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Clinical Significance of Colorectal Cancer: Metastases in Lymph Nodes <5 mm in Size

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Background: The clinical significance of metastases in small lymph nodes is not known. Our objective was to evaluate possible relationships between the number and size of lymph node metastases and survival after potentially curative colorectal resection.

Methods: A retrospective chart review was performed in patients with Dukes' C (any T, N_{1-3}, M_0) colorectal cancers from July 31, 1971 to December 31, 1987. All specimens underwent the lymph node clearing technique. Statistical analysis was performed with the log rank test and the Cox proportional hazards model.

Results: In 77 patients there were 253 (8%) of 3,087 cleared lymph nodes with metastases. One hundred seventy-five (69%) of these metastatic nodes were 5 mm or less in diameter. The distal margin of resection ($p = 0.011$) and number of positive lymph nodes ($p = 0.036$) were statistically significant factors influencing overall survival. There was no significant difference in overall survival ($p = 0.73$) or disease-free survival ($p = 0.56$) whether the involved lymph nodes were < or > 5 mm in size.

Conclusion: Most metastatic lymph nodes were <5 mm in diameter. Based on our results, the size of lymph node metastases do not affect disease-free or overall survival in colorectal carcinoma.

Key Words: Colorectal cancer—Metastases—Lymph nodes.

The most important prognostic factor in colorectal carcinoma is lymph node metastases. Several studies have shown that when the lymph node clearing technique is used, both the total number of lymph nodes and the number of metastatic lymph nodes examined in surgical specimens increase (1–4). Furthermore, the majority of the lymph nodes detected are <5 mm in size (2,4). The clinical significance of metastases in small lymph nodes is not known. The purpose of this study was to explore possible relationships, if any, between the number and size of the metastatic lymph nodes and the disease-free and overall survival in patients who underwent curative resections for colorectal cancer.

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MATERIALS AND METHODS

After approval by the Institutional Review Board, the medical records of 88 patients who had colorectal carcinoma and lymph node metastases and who underwent primary curative resection at Roswell Park Cancer Institute from July 31, 1971 to December 31, 1987 were retrospectively reviewed. A curative resection was described as one in which all the gross tumor and its mesentery were removed with clear margins of resection. The medical records were examined for age, sex, Dukes' stage (Gastrointestinal Tumor Study Group modification; Dukes' C1 — one to four involved lymph nodes; Dukes' C2 — more than four involved lymph nodes irrespective of bowel wall penetration) (5,6), TNM stage (American Joint Commission on Cancer) (7), site of the primary tumor, margins of resection, de-

gree of differentiation, number and size of lymph nodes cleared, adjuvant therapy, recurrence, and survival. All pathology slides were reviewed (SM, RBP) and the number and size of the lymph nodes cleared, both positive and negative recorded. In cases in which there was more than one neoplasm in the resected specimen, the highest Dukes' classification was used. Eleven patients were excluded from the study for the following reasons: three patients — lymphatic vessel involvement but no actual lymph node metastases on review of slides, four patients — slides not available, four patients — postoperative deaths. The remaining 77 patients form the basis of this report. Fifty six patients (73%) received no adjuvant therapy, whereas 21 received adjuvant therapy, which included chemotherapy — 7 patients, chemotherapy and radiation — 12 patients, immunotherapy — 1 patient, and chemotherapy and immunotherapy 1 patient. The majority of the patients receiving adjuvant therapy were enrolled in various national protocols. The chemotherapy administered was mainly 5-fluorouracil based. All patients were followed up either in the clinics, by contact with their primary physician, or until death. Statistical analysis was performed using the log rank test (8) and the Cox proportional hazard model for multivariate analysis (9).

The lymph node clearing technique used has been previously described (10). Namely, after opening and rinsing the specimen with water, all gross pathologic changes were recorded. The specimen was then pinned in a cork or a polystyrene board and fixed with Lillie's solution for 24 h. After sections for routine processing were taken from the tumor and margins, the specimen was dehydrated by using two changes of 95% alcohol, and three changes of absolute alcohol every 12 h. The specimen was squeezed between changes to remove the dissolved fat. Subsequently the specimen was kept in cedar wood oil for 4 h at 60°C. Once the fat clearing was complete, the specimen was drawn on bonded paper. As the lymph nodes were retrieved, they were placed in the exact location in the diagram and given a number before being fixed in paraffin. After fixation in paraffin, each lymph node was sectioned at three different levels for histological examination.

