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CLINICAL–ALIMENTARY TRACT

Risk Factors for an Adverse Outcome in Early Invasive Colorectal Carcinoma

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Background & Aims: **Various histologic findings exist for managing patients with malignant polyps. Our goal was to determine the criteria for a conservative approach to patients with locally excised early invasive carcinoma.** ***Methods:*** **In 292 early invasive tumors (local resection followed by laparotomy [80 tumors, group A], local resection only [41 tumors, group B], and primarily laparotomy [171 tumors, group C], potential parameters for nodal involvement were analyzed. The status of the endoscopic resection margin also was examined for the risk for intramural residual tumor.** ***Results:*** **Unfavorable tumor grade, definite vascular invasion, and tumor budding were the combination of qualitative factors that most effectively discriminated the risk for nodal involvement in patients in groups A–C. The nodal involvement rate was 0.7%, 20.7%, and 36.4% in the no-risk, single-risk, and multiple-risks group, respectively. Thirty-two and 9 patients from group B were assigned to the no-risk and one-risk group, respectively; extramural recurrence occurred in 2 patients with risk factors. Considering quantitative risk parameters for submucosal invasion (i.e., width ≥4000 μm or depth ≥2000 μm), nodal involvement (including micrometastases) was not observed in the redefined no-risk group that accounted for about 25% of the patients from groups A and C. An insufficiency of endoscopic resection could be evaluated most precisely based on the coagulation-involving tumor, rather than the 1-mm rule for the resection margin.** ***Conclusions:*** **Provided that the criterion of sufficient excision is satisfied, the absence of an unfavorable tumor grade, vascular invasion, tumor budding, and extensive submucosal invasion would be the strict criteria for a wait-and-see policy.**

There have been various opinions regarding treatment policy after endoscopic removal for patients with early invasive colorectal cancer, including extreme cases. One opinion is that all patients with polyps containing invasive carcinoma should undergo standard resection[1]; another opinion is that a conservative approach should be maintained under the condition of an absence of the cancer at the resection line.[2] The present mainstream opinion, however, is that malignant polyps can be treated successfully by endoscopic resection alone, provided that both the laboratory techniques of examination and the histopathologic criteria are strictly applied.[3] A matter of controversy in this field involves which parameters should be integrated into such criteria among various candidates, including qualitative parameters relating to tumor aggressiveness, quantitative parameters, and the status of the resection margin. For example, a combination of qualitative parameters such as tumor grade and vascular invasion often has been argued as being valuable regarding the criteria for treatment choice[4–6]; Volk et al.,[7] however, have denied the importance of vascular invasion, and Netzer et al.[8] have insisted that these parameters do not have independent predictive value with regard to adverse outcomes. In addition, some investigators have emphasized the clinical value of the level of submucosal invasion,[9,10] but quantitative parameters have not been evaluated frequently in related studies.

One of the reasons for such inconsistencies might be the sample size of studies in which only a small number of patients had adverse outcomes such as nodal involvement (Table 1). Furthermore, the inconsistency of the kind of adverse outcome analyzed could be another reason, that is, an intramural remnant tumor (or intramural recurrence) caused by insufficient endoscopic resection, lymph node metastases (or extramural recurrence caused

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Table 1. Literature Series of Treatment Indicators for Early Invasive Colorectal Cancers

Author (*yr*)	Number of tumors analyzed[a]	Number of adverse outcomes analyzed	Recommended indicators for additional laparotomy
Colacchio,[1] 1981	24 (A 24)	6 (LN 6)	None
Lipper,[2] 1983	51 (A 23, B 28)	2 (residual 1, LR 1)	Margin
Haggitt,[9] 1985	64 (A 13, B 26, C 25)	8 (LN 4, LR 2, others 2)	Level
Cranley,[4] 1986	38 (A 20, B 18)	10 (LN 3, residual 7, LR 2)[b]	Grade, margin, lymphatic invasion
Richards,[30] 1987	80 (A 44, B 36)	10 (LN 6, residual 6)[b]	Grade, margin, stalk invasion, vascular invasion
Coverlizza,[5] 1989	31 (A 18, C 13)	6 (LN 5, residual 1)	Margin, grade, vascular invasion
Kyzer,[10] 1992	44 (A 29, B 15)	3 (LN 1, residual 3)[b]	Level
Minamoto,[31] 1993	40 (Not described)	6 (LN 6)	Grade, level, lymphatic invasion, growth pattern, adenomatous component
Kikuchi,[32] 1995	182 (A 23, B 74, C 85)	21 (LN 13, residual 4, LR 4)	Level, tumor configuration, location
Hase,[19] 1995	79 (A 25, C 54)	11 (LN 11)	Tumor budding, growth pattern, grade, level, lymphatic invasion
Cooper,[6] 1995	140 (A 104, B 36)	16 (LN 13, residual 1, LR 2)	Margin, grade, vascular invasion
Volk,[7] 1995	47 (A 21, B 26)	10 (residual 6, LR 2, others 2)	Grade, margin
Whitlow,[15] 1997	59 (A 37, B 22)	4 (residual 3, LR 1)	Level, margin, grade
Netzer,[8] 1998	70 (A 31, B 39)	16 (LN 2, residual 12, LR 2, others 1)[b]	Margin, vascular invasion, grade
This series	292 (A 80, B 41, C 171)	50 (LN 33, residual 4, LR 3) (extramural 2, intramural 1, micrometastasis 10)	Margin, vascular invasion, grade, tumor budding, depth/width of submucosal invasion

LN, lymph node metastases; residual, residual tumor observed at endoscopic excision site; LR, local recurrence after local excision; margin, resection margin; level, level of submucosal invasion; grade, tumor grade; vascular invasion, lymphatic/venous invasion
[a]A, local resection followed by laparotomy; B, local resection only; C, primarily laparotomy.
[b]There were patients with both nodal involvement and residual tumor.

by undissected metastatic nodes), and distant metastases have been variously analyzed together as adverse outcomes (Table 1).

