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Extramural Extension as Indicator for Postoperative Adjuvant Chemotherapy in Stage IIA (pT3N0) Colon Cancer

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The usefulness of adjuvant chemotherapy (CMT) in patients with Stage IIA colon cancer remains unclear. The present study aimed to investigate extramural extension as an indicator for adjuvant CMT. Data were reviewed from 202 consecutive patients with Stage IIA colon cancer that underwent curative surgery between 1995 and 2007. The distance of the extramural extension (DEE) was measured histologically. The optimal prognostic cut-off point of the DEE for oncologic outcomes was statistically determined. The eligible surviving patients had been followed for a median period of 75 months (range: 2–210 months). Patients were subdivided into two groups according to the optimal cut-off point; DEE $\leq$5 mm (pT3a) and DEE >5 mm (pT3b). The pT3b was the most powerful independent risk factor for postoperative recurrence ($P = 0.0324$, HR: 3.04, 95% CI: 1.098–8.408), and was significantly correlated with distant metastasis ($P = 0.0161$ HR: 5.19, 95% CI: 1.765–15.239). The recurrence-free and cancer-specific 5-year survival rates in patients with pT3b were significantly lower than in patients with pT3a (81.5% vs. 95.4%, $P = 0.0003$ and 85.9% vs. 97.4%, $P = 0.0007$, respectively). pT3b could be an important risk factor for distant metastasis in Stage IIA colon cancer. Postoperative adjuvant CMT may be indicated for patients with pT3b.

KEY WORDS: colon cancer; extramural extension; depth of invasion; risk factor

INTRODUCTION

Colorectal cancer is the third-leading cause of cancer mortality in Japan [1]. Although surgical treatment is the best approach to cure colorectal cancer, postoperative recurrence occurs in some patients after curative resection. The most important prognostic factor for recurrence and survival is the stage of disease, which is determined by the TNM7th staging system [2]. Among colon cancers, 30–40% of patients are diagnosed as Stage II disease [3], and these patients have a good prognosis with a 5-year survival rate of approximately 80% after surgery alone [4,5]. In other words, 20% have a worse prognosis. Postoperative adjuvant chemotherapy (CMT) is essential for these patients to prevent postoperative recurrence and to improve survival, whereas the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) treatment guidelines do not recommend the routine use of adjuvant CMT for Stage II colon cancer patients. On the other hand, ASCO and NCCN guidelines do state that adjuvant CMT could be considered for patients with high risk factors, including T4 tumor leading to obstruction, perforation, and for patients with fewer than 12 lymph nodes [6,7]. However, the high risk factors of Stage II colon cancer have not yet been determined. Therefore, it is important to identify which patients with Stage II colon cancer are at a higher risk of recurrence and have a poorer prognosis following curative resection. Here, we have investigated the distance of extramural extension (DEE) which has not yet been included as being among the high risk factors of Stage II colon cancer. Recently, a distance of mesorectal extension more than 4 mm has been reported as a higher risk factor for distant metastasis in Stage IIA rectal cancer [8,9]. However, the prognostic significance of DEE in Stage IIA (pT3N0) colon cancer remains unclear. The aim of the present study was to investigate the significance of DEE for postoperative recurrence and to select patients requiring postoperative adjuvant CMT.

MATERIALS AND METHODS

All protocols contained within this study were approved by the local Institutional Review Board. Between 1995 and 2007, patients with a colon cancer underwent curative surgery at Kurume University Hospital. Data of 202 consecutive Stage IIA (pT3N0) colon cancers including rectosigmoid colon were derived from our computerized database (CDB) which was established in 1982. All patients were prospectively registered into the CDB and had histologically confirmed adenocarcinoma in the present study. None of the patients had received radiotherapy or neoadjuvant CMT prior to operative management in this study. Histologically defined curative surgery (R0) was performed in each patient by well-trained five colorectal surgeons, and colon resection was performed with standard regional lymph nodes dissection according to the rules defined by the Japanese Society for Cancer of the Colon and Rectum (JSCCR) [10]. The root of the ileocolic, right colic, and middle colic artery was cut in cecum, ascending colon, and transverse colon cancer, respectively, and the root of the inferior mesenteric artery was cut in descending, sigmoid colon, and rectosigmoid colon cancer.

The surgical 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. The CRM positive case was not included in this study. The baseline characteristics of patients and tumors are shown in Table I. The mean number of retrieved lymph nodes was 32 ± 19 (median: 28, range: 5–117). In 20 patients (10%), the number of retrieved lymph

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nodes was less than 12. Postoperative CMT was administered without standardized protocol for 76 patients (37.6%) who had traditional risk factors such as moderately–poorly differentiation, moderate-marked lymphatic and venous invasion. Peroral 5-fluorouracil (5-Fu) based anti-cancer agents including doxifluridine (5′DFUR), 1-hexylcarbamoyl-5-fluorouracil (HCFU), or uracil–tegafur (UFT) were most frequently used.