TABLE 1. *Clinical and pathological characteristics of patients with colorectal cancer and lymph node metastases*

Site of neoplasm						
Cecum						9
Ascending colon						4
Hepatic flexure						2
Transverse colon						3
Splenic flexure						1
Descending colon						2
Sigmoid colon						20
Rectum						43
Degree of differentiation						
Well differentiated						17
Moderately differentiated						49
Poorly differentiated						14
Mucin producing						4
TN stage[a]	T		N		Dukes' stage[b]	
	T1	11	N1	50	C1	60
	T2	15	N2	27	C2	17
	T3	46				
	T4	12				

[a] AJCC staging; N1: one to three involved nodes; N2: four or more involved nodes (7).

[b] Gastrointestinal Tumor Study Group Dukes' Modification (5,6).

TABLE 2. *Size and tumor involvement of lymph nodes cleared*

	Size (mm)										
Status	1	2	3	4	5	6	7	8	9	10	≥10
Positive	10	35	54	46	30	27	15	15	12	5	4
Negative	646	703	593	427	208	112	66	35	21	6	17

RESULTS

There were 42 women and 35 men. The median age was 62 years (range 23–83 years). Table 1 demonstrates other clinical and pathological characteristics of the 77 patients. There were 84 adenocarcinomas in 77 patients. Seventy-five percent of the cancers were located in the rectum and sigmoid. Histologically, 58% of the tumors were moderately differentiated. The median follow-up was 82 months (range 4–254 months). There were 3,087 lymph nodes cleared in 77 patients, of which 2,834 (92%) were negative and 253 (8%) had metastatic involve-

TABLE 3. *Size and number of metastatic lymph nodes in patients with positive lymph nodes ≤5 mm only*

No. of patients	Size and number of positive lymph nodes cleared (mm)				
	5	4	3	2	1
34	13	16	25	23	9
25		13	19	20	8
15			13	9	6
6				7	5
0					0

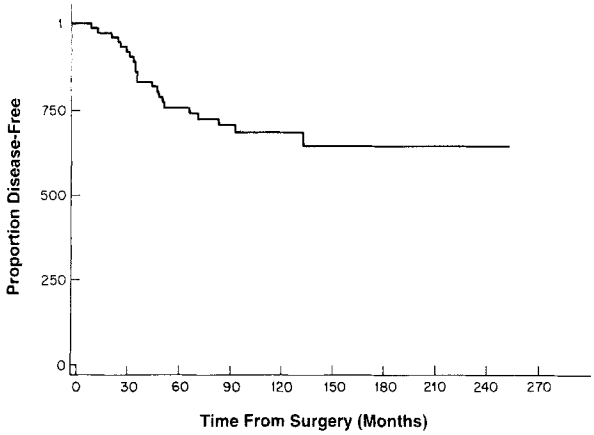

FIG. 1. Overall survival for all patients.

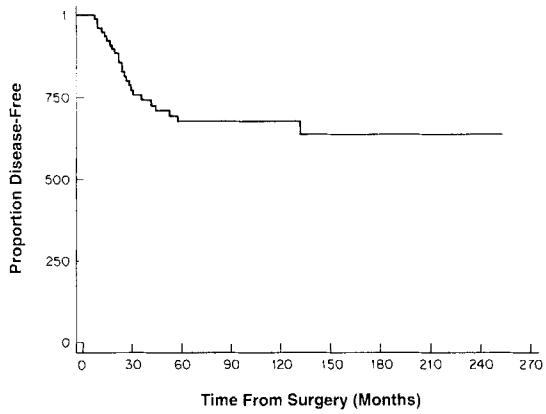

FIG. 2. Disease-free survival for all patients.

ment by tumor. The mean and median number of lymph nodes cleared per specimen were 40 and 30, respectively (range 9–189). The mean and median number of positive lymph nodes obtained were 3 and 2, respectively (range 1–30). Table 2 demonstrates the size and tumor involvement of the lymph nodes cleared. There were 2,752 (89%) small lymph nodes cleared (1–5 mm) and 335 (11%) lymph nodes 6 mm or greater. Of the 253 metastatic lymph nodes cleared, 175 (69%) were 5 mm or less in size whereas 78 (31%) were 6 mm or greater. Table 3 demonstrates the size and number of positive lymph nodes in patients whose metastatic lymph nodes were 5 mm or less in size. In 34 (44%) patients all the positive lymph nodes were 5 mm or less.