In the present study, early invasive colorectal cancers treated in multiple hospitals were examined together to obtain the indicators of nodal involvement and insufficient excision. We enumerated potential parameters, including novel ones such as tumor budding, as a qualitative parameter and measurements of submucosal invasion as a quantitative parameter, and analyzed their value. The unfavorable events assessed were as follows: (1) lymph node metastases, including micrometastases, in patients with laparotomy; (2) extramural local recurrence caused by undissected involved nodes in patients with local excision only; (3) submucosal tumor remaining at the endoscopic resection site in laparotomy specimens; and (4) intramural recurrence caused by insufficient local excision in patients with local excision only. It was the goal of the present study to determine the criteria for a conservative approach in patients with local excision of early invasive colorectal cancer.

Patients and Methods

Early Invasive Colorectal Cancers Examined

Data on 292 early invasive colorectal adenocarcinomas from 285 consecutive patients treated between 1980 and 2002 were gathered from the National Defense Medical College Hospital (251 cancers, including 33 cancers treated first with local excision at other hospitals and National Defense Medical College Hospital provided the second opinions about their additional laparotomy) and the Self-Defense Forces Central Hospital (41 cancers). These tumors were confirmed pathologically to invade through the muscularis mucosae and into the submucosa. The median age of patients was 62 years (range, 32–91 yr), and the ratio of women to men was 1:1.5. All clinical data for tumors, including tumor diameter, location, configuration, and patient background including treatment and follow-up status, were collected from pathologic, endoscopic, or clinical records. A total of 171 tumors were excised with laparotomy with nodal dissection and 80 were resected with local excision (endoscopic resection, 73; transanal resection, 7) followed by laparotomy. A conservative approach was chosen for 41 tumors after their local excision (endoscopic resection, 36; transanal resection, 3; York–Mason, 2). The background of tumors grouped by their resection method is shown in Table 2. The median follow-up period for patients with the conservative approach was 41 months (range, 14–174 mo).

Parameters in Primary Tumors for Their Metastatic Potential

The parameters in primary tumors assessed pathologically to determine their correlation with nodal involvement were as follows: Haggitt's classification,[9] width and depth of submucosal invasion (Figure 1), type of growth pattern (polypoid growth/nonpolypoid growth),[11] presence or absence of a

Table 2. Characteristics of Early Invasive Colorectal Cancers Grouped by Their Resection Method

Parameters	Resection method			*P* value
	A, local resection followed by laparotomy (n = 80)	B, local resection only (n = 41)	C, primarily laparotomy (n = 171)	
Age (average)	61.0	61.3	63.2	NS
Sex: male/female	50 (62.3)/30 (37.5)	27 (65.9)/14 (34.1)	97 (56.7)/74 (43.3)	NS
Tumor location: colon/rectum	50 (62.3)/30 (37.5)	24 (58.5)/17 (41.5)	104 (60.8)/67 (39.2)	NS
Tumor diameter (average)	15.0 mm	13.4 mm	22.4 mm	<0.0001 (A vs. C), 0.0003 (B vs. C)
Macroscopic tumor configuration: sessile and pseudopedunculated/pedunculated	65 (81.3)/15 (18.8)	28 (68.3)/13 (31.7)	145 (84.8)/26 (15.2)	0.01 (B vs. C)
Depression zone: presence/absence	4 (5.0)/76 (95.0)	2 (4.9)/39 (95.1)	48 (28.1)/123 (71.9)	<0.0001 (A vs. C), 0.002 (B vs. C)
Tumor grade: unfavorable/favorable	31 (38.8)/49 (61.3)	3 (7.3)/38 (92.7)	44 (25.7)/127 (74.3)	0.0003 (A vs. B), 0.04 (A vs. C), 0.01 (B vs. C)
Vascular invasion: presence/absence	21 (26.3)/59 (73.8)	6 (14.6)/35 (85.4)	54 (31.6)/117 (68.4)	0.03 (B vs. C)
Tumor budding: positive/negative	11 (13.8)/69 (86.3)	0/41 (100.0)	27 (15.8)/144 (84.2)	0.02 (A vs. B), 0.007 (B vs. C)
Width of submucosal invasion: ≥4000/<4000 (μm)	52 (65.0)/28 (35.0)	19 (46.3)/22 (53.7)	118 (69.0)/53 (31.0)	0.05 (A vs. B), 0.006 (B vs. C)
Depth of submucosal invasion: ≥2000/<2000 (μm)	58 (72.5)/22 (27.5)	22 (53.7)/19 (46.3)	117 (68.4)/54 (31.6)	0.04 (A vs. B)

NS, not specified.

