Clinicopathological Characteristics of Colorectal Cancers That Invade the Muscularis Propria

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Abstract: Purpose. This study investigated the clinicopathological characteristics of pT2 colorectal cancers.

Methods. We studied 91 patients with pT2 colorectal cancers who underwent resection. The prognostic values of various pathological parameters, including tumor budding, were investigated.

Results. Excluding four patients who underwent palliative resection, postoperative recurrence was seen in four patients (4.6%). The tumor differentiation type of the latter four patients was moderately differentiated adenocarcinoma (P=0.009). Metastasis to lymph nodes correlated significantly with postoperative recurrence (P=0.004). Recurrences tended to be more frequent in patients with tumor budding (5.3%) than in those without tumor budding (4.1%), although this difference did not achieve statistical significance. Multivariate analysis identified lymph node metastasis (P=0.014) and lymphatic invasion (P=0.010) as the only factors that had independent prognostic value.

Conclusions. Patients with pT2 colorectal cancers who had lymph node metastases (stage Ⅲ) and lymphatic invasion had a poor prognosis. Along with these two variables, tumor budding and tissue differentiation may be useful prognostic indicators that can be used to identify those patients with pT2 colorectal cancers who are at a high risk of disease recurrence after curative surgery. Such cases may demand postoperative adjuvant chemotherapy or intensive observation aimed at detecting recurrences.

Key Words: Colorectal Cancer; Muscularis Propria; Tumor budding.

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Introduction

Colorectal cancers that invade the muscularis propria (pT2) are classed as an advanced form of cancer that is associated with a relatively good prognosis (according to the UICC/TNM classification[1]). However, a subgroup of patients with pT2 colorectal cancers is at high risk of tumor recurrence. Therefore, a better method of predicting the prognosis of these patients is needed. The Dukes staging system is currently the most widely employed system of postoperative prognostic classification[2]. This staging system is based on two fundamental parameters, namely tumor penetration of the bowel wall and lymph node involvement[3]. In particular, lymph node status is considered to be the most important determinant in the decision to initiate postoperative therapies in colorectal cancer. However, neither of these parameters reflects biological behaviors of individual cancers that correlate with tumor aggressiveness and risk of recurrence[4]. In contrast, tumor budding, which is the formation of small clusters of undifferentiated cancer cells ahead of the invasive front of the lesion, is the first and most significant sign of tumor invasion[5][6]. Tumor budding has been reported to be useful for identifying high-risk patients with colorectal cancer, but the results were preliminary[4-13].

In the present study, we analyzed the association between various clinicopathological characteristics of pT2 colorectal cancers, including tumor budding, and tumor recurrence and patient survival. The aim was to identify risk factors that correlate with lower survival. This will facilitate the identification of those patients with pT2 colorectal cancer who could benefit from adjuvant chemotherapy.

Patients and Methods

The study group consisted of 91 patients [49 men and 42 women; average age, 65.9 (range, 32-89) years] with pT2 colorectal cancer who underwent tumor resection in the Department of Gastroenterological Surgery, Kyoto Prefectural University School of Medicine between March, 1998 and October, 2007. Patients with polyposis syndrome, multiple colon cancers, or inflammatory bowel disease were excluded. The rectum was the most common tumor site as the cancers of 47 patients (51%) were located in the rectum. Of the remaining patients, the cancer was located in the sigmoid colon in 25 (27%), the transverse colon in seven (8%), the ascending colon in seven (8%), the descending colon in three (3%), and the cecum in two (2%) patients. When the patients first underwent surgery, distant metastases were found in four (4.4%) (three had liver metastases and one had a lung metastasis). Seventeen patients had lymph node metastases and received adjuvant chemotherapy with oral 5-FU derivatives or drips of 5FU/l-LV for approximately one year after surgery. With the exception of the four patients with distant metastases, all patients underwent a potentially curative surgical resection.

All patients were regularly followed up by clinical examinations in the outpatient clinic (every 2-4 months), which also involved measuring the serum carcinoembryonic antigen levels (every 3-12 months). In addition, barium enema radiography or colonoscopy, ultrasonography, and computer-aided tomography were performed every 6-12 months. The mean follow-up period of the survivors (n=72) was 57 months (range, 10-123 months). Recurrence was diagnosed on the basis of the examinations described above.