Figures 1 and 2 show the overall survival and disease-free survival in the 77 patients. The estimated survival rate at 65 months was 74% (95% confidence interval [CI] 63–85%). The estimated disease-free survival at 57 months was 68% (95% CI 57–74%). Figures 3 and 4 illustrate overall survival according to whether the number of lymph nodes cleared was 30 or less versus >30. Using the log rank test, there was no significant difference between these two groups in either survival ($p = 0.26$) or disease-free survival ($p = 0.33$). A multivariate analysis using the Cox model was performed. In terms of overall survival, margins of resection and number of positive lymph nodes were statistically significant ($p = < 0.05$). Table 4 reveals the results

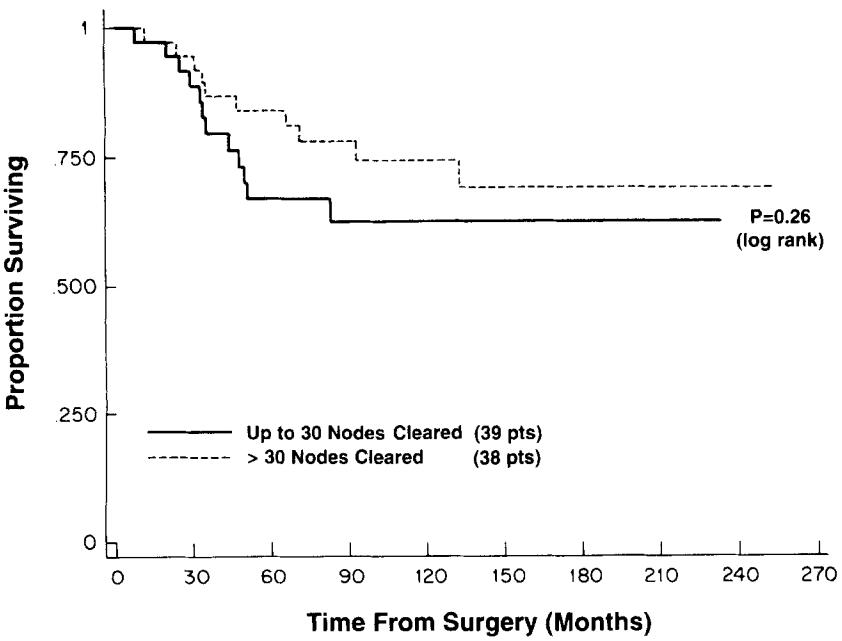

FIG. 3. Overall survival according to number of lymph nodes cleared.