depression zone, adenoma component, mucin-producing, cribriform formation, tumor grade, vascular invasion (definite cancer involvement of lymphatic vessels and/or venous vessels), and tumor budding (Figure 2).[12,13] Tumor grade was assessed at the deepest part of the tumor containing the most unfavorable histologic feature, and was classified as favorable grade (well and moderately differentiated adenocarcinoma) or unfavorable grade (poorly differentiated adenocarcinoma and mucinous carcinoma). Tumor budding was defined as an isolated single cancer cell or a cluster composed of fewer than 5 cancer cells, as previously reported.[12] After choosing one field where budding was the most intensive, a budding count was made in the field measuring 0.785 mm^2 using a 20× objective lends. A field with 5 or more buds was viewed as positive.[13]

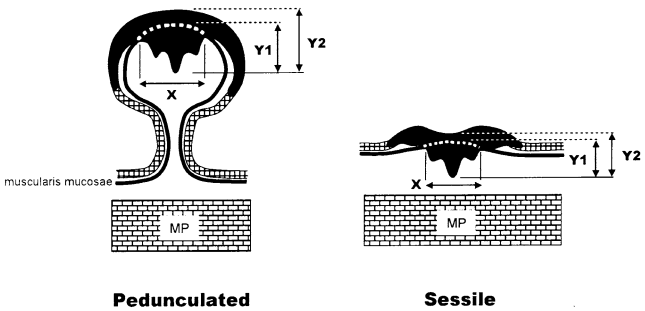

Figure 1. Measurement of the extent of invasion in the submucosal layer. X, width of submucosal invasion; Y1, depth of submucosal invasion (for tumors in which muscularis mucosae can be estimated as the upper yardstick of the submucosal layer); Y2, depth of submucosal invasion (for tumors with no muscularis mucosae to be the yardstick).

The material was processed routinely and stained with H&E for histologic diagnosis. Additional staining was performed in 134 patients whose paraffin-embedded tumors were available; that is, Elastica van Gieson staining and immunohistochemical staining using mouse monoclonal anti-human CD34 antigen (Novocastra Laboratories, Newcastle upon Tyne, UK) for the detection of vascular invasion, and immunohistochemical staining using mouse monoclonal anti-human Desmin (Dako Corporation, Glostrup, Denmark) for the detection of muscularis mucosae fragmented by cancer cells and desmoplasia to measure the depth of submucosal invasion. All pathologic slides of tumors, without knowledge of the nodal status and clinical outcome, were reviewed by one of the authors (H.U.) and recorded. The median number of pathologic slides examined for respective tumor was 4 (range, 1–22), and the median number of slides containing parts of tumors invading the submucosa was 2 (range, 1–11).

Examination of Lymph Node Metastases

The median number of lymph nodes examined pathologically in patients undergoing laparotomy with nodal dissection was 12 (range, 1–51). Lymph node involvement was observed by conventional pathologic examination in 13.1% (33 of 251) of the tumors examined.

Among the 218 tumors without nodal involvement, 98 tumors treated at the National Defense Medical College Hospital were examined for their micrometastases in the regional lymph nodes based on immunohistochemical techniques. All regional lymph node specimens that had been dissected and embedded in paraffin wax were sectioned and stained with mouse monoclonal anti-human cytokeratin antibodies (AE1/

