III tumors (40% *vs.* 27%) at a cut-off value of 6 mm.[1,6] In our statistical analyses, DME was a powerful predictor for stratifying patients in Stages IIA and IIIB. However, DME may be not a useful predictor in patients with Stage IIIC because of extremely advanced disease. Thus, DME is a useful predictor of postoperative recurrence and survival, and improves the utility of the TNM 7th staging system except for Stage IIIC. In addition, these findings raise questions regarding the optimal management of rectal cancer patients with a DME $>$ 4 mm. How does this apply to preoperative and/or postoperative treatments? Willett *et al.*[3] recommended selecting patients with rectal cancer for postoperative adjuvant therapy according to the depth of tumor invasion into the perirectal fat. Diagnostic techniques using MRI enable accurate measurement of the DME, which correlates well with pathological measurements.[24,25] Indeed, use of a cut-off value that can be assessed by preoperative MRI would present an efficient strategy to select patients for pre- and/or postoperative adjuvant treatments including chemoradiotherapy (CRT). In this series, between 1995 and 1999, postoperative adjuvant chemotherapy was given perorally according to the local criteria at each institute.

In European countries, preoperative CRT is the standard strategy for T3 rectal cancer to control local recurrence. In Japan, prophylactic pelvic lymph node dissection has been often performed rather than using preoperative CRT for mid-lower rectal cancer to control local recurrence.[26,27] Recently, the Dutch Colorectal Cancer Group has reported that

preoperative CRT has decreased local recurrence rate to 10.6% in Stage III rectal cancers, [28] which is consistent with findings from this study without using preoperative CRT (55/512: 10.7%, Table 3). Moreover, there was no survival benefit in those who received irradiation.[28] That is why, neoadjuvant CRT for Stage III rectal cancer has been seldom performed in Japan.

More intensive adjuvant treatments including CRT may be needed for patients with a DME > 4 mm or with Stage IIIC disease to eradicate isolated tumor cells, to prevent postoperative recurrence and to improve survival.

In conclusion, a DME value of 4 mm provides the best prognostic cut-off point to stratify patients with pT3 rectal cancer and predict oncologic outcomes. A subclassification based on a 4-mm cut-off point may improve the utility of the TNM 7th staging system except for Stage IIIC. Intensive chemotherapy is needed for patients with a DME > 4 mm or with Stage IIIC disease. These findings warrant further prospective studies to determine the reliability and validity of this cut-off point.

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進行直腸癌における肛門温存手術

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はじめに

直腸癌の治療の歴史を紐解くと，1908年にMilesにより発表された根治的な腹会陰式直腸切断術（abdominoperineal resection：APR）が，論理性と治癒性に優れ安全性も比較的高いと認められ，過去数十年にわたって標準的術式として実施されてきた。しかし，人工肛門の管理は進歩したとは言え，患者にとっての社会的・精神的負担はやはり少なくない。直腸切断術を回避し肛門温存を行うことは，大腸癌を扱う外科医の大きな願いである。

近年の器械吻合の進歩により，下部直腸癌の多くの症例で肛門温存が可能となった。また適正な肛門側断端（distal margin：DM）に関する臨床病理学的研究により，肛門温存手術の妥当性も示されている[1)~6)]。直腸癌において肛門温存手術を実施する場合，低位前方切除（low anterior resection；LAR），超低位前方切除（very low anterior resection；v-LAR），腹膜反転法（prolapsing法），経肛門吻合（conventional coloanal anastomosis：CAA），さらに一部の施設では内肛門括約筋を切除して肛門吻合を行うintersphincteric resection（ISR）を主とした肛門括約筋部分温存手術などが行われている。現時点での下部進行直腸癌の治療戦略を**表1**に示す。

現在の下部直腸癌における肛門温存術の大半は，double stapling technique（DST）による（超）低位前方切除術で実施されている。一般的にこの方法による肛門温存が不可能な場合，APRの適応とされることが多い。この理由として，①この部位の癌では坐骨直腸窩や肛門挙筋に沿うリンパ節転移の可能性があること，②肛門温存が手技的にきわめて困難であること，③肛門括約筋切除により排便機能が廃絶する可能性が大きいこと，などがあげられていたためである。しかし最近では，肛門縁から腫瘍の下縁が5 cm以内に存在する下部直腸癌に対しても，ISRを主とした肛門括約筋の部分切除を行って肛門を温存する手術法も臨床応用されるようになりつつある。これまでの報告によると①の項目については否定的であり[1)2)]，また③の排便機能はさまざまな排便障害は存在するものの，容認できる結果であるとされている[2)~4)]。下部直腸癌の治療では根治性と機能温存という，相反する面が問題となり，両者のバランスをとることが重要である。もちろん，肛門温存のために局所再発の増加があってはならず，その適応は厳しく選別しなければならない。