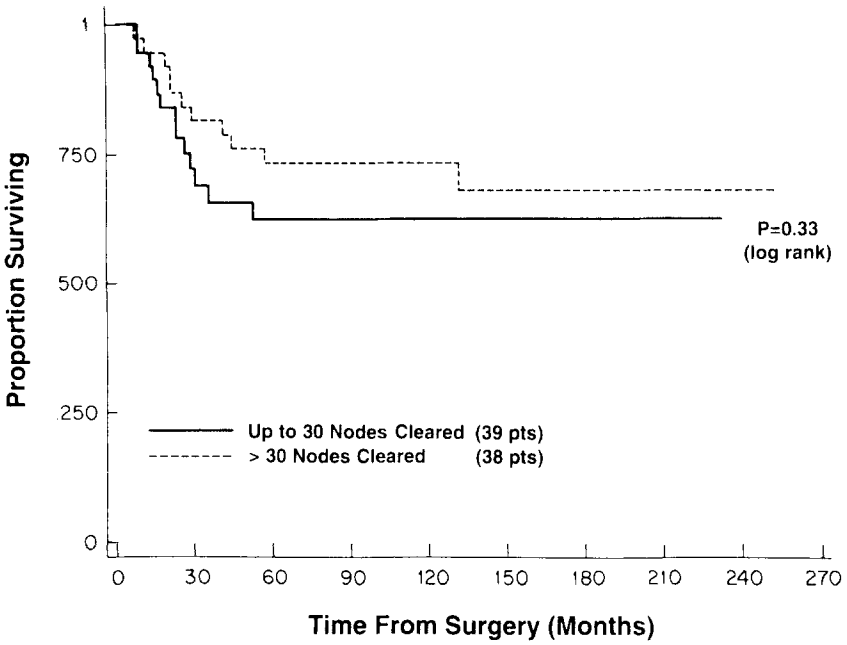

FIG. 4. Disease-free survival according to number of lymph nodes cleared.

of the multivariate analysis where an increase in distal margin of resection or an increase in lymph nodes cleared increases the expected chance of survival. Other variables found not to be significant with regard to survival were age, adjuvant therapy, Dukes' stage, or T stage. Among the variables examined, only distal margin of resection was significant ($p = 0.008$) in terms of disease-free survival.

A multivariate Cox proportional hazard analysis using overall and disease-free survival as the endpoints with the largest positive lymph node as a parameter was performed. The size of the largest metastatic lymph node had no statistically significant effect on overall or disease-free survival by itself or after adjusting for other parameters. A similar analysis was performed with colon and rectal tumors only. Again, no statistically significant effect by itself or after adjusting for other parameters was found for the largest positive lymph node. Subsequently, a dichotomous variable was defined for when the largest positive node was ≤5 mm versus 6 mm or larger. Figures 5 and 6 demonstrate that there is no statistically significant advantage in terms of overall survival ($p = 0.73$) or disease-free survival ($p = 0.56$). When the same analysis was performed for patients with 30 or less lymph nodes cleared, no difference was noted in overall ($p = 0.94$) or disease-free survival ($p = 0.77$). The same was true for patients with >30 lymph nodes cleared for overall survival ($p = 0.55$) and disease-free survival ($p = 0.45$).

Twenty-four patients developed recurrent disease. There were 97 metastatic lymph nodes cleared in these patients. The median number and size of positive lymph nodes cleared were 2 (range 1–30) and 4 mm (range 1–>10 mm), respectively. In two patients the metastatic lymph nodes were >10 mm in size. Table 5 illustrates the size of the largest metastatic lymph node and the site of recurrence in these patients. Sixteen of the 24 patients (67%) with

TABLE 4. *Multivariate analysis with regard to overall survival in 77 patients with colorectal cancer*

Variable	Coefficient	p value	Exp. (coeff.)
Distal margin of resection	−0.092	0.011	0.91
Rectum	1.337	0.200	3.80
Positive lymph nodes	0.156	0.036	1.17
Lymph nodes cleared	−0.019	0.061	0.98
Differentiation	0.925	0.064	2.52

TABLE 5. *Site of recurrence and size of largest metastatic lymph node*

Site of recurrence	Size of largest metastatic lymph node (mm)[a]									
	1	2	3	4	5	6	7	8	9	≥10
Local				3		1				
Regional			1					2	1	1
Distant		1	2		1	4		1	1	1
Local and regional						1				
Regional and distant		1					1		1	

[a] Each number represents a patient.