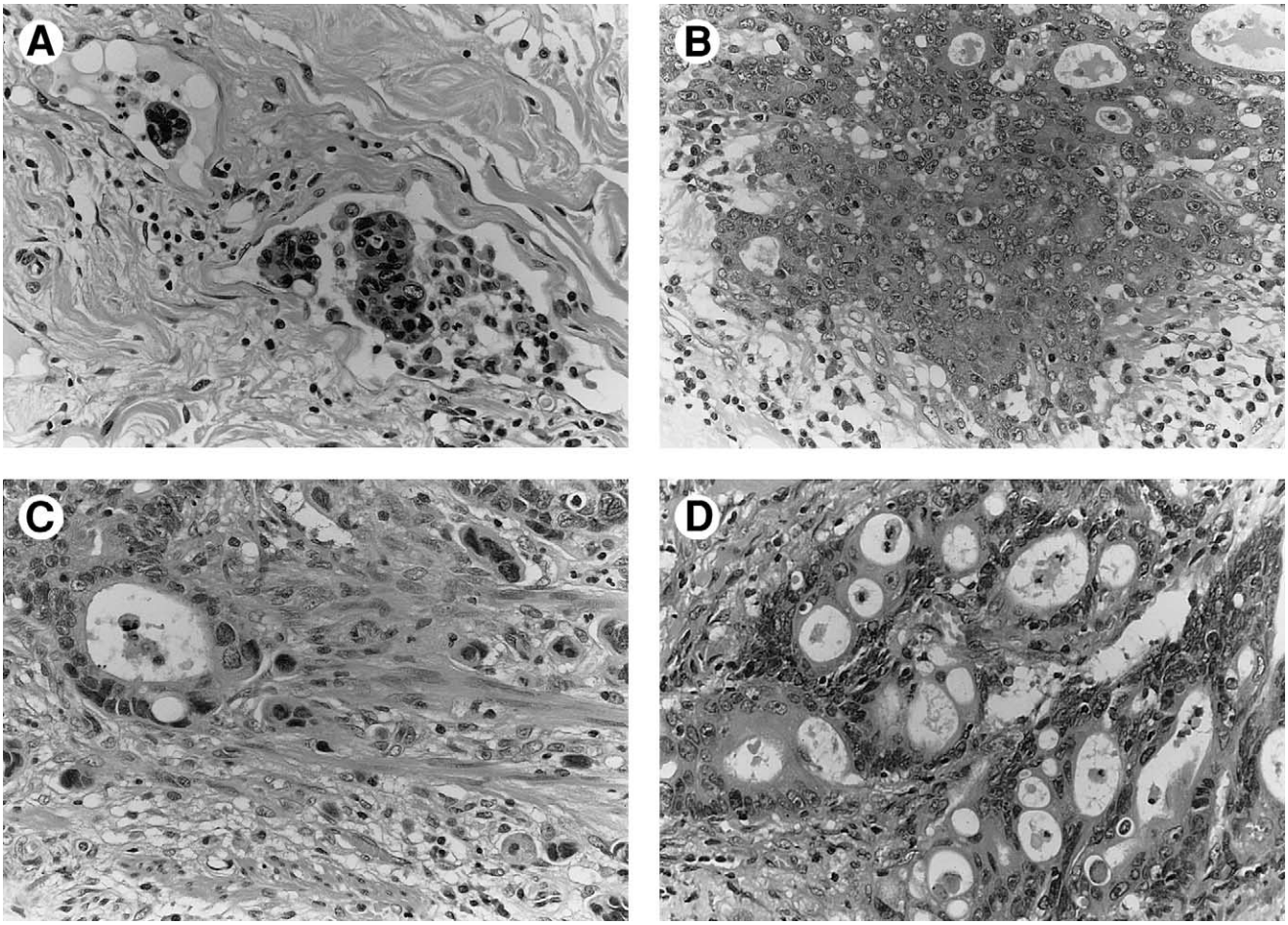

Figure 2. Unfavorable histologic features in early invasive colorectal cancer. (*A*) Lymphatic invasion (original magnification: 100×). Only the definite involvement of lymphatic vessels or venous vessels was regarded as positive vascular invasion. (*B*) Poor differentiation (100×). Tumor loses the acinar gland formation at the invasive front and forms the region of poorly differentiated carcinoma. Judgment of tumor grade was based on the most unfavorable part, even if it was a small region. (*C*) Tumor budding (100×). An isolated single cancer cell or a cluster composed of fewer than 5 cancer cells was defined as a budding focus. (*D*) Cribriform pattern (100×). In cribriform-pattern tumors, small acinus structure, lined by cuboidal to columnar cancer cells, making back-to-back formation, was dominantly observed at the advancing region of tumor.

AE3; Dako Corporation, Carpinteria, CA). The median number of lymph nodes examined was 10 (range, 1–44) per patient. Lymph nodes were considered as having a micrometastasis when they showed one or more cells positive to AE1/AE3 antibodies (Figure 3). Sixteen lymph nodes in 10 patients (10.2%), who were all treated primarily by laparotomy, contained micrometastases.

Parameters in Primary Tumor for the Insufficiency of Endoscopic Excision

As a potential index for the insufficiency of excision in the endoscopically excised specimens, the circumferential excision margin (cancer-free distance) as well as the correlation between the tumor front and coagulation region, was evaluated. The insufficiency of endoscopic excision was determined based on the residual submucosal tumor at the site of the endoscopic resection in the laparotomy specimens and intramural recurrence in patients with endoscopic treatment only. The residual tumor at the site of the endoscopic resection in the laparotomy specimens was examined in 68 among 73 patients with endoscopic resection followed by laparotomy; the median number of pathologic slides (H&E staining) examined was 4 (range, 1–9). The intramural local recurrence was studied in 35 among 36 patients with endoscopic resection only. Six patients (5 with endoscopic excision followed by laparotomy and 1 with endoscopic excision only) whose endoscopic resection margin could not sufficiently be assessed histologically were excluded from the study.

Analyses

Statistical analyses were performed using the SPSS software package (SPSS Inc., Chicago, IL). Differences in the nodal involvement rate between groups were estimated using the χ^2 test or Fisher exact test. Logistic regression analysis was performed to estimate the influence of various factors on nodal involvement. Regarding the quantitative continuous variables, the threshold of the extent of submucosal invasion that had the biggest impact on the possibility of nodal involvement was

