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Predictive value of histology at the invasive margin in the prognosis of early invasive colorectal carcinoma

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Abstract: To accurately select patients with malignant colorectal polyps who are at high risk of adverse outcome, we examined the predictive value of clinicopathological factors, with special attention paid to the histology at the invasive margin. We examined 75 submucosal carcinomas from 75 patients, initially resected by polypectomy, including endoscopic, trans-anal, trans-sacral, and trans-sphincteric local excision. The associations between clinicopathological features such as sex and age; tumor size, location, shape, depth of submucosal invasion, vascular invasion, histology at the central part, and histology at the invasive margin; and the presence or absence of a residual adenomatous component and adverse outcome were examined by univariate and multivariate logistic regression analyses. Lymph node metastases were found in 2 patients, local recurrence in 4, and distant metastases in 2. Univariate logistic regression analysis showed that unfavorable histology at the invasive margin was significantly associated with lymph node metastasis or local recurrence ($P = 0.0373$), whereas the association of lymphatic invasion and vascular (lymphatic or venous) invasion with lymph node metastasis or local recurrence had marginal significance ($P = 0.0785$; $P = 0.0990$). Multivariate logistic regression analysis, with unfavorable histology at the invasive margin and lymphatic invasion as independent variables, showed that unfavorable histology alone had significance ($P = 0.0373$) in predicting adverse outcome. Widely accepted criteria such as massive submucosal invasion, positive vascular invasion, and poorly differentiated histology, were less useful in predicting adverse outcome. These results suggest that unfavorable histology at the invasive margin is a useful risk factor for predicting lymph node metastasis or local recurrence in patients with malignant colorectal polyps.

Key words: malignant colorectal polyp, lymph node metastasis, rick factor, endoscopic polypectomy, local excision

Introduction

In the past two decades, endoscopic polypectomy has been widely used for the treatment of neoplastic lesions of the large intestine, and this technique is now assumed to be satisfactory for the treatment of colorectal adenomas. However, it is still controversial whether endoscopic polypectomy is suitable once carcinomatous cells have penetrated the muscularis mucosae.[1–7] Lymph node metastasis, residual carcinoma, local recurrence, and hepatic involvement have been reported to occur in about 6%, 6%, 4%, and 1%, respectively, of early invasive colorectal carcinomas removed by polypectomy.[7,8] To reduce the adverse outcome in these patients, risk factors have been proposed by some researchers.[2,5,9–11] If polypectomized specimens have lymphatic or vessel invasion, poorly differentiated histology, or invasion close to the cut end, additional bowel resection is recommended. Although poorly differentiated histology is easily identified, it is an extremely rare pathological finding. Lymphatic invasion is not always easy to detect in routine pathology practice, and diagnosis of invasion close to the cut end may be biased by the resection line, that is, the endoscopist's technique.

Hase et al.[12] and Ono et al.[13] have recently reported that the presence of microscopic clusters of undifferentiated cancer cells at the invasive front of the lesion ("budding" or "focal dedifferentiation", respectively) is one of the most useful factors for selecting groups

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at high risk of hematogenous or regional metastasis among patients with advanced colorectal cancer. Further, Okabe[14] has reported that the mucinous component at the invasive margin was associated with adverse outcomes in early invasive colorectal carcinomas. Therefore, we hypothesized that the presence of the abovementioned histological features at the invasive margin could be an alternative risk factor for predicting lymph node metastasis or local recurrence in early invasive carcinomas, and we attempted to prove this using logistic regression analysis.

