Long-Term Results of Curative Resection of "Minimally Invasive" Colorectal Cancer

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PURPOSE: The aim of this study was to determine the long-term outcome after curative resection of colorectal cancers that extend only into the submucosa ("minimally invasive") and to evaluate potential histologic predictors of lymph node metastases. METHODS: Seventy-nine patients who underwent curative resection of minimally invasive colorectal cancer and were followed for at least five years were studied retrospectively. RESULTS: The series was comprised of 53 men and 26 women, with a mean age of 61 years. The lesion was in the colon in 47 patients and the rectosigmoid or rectum in 32 patients. Open surgery followed attempted endoscopic tumor removal in 25 patients. Lymph node metastasis, found in 11/79 patients (13.9 percent), was associated with worse outcome: 36.4 percent of node(+) patients developed recurrence, *vs.* only 5.9 percent of node(−) patients ($P < 0.005$). The cumulative survival rate was also worse in node(+) *vs.* node(−) patients: 72.7 percent *vs.* 91.1 percent at five years ($P < 0.05$) and 45.5 percent *vs.* 65.3 percent at ten years ($P < 0.05$). Five histopathologic characteristics were identified as risk factors for lymph node metastasis: 1) small clusters of undifferentiated cancer cells ahead of the invasive front of the lesion ("tumor budding"); 2) a poorly demarcated invasive front; 3) moderately or poorly differentiated cancer cells in the invasive front; 4) extension of the tumor to the middle or deep submucosal layer; 5) cancer cells in lymphatics. Whereas patients with three or fewer risk factors had no nodal spread, the rate of lymph node involvement with four or more risk factors was 33.3 percent and 66.7 percent, respectively. CONCLUSIONS: Metastasis is not infrequent in "minimally invasive" colorectal cancer. Appropriate bowel resection with lymph node dissection is indicated if such a lesion exhibits more than three histologic risk factors for metastasis. [Key words: Minimally invasive colorectal cancer; Colonoscopic polypectomy; Lymph node metastasis risk factors]

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Whereas intramucosal colorectal cancer has not been reported to metastasize and colonoscopic removal of these lesions is sufficient therapy,[1-9] there is a risk of nodal spread when cancer cells have invaded the submucosa.[1, 3-7, 10-12] Polypectomy may then be inadequate treatment. In particular, it has not been established whether subsequent open surgery is needed after endoscopic removal of "minimally invasive" colorectal cancers, defined as tumors extending in direct continuity into the submucosa but not the muscularis propria (Fig. 1). Furthermore, long-term outcome of curative resection of these lesions has not been elucidated. In this study, we attempt to clarify these issues.

METHODS

A review was made of the hospital records of all patients who underwent surgery for minimally invasive adenocarcinoma of the colon or rectum at Santa Clara Valley Medical Center and the Palo Alto Veterans Administration Hospital from 1970 to 1985, Stanford University Medical Center from 1980 to 1985, and National Defense Medical College from 1978 to 1985. From this group the following patients were eliminated from the study: 1) those with multiple cancers; 2) those who had hereditary polyposis or other syndromes associated with an increased incidence of colorectal cancer; 3) those with inflammatory bowel disease; 4) those who had gross or histologic residual cancer after surgery; 5) those who were lost to follow-up. Thus, all patients entered into the study underwent a "curative" resection and were followed for at least five years or until death. Follow-up information was obtained from outpatient records, tumor registries, and telephone interviews with patients or family members.

All surgical specimens were examined histologi-

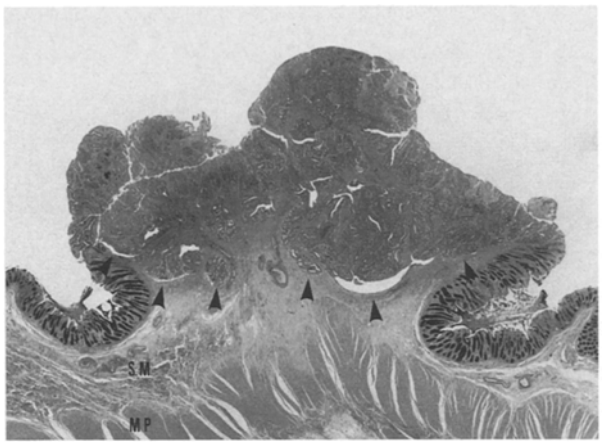

Figure 1. Minimally invasive colorectal cancer, defined as tumor extending only into the submucosa (*arrows*) (victoria blue, eosin; ×4).