The clinicopathological data and follow-up system were based on the rules defined by the JSCCR. Patients were re-staged according to the pathological TNM classification (7th edition) [2]. 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 and/or ultrasonography, the final diagnosis was made using computerized tomography (CT) and/or magnetic resonance imaging (MRI) and other diagnostic tools.

Distant metastasis included hematogenous metastases to the liver, lung, bone, brain, kidney, or other organs. Local recurrence was defined as a single tumor within the initial operation field. Peritoneal dissemination was defined as intra-abdominal multiple tumors with or without ascites. Lymph node recurrence was defined as intra-abdominal, para-aortic, subclavicular, and mediastinal lymph node metastases. These recurrence tumors were radiologically confirmed and/or histologically proven.

The outcomes of all patients were precisely investigated. As of January 1995, the eligible surviving patients had been followed for a median period of 75 months (range: 2–210 months).

Measurement of Distance of Extramural Extension

All surgically resected specimens were opened along the anti-tumor 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, the 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., DEE). The measurement was determined without prior knowledge of patient clinical information. 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 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 (Fig. 1b).

This methodology was established as a standardized measurement by the pathological workshops held by six specialized pathologists belonging to the JSCCR [9], but external pathological review was not performed in the present study, because one of the authors (KS) is a surgeon who is familiar with surgical pathology.

TABLE I. Patient and Tumor Characteristics

Number of patients with Stage IIA colon cancer	202
Age (years)[a]	68 ± 11 (range: 32–91)
Gender: male/female	135/67
Preoperative CEA (ng/ml)[a]	7.7 ± 16.4 (range: 0–176)
Preoperative ileus: yes/no	10/192
Location of tumor: C/A/T/D/S/RS	13/39/32/12/66/40
Operative method: ICR/RH/TR/DR/LH/SD/AR/LAR	8/55/16/5/10/58/29/21
Size of tumor (mm)[a]	52 ± 21 (range: 15–130)
Gross type: expansive/infiltrative	193/9
Circumference of tumor: total/non-total	71/131
Histology: well/moderate/poorly/mucinous	140/51/2/9
Lymphatic invasion: ly0/ly1/ly2/ly3	102/78/15/7
Venous invasion: v0/v1/v2/v3	49/141/12/0
Perineural invasion: negative/positive	179/23
Number of retrieved lymph nodes[a]	32 ± 19 (range: 5–117)
Postoperative chemotherapy: yes/no	76/126

CEA, carcinoembryonic antigen; C, cecum; A, ascending colon; T, transverse colon; D, descending colon; S, sigmoid colon; RS, rectosigmoid colon; ICR, ileocecal resection; RH, right hemicolectomy; TR, transverse colon resection; DR, descending colon resection; LH, left hemicolectomy; SD, sigmoidectomy; AR, anterior resection; LAR, low anterior resection; well, well differentiated; moderate, moderately differentiated; poorly, poorly differentiated; ly0/v0, negative invasion; ly1/v1, mild invasion; ly2/v2, moderate invasion; ly3/v3, marked invasion.
[a]Mean ± SD.

Statistical Analysis

Statistical analysis was performed using StatView (version 5.0) for Windows. All clinicopathological independent variables (15 items) were coded for analysis. These were: gender (male: 0, female: 1); age (>70: 0, ≤70: 1); preoperative carcinoembryonic antigen (CEA; >5.0: 0, ≤5.0: 1); size of tumor (>5 cm: 0, ≤5 cm: 1); preoperative ileus (yes: 0, no: 1); location of tumor (right: 0, left: 1, defined, respectively, as proximal or distal to the splenic flexure); gross type (infiltrative: 0, expansive: 1); circumference of tumor (total: 0, non-total: 1), histology (moderately/poorly-differentiated/mucinous adenocarcinoma: 0, well-differentiated adenocarcinoma: 1); lymphatic invasion (positive: 0, negative: 1); venous invasion (positive: 0, negative: 1); perineural invasion (positive: 0, negative: 1); number of retrieved LN (<12: 0, ≥12: 1); postoperative CMT (yes: 0, no: 1); and DEE (>X mm: 0, ≤X mm: 1). Overall recurrence (absent: 0, present: 1), distant metastasis (absent: 0, present: 1), local recurrence, peritoneal dissemination, and others (absent: 0, present: 1), and survival (alive: 0, dead: 1) were coded as dependent variables. Cox regression analysis was used to determine independent risk factors for overall postoperative recurrence and the optimal cut-off point of the DEE 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

Histogram of the Distance of Extramural Extension

The mean DEE for the 202 cases of Stage IIA (pT3N0) colon cancer was 4.7 ± 4.6 mm (median: 4.0 mm; range: 0.1–40 mm).