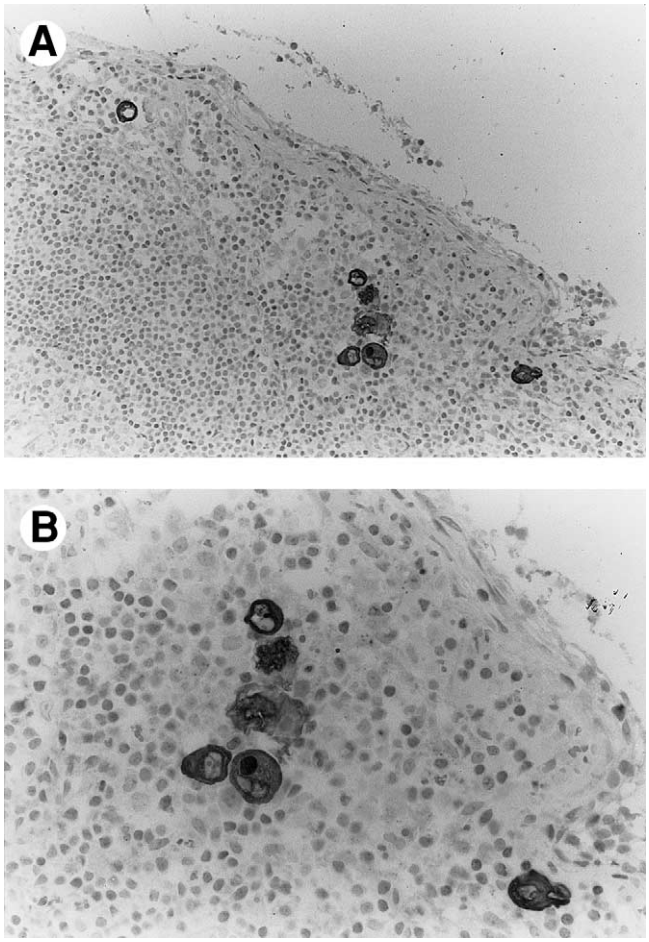

Figure 3. Micrometastases in the regional lymph node. Lymph node containing multiple stained cells (anticytokeratin antibody [AE1/AE3]). Original magnification: *A*, 66×; *B*, 132×.

determined based on the odds ratios calculated by logistic analysis. Various combinations of parameters were made, and their influence on unfavorable outcomes was compared to determine the optimal combination of parameters to be integrated into the criteria for treatment choice.

Results

Qualitative Parameters as Risk Factors for Lymph Node Metastases

Neither the type of growth pattern, the presence of a depression zone on the tumor surface, the presence of an adenoma component, or mucin production was found to have a significant impact on lymph node metastases. The incidence of nodal involvement was, however, significantly affected by the following histologic parameters: cribriform formation, tumor grade, vascular invasion, and tumor budding (Table 3). Multivariate logistic analysis showed that these 4 parameters have an independent impact on nodal involvement.

A comparison of the various combinations of the 4 earlier-described qualitative parameters showed that tumor grade, vascular invasion, and tumor budding are the combination having discrimination ability with regard to nodal involvement with the highest odds ratio (Table 4). A grading system that included these 3 parameters and cribriform formation as an additional feature increased the number of risk-positive patients having no nodal involvement. Regarding (1) unfavorable tumor grade, (2) the presence of vascular invasion, and (3) positive tumor budding as risk factors, patients were divided into 3 groups with different nodal involvement rates based on a simple scoring method. Specifically, nodal involvement rates were only 0.7% in tumors with no risk factor, whereas they were 20.7% in those with a single risk factor, and 36.4% in those with multiple risk factors (Table 5). Similarly, in tumors treated primarily by local excision, the nodal involvement rate was small in those with no risk factor (2.3%, 1 of 44), it was 28.6% (4 of 14) in those with a single risk factor, and 22.7% (5 of 22) in those with multiple risk factors.

Table 3. Univariate and Multivariate Analyses for Nodal Involvement With Regard to Qualitative Characteristics

			Univariate analysis		Multivariate analysis	
Qualitative parameters	Number of tumors	Nodal involvement (%)	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Tumor grade						
Favorable	176	10 (5.7)	1		1	
Unfavorable	75	23 (29.2)	7.3 (3.3–16.4)	<0.0001	2.9 (1.2–7.4)	0.023
Vascular invasion						
Absence	176	10 (5.7)	1		1	
Presence	75	23 (30.7)	7.3 (3.3–16.4)	<0.0001	2.7 (1.1–7.0)	0.039
Cribriform pattern						
Absence	192	14 (7.3)	1		1	
Presence	59	19 (32.2)	6.0 (2.8–13.1)	<0.0001	3.9 (1.6–9.4)	0.002
Tumor budding						
Negative	213	17 (8.0)	1		1	
Positive	38	16 (42.1)	8.4 (3.7–18.9)	<0.0001	3.7 (1.4–9.9)	0.008

CI, confidence interval.

Table 4. Comparison of the Combination of Qualitative Parameters to be Integrated Into a Grading System to Discriminate the Risk for Nodal Involvement

Grading system	Number of parameters composing the grading system	Combinations of parameters				Incidence of nodal involvement		Odds ratio of nodal involvement (95% CI)	*P* value
		Tumor grade	Vascular invasion	Tumor budding	Cribriform formation	Risk negative	Risk positive		
1		●	●			1.4 (2/143)	28.7 (31/108)	28.4 (6.6–121.8)	<0.0001
2	2	●		●		4.2 (7/163)	29.5 (26/62)	9.3 (3.9–22.6)	<0.0001
3		●			●	3.4 (5/148)	27.2 (28/103)	10.7 (4.0–28.8)	<0.0001
4	3	●	●	●		0.7 (1/138)	28.3 (32/113)	54.0 (7.3–402.4)	<0.0001
5		●	●		●	1.6 (2/124)	24.4 (31/127)	19.6 (4.6–83.9)	<0.0001
6	4	●	●	●	●	0.8 (1/119)	24.2 (32/132)	37.7 (5.1–280.9)	<0.0001

NOTE. ● indicates parameters integrated into grading system.
CI, confidence interval.

Quantitative Parameters as Risk Factors for Lymph Node Metastases

There was no correlation between the maximum tumor diameter and the incidence of nodal involvement (Table 6). None of the 42 tumors that were classified as Haggitt's level 1 or level 2 had nodal involvement.