cally by one of the authors (K.H.), who was blinded as to patient outcome. Specimens were examined in detail, as recommended by experienced pathologists,[7, 13, 14] for the following histologic features reported to be associated with metastasis: 1) "tumor budding," small clusters of undifferentiated cancer cells ahead of the invasive front of the lesion (Fig. 2); 2) the pattern of cancer growth in the submucosal invasive front (Fig. 3); 3) tumor differentiation at the leading edge of the lesion; 4) depth of submucosal cancer invasion (Fig. 4); 5) cancer cells in lymphatics. Long-term survival, death rate from cancer, and tumor recurrence rates were used to assess patient outcome. Comparisons of survival curves were made by the generalized Wilcoxon test. Differences in survival at specific follow-up intervals were evaluated by the Z test. For the remaining data significant differences were determined by the chi-squared test.

RESULTS

Among the 79 patients entered into the study, 48 patients were treated in the United States, and 31 patients underwent treatment in Japan. There were no major differences between the two populations in clinicohistopathologic characteristics. There were 53 men and 26 women, whose ages ranged from 27 to 86 (mean, 60.7) years. Forty-seven patients had colon cancer, and 32 patients had rectosigmoid or rectal tumors (Table 1). Sixty-one patients had symptoms that led to the discovery of colorectal cancer: lower gastrointestinal bleeding in 46 patients; nonspecific abdominal pain in 10 patients; constipation in 5 patients; diarrhea in 5 patients. In the 18 asymptomatic patients cancer was discovered during routine physical examinations. Bowel resection and lymph node dissection followed attempted endoscopic removal of the cancer in 25 patients, whereas surgical resection was undertaken initially in 54 patients. There were no postoperative deaths.

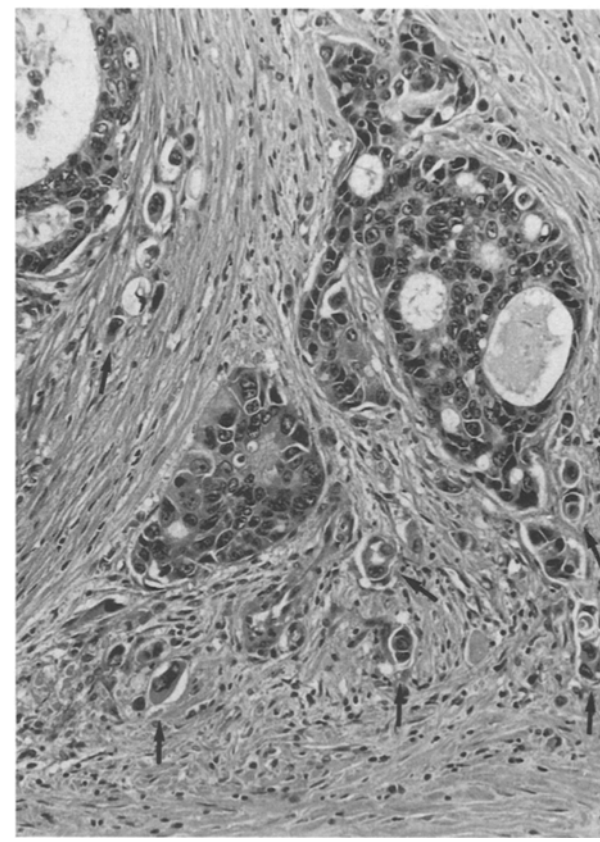

Figure 2. Tumor budding (*arrows*), defined as small clusters of undifferentiated cancer cells ahead of the invasive front (hematoxylin and eosin; ×50).