Patients and methods

Seventy-five submucosal carcinomas from 75 patients were collected from the pathology files of our Department of Surgery, the University of Tokyo. Exclusion criteria were: (1) patients initially treated by radical surgery, (2) patients with inflammatory bowel disease or familial adenomatous polyposis, (3) patients with coexistent advanced malignancy of the colorectum or other organs, (4) patients with previous cancer treatment. Forty-nine patients had initially undergone endoscopic polypectomy (EP group), and the remaining 26 had undergone local excision via the trans-anal, trans-sacral, or trans-sphincteric approach (LE group). After histological examinations of the resected specimens, additional treatment was attempted in 39 patients. Local excision was added in 2 patients in the EP group, and radical surgery was added in 29 patients in the EP group and in 8 patients in the LE group. In 37 of the 38 patients who underwent endoscopic or local excision without radical surgery, the cut end was negative for cancer. In the remaining patient, who underwent trans-anal resection for a 17-mm IIa + IIc type tumor, the surgical cut end was positive for cancer; however, no radical surgery was attempted because of his advanced age. No local recurrence or distant metastasis was observed in this patient during a 5-year follow-up period. These findings suggest that none of these 38 patients had residual cancer after endoscopic polypectomy or local excision. The age and sex of the patients were obtained from their hospital records. The tumor size, location, and gross appearance (pedunculated, broad-based, or sessile/ulcerated) were determined from the endoscopic or pathological reports. We reviewed representative histologic sections of polypectomized or resected specimens, focusing on histology, lymphatic or venous invasion, and depth of submucosal invasion. Histological differentiation was graded as: well, moderate, poor, or mucinous, based on the standard criteria,[15] and superficial and invasive parts were graded separately. We focused on the presence or absence of small nests of cancer cells with poorly differentiated or mucinous histology (unfavorable histology) at the invasive margin of the tumor (Fig. 1). The small nests of cancer cells with poorly differentiated histology were assumed to be identical to the findings that Hase et al.[12] and Ono et al.[13] have recently reported as one of the most useful factors for determining the subset of patients with advanced colorectal cancer who are at high risk for hematogenous or regional metastasis. These small nests of cancer cells may be easily overlooked in routine pathological practice.

Specimens containing adenomatous tissue with mild-to-moderate dysplasia were classified as "positive for residual adenomatous component". Submucosal invasion was graded into three levels according to the following criteria:

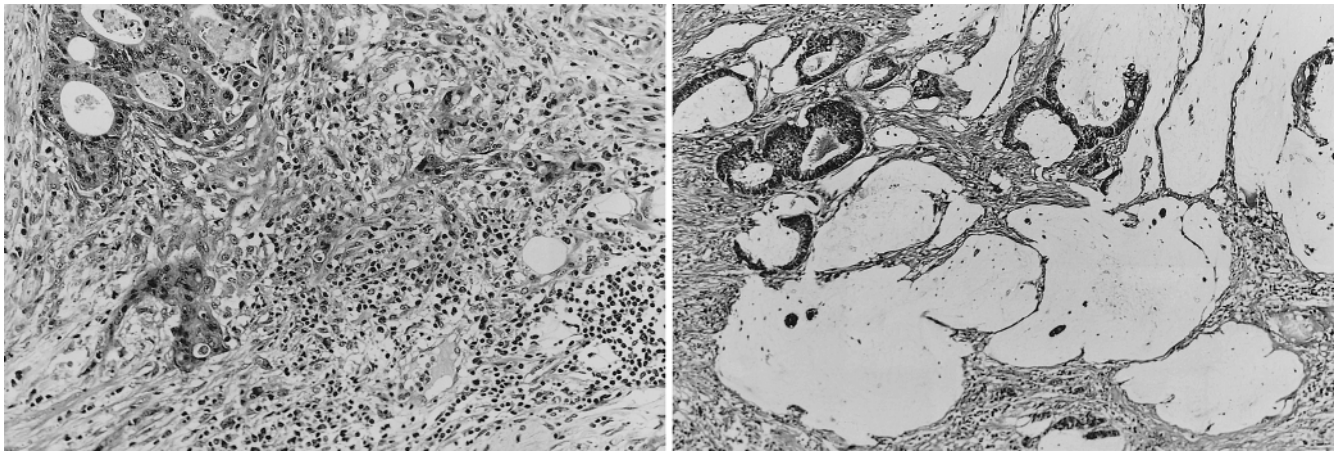

Fig. 1a,b. Representative photographs of unfavorable histology at the invasive margin. **a** Small nests of cancer cells with poorly differentiated histology are seen at the invasive margin of the tumor. **b** Cancer cells are floating in an abundant mucinous lake at the invasive margin of the tumor. **a** H&E, ×50; **b** H&E, ×25