Cut-Off Points of Distance of Extramural Extension for Recurrence-Free Survival

Results from the Cox regression and log-rank analyses for recurrence-free 5-year survival are summarized in Table II. A cut-off value of 5 mm showed the lowest *P*-value ($P = 0.0003$) and highest hazard ratio (HR) of 4.71, when this cut-off point was compared with other cut-off points. A cut-off value of 5 mm had the greatest influence on recurrence-free survival at 5 years. Therefore, the best prognostic cut-off point for DEE was determined as 5 mm, and Stage IIA patients were stratified into two categories according to this value (DEE ≤5 mm: pT3a, and DEE >5 mm: pT3b).

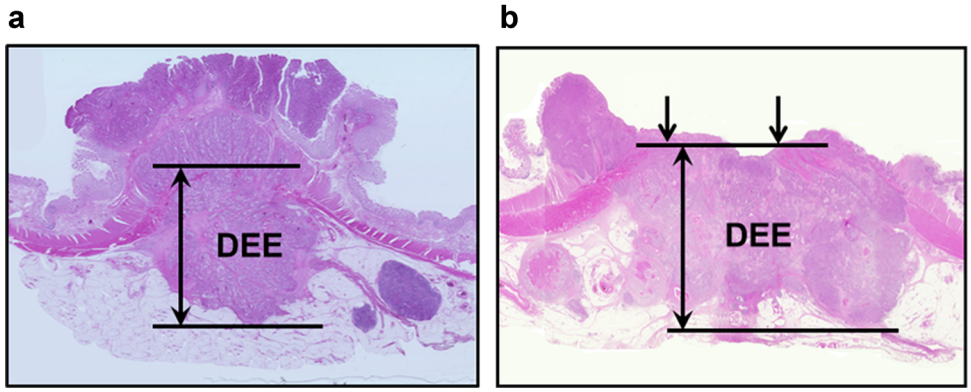

Fig. 1. Measurement of distance of extramural extension. **a**: When the outer border of the muscular layer was completely identifiable, the distance from the outer border of the muscular layer to the deepest part of the invasion was measured. **b**: When the outer border of the muscular layer was not 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. DEE, distance of extramural extension.

Independent Risk Factors for Postoperative Overall Recurrence

Univariate analysis showed that CEA level ($P = 0.0622$), gross type ($P = 0.0003$), circumference of tumor ($P = 0.0105$), lymphatic invasion ($P = 0.0735$), perineural invasion ($P = 0.0408$), and DEE ($P = 0.0003$) were high risk factors for overall postoperative recurrence and recurrence-free 5-year survival rate (Table III). Of those, the DEE was extracted as the most powerful independent risk factor by multivariate analysis (HR 3.04, 95% CI: 1.098–8.408, $P = 0.0324$).

Postoperative Recurrence After Curative Surgery

The first site of recurrence after curative resection is shown in Table IV. Twenty patients (9.9%) had postoperative recurrences including 12 patients (19.4%) in pT3b category ($P = 0.0062$). Lung metastasis occurred at a higher rate of 6.5% ($P = 0.0083$). As shown in Table V, Cox regression analysis showed that distant metastases including liver and/or lung occurred at a significantly higher rate (16.1%) in pT3b category (HR: 5.19, 95% CI: 1.765–15.239, $P = 0.0028$).

Treatment for Postoperative Recurrence and Survival

Radical salvage surgery (R0) including pulmonary and/or liver resection was performed in nine patients followed by 5-Fu based CMT. Eleven patients received 5-Fu based CMT, radiotherapy, and best supportive care. The 5-Fu based regimen included UFT + UZEL (leucovorin), TS-1 (tegafur–gimeracil–oteracil potassium), CPT-11 (irinotecan) + 5′FUDR (doxifluridine), FOLFOX (folinic acid–fluorouracil–oxaliplatin), and/or FOLFIRI (folinic acid–fluorouracil–irinotecan) with or without bevacizumab. As shown in Figure 2, the 5-year-survival rate in patients (n = 9) with radical salvage surgery + CMT was higher than that in patients (n = 11) with CMT alone ($P = 0.0682$, HR: 2.93, 95% CI: 0.871–9.835).

Recurrence-Free and Cancer-Specific Survival Rates

As shown in Figure 3, the recurrence-free 5-year-survival rate was significantly lower in patients with pT3b than in patients with pT3a (81.5% vs. 95.4%, $P = 0.0003$, HR: 4.71, 95% CI: 1.875–11.849). In addition, the cancer-specific 5-year-survival rate in patients with pT3b was significantly lower than that in patients with pT3a (85.9% vs. 97.4%, $P = 0.0007$, HR: 5.84, 95% CI: 1.831–18.632) as shown in Figure 4.