Among the 25 patients undergoing initial colonoscopic polypectomy, 23 patients had pedunculated tumors, and two patients had sessile lesions. In 20 patients tumor diameter was ≤2.2 cm; the largest lesion was 5.5 cm. Indications for subsequent open surgery included cancer at the margin of the polypectomy specimen (10), lymphatic invasion (9), and inadequate tissue for histologic assessment (5). In one patient the reason for bowel resection was not stated. All 25 patients had well-differentiated or moderately differentiated tumors. Three patients had residual cancer at the polypectomy site, and two other patients had lymph node metastasis without residual tumor.

In the entire study group the mean tumor diameter was 2.5 cm (Table 1). The diameter of the lesion was <1.0 cm in 10 patients, 1.1 to 2.0 cm in 36 patients, 2.1 to 3.0 cm in 16 patients, and >3.1 cm in 17 patients. Cancers were pedunculated, with either a narrow or

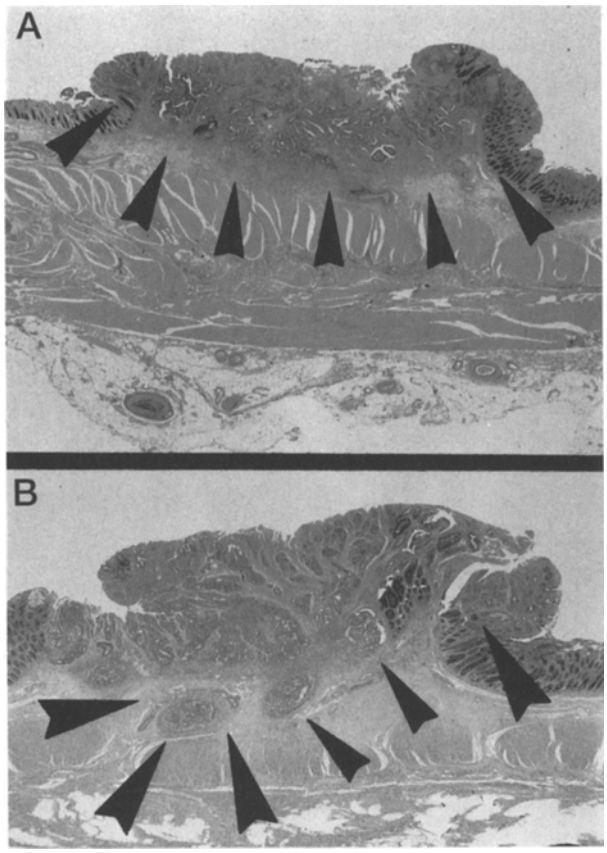

Figure 3. Patterns of cancer growth at invasive front: clearly demarcated (*A*) and poorly demarcated (*B*) (victoria blue; ×4).

broad stalk, in 46 patients (58.2 percent) and sessile in 33 patients (41.8 percent). The follow-up interval has ranged from 5 to 173 (median, 81.1) months. Eight patients (10.1 percent) have developed cancer recurrence (Fig. 5), diagnosed at 8, 12, 21, 25, 28, 34, 55, and 60 (mean, 30.3) months after surgery. Twenty patients have died, 8 from colorectal cancer and 12 from other causes (Figs. 6 and 7). Lymph node metastasis was found in 11/79 patients (Fig. 5). Nine patients had cancer in nodes adjacent to the the tumor, whereas two patients had metastases in lymph nodes along the course of a major named vascular trunk. Nodal involvement was associated with a worse prognosis; 36.4 percent of node(+) patients developed cancer recurrence *vs.* only 5.9 percent of node(−) patients ($P < 0.005$). Cumulative survival rate was also worse in node(+) *vs.* node(−) patients (Fig. 6): 72.7 percent *vs.* 91.1 percent at five years ($P < 0.05$) and 45.5 percent *vs.* 65.3 percent at ten years ($P < 0.05$). Cumulative death rate from cancer was also higher in node(+) *vs.* node(−) patients (Fig. 7): 19.2 percent *vs.* 3.1 percent at five years ($P < 0.05$) and 43.4 percent *vs.* 7.2 percent at ten years ($P < 0.05$).