本稿では下部直腸癌，とりわけ進行癌における

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key words
下部直腸癌，超低位前方切除術，肛門括約筋部分温存術

表1　下部直腸癌の根治手術

(1) 標準的手術

○(超)低位前方切除（肛門温存）
器械吻合：Double stapling technique（DST）

↓ 不可

直腸反転法（prolapsing 法）
手縫い吻合：Conventional CAA

↓ 不可

○直腸切断術（永久人工肛門）
（Miles 手術）
Abdominoperineal resection（APR）

不可 → ※適応を厳密にした上で(2) を選択

(2) 標準化されていない手術および治療

○肛門括約筋部分温存手術（APR の回避）
・Intersphincteric resection（ISR）
・ISR plus（Partial）external sphincter resection（ESR）

最近の肛門温存手術について超低位前方切除やISR を中心に述べることにする。

Ⅰ．超低位前方切除

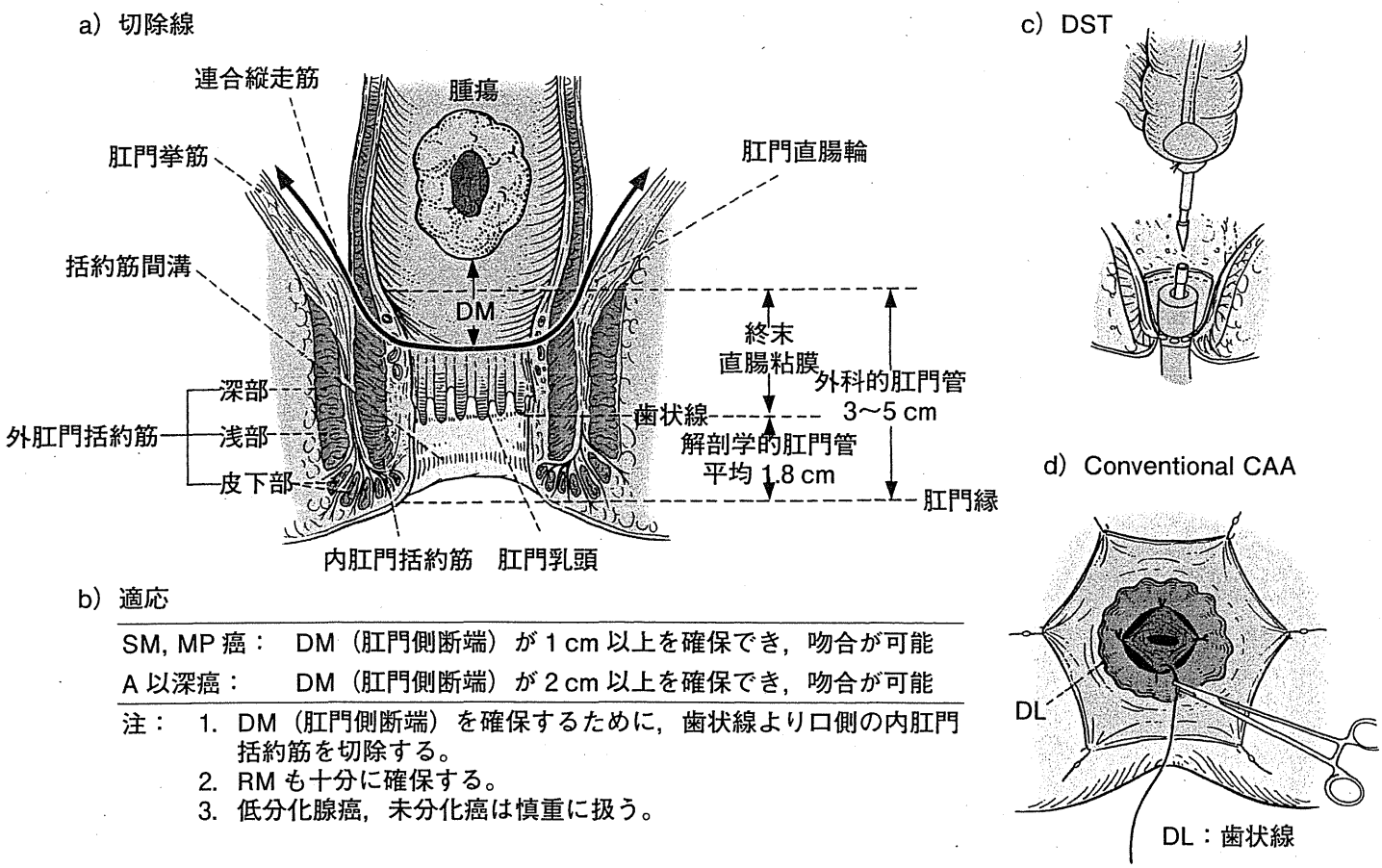
腫瘍細胞の肛門側壁内進展など臨床病理学的な知見の集積と，狭い骨盤内での吻合技術の進歩と普及に伴い，上部直腸（Ra）までの癌に対して自然肛門温存手術を施行することはコンセンサスが得られている。問題となるのは腫瘍占居部位が腹膜反転部より肛門側にある下部直腸（Rb）癌に対して自然肛門温存手術を行うのか，あるいは直腸切断術を行うのかである。日常生活に支障のない術後の排便機能を得るためには，肛門管とそれを構成する括約筋群の温存が不可欠である。詳述は省略するが，安全なDM と外科的剝離面（radial margin：RM）の確保は重要であり，T3 以深症例では病理組織学的検討により2 cm とされている。またT2 までの症例では，DM は最短1 cm でよいと考えている。T4 症例でも合併切除によりRM が確保できれば，可能な限り肛門温存を行ってよいと考える。すなわち低分化腺癌や印環細胞癌，リンパ節転移が高度な例を除けば，約1 cm のDM を保って切除できれば肛門管への癌の遺残は少ないと考えられている。このような背景から，腹腔側から直腸を切離できる症例が増える要因の1つとなっていると思われる。