No nodal involvement was observed in tumors with a submucosal invasion width <2000 μm or a depth <500 μm. The odds ratios of nodal involvement with minimum *P* value were 8.8 (range, 2.1–38.5) at the threshold of 4000 μm for width and 5.0 (range, 1.5–17.0) at the threshold of 2000 μm for depth (Figure 4). The incidence of nodal involvement in tumors with a width <4000 μm (2.5%) and a depth <2000 μm (3.9%) was much less than that in tumors with a width ≥4000 μm (18.2%) ($P = 0.0005$) and in patients with a depth ≥2000 μm (17.1%) ($P = 0.0045$) (Table 7).

Follow-up Outcomes of Patients Without Ensuring Laparotomy

Among the 41 patients treated with local excision only, none had multiple qualitative risk factors in their specimens. Thirty-two patients were classified in the no-risk group and 9 were classified in the one-risk group. Extramural local recurrence occurred in 2 patients; in 1 patient (a 74-year old woman with sigmoid colon cancer) the laparotomy had been abandoned owing to cardiac arrest during surgery, and another patient (a 36-year old man with lower rectal cancer) refused radical surgery. The timing of these recurrences was 14 months and 22 months after local excision, respectively. Both patients belonged to the one-risk group.

Predictive Model For Nonnodal-Involvement Tumors Using Qualitative and Quantitative Parameters

Even in the tumors with no qualitative risk factors (unfavorable tumor grade, vascular invasion, and tumor budding), nodal involvement was observed in 0.7% and 6.8% of tumors shown to have micrometastasis in the regional nodes (Table 5). Given that a ≥4000 μm width of submucosal invasion was regarded as a risk factor together with the 3 earlier-described qualitative risk factors, no overt nodal involvement or micrometastasis in the nodes existed in the no-risk group. In the same way, neither overt nodal involvement nor micrometastasis was observed in the group having none of the

Table 5. Combination of Qualitative and Quantitative Risk Factors and the Incidence of Nodal Involvement

Number of risk factors	Qualitative risk factors 1–3[a]		Qualitative risk factors 1–3[a] plus Haggitt's level 3–4		Qualitative risk factors 1–3[a] plus width ≥4000 μm		Qualitative risk factors 1–3[a] plus depth ≥2000 μm	
	Nodal involvement	Micrometastasis	Nodal involvement	Micrometastasis	Nodal involvement	Micrometastasis	Nodal involvement	Micrometastasis
None	0.7% (1/138)[b]	6.8% (4/59)[c]	0.0% (0/27)[d]	15.4% (2/13)[c]	0.0% (0/62)[e]	0.0% (0/26)[f]	0.0% (0/56)[g]	0.0% (0/19)[c]
1	20.7% (12/58)	14.3% (3/21)	0.8% (1/118)	4.3% (2/47)	2.3% (2/87)	10.8% (4/37)	3.3% (3/92)	8.9% (4/45)
2 or more	36.4% (20/55)	16.7% (3/18)	30.2% (32/106)	15.8% (6/38)	30.4% (31/102)	17.1% (6/35)	29.1% (30/103)	17.6% (6/34)

NOTE. Nodal involvement was based on the conventional examination.
[a]Risk factors: 1, unfavorable grade; 2, vascular invasion; 3, tumor budding. [b]$P < 0.0001$; [c]$P > 0.1$; [d]$P = 0.031$ (Fisher exact test); [e]$P = 0.0004$; [f]$P = 0.058$ (Fisher exact test); [g]$P = 0.0010$.

Table 6. Correlation Between Quantitative Parameters of Tumors and the Incidence of Nodal Involvement

Quantitative parameters		Number of cases	Nodal involvement (%)	*P* value
Maximum diameter: D (*mm*)	< 10	26	3 (11.5)	>0.1
	$10 \leq D < 20$	126	15 (11.9)	
	$20 \leq D < 30$	58	10 (17.2)	
	≥ 30	41	5 (12.2)	
Haggitt's classification	Level 1/2	42	0	0.0057[a]
	Level 3	24	6 (25.0)	
	Level 4	185	27 (14.6)	
Width of submucosal invasion: X (μm)	< 2000	35	0	0.0005[b]
	$2000 \leq X < 3000$	22	1 (4.5)	
	$3000 \leq X < 4000$	24	1 (4.2)	
	$4000 \leq X < 5000$	19	4 (21.1)	
	$5000 \leq X < 6000$	23	4 (17.4)	
	$6000 \leq X < 7000$	10	2 (20.0)	
	$7000 \leq X < 8000$	26	4 (15.4)	
	≥ 8000	92	17 (18.5)	
Depth of submucosal invasion: Y (μm)	< 500	23	0	0.0045[c]
	$500 \leq Y < 1000$	15	1 (6.7)	
	$1000 \leq Y < 2000$	38	2 (5.3)	
	$2000 \leq Y < 3000$	61	11 (18.0)	
	$3000 \leq Y < 4000$	45	5 (11.0)	
	$4000 \leq Y < 5000$	31	6 (19.4)	
	≥ 5000	38	8 (21.1)	

[a]Level 1/2 vs. level 3/4.
[b]$X < 4000$ vs. $X \geq 4000$.
[c]$Y < 2000$ vs. $Y \geq 2000$.

3 earlier-described qualitative risk factors and a $\geq$2000 μm depth of submucosal invasion.