Data on histologic risk factors for lymph node metastasis are summarized in Table 2. Patients with moderate or severe tumor budding had a 25 percent incidence of nodal spread, whereas those with no or minimal budding experienced no lymph node involvement. In patients harboring cancer with a poorly demarcated invasive front, nodal spread was much more common than in those with tumors having a clean interface with the underlying tissue. Patients with moderately or poorly differentiated cancer cells in the submucosal invasive front (44.3 percent of the population) also experienced a higher incidence of lymph node metastasis than those with well-differentiated cancer cells (28.6 percent *vs.* 2.5 percent; $P < 0.005$). In patients with middle or deep submucosal invasion, the incidence of nodal spread was 23.4 percent *vs.* 0 percent in those with superficial invasion ($P < 0.005$). Patients with cancer cells in lymphatics also exhibited a significantly higher incidence of lymph node involvement than patients without lymphatic permeation. Further assessment of these data revealed that, whereas patients with fewer than four risk factors had no nodal metastasis, those with four or five risk factors experienced rates of lymph node involvement of 33.3 percent and 66.7 percent, respectively. These findings were noted in both colon and rectal cancer patients and were not affected by the initial mode of therapy (Table 3). Patients with four or more risk factors accounted for 26.6 percent of the study group, and this population had a 52.4 percent incidence of nodal metastasis.

There was no correlation between lymph node involvement and tumor size. Nodal metastasis occurred in 3/10 patients (30 percent) with a tumor

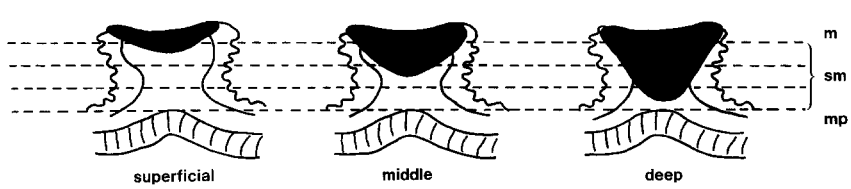

Figure 4. Illustration of superficial, middle, and deep submucosal invasion.

Table 1.
Clinicopathologic Characteristics of Patients with "Minimally Invasive" Colorectal Cancer

	Tumor Location					
	Ascending Colon	Transverse Colon	Descending Colon	Sigmoid Colon	Rectosigmoid	Rectum
No. of patients	6	3	4	34	10	22
Tumor diameter (cm)	1.2–10.5	1.2–2.2	0.6–4.5	0.4–8.0	1.0–10.0	0.3–7.0
Initial polypectomy	2	1	1	15	0	6
Partial colectomy	6	3	4	1*		
Sigmoidectomy				25		
Anterior resection				8	9	14
Abdominoperineal resection					1	8
Nodal metastasis	0	0	0	6	1	4
Cancer recurrence	0	0	0	5	2	1

* Left hemicolectomy.

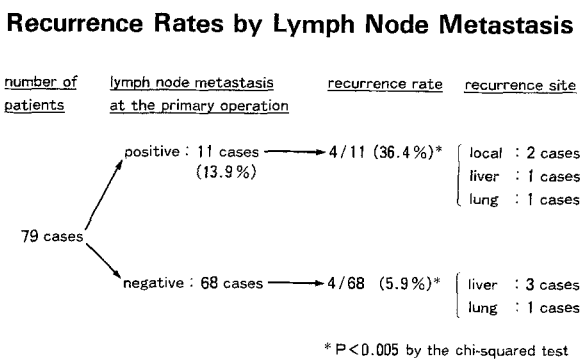

Figure 5. Tumor recurrence after curative surgery in patients with minimally invasive colorectal cancer.

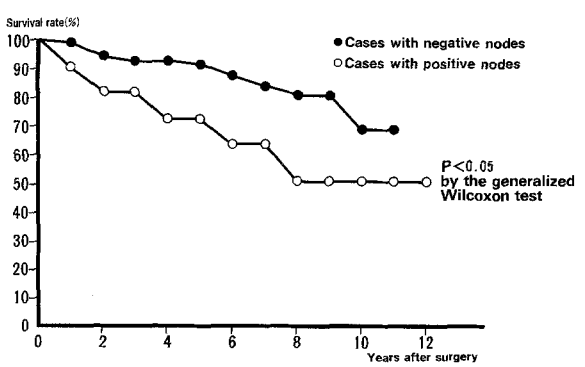

Figure 6. Cumulative long-term survival in patients with minimally invasive colorectal cancer. (The generalized Wilcoxon test compares the survival curves of two populations.)