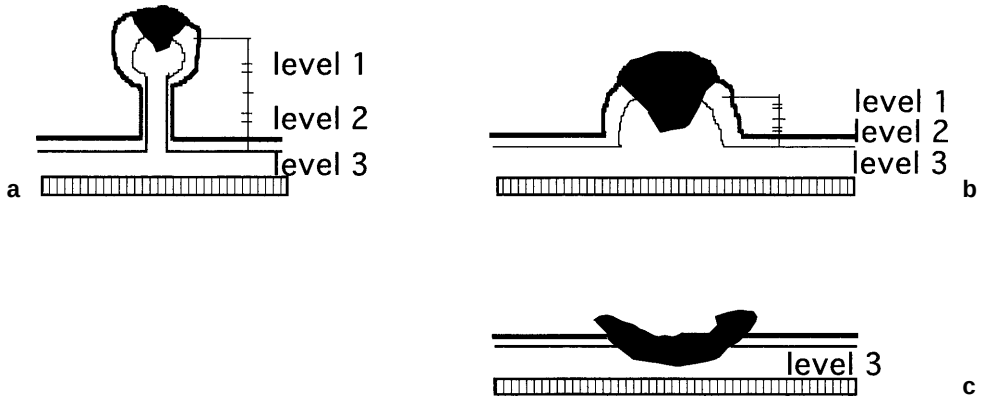

Fig. 2a–c. Level of invasion into submucosal layer. **a** and **b** In pedunculated and broad-based lesions, the submucosal layer above the level of the muscularis mucosae of the surrounding normal mucosa is divided equally into two, and *levels 1* and *2* are determined. *Level 3* denotes the level beneath the muscularis mucosae of the surrounding normal mucosa. **c** In a sessile lesion, the submucosal layer of the lesion is located beneath the level of the muscularis mucosae of the surrounding normal mucosa, which implies *level 3*

(1) In tumors with pedunculated or broad-based morphology, the height of the submucosal layer above the adjacent muscularis mucosae was equally divided into two levels. Submucosal invasion limited to the upper half was defined as level 1, and that extending into the lower half was defined as level 2. If cancer cells had invaded below the level of the adjacent muscularis mucosae, invasion was defined as level 3 (Fig. 2a,b). If the adjacent mucosa was not included in the polypectomized specimen, accurate differentiation of level 1 and 2 on the slides was theoretically impossible. In such cases, the size of the head and stalk was obtained from the endoscopic report and the approximate level of submucosal invasion was determined.
(2) In tumors with sessile or ulcerated morphology, submucosal invasion was always below the level of the adjacent muscularis mucosae, and consequently, the invasion was defined as level 3 (Fig. 2c).

Patients' clinical records and pathological reports were reviewed with special attention to the presence or absence of lymph node metastases, local recurrence, and distant metastases. All patients were followed for at least 5 years after initial treatment or until death. The χ^2 test with Yates' correction was used to analyze the contingency table, and the Mann-Whitney *U*-test was used to compare mean values in unpaired samples. The associations between clinicopathological features and adverse outcome were examined using univariate and multivariate logistic regression analyses (software, SPSS for the Macintosh, version 4.0 (Chicago, IL, USA)). The *P* values computed were two-tailed, and $P < 0.05$ was considered statistically significant.

Results

Demographic details of the seven patients with adverse outcome

As shown in Table 1, lymph node metastases were found in the radically resected specimens in two patients, local recurrence in four patients (1.5 to 8 years after the initial treatment), and distant metastases in two patients (4 years and 3 months, and 10 years after initial treatment). Submucosal invasion was deeper than or equal to level 2 in all patients. Lymphatic invasion was positive in six patients and venous invasion was positive in one patient. The cut end of the locally resected specimen was positive in one patient, and radical surgery was added.

Clinicopathological features and lymph node metastasis or local recurrence (univariate analysis)

Table 2 shows the associations between clinicopathological features and lymph node metastases or local recurrence. Unfavorable histology at the invasive margin was positive in 24 of 65 patients for whom histological review was possible (37%), and lymph node metastasis or local recurrence was found in 5 patients (21%). However, one patient with local recurrence had no unfavorable histology at the invasive margin. Univariate logistic regression analysis showed that unfavorable histology at the invasive margin was significantly associated with adverse outcome ($P = 0.0373$); however, lymphatic invasion and vascular invasion (lymphatic or venous invasion) showed marginal significance ($P = 0.0785$; $P = 0.0990$).