DISCUSSION

It remains unclear whether or not adjuvant CMT improves prognosis in patients with Stage II colon cancer, because surgery alone is usually curative for Stage II colon cancer. But, postoperative recurrences occur at approximately 20% of these patients, and some patients die of metastatic disease [6]. Some risk factors including T4 tumor, lymphatic permeation, venous invasion, bowel obstruction, perforation, low grade histological differentiation, and the number of retrieved lymph nodes less than 12 have been identified in an attempt to stratify Stage II colon

TABLE II. Extramural Extension for Recurrence-Free 5-Year Survival Using Cox Regression Analysis: Cut-Off Points

DEE (mm)	Number of patients	RF survival at 5 years	Chi-square	HR (95% CI)	Log-rank *P*-value
>1 vs. ≤1	159 vs. 43	91% vs. 92%	0.428	1.50 (0.440–5.137)	0.5130
>2 vs. ≤2	129 vs. 73	89% vs. 94%	1.331	1.80 (0.653–4.969)	0.2487
>3 vs. ≤3	107 vs. 95	88% vs. 94%	2.623	2.16 (0.830–5.633)	0.1053
>4 vs. ≤4	89 vs. 113	87% vs. 94%	3.961	2.47 (0.983–6.183)	0.0544
>5 vs. ≤5	62 vs. 140	82% vs. 95%	13.202	4.71 (1.875–11.849)	0.0003
>6 vs. ≤6	36 vs. 166	86% vs. 92%	0.757	1.56 (0.567–4.300)	0.3844
>7 vs. ≤7	29 vs. 173	86% vs. 92%	0.499	1.48 (0.495–4.429)	0.4800
>8 vs. ≤8	23 vs. 179	82% vs. 92%	1.332	1.89 (0.630–5.648)	0.2485
> 9 vs. ≤9	22 vs. 180	81% vs. 92%	1.541	1.98 (0.660–5.918)	0.2145
> 10 vs. ≤10	15 vs. 187	86% vs. 92%	0.055	1.19 (0.275–5.152)	0.8143

HR, hazard ratio; CI, confidence interval; DEE, distance of extramural extension; RF, recurrence-free.

TABLE III. Independent Risk Factors for Recurrence and Recurrence-Free 5-Year Survival Using Cox Regression Analysis

			Univariate analysis		Multivariate analysis	
Variable (n)	Rate of recurrence (n)	RF 5-year survival	HR (95% CI)	*P*-Value	HR (95% CI)	*P*-Value
Gender						
Male (135) vs. female (67)	11% (15) vs. 8% (5)	89.7% vs. 93.5%	1.69 (0.611–4.676)	0.3059		
Age (years)						
>70 (96) vs. ≤70 (106)	11% (11) vs. 8% (9)	90.2% vs. 92.1%	1.59 (0.656–3.829)	0.3018		
Preoperative CEA (ng/ml)						
>5 (77) vs. ≤5 (122)	14% (11) vs. 7% (9)	84.9% vs. 94.7%	2.28 (0.936–5.528)	0.0622	1.37 (0.502–3.726)	0.5399
Preoperative ileus						
Yes (10) vs. no (192)	20% (2) vs. 9% (18)	80% vs. 91.6%	2.47 (0.569–10.693)	0.2118		
Size of tumor (cm)						
>5 (92) vs. ≤5 (110)	11% (10) vs. 9% (10)	90.9% vs. 91.2%	1.07 (0.445–2.592)	0.8735		
Location of tumor						
Right (63) vs. left (139)	8% (5) vs. 11% (15)	92.0% vs. 90.5%	0.7 (0.254–1.922)	0.4845		
Gross type						
Infiltrative (9) vs. expansive (193)	44% (4) vs. 8% (16)	55.6% vs. 92.9%	5.92 (1.976–17.740)	0.0003	2.44 (0.677–8.790)	0.1724
Circumference of tumor						
Total (71) vs. non-total (131)	17% (12) vs. 6% (8)	84.0% vs. 95.0%	3.04 (1.241–7.467)	0.0105	1.47 (0.530–4.079)	0.4590
Histology						
Others[a] (62) vs. well (140)	11% (7) vs. 9% (13)	91.3% vs. 91.0%	1.20 (0.479–3.012)	0.6946		
Lymphatic invasion						
Positive (100) vs. negative (102)	14% (14) vs. 6% (6)	88.3% vs. 93.8%	2.34 (0.896–6.089)	0.0735	1.63 (0.595–4.456)	0.3424
Venous invasion						
Positive (153) vs. negative (49)	11% (17) vs. 6% (3)	90.1% vs. 93.8%	1.76 (0.514–6.007)	0.3622		
Perineural invasion						
Positive (23) vs. negative (179)	22% (5) vs. 8% (15)	78.3% vs. 92.8%	2.77 (1.000–7.648)	0.0408	1.38 (0.464–4.107)	0.5618
DEE (mm)						
>5 (pT3b:62) vs. ≤5 (pT3a:140)	21% (13) vs. 5% (7)	81.5% vs. 95.4%	4.71 (1.875–11.849)	0.0003	3.04 (1.098–8.408)	0.0324
Number of retrieved LNs						
<12 (20) vs. ≥12 (182)	10% (2) vs. 10% (18)	85.5% vs. 91.4%	1.19 (0276–5.159)	0.8119		
Postoperative chemotherapy						
Yes (76) vs. no (126)	11% (8) vs. 10% (12)	90.7% vs. 91.2%	0.83 (0.329–2.070)	0.6822		