diameter below 1.0 cm, in 4/36 patients (11.1 percent) with cancers from 1.1 cm to 2.0 cm, in 3/16 patients (18.7 percent) with lesions from 2.1 cm to 3.0 cm, and in 1/17 patients (5.9 percent) with tumors over 3.1 cm. There was no significant difference in the rate of nodal involvement between patients with moderately

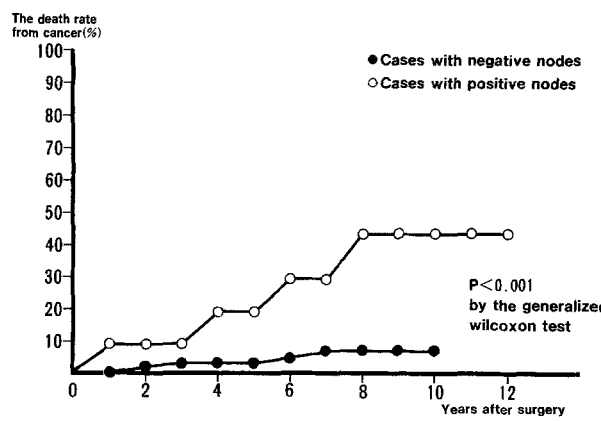

Figure 7. Death rate from cancer after curative resection of minimally invasive colorectal cancer.

or poorly differentiated *vs.* well-differentiated tumors (20.8 percent *vs.* 11.1 percent). No difference was noted in the incidence of lymph node metastasis between patients with colon cancer (6/47; 12.8 percent) or rectal cancer (5/32; 15.6 percent). There was also no significant difference in the rate of nodal involvement between patients with pedunculated cancers (5/46; 10.9 percent) *vs.* sessile tumors (6/33; 18.2 percent).

DISCUSSION

Widespread use of colonoscopy has enchanced our ability to encounter small, early cancers of the colon and rectum. However, this technology has also created a therapeutic dilemma; namely, is colonoscopic removal sufficient therapy for tumors that have invaded the submucosa or should subsequent bowel resection and lymph node dissection be performed? This problem has not been resolved satisfactorily, and the aim of the present study was to provide guidelines

Table 2.
Relationship Between Lymph Node Metastasis and Histologic Risk Factors in Minimally Invasive Colorectal Cancer

	No. of Patients (%)		
	(+) Lymph Nodes	(−) Lymph Nodes	*P* value
Tumor budding			
(−)	0	35 (100)	$P < 0.005$
(+)	11 (25.0)	33 (75.0)	
Demarcation of cancer at the invasive front			
Clear	1 (2.6)	37 (97.4)	$P < 0.01$
Poor	10 (24.4)	31 (75.6)	
Tumor differentiation in submucosal invasive front			
Well	1 (2.5)	39 (77.5)	
Moderate	9 (17.4)	24 (82.6)	$P < 0.01$
Poor	1 (50.0)	1 (50.0)	
Mucinous	0	4 (100)	
Depth of submucosal cancer invasion			
Superficial	0	32 (100)	
Middle	7 (30.4)	16 (69.6)	$P < 0.01$
Deep	4 (16.7)	20 (83.3)	
Lymphatic invasion			
(−)	2 (4.0)	48 (96.0)	
(+)	9 (31.0)	20 (69.0)	$P < 0.005$

Table 3.
Relationships Between Risk Factors and Incidence of Lymph Node Metastasis