Histologic Completeness of Endoscopic Excision

In the 32 tumors for which endoscopic resection was performed followed by an ensuring surgery and for which the invasive front involved coagulation (burn-effect region), 4 tumors had residual tumors in the submucosa of the surgical specimens. In contrast, among tumors for which the fronts were away from the coagulation, including 19 tumors having $<$1 mm excision margin, no intramural residual tumors were observed in the laparotomy specimens obtained after endoscopic resection (Table 8).

With regard to tumors treated by local excision only, intramural recurrence occurred in 1 of 3 tumors for which the front was involved by coagulation. None of the 32 tumors not involved by coagulation, including 14 tumors with a $<$1-mm excision margin, had intramural recurrence during their follow-up period (Table 8).

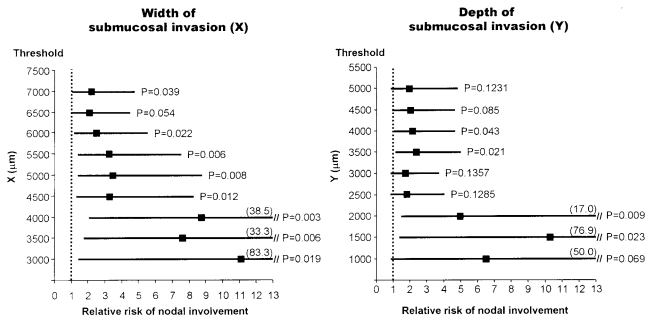

Figure 4. Correlation between the extent of submucosal invasion and the relative risk for nodal involvement. Relative risks for nodal involvement in tumors with more extensive invasion than the thresholds (logistic analysis; bar, 95% confidence interval).

Discussion

In specimens of early invasive colorectal cancer, there are more than a few potential indicators of adverse outcomes after minor excision (Table 1). Qualitative parameters such as the tumor grade, vascular invasion, tumor budding, and cribriform formation, and quantitative parameters such as Haggitt's system and the width and depth of submucosal invasion, are the parameters significantly related to nodal involvement. Obviously, what is practically important is to determine the ultimate combination of parameters to be integrated into the criteria of treatment choice that minimizes both unnecessary additional laparotomy and survival impairment accompanying a conservative approach after local excision. Based on the present results, neither an unfavorable tumor grade, the presence of vascular invasion, nor positive tumor budding would be recommended minimum requirements for a conservative policy. Furthermore, nu-

Table 7. Correlation Between Quantitative Risk Factors and Nodal Involvement and Qualitative Risk Factors

		Lymph node metastasis (conventional examination)		Micrometastasis (immunohistologic stain)		Qualitative risk factors[a]	
Quantitative parameters		Positive	*P* value	Positive	*P* value	Positive	*P* value
Haggitt's classification	Level 1/2	0.0% (0/42)	0.0057	15.8% (3/19)	>0.1	35.7% (15/42)	>0.1
	Level 3/4	15.8% (33/209)		8.9% (7/79)		46.9% (98/209)	
Width of submucosal invasion	<4000 μm	2.5% (2/81)	0.0005	3.0% (1/33)	>0.1	23.5% (19/81)	<0.0001
	≥4000 μm	18.2% (31/170)		13.8% (9/65)		55.3% (94/170)	
Depth of submucosal invasion	<2000 μm	3.9% (3/76)	0.0045	3.6% (1/28)	>0.1	26.3% (20/76)	<0.0001
	≥2000 μm	17.1% (30/145)		12.9% (9/70)		53.1% (93/175)	

[a]Unfavorable grade, vascular invasion, and tumor budding.

meric data regarding the extent of submucosal invasion was shown to aid in choosing tumors having very little risk for nodal involvement by estimating the extent of invasion together with the earlier-described 3 qualitative parameters.

Tumor grade has been regarded as the most important indicator of nodal involvement.[4–7,14,15] Cribriform formation, which indicates a loss of normal architectural relationships and is therefore a feature of poor differentiation, in particular was found to have a significant value in the multivariate analysis. However, a scoring system that included cribriform formation as its composing category would increase the incidence of unnecessary laparotomy rather than decrease the number of potential patients who could develop local recurrence.

Dealing with lymphatic invasion has been an extremely controversial issue.[16] Some investigators have argued that lymphatic invasion is not necessarily a useful indicator of nodal involvement because distinguishing true lymphatic invasion from venous invasion, or retraction artifact, frequently is difficult,[7] and lymphatic invasion without other unfavorable pathologic features is rare.[8] The results of the present study, however, show that it is not necessarily essential to distinguish lymphatic invasion from venous invasion in assessing the probability of nodal involvement, and that definite vascular invasion accompanied by no other unfavorable parameters actually is associated with an adverse outcome.