Tumor location in the large intestine was categorized as cecum/colon or rectum. Sections of the invasive tumor margin were made from specimens that were fixed in formalin and embedded in paraffin.

These sections were stained with hematoxylin and eosin (H&E) for microscopic examination. The tumors were classified according to differentiation stage, namely as well differentiated or others (moderately differentiated, poorly differentiated, or mucinous). The presence of lymph node metastasis, lymphatic invasion, or venous invasion was determined on the basis of histological analysis. The tumors were also classified according to the presence or absence of tumor budding upon examination of H&E-stained sections viewed at a magnification of 200x. Tumor budding is defined as an isolated single cancer cell or a cluster composed of fewer than five undifferentiated cancer cells that appears at the invasive front of the tumor[6]. Tumor budding was classified into positive or negative: positive, corresponding to 5 or more foci of tumor budding in the area with the highest density of them, or negative, corresponding to none or less than 5 foci1[5].

Statistical Analysis

Chi-squared tests were used to compare the data of the different groups. Survival curves were generated by the Kaplan-Meier method[16], and survival rates were compared by the log-rank test. Correlations between clinicopathological variables and recurrence or survival were examined by univariate and multivariate analyses. For multivariate analysis, Cox's regression analysis17, a step-wise backward variable elimination method, was used and a value of $P<0.05$ was considered to indicate statistical significance. Statistical analyses were performed by using Microsoft Office Excel 2007® and JMP® software, version 7.0.

Results

The relationship between various clinicopathological factors and recurrence is shown in Table 1. Excluding those patients who underwent palliative resection, postoperative recurrence was seen in four of the patients (4.6%, two had lung metastases and local recurrences, one had a liver metastasis, and one had a brain metastasis). The tumors of all four patients with postoperative recurrence were moderately differentiated adenocarcinomas. Univariate analysis revealed that two factors, namely tumor differentiation type ($P=0.009$) and lymph node metastasis ($P=0.004$), correlated significantly with postoperative recurrence. Even though all four patients with postoperative recurrence had hematogenous metastasis, venous invasion did not correlate with recurrence. While recurrences were more frequent in patients with tumor budding (5.3%) than those without tumor budding (4.1%), there was no statistically significant correlation between the two variables.

When the relationship between lymph node metastasis and tumor budding was investigated, tumor budding was found in 12 of 18 patients (66.7%) with lymph node metastasis but in only 26 of 73 patients (35.6%) without lymph node metastasis ($P=0.017$) (Table 2). In addition, when we investigated the relationship between lymph node metastasis and lymphatic invasion, lymphatic invasion was found in 12 of 18 patients (66.7%) with lymph node metastasis, compared to 22 of 73 patients (30.1%) without lymph node metastasis ($P=0.004$).

The survival rates of the patients were then evaluated (Table 3). Univariate analysis revealed that two factors, namely lymph node metastasis ($P=0.001$) and lymphatic invasion ($P=0.009$), correlated significantly with survival (Fig. 1 and 2). The cumulative five-year survival rate of patients without lymph node metastasis (93.3%) was significantly higher than that of patients with lymph node metastasis (57.1%). Patients without lymphatic invasion (95.7%) also had a significantly higher

Table 1. Relationship between clinicopathological factors and recurrence in pT2 colorectal cancer

Factors	With tumor recurrence	Without tumor recurrence	Odds ratio (95%CI)	P value (Univariate analysis)
Gender				0.389
Male	3	44	2.66 (0.27–26.62)	
Female	1	39		
Age (yr)				0.789
＜60	1	26	1.37 (0.14–13.79)	
≧60	3	57		
Location				0.389
Cecum/Colon	1	39	0.38 (0.04–3.77)	
Rectum	3	44		
Differentiation				*0.009
Well	0	54	0	
Others (Moderately, poorly, mucinous)	4	29		
Lymph node metastasis				*0.004
Positive	3	14	14.79 (1.43–152.7)	
Negative	1	69		
Lymphatic invasion				0.118
Positive	3	30	5.3 (0.53–53.24)	
Negative	1	53		
Venous invasion				0.778
Positive	1	16	1.40 (0.14–14.32)	
Negative	3	67		
Tumor budding				0.794
Positive	2	36	1.31 (0.18–9.72)	
Negative	2	47		

*P<0.05 is considered significant.