	Number of Risk Factors					
	0	1	2	3	4	5
Overall rate (%) of lymph node involvement	0/10 (0)	0/9 (0)	0/24 (0)	0/15 (0)	3/9 (33.3)	8/12 (66.7)
Lymph node metastatic rate (%) by tumor site						
Colon cancer	0/10 (0)	0/6 (0)	0/13 (0)	0 /7 (0)	1/4 (25.0)	5/7 (71.4)
Rectal cancer	0/0 (0)	0/3 (0)	0/11 (0)	0 /8 (0)	2/5 (40.0)	3/5 (60.0)
Nodal metastatic rate (%) related to treatment						
Open surgery after attempted polypectomy	0/3 (0)	0/2 (0)	0/9 (0)	0 /6 (0)	1/2 (50.0)	1/3 (33.3)
Open surgery initially	0/7 (0)	0/7 (0)	0/15 (0)	0 /9 (0)	2/7 (28.6)	7/9 (77.8)

for appropriate treatment of minimally invasive colorectal cancer. To address this issue we elected to review only patients who had undergone curative resection of colorectal cancers that were diagnosed histologically as minimally invasive. In this fashion lymph node status of all such patients could be ascertained. We also elected to evaluate only patients who had been followed beyond five years, postoperatively, because previous work showed that five-year survival is inadequate to assess results of treatment in cancer of the colon or rectum.[15]

Our study revealed that patients with minimally invasive colorectal cancer have a surprisingly high (14 percent) risk of lymph node metastases at the time of diagnosis and also have a worrisome incidence (10 percent) of cancer recurrence over the long term. These rates are slightly higher than those reported previously, probably because our follow-up interval is much longer. In previous investigations the incidence of lymph node metastasis varied from 3 percent to 12 percent,[1, 4, 8, 10–13, 16] and cancer recurrence rate has ranged from 6.3 percent to 8.9 percent.[1, 13, 16, 17] Of even greater significance, minimally invasive cancer of the colon or rectum is a potentially lethal disease, as evidenced by the fact that eight of our patients died from colorectal cancer.

Our results indicate that the long-term outcome in patients with minimally invasive colorectal cancer is related to lymph node status at the time of initial diagnosis and definitive treatment. Patients with nodal metastases had a much higher incidence of recurrence than those without nodal spread (36 percent *vs.* 6 percent). In addition, the ten-year death rate from cancer in node(+) patients was 43 percent *vs.* 7

percent in node(−) patients. Thus, nodal involvement in patients with minimally invasive cancer of the colon or rectum indicates vigorous biologic activity of the tumor. For this reason, it is necessary to identify and properly treat such patients. Because the nodal status can be ascertained only by harvesting lymph nodes and examining them histologically, treatment of minimally invasive colorectal cancer solely by colonoscopic removal will be inadequate for some patients. On the other hand, because the majority of patients with these lesions do not have nodal metastases, open surgery is clearly not necessary in all patients. Thus, in this era of increasing endoscopic removal of small colorectal cancers, guidelines are needed regarding the likelihood of lymph node metastases and the need for subsequent resection of the involved bowel and its nodal drainage.

It is generally agreed that patients with incomplete endoscopic excision of invasive colorectal cancers should undergo bowel resection.[1–3, 5, 7, 18] However, controversy exists regarding other indicators for open surgery following colonoscopic removal of minimally invasive cancer. Some investigators[6, 19, 20] have contended that all patients with submucosal colorectal cancer should undergo bowel resection, because of the lack of definitive risk factors for metastases. Several other authors[1, 2, 4, 5, 7–10, 13, 17, 18, 21, 22] have proposed numerous histopathologic criteria for subsequent open surgery after initial colonoscopic removal of early colorectal cancer: Level 4 invasion; poorly differentiated carcinoma; lymphatic invasion; aneuploidy; all sessile lesions; stalk invasion in pedunculated tumors. Unfortunately, each of these tumor characteristics has a high rate of false positivity and is of limited usefulness in clinical practice. Hence, using five risk factors for lymph node metastases, we sought to develop a means of reliably predicting nodal involvement in patients with minimally invasive colorectal carcinoma.

In our series, 31 percent of patients with cancer cells in lymphatics had nodal metastasis. This incidence is similar to that reported by others.[4, 10, 12] It should be noted, however, that definitive diagnosis of lymphatic permeation can be troublesome.[3, 11, 18] Cranley and associates,[3] in particular, have emphasized difficulty in distinguishing histologically true lymphatic invasion from either vascular invasion or retraction artifact and have questioned the reliability of lymphatic permeation as a criterion for possible nodal metastasis. Although these concerns are valid, they also highlight the need for examination of colorectal cancer specimens by a pathologist who is familiar with and can accurately assess prognostic histologic features.[4, 7, 13, 14] With such capability, as shown by our data, lymphatic involvement is useful as an indicator of lymph node metastasis.