HR, hazard ratio; CI, confidence interval; RF, recurrence-free; CEA, carcinoembryonic antigen; well, well-differentiated adenocarcinoma.
[a]Others, moderately differentiated, poorly differentiated, and mucinous adenocarcinoma; DEE, distance of extramural extension; LN, lymph node.

cancers as a high risk group. Adjuvant CMT may bring some improvement in survival rate in some patients of this group. However, many of these factors might lack utility and reliability.

The 7th edition of TNM staging system [2] gives the strong predictors for prognosis in colorectal cancer. The recurrence rate of Stage II colon cancer is reported to range from 7.9% to 22%, and the 5-year survival rate, to range from 75% to 92% [4,11,12], similar to our results. For further improvement in prognosis, it is important to identify the highest risk factor for recurrence following curative resection. The aim of the present study was to investigate DEE in Stage IIA (pT3N0) colon cancers as a convenient indicator for postoperative recurrence, and for selecting patients for adjuvant CMT.

Cawthorn et al. [13] advocated stratifying mesorectal extension using a cut-off point of 4 mm in 1990, and subsequently, the International Union Against Cancer (UICC) proposed an optional cut-off point for mesorectal extension in the pT3/pT4 tumors [14]. Thereafter, several studies have described prognostic heterogeneity in patients with pT3 rectal cancers, and they used different cut-off points which varied from 2 to 8 mm [15–21]. These cut-off points showed a prognostic significance except for a cut-off point of 3 mm [20]. A recent multi-institutional study carried out by our group demonstrated that a cut-off point of 4 mm could best independently delineate adverse prognosis of Stage IIA (pT3N0) rectal cancers [8,9].

TABLE IV. First Site of Recurrence After Curative Surgery

First site of recurrence	Total (n = 202)	pT3a (n = 140)	pT3b (n = 62)	*P*-Value
Liver	10 (5.0%)	5 (3.6%)	5 (8.1%)	n.s.
Lung	4 (2%)	0	4 (6.5%)	0.0083
Liver + lung	1	0	1	n.s.
Peritoneal dissemination	3	1	2	n.s.
Lymph nodes	1	1	0	n.s.
Local	1	1	0	n.s.
Total	20 (9.9%)	8 (5.7%)	12 (19.4%)	0.0062

pT3a, distance of extramural extension ≤5 mm; pT3b, distance of extramural extension >5 mm.

As to colon cancer, in 2001, the Erlangen Registry of Colorectal Carcinoma (ERCRC) and Study Group for Colorectal Carcinoma (SGCRC) Studies subdivided extramural invasion into two groups (≤15 and >15 mm) according to the histological measurement, and reported its noticeable importance as a prognostic indicator although no statistical significance was shown by multivariate analysis [22]. However, the heterogeneity of pT3 concerning lymph node and distant metastases was reported when pT3 was subdivided into four groups; pT3a (<1 mm), pT3b (1–5 mm), pT3c (>5–15 mm), and pT3d (>15 mm) [23]. Another investigator has reported that the extramural invasion >1 cm was associated with a high-risk of recurrence by univariate analysis, but no prognostic significance was shown by multivariate analysis [24].

In the present study, the best cut-off point of DEE predicting postoperative recurrence was 5 mm, and DEE >5 mm (pT3b) was the most powerful independent risk factor for postoperative recurrence by multivariate analysis, different from other reports [22,24]. These discrepancies may be caused by the differences in tumor malignancy, cohort, sample size, and statistical techniques.

TABLE V. Postoperative Recurrence at the Cut-Off Value of 5 mm Using Cox Regression Analysis

	Distant metastasis			Non-hematogenous recurrence[a]		
TNM stage (7th ed.)	Number of patients (%)	HR (95% CI)	*P*-Value	Number of patients (%)	HR (95% CI)	*P*-Value
Stage IIA (n = 202)						
pT3a (n = 140)	5 (3.6)	1		2 (1.4)	1	
pT3b (n = 62)	10 (16.1)	5.19 (1.765–15.239)	0.0028	3 (4.8)	3.58 (0.597–21.398)	0.1629

HR, hazard ratio; CI, confidence interval; pT3a, distance of extramural extension ≤5 mm; pT3b, distance of extramural extension >5 mm.
[a]Non-hematogenous recurrence includes peritoneal dissemination, lymph node metastases, and local recurrence.