Tumor budding is a cancer growth form representing the events of dedifferentiation and a dissociation of cancer cells that can be regarded as an initial phase of invasion preceding the process of vascular invasion. Although the concept of this pathologic feature might be thought to overlap with that of poor differentiation, tumor budding usually is observed in only a confined region of the invasive front, and, practically, the diagnosis of poorly differentiated carcinoma would not be applied to the tumors representing well or moderate differentiation except for this region. In addition, multivariate analysis in the present study showed that these 2 parameters are independent in terms of their impact on nodal involvement. A significant correlation between tumor budding and nodal involvement already has been shown in advanced colorectal cancer,[12,17,18] and the present study has confirmed the results of several other studies showing this correlation applied to early invasive colorectal cancers.[19–22]

By using 3 qualitative parameters for cancer (tumor grade, vascular invasion, and budding), we could determine a population having a small possibility of nodal involvement that would account for approximately 55% of the overall early invasive colorectal cancers. Absence of an unfavorable tumor grade, vascular invasion, and tumor-budding would be the most informative combination of criteria for selecting patients with a low recurrence risk, if we attach importance to avoiding

Table 8. Correlation Between Resection Margin and Intramural Residual and Intramural Local Recurrence

		Tumors with endoscopic excision followed by laparotomy (n = 68)		Tumors with endoscopic excision alone (n = 35)	
Location of tumor front	Circumferential excision margin	Number of tumors	Residual tumor in the submucosa	Number of tumors	Intramural local recurrence
Within the coagulation region	<1 mm	31	4 (12.9%)	2	1 (50.0%)
	1 mm ≤ margin <2 mm	1	0	1	0
Outside the coagulation region	<1 mm	19	0	14	0
	1 mm ≤ margin <2 mm	10	0	7	0
	≥2 mm	7	0	11	0

unnecessary laparotomy. We previously reported that these 3 parameters observed in the biopsy specimens of the submucosal horizontal invasive frontal region in advanced rectal cancers are relevant to the extent of extramural[13] and intramural spread.[23] It would be said that these parameters are appropriate to evaluate a cancer's potential for invasion and metastasis.

Unfortunately, however, exceptional cases would arise from the no-risk group based on the earlier-described minimum requirements consisting of 3 qualitative parameters, and patients should be informed of this risk. It was shown in our series that 1 in 138 tumors (0.7%) had overt nodal involvement and 4 in 59 tumors (6.8%) had micrometastasis in the group having neither the unfavorable tumor grade, vascular invasion, nor tumor budding. The value of immunohistochemically detected micrometastasis for prognostication in node-negative colorectal cancer remains controversial,[24–28] and some immunohistochemical studies have shown no relationship between the existence of micrometastasis and unfavorable prognosis if treated by resection.[26,27,29] However, we still cannot neglect the possibility that micrometastasis, if remained untreated, could be the origin of recurrence focus. The property of quantitative parameters in terms of its relevance to nodal involvement would be different from that of parameters of a qualitative nature. Specifically, the quantitative parameters could enable us to distinguish tumors with no nodal involvement by themselves, for example, Haggitt's level 1 or 2, a submucosal invasion width of less than 2000 μm, or a depth of less than 500 μm, although the proportion of tumors meeting these conditions is too small to use these categories as the criterion for a conservative approach. One notable result of the present study was that counting a width $\geq$4000 μm (or depth $\geq$2000 μm) of submucosal invasion among the risk factors together with the 3 earlier-described qualitative parameters, we could determine the group that had no nodal involvement, although the number of tumors belonging to the no-risk group was reduced by half. The range for the estimated risk for recurrence for which the conservative approach is selected (acceptable recurrence rate) differs individually. This range could be determined with careful consideration of the operative mortality risk and the postoperative morbidity state, which are greatly affected by the patient's preoperative complications and the tumor location, respectively. In this circumstance, numeric data concerning the extent of submucosal invasion, which allowed us to have the strict criteria identifying the patient group for which a conservative approach would virtually never compromise a patient's life, would be quite valuable.

It is naturally accepted that the presence of a tumor extending to the edge of the endoscopic resection is a histologic finding that signifies the potential for a remnant tumor, but the definite requisite resection margin is still under discussion. Tumor near the resection edge has been variously defined: for example, cancer cells $\leq$1 mm from the edge,[6] $\leq$2 mm from the edge,[7] or cancer within the diathermy.[3] Based on the present results, it is of concern that unnecessary surgery would be performed too frequently if a 1-mm rule, not to mention a 2-mm rule, were widely adopted. On the condition that appropriate pathologic specimens containing a sufficient resection region were evaluated, the criterion for additional laparotomy would be the finding that the diathermy effect ranged over the tumor's invasive front.

The criteria for a wait-and-see policy based on the possibility of nodal involvement and insufficient excision, which were established using the clinicopathologic data of patients undergoing radical surgery, were supported by the follow-up data of patients treated with only local excision. Extramural recurrence was observed in none of the 32 patients meeting the minimum requirements for the observation policy, whereas it occurred in 2 of 9 patients having some qualitative risk. Intramural recurrence after local excision was observed in none of the 32 patients without risk for a remnant intramural tumor (i.e., cancer involved by diathermy), whereas it occurred in 1 of 3 patients with this risk.

Even if the majority of malignant polyps are curable by minor excision, a misguided conservative approach compromises a patient's life, which could be saved with radical surgery. A prudent attitude to determine the treatment criteria is indispensable to eliminating an undiagnosed origin of recurrence. Provided that the criterion of sufficient excision (i.e., absence of the pathologic finding of tumor front involved by coagulation) is satisfied, absence of an unfavorable tumor grade, vascular invasion, tumor budding, and extensive submucosal invasion must be fulfilled for a wait-and-see strategy (strict criteria); and depending on the individual acceptable recurrence rate, the minimum requirements (i.e., the absence of an unfavorable tumor grade, vascular invasion, or tumor budding) would be adopted for a wait-and-see policy. We believe the results of the present study should be verified in other cohorts including a large number of patients with unfavorable outcomes.

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