Another histologic characteristic evaluated in our study was the depth of submucosal tumor invasion. Patients with middle or deep submucosal invasion had a 23.4 percent incidence of nodal involvement. These findings corroborate the report of Haggitt and colleagues,[5] who found no lymph node metastases when tumor invasion was limited to the head, neck, or stalk of the polyp (Levels 1, 2, 3). In contrast when the cancer reached the base of the stalk or the polyp was sessile (Level 4), lymph node metastasis was frequent. Nivatvongs and coauthors[10] reported similar findings. In our series there was no significant difference in the incidence of nodal involvement between sessile (18 percent) or pedunculated (11 percent) cancers. Thus, the depth of submucosal invasion by the tumor appears to be more important than whether the tumor is sessile or pedunculated.

Current data suggest that the biologic activity of large bowel cancer is more accurately reflected by histologic characteristics at the invasive front of the lesion, rather than in the body of the tumor.[15, 23, 24] For example, in our study and in other recent reports,[10, 16] there was no relationship between tumor size or cellular differentiation and nodal spread. Because the invasive front of a tumor has ample blood supply, there is an optimal chance for the cancer to reflect its true aggressiveness. Consequently, we carefully assessed events at the leading edge of the tumor as risk factors for lymph node metastasis.

Patients with moderately or poorly differentiated cancer cells in the submucosa at the invasive front had a high incidence of lymph node involvement, compared with those with well-differentiated cancer cells at the leading edge. In contrast, patients with moderately or poorly differentiated cells in the main body of the tumor did not have a higher rate of lymph node involvement than those with well-differentiated lesions. This finding, plus the low incidence of poorly differentiated tumors in patients with minimally invasive colorectal cancer,[3, 7, 23] underscores the importance of close examination of histologic events at the leading edge of the tumor. This point is further emphasized by our analysis of tumor budding. Recent data[15, 25] suggested that budding is a prelude to lymphatic invasion and indicates vigorous biologic activity of colorectal cancer. In this series, 25 percent of

patients with severe tumor budding had lymph node metastases, whereas patients with no or minimal budding did not have nodal involvement. Finally, patients harboring tumors with a poorly demarcated invasive front had a much higher incidence of nodal spread than those with a sharp delineation between cancer and normal tissue (24.4 percent *vs.* 2.6 percent).

Although any one of the histologic features we evaluated *can* be helpful in indicating the presence of lymph node metastases, the sensitivity and specificity of each criterion is fairly low. Because one of our goals was to develop guidelines for bowel resection and lymph node dissection after colonoscopic removal of minimally invasive colorectal cancer, we examined the relationship between number of predictors present and lymph node metastases. Patients with fewer than four histologic risk factors had no lymph node metastases. In contrast, patients with four or five risk factors had a 33.3 percent and 66.7 percent incidence of lymph node involvement, respectively. Thus, we recommend that among patients who have initial colonoscopic removal of minimally invasive cancer, those whose lesions exhibit four or more histologic risk factors should undergo appropriate bowel resection with lymph node dissection. Patients with three or fewer risk factors should not be subjected to a subsequent open surgical procedure. Our data also indicate that the extent of bowel resection and lymph node dissection in patients with minimally invasive colorectal cancer should be the same as in patients with more advanced stages of the disease. Two of our patients with nodal metastases had involvement of lymph nodes along the course of a major named vascular trunk. Moreover, two patients who experienced local recurrence of their cancer had segmental bowel resection at their original operation.

CONCLUSIONS

Minimally invasive colorectal cancer can be an aggressive disease; 14 percent of our patients had nodal metastases, 10 percent experienced tumor recurrence, and 10 percent died of cancer. Lymph node involvement portends a worse outcome. Thus, patients who have colonoscopic removal of these tumors should undergo subsequent formal bowel resection if a lesion exhibits four or more of the following histologic features: severe tumor budding; a poorly demarcated leading edge; poorly differentiated cells in the invasive front; lymphatic involvement; deep submucosal invasion.

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