超低位前方切除は，低位前方切除に含まれるものである。厳密な意味での超低位前方切除術の定義はないが，吻合が外科的肛門管またはその直上で実施されたものと理解している。したがって直腸肛門側の剝離は外科的肛門管に及び，DST により再建される。標準的な（超）低位前方切除の適応を**図1**に示す。本法の適応は，安全なsurgical margins（DM, RM）が確保され吻合が可能であるかどうかで決定される。手術の実際はLAR に準ずるものであり，上方郭清，total mesorectal excision（TME）±自律神経温存，±側方郭清，吻合，で構成される。

なお，前方切除とは直腸の切離・吻合を腹腔側（前方）から行う手術の呼称であり，経肛門的吻合と超低位前方切除は厳密な意味で区別して扱うほうがよいと考えられる。

Ⅱ．直腸反転法（Prolapsing 法），Conventional CAA

超低位前方切除術のほとんどはDST により実施されるが，腫瘍が低位になれば時に切離に困難を伴うことがある。とくに男性の狭骨盤例などでは，器械の安全な装着や挿入が煩雑になることがある。このような場合は，直腸反転法（prolaps-



b) 適応

SM, MP 癌：	DM（肛門側断端）が 1 cm 以上を確保でき，吻合が可能
A 以深癌：	DM（肛門側断端）が 2 cm 以上を確保でき，吻合が可能

注：
1. DM（肛門側断端）を確保するために，歯状線より口側の内肛門括約筋を切除する。
2. RM も十分に確保する。
3. 低分化腺癌，未分化癌は慎重に扱う。

図 1　Very low anterior resection (V-LAR), Conventional colo-anal anastomosis (CAA)
文献 11 より引用。

ing 法）にするか，経肛門吻合（conventional CAA）にするかの選択となる。

直腸反転法で行う場合，あらかじめ切離した口側断端を鉗子でつまみ肛門外に反転させる。腫瘍と歯状線を直視下に確認し，DM または肛門側を確保する。その上で，器械を用いて切離し DST で再建を行うか，全周性に電気メスで切離して再建を CAA で行うという手法である。その適応は肛門直腸輪付近の腫瘍で以下の条件になる。①半周以下の腫瘍径，②SM〜MP 程度の深達度，③EMR 後の追加切除，などである。このため，本手法は腫瘍径の大きい進行癌には適さない（図 2）。

直腸反転法が適さない場合の次なる手段としては，手縫いの conventional CAA を行うことで肛門温存は可能となる。この conventional CAA は後述する ISR とは別の術式であり，ほとんどの内肛門括約筋が残存する。本術式により自然肛門から排便できることの恩恵は大きいが，排便障害を認めることもしばしばあり，術前よりしっかりと説明する必要がある。また吻合部が低位になるほど縫合不全の危険が増加するため，一時的人工肛門造設も考慮する必要がある。

Ⅲ．ISR を主とした肛門括約筋部分温存手術

ISR の臨床は 1977 年に Parks らにより報告され[7]，1990 年代初頭のヨーロッパのグループからシリーズで発表されている[5]。本邦においては施行され始めたのは 1990 年代後半である[3]。ISR を主とした肛門括約筋部分温存手術である。ISR という言葉を最初に提唱したのは，1977 年の Parks らの報告であろう[7]。この原著に従えば，ISR とはあくまでも intersphincteric に内外括約筋間の剝離を肛門側より行い，続いて手縫いによる結腸肛門吻合を行う手技に対して適用された言葉である。しかし，近年の骨盤底解剖の理解の進