Table 2. Relationship between lymph node metastasis and two pathological factors in pT2 colorectal cancer

Factors	With lymph node metastasis	Without lymph node metastasis	Odds ratio (95%CI)	P value (Univariate analysis)
Tumor budding				*0.017
Positive	12	26	3.62 (1.21–10.76)	
Negative	6	47		
Lymphatic invasion				*0.004
Positive	12	22	4.64 (1.54–13.93)	
Negative	6	51		

*P<0.05 is considered significant.

cumulative five-year survival rate than patients with lymphatic invasion (67.9%). However, we did not detect a significant correlation between venous invasion and the clinical outcome. Cox's multivariate regression analysis was conducted with a model that included eight factors, namely gender, age, tumor location, tumor differentiation, lymph node metastasis, lymphatic invasion, venous invasion, and tumor budding (Table 4). Lymph node metastasis (P=0.014) and lymphatic invasion (P=0.010) were demonstrated to be independent prognostic factors.

Table 3. Univariate analysis of survival by patients with pT2 colorectal cancer.

Factors	No. of patients	Five-year survival (%)	P value
Gender			0.999
Male	49	88.2	
Female	42	86.4	
Age (yr)			0.695
＜60	27	88.4	
≧60	64	87.6	
Location			0.717
Rectum	47	87.9	
Cecum/Colon	44	87.1	
Differentiation			0.279
Well	57	90.6	
Others (Moderately, poorly, mucinous)	34	82.1	
Lymph node metastasis			*0.001
Negative	73	93.3	
Positive	18	57.1	
Lymphatic invasion			*0.009
Negative	57	95.7	
Positive	34	67.9	
Venous invasion			0.79
Negative	73	89.1	
Positive	18	81.7	
Tumor budding			0.773
Negative	53	89.6	
Positive	38	84.8	

*P<0.05 is considered significant.

Univariate analysis revealed that two factors, namely lymph node metastasis (P=0.001) and lymphatic invasion (P=0.009), correlated significantly with survival.

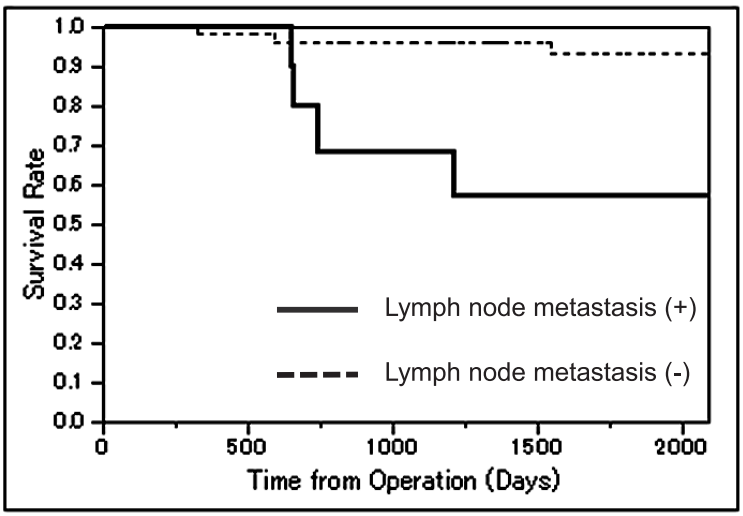

Fig. 1. Comparison of patients with or without lymph node metastases in terms of postoperative survival.

The two groups differed significantly in terms of overall survival (P= 0.001).