Preoperative CEA, gross type, circumference of tumor, lymphatic invasion, and perineural invasion were relatively associated with postoperative recurrence, similar to other reports [25–27]. However, histology, preoperative ileus, venous invasion, and the number of retrieved lymph nodes <12 were not correlated with postoperative recurrence, different from other reports [26,28–30]. Detailed clinicopathological examination, long-term follow-up, and optimal statistical analysis might have caused these results.

An increased DEE may be associated with undetectable lymphovascular invasion and microtumor deposits in the extramural adipose tissues, which increase the risk to distant and/or lymph node metastases, as suggested by another investigator [23]. Especially, the pT3b category in Stage IIA colon cancer seems to be a heterogeneous group which is strongly associated with distant metastases (Table IV), similar to that of Stage IIA rectal cancer [8,9]. This is because the mechanism of distant metastases may be each similar in the Stage II disease, but different from that of local recurrence often caused in the Stage III disease and by positive circumference resection margin.

The DEE can be easily evaluated on a histological glass slide with efficient cost benefit and without technical complexity. Therefore, DEE is a useful and convenient predictor for postoperative recurrence and survival. A sub-classification based on a 5-mm cut-off point may improve the utility of the TNM 7th staging system.

However, these findings raise questions regarding the optimal management of pT3b (DEE >5 mm) category in patients with Stage IIA disease. Willett et al. recommended selecting patients for postoperative adjuvant therapy according to the depth of tumor invasion into the perirectal fat [15]. In the present series, between 1995 and 2007, postoperative adjuvant CMT was given perorally to patients who had traditional pathologic risk factors such as tumor differentiation, lymphatic and venous invasion. But, these traditional factors and 5-Fu based adjuvant CMT were not useful for evaluating recurrence and survival. This may be caused by the insufficient treatment strategy. The Quick and Simple and Reliable (QUASAR) trial showed a small survival benefit of 3.6% in Stage II colon cancer using 5-Fu plus leucovorin [31]. Therefore, the subsets of patients who truly benefit from CMT need to be identified. Treatment strategy should be changed and more aggressive adjuvant treatments may be needed for patients with the pT3b category to prevent postoperative recurrence. The MOSAIC (Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer) trial reported that high-risk Stage II colon cancer patients may benefit from adjuvant CMT using oxaliplatin, 5-Fu, and leucovorin (FOLFOX) [32]. Recently, molecular markers such as microsatellite instability/stability appear useful to select high-risk Stage II patients and to guide individualized therapy [33,34]. However, it may be difficult to decide optimal duration and management of toxicities of the new anti-cancer agents such as FOLFOX, but special attention to the combination of this simple pathological predictor and molecular markers may initiate a new treatment strategy for high-risk Stage II patients, who could benefit from the adjuvant CMT. Additionally, radical salvage surgery after recurrence should be performed to improve survival, if possible.

In conclusion, a DEE value of 5 mm provides the best prognostic cut-off point to stratify patients with Stage IIA colon cancer and predict oncologic outcomes. Postoperative adjuvant CMT may be indicated for patients with pT3b category. Further studies are essential to confirm the reliability and reproducibility of this study and to use this pathological predictor in routine clinical practice.

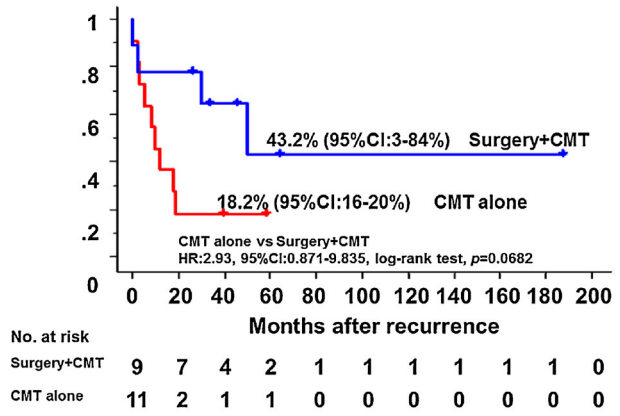

Fig. 2. Survival after recurrence. The 5-year survival rate was higher in patients (n = 9) with radical salvage surgery + CMT as compared to that of patients (n = 11) with CMT alone ($P = 0.0682$, HR: 2.93, 95% CI: 0.871–9.835). CMT, chemotherapy.