Table 1. Clinicopathologic details of patients with adverse outcome

Age (years)	Sex	Tumor features				Risk factors	UHI	Treatment	LN met	Distant met	Local recurrence[a]
		Location	Shape	Size (mm)	Histology						
75	F	Rs	S	30	M	sm3, ly+	+	EP	–	–	+ (3 Years, 6 months)
38	M	Ra	SP	11	W	sm3, ly+	–	EP + TSR	–	–	+ (8 Years)
63	F	Rb	B	23	W	sm2, ly+	+	TAR	–	–	+ (1 Year, 6 months)
54	M	Rs	B	10	W	sm3, ly+, v+	+	EP + RS	+	Liver (10 years)	–
61	M	Rb	B	25	W	sm2, ly+, cut end+	+	TAR + RS	+	–	–
75	M	S	B	22	W	sm2	+	EP + RS	–	–	+ (2 Years, 6 months)
47	F	Rb	B	15	M	sm3, ly+	+	TAR + RS	–	Lung, brain (4 Years, 3 months)	–

UHI, unfavorable (poorly differentiated/mucinous) histology at the invasive margin; LN, lymph node; Rs, upper rectum; Ra, middle rectum; Rb, lower rectum; S, sigmoid colon; SP, subpedunculated; B, broad-based; S, sessile; W, well differentiated; M, moderately differentiated; EP, endoscopic polypectomy; TAR, trans-anal resection; TSR, trans-sacral resection; RS, radical surgery; met, metastasis; sm, level of submucosal invasion; ly, lymphatic invasion; v, venous invasion

[a] The period after initial treatment to adverse outcome is shown in parentheses

Multivariate analysis

As shown in Table 3, backward stepwise logistic regression analysis, using unfavorable histology at the invasive margin and lymphatic invasion as independent variables, showed that unfavorable histology at the invasive margin alone was significantly associated with lymph node metastasis or local recurrence ($P = 0.0373$).

Discussion

In the new classification of depth of invasion proposed by Haggitt et al.[4] in 1985, polyps with invasive carcinoma were classified as of two types only, pedunculated and sessile. However, about 40% of polyps with invasive carcinoma in our series had intermediate morphology, having a broad-based shape. Those polyps had no stalk; however, histologically, the muscularis mucosae was always lifted above the level of the adjacent muscularis mucosae, and such polyps were not categorized by Haggitt et al., as, in these polyps, levels 2 and 3 of the classification of Haggitt et al. could not be determined. On the other hand, our system is assumed to be applicable to all types of polyps with invasive carcinoma.

Nivatvongs et al.[11] collected 151 colorectal polyps containing invasive adenocarcinoma treated by resection, 13 of which were associated with lymph node metastasis. The depth of invasion in all these 13 specimens was level 4 of the Haggitt et al.[4] classification (level 3 according to our study), and they stressed the importance of level 4 invasion as a risk factor for lymph node metastasis. However, they did not discuss the predictive value of risk factors. The positive predictive value of level 4 invasion, vascular invasion, and grade III/mucinous histology in the series of Nivatvongs et al.,[11] calculated with reference to their Tables 4, 6 and 8 was 12.0%, 31.0%, and 11.0%, respectively. Level 4 invasion was assumed to be inferior to vascular invasion as a risk factor for lymph node metastasis.

In this study, we paid special attention to the presence or absence of poorly differentiated or mucinous histology at the infiltrating portion of early invasive carcinomas, and found that this unfavorable histology was superior to vascular invasion as a risk factor for predicting adverse outcome. Coverlizza et al.[10] classified adenomas containing well or moderately differentiated adenocarcinoma with a focus of poorly differentiated or undifferentiated histology as presenting a high risk for lymph node metastasis. The cancer cells with poorly differentiated or undifferentiated histology have been regarded as more malignant and aggressive in character,[10,16] and our follow-up data support this concept. Hase et al.[12] and Ono et al.[13] also stressed the impor-

Table 2. Clinicopathologic features and LN metastasis/local recurrence

		LN metastasis/Local recurrence			
		Present	Absent	*P* value	Odds ratio (95% CI)
Sex	Male	4	39	$P = 0.9542$[a]	
	Female	2	30		
Age (years)		61 ± 6	58 ± 1	$P = 0.5580$[b]	
Size (mm)		20.2 ± 3.3	16.8 ± 0.9	$P = 0.2348$[b]	
Location	Rt. colon	0	2		
	Lt. colon	1	26	$P = 0.7129$[a]	
	Rectum	5	41		
Shape	Pedunculated	2	30	$P = 0.8330$[c]	1.12 (0.38–3.30)
	Broad-based	3	24		
	Sessile/ulcerated	1	14		
SM inv	Level 1	0	15	$P = 0.2779$[c]	2.02 (0.56–7.23)
	Level 2	3	25		
	Level 3	3	24		
Differentiation	Well	5	65	$P = 0.6218$[c]	1.54 (0.27–8.80)
	Moderate	1	2		
	Poor	0	2		
ly	+	5	27	$P = 0.0785$[c]	7.21 (0.79–65.29)
	−	1	39		
v	+	1	3	$P = 0.2543$[c]	4.13 (0.36–47.40)
	−	5	62		
ly/v	+	5	29	$P = 0.0990$[c]	6.37 (0.70–57.63)
	−	1	37		
UHI[d]	+	5	19	$P = 0.0373$[c]	10.52 (1.14–96.39)
	−	1	40		
Adenomatous component	+	1	38	$P = 0.1001$[c]	6.33 (0.70–57.11)
	−	5	30		