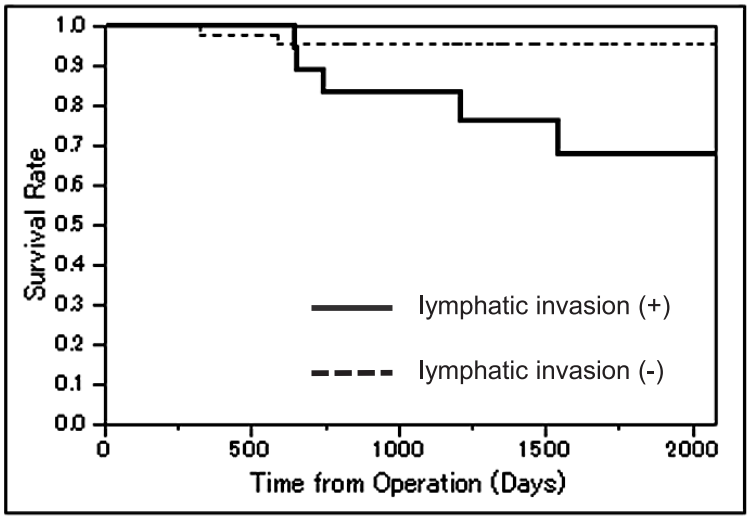

Fig. 2. Comparison of patients with or without lymphatic invasion in terms of postoperative survival.
The two groups differed significantly in terms of overall survival (P=0.009).

Table 4. Multivariate analysis of survival by patients with pT2 colorectal cancer

Factors	Hazard ratio	95% confidence interval	P value
Gender			
Male	1		
Female	1.351	0.116–5.069	0.747
Age (yr)			
＜60	1		
≧60	4.825	0.512–63.773	0.173
Location			
Rectum	1		
Cecum/Colon	1.139	0.075–8.085	0.911
Differentiation			
Well	1		
Others (Moderately, poorly, mucinous)	7.401	0.497–224.061	0.156
Lymph node metastasis			
Negative	1		
Positive	23.793	1.855–468.849	*0.014
Lymphatic invasion			
Negative	1		
Positive	12.045	1.781–140.392	*0.010
Venous invasion			
Negative	1		
Positive	1.666	0.195–12.239	0.613
Tumor budding			
Negative	1		
Positive	1.161	0.123–15.181	0.871

*P<0.05 is considered ignificant.

Multivariate analysis revealed that two factors, namely, lymph node metastasis (P=0.014) and lymphatic invasion (P=0.010), correlated significantly with survival.

Discussion

Our study shows that lymph node metastasis and lymphatic invasion were the only independent prognostic factors in patients with pT2 colorectal cancer. The patients with lymph node metastases and/or lymphatic invasion had lower survival rates than the patients without these factors.

The presence of lymph node metastasis is undoubtedly the most important prognostic factor. Indeed, Dukes[2] had already recognized the significance of nodal status in 1932 and therefore incorporated this factor in his staging system. All subsequent staging systems used for patients with colorectal cancer, including the tumor node metastasis system, have continued to recognize the importance of lymph node involvement and patients with lymph node metastases now routinely undergo adjuvant chemotherapy[18]. The literature strongly suggests that not only lymphatic invasion but also venous invasion by tumors may be of prognostic importance[3)19)]. Moreover, most of the studies that reported a prognostic value for venous invasion included patients with colorectal cancer[3]. However, we found that venous invasion did not correlate significantly with survival. Indeed, although all four patients with recurrence had hematogenous metastasis, only one of these patients exhibited venous invasion. Thus, venous invasion may not be very useful as a prognostic predictor in pT2 colorectal cancer. It may be that the invasion of blood vessels is a late event in the tumor-spreading process and thus is only detected in patients with advanced stage tumors[20]. In any case, since lymph node metastasis is a useful prognostic factor, clinicians who observe lymph node metastasis in a patient with pT2 colorectal cancer must be alert to the possibility of recurrence, even if venous invasion is not detected.