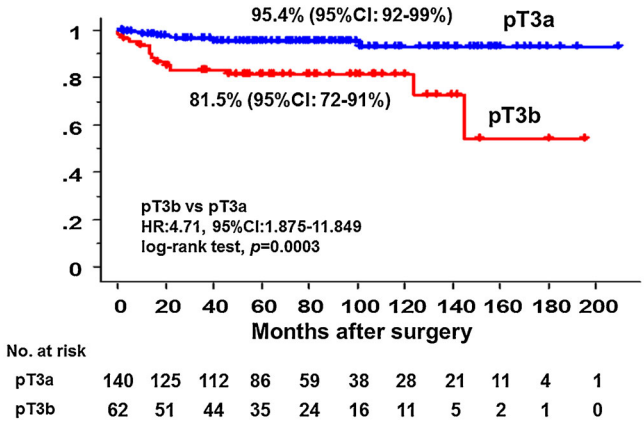

Fig. 3. Recurrence-free survival. The recurrence-free 5-year-survival rate was 81.5% in patients with pT3b, and 95.4% in patients with pT3a. Significant difference was noted between the groups ($P = 0.0003$, HR: 4.71, 95% CI: 1.875–11.849). pT3a, distance of extramural extension ≤5 mm; pT3b, distance of extramural extension >5 mm.

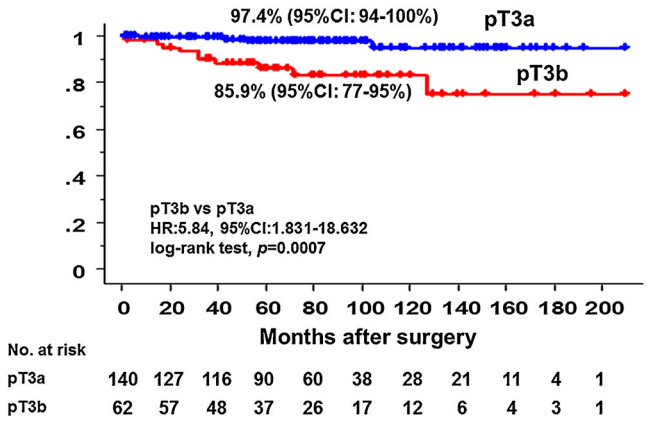

Fig. 4. Cancer-specific survival. The cancer-specific 5-year-survival rate was 85.9% in patients with pT3b, and 97.4% in patients with pT3a. Significant difference was noted between the groups (HR: 5.84, 95% CI: 1.831–18.632, $P = 0.0007$). pT3a, distance of extramural extension $\leq$5 mm; pT3b, distance of extramural extension >5 mm.