SM inv, level of submucosal invasion; ly, lymphatic invasion; v, venous invasion; UHI, unfavorable (poorly differentiated/mucinous) histology at the invasive margin; CI, confidence intervals
[a] χ^2 test with Yates' correction
[b] Mann-Whitney *U*-test
[c] Univariate logistic regression analysis
[d] Histological review was possible in 65 patients

Table 3. Multivariate logistic regression analysis

Variable	*P* value	Odds ratio	95% CI
ly	0.1731	4.89	0.49–48.08
UHI	0.0873	7.24	0.74–70.18

χ^2 8.354; df 2; P value = 0.0153

Variable	*P* value	Odds ratio	95% CI
UHI	0.0373	10.52	1.14–96.39

χ^2 6.054; df 1; P value = 0.0139
ly, lymphatic invasion; UHI, unfavorable (poorly differentiated/mucinous) histology at the invasive margin; df, degrees of freedom

tance of these cancer cells (termed "budding" by Hase et al.[12] and "focal dedifferentiation" by Ono et al.[13]) as a prognostic indicator for advanced colorectal cancers. We showed that this histological feature at the invasive margin was also useful for predicting adverse outcome in early invasive colorectal cancers. Okabe[14] reported that, although the finding was not statistically significant, a mucinous component at the invasive margin was found more frequently in patients with early invasive colorectal cancer with adverse outcomes than in those without. In our study, multivariate logistic regression analysis showed that mucinous histology at the invasive margin was a significant risk factor in predicting lymph node metastasis or local recurrence.

The diagnosis of vascular invasion, especially lymphatic invasion, is often subjective and uncertain because of interobserver variation, sampling error, or

artifacts. Tissue retraction around tumor foci may mimic lymphatic invasion. The validity of immunohistochemical staining, using specific antibodies for the accurate detection of lymphatic invasion, was studied by Muller et al.[17] However, lymphatic invasion was not confirmed by this method, and they concluded that immunostaining was disappointing for this purpose. Geraghty et al.[18] also stressed that the histological features of lymphatic invasion were too subjective to be of value. They also emphasized that venous invasion by a tumor was a common finding (in their series, 30 polyps [37%] had venous invasion), and seemed to have no prognostic importance. However, it seemed that their series had a case selection bias, because their treatment policy was that polyps should be removed in one piece as a total excisional biopsy, which limited the patients amenable to endoscopic polypectomy. Although they concluded that even patients with histologically incompletely excised polyps, containing well or moderately differentiated carcinoma, could be safely managed by conservative treatment, provided the endoscopist was certain that there was no residual tumor, it may well be that, with their treatment policy, those patients were originally biased toward a better prognosis. Wilcox et al.[19] critically reviewed all known English-language studies of early invasive carcinoma in colonic polyps and pointed out that the selection bias existing in these studies made accurate comparison impossible. To minimize this case selection bias, we analyzed patients treated by polypectomy alone and those treated by additional bowel resection following polypectomy all together as the polypectomy group.

On our backward stepwise logistic regression analysis, unfavorable histology at the invasive margin alone showed statistical significance in predicting lymph node metastasis or local recurrence. However, prospective studies will be needed before conclusions can be reached on this point. Furthermore, we found that widely accepted risk factors such as massive submucosal invasion, positive vascular invasion, and poorly differentiated histology were less useful than expected in predicting adverse outcome. These findings have never been reported before in the management of malignant polyps of the large intestine.

In conclusion, unfavorable histology at the invasive margin is assumed to be a very useful prognostic indicator, because it can be more easily and objectively diagnosed in routine pathology practice than vascular invasion. We believe that the use of this new risk factor will facilitate the accurate selection of patients with a high risk of adverse outcome, and eventually aid in improving their prognosis.

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