Several studies have shown that patients with tumor budding have a worse prognosis than those without budding[4-13]. Budding is a histological feature that is characterized by single cells or small clusters of cells located ahead of the invasive front of the lesion[6)14)]. Budding reflects the biological aggressiveness of the tumor itself[4]. Budding at the invasive front of the tumor reflects the biological aggressiveness of the tumor itself[4]. The term was first advocated by Morodomi et al. in 19896 and Hase et al. subsequently showed clearly that tumor budding is a good predictor of recurrence and long-term survival in patients with colorectal cancer[7]. While recent studies have found that tumor budding is significantly associated with poor differentiation, vascular invasion, metastasis, recurrence, and poor prognosis[4-13], the prognostic relevance of tumor budding in pT2 colorectal cancer was unclear. In the present study, we found that patients with budding tended to have recurrences more frequently and had a slightly lower cumulative five-year survival rate than patients without tumor budding (84.8 and 89.6%, respectively). However, neither of these differences achieved statistical significance. Specifically, in a study of 83 patients with pT3 rectal cancer by Okuyama et al.[22], 57.9% were found to exhibit tumor budding and their postoperative survival rate was significantly lower than that of the patients with budding-negative lesions (the cumulative five-year survival rates were 51.8 and 85.0%, respectively). Use of a multivariate proportional hazard model revealed that the presence of budding was the only significant indicator of reduced postoperative survival. Notably, the cumulative five-year survival rate of the patients with budding pT3 rectal cancers was much lower than that of our patients with budding pT2 colorectal cancer (51.8% vs. 84.8%), whereas the rates for the patients with budding-negative lesions were similar (85.0 vs. 89.6%, respectively). This reflects the fact that pT2 (not so deeply invaded) colorectal cancers are an advanced form of cancer with a relatively good prognosis and may explain why we could not detect an obvious correlation between tumor budding and survival.

Several studies have also examined the relationship between budding and lymph node metastasis and have shown that tumor budding in combination with lymphatic invasion is a predictive marker of lymph node metastasis in colorectal cancer[5)21-24)]. Moreover, in our study, tumor budding and lymph node metastasis correlated strongly (P=0.017), as did lymphatic invasion and lymph node metastasis (P=0.004). These observations suggest that in cases where pathological specimens are not available for the assessment of nodal status, such as in locally excised or polypectomized cancers, it may be worthwhile to evaluate whether tumor budding is present, as this information could suggest that an additional colectomy may be necessary. This approach is facilitated by the fact that tumor budding is a simple marker that is readily measured by examining H&E-stained specimens; special procedures are not required.

Previous studies have confirmed that tumor differentiation correlates closely with lymph node metastasis[25-27)]. Although we did not detect a statistically significant association between tumor differentiation and lymph node metastasis in our study, all four patients with postoperative recurrences had moderately differentiated adenocarcinomas (P=0.009). This supports the notion that moderately differentiated adenocarcinomas may be associated with a more severe prognosis.

Conclusions

Patients with pT2 colorectal cancers who had lymph node metastases (stage Ⅲ) and lymphatic invasion had a poor prognosis. These parameters, along with tumor budding and tissue differentiation, may be useful prognostic indicators that can help to identify patients with pT2 colon cancers who are at high risk of disease recurrence after curative surgery. Such cases may demand postoperative adjuvant chemotherapy or intensive observation aimed at detecting recurrences.

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〈和文抄録〉

mp 大腸癌の臨床病理学的検討

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【目的】当科において手術を施行した pT2 大腸癌について臨床病理学的検討を行った．【方法】当科にて切除手術を行った pT2 大腸癌 91 例に関して，腫瘍先進部において 5 個未満の癌細胞が組織間隙へ散布するように認められる所見，即ち budding を含めた臨床病理学的因子について比較検討した．【結果】pT2 大腸癌 91 例中 4 例（4.4％）は術前から血行性転移（肝転移 1 例，肺転移 2 例，脳転移 1 例）を認めていた．根治手術を施行した 87 例中 4 例（4.6％）に術後再発を認めた．再発を認めた 4 例の組織型はすべて中分化腺癌であった（P＝0.009）．またリンパ節転移陽性症例で有意に再発を多く認めた（P＝0.004）．budding 陽性症例で，有意差はみられなかったが再発を多く認めた（5.3％ vs. 4.1％）．多変量解析ではリンパ節転移（P＝0.014）とリンパ管侵襲（P＝0.010）が予後規定因子であった．【まとめ】pT2 大腸癌ではリンパ節転移陽性症例（stage Ⅲ），リンパ管侵襲陽性症例が有意に予後不良であった．加えて budding 陽性症例，中分化腺癌症例も再発の危険因子である可能性が示唆された．これらの症例は術後補助化学療法や注意深い術後経過観察が必要と考えられた．

キーワード：pT2 大腸癌，再発，予後．