REFERENCES

1. Kotake K, Honjo S, Sugihara K, et al.: Changes in colorectal cancer during a 20-year period: An extended report from the multi-institutional registry of large bowel cancer, Japan. Dis Colon Rectum 2003;46:32–43.
2. Sobin LH, Gaspodarowicz MK, Wittekind C: TNM classification of malignant tumors, 7th edition. New York, NY: Wiley-Blackwell; 2009.
3. Jessup JM, McGinnis LS, Steele GD ,Jr, et al.: The National Cancer Data Base. Report on colon cancer. Cancer 1996;78:918–926.
4. Schrag D, Rifas-Shiman S, Saltz L, et al.: Adjuvant chemotherapy use for medicate beneficiaries with stage II colon cancer. J Clin Oncol 2002;19:3999–4005.
5. IMPACT B2: Efficacy of adjuvant fluorouracil and folinic acid in B2 colon cancer trials investigators. J Clin Oncol 1999;17:1356–1363.
6. Benson AB III, Schrag D, Somerfield MR, et al.: American Society of Clinical Oncology recommendations on adjuvant chemotherapy for stage II colon cancer. J Clin Oncol 2004;22:3408–3419.
7. Engstrom PF, Amoletti JP, Benson AB III, et al.: NCCN clinical practice guidelines in oncology: Colon cancer. V.3.2010. J Clin Oncol 1999;17:1356–1363.http://www.nccn.org/2010
8. Shirouzu K, Akagi Y, Fujita S, et al.: Clinical significance of the mesorectal extension of rectal cancer: A Japanese multi-institutional study. Ann Surg 2011;253:704–710.
9. Akagi Y, Shirouzu K, Fujita S, et al.: Predicting oncologic outcomes by stratifying mesorectal extension in patients with pT3 rectal cancer: A Japanese multi-institutional study. Int J Cancer 2012;131:1220–1227.
10. Japanese Society for Cancer of the Colon and Rectum (JSCCR): Japanese classification of colorectal carcinoma, 2nd English edition. Tokyo, Japan: Kanehara & Co., Ltd.; 2009.
11. Gertler R, Rosenberg R, Schuster T, et al.: Defining a high-risk subgroup with colon cancer stages I and II for possible adjuvant therapy. Eur J Cancer 2009;45:2992–2999.
12. O'Connel JB, Maggard MA, Ko CY: Colon cancer survival rates with New American Joint Committee on cancer sixth edition staging. J Natl Cancer Inst 2004;96:1420–1425.
13. Cawthorn SJ, Parums DV, Gibbs NM, et al.: Extent of mesorectal spread and involvement of lateral resection margin as prognostic factors after surgery for rectal cancer. Lancet 1990;1:1055–1059.
14. Hermanek P, Henson DE, Hutter RVP, et al.: editors. UICC TNM supplement. New York, NY: Springer; 1993.
15. Willett CG, Badizadegan K, Ancukiewicz M, et al. Prognostic factors in stage T3N0 rectal cancer: Do all patients require postoperative pelvic irradiation and chemotherapy? Dis Colon Rectum 1999;42:167–173.
16. Steel MC, Woods R, Mackay JM, et al. Extent of mesorectal invasion is a prognostic indicator in T3 rectal carcinoma. Anz J Surg 2002;72:483–487.
17. Miyoshi M, Ueno H, Hashiguchi Y, et al. Extent of mesorectal tumor invasion as a prognostic factor after curative surgery for T3 rectal cancer patients. Ann Surg 2006;243:492–497.
18. Bori R, Sejben I, Svébis M, et al.: Heterogeneity of pT3 colorectal carcinomas according to the depth of invasion. Pathol Oncol Res 2009;15:527–532.
19. Pollheimer MJ, Kornprat P, Pollheimer VS, et al.: Clinical significance of pT sub-classification in surgical pathology of colocolon cancer. Int J Colorectal Dis 2010;25:187–196.
20. Picon AI, Moore HG, Sternberg SS, et al.: Prognostic significance of depth of gross or microscopic perirectal fat invasion in T3 N0 M0 rectal cancers following sharp mesorectal excision and no adjuvant therapy. Int J Colorectal Dis 2003;18:487–492.
21. Merkel S, Mansmann U, Siassi M, et al.: The prognostic inhomogeneity in pT3 rectal carcinomas. Int J Colorectal Dis 2001;16:298–304.
22. Merkel S, Wein A, Günther K, et al.: High-risk groups of patients with Stage II colon carcinoma. Cancer 2001;15:1435–1443.
23. Yoo HY, Shin R, Ha HK, et al.: Does T3 subdivision correlate with nodal or distant metastasis in colorectal cancer. J Korean Soc Coloproctol 2012;28:160–164.
24. Burdy G, Panis Y, Alves A, et al.: Identifying patients with T3-T4 node-negative colon cancer at high risk of recurrence. Dis Colon Rectum 2001;44:1682–1688.
25. Ogata Y, Murakami H, Sasatomi T, et al.: Elevated preoperative serum carcinoembryonic antigen level may be an effective indicator for needing adjuvant chemotherapy after potentially curative resection of stage II colon cancer. J Surg Oncol 2009;99:65–70.
26. Sato H, Maeda K, Sugihara K, et al.: High-risk Stage II colon cancer after curative resection. J Surg Oncol 2011;104:45–52.
27. Santos C, López-Doriga A, Navarro M, et al.: Clinico-pathological risk factors of stage II colon cancer: Results of a prospective study. Colorectal Dis 2013;15:414–422.
28. Biffi R, Botteri E, Bertani E, et al.: Factors predicting worse prognosis in patients affected by pT3 N0 colon cancer. Long-term results of a monocentric series of 137 radically resected patients in a 5-year period. Int J Colorectal Dis 2013;28:207–215.
29. Wolmark N, Wieand HS, Rockette HE, et al.: The prognostic significance of tumor location and bowel obstruction in Dukes B and C colorectal cancer. Findings from the NSABP clinical trials. Ann Surg 1983;198:743–752.
30. Le Voyer TE, Sigurdson ER, Hanlon AL, et al.: Colon cancer survival is associated with increasing number of lymph nodes analyzed: A secondary survey of intergroup trial INT-0089. J Clin Oncol 2003;21:2912–2919.
31. Gray R, Barnwell J, McConkey C, et al.: Adjuvant chemotherapy versus observation in patients with colorectal cancer: A randomised study. Lancet 2007;370:2020–2029.
32. André T, Boni C, Navarro M, et al.: Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. J Clin Oncol 2009;27:3109–3116.
33. Merok MA, Ahlquist T, Røyrvik EC, et al.: Microsatellite instability has a positive prognostic impact on stage II colorectal cancer after complete resection: Results from a large, consecutive Norwegian series. Ann Oncol 2013;24:1274–1282.
34. Benatti P, Gafà R, Barana D, et al.: Microsatellite instability and colorectal cancer prognosis. Clin Cancer Res 2005;11:8332–8340.