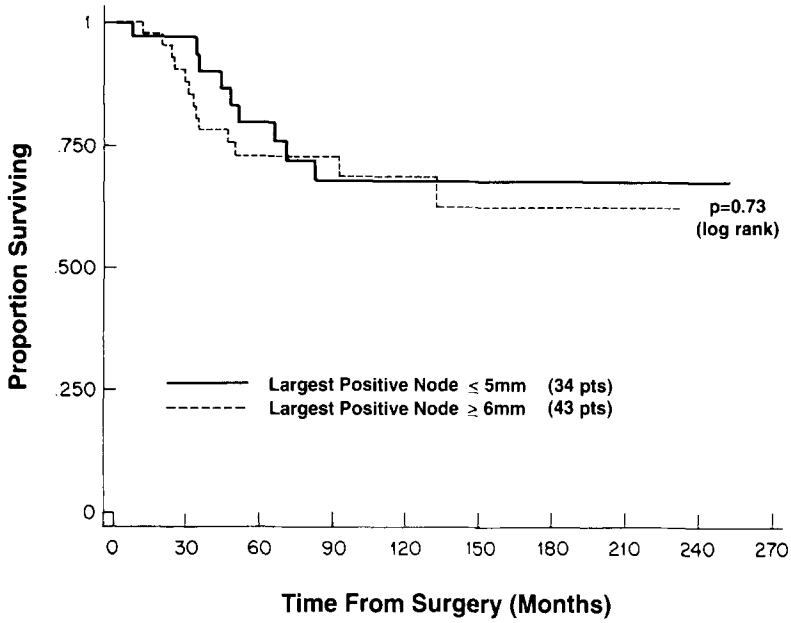

FIG. 5. Overall survival according to size of largest positive lymph node.

recurrence had a primary rectal cancer. The median distal margin of resection in the patients who had primary rectal cancer and who developed recurrence was 4.0 cm (range 0.5–9.0 cm).

DISCUSSION

Several investigators have reported that with the fat-clearing technique the number of lymph nodes examined per specimen after colorectal cancer resection is increased when compared with conventional pathologic investigation. Moorman et al. reported an increase from 3.1 to 10.6 lymph nodes per patient when the clearing method was used (11). Similar experiences were reported by Cawthorne et al. (1) and Scott and Grace (3). The latter two series reported an increase in lymph nodes detected in cleared specimens from 6.1 to 18.9 and 10.5 to 23.1, respectively. Hida et al. (4) reported an increase from 18.1 to 76.4 in the colon and 21.2 to 73.7 in the

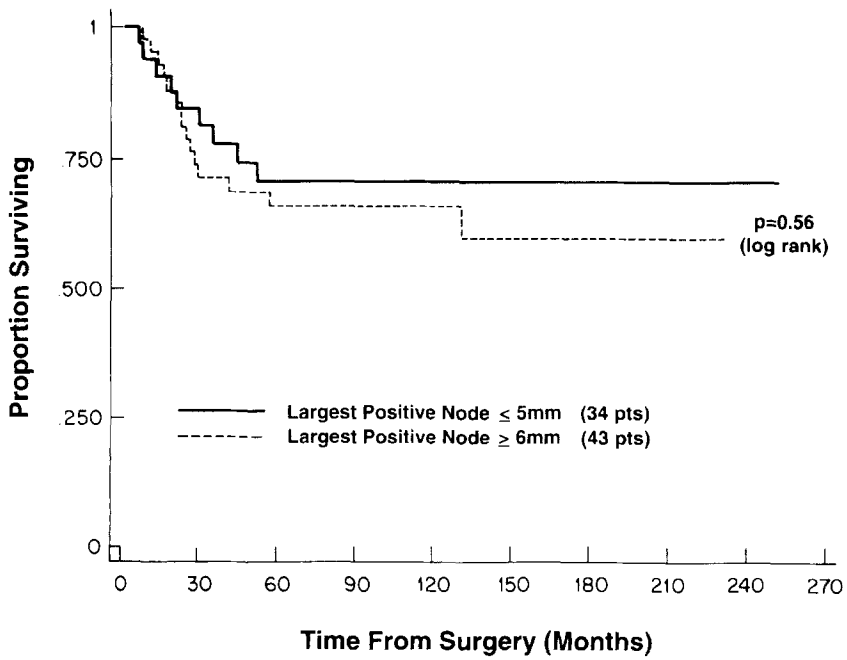

FIG. 6. Disease-free survival according to size of largest positive lymph node.

rectum after fat clearance. This was not the case in the experience reported by Jass et al., who found no significant difference in the number of lymph nodes harvested with or without the fat-clearing technique (12). Aside from the extent of surgical resection, the most important aspect of detecting the lymph nodes in pathological specimens is the perseverance of the pathologist's search for them. It has been reported that lymph nodes <4–5 mm in size are not detected by the conventional dissection. Our data clearly show that the majority of the metastatic lymph nodes detected in resected specimens (69%) are 5 mm or less. This was previously documented in a report from our institution in which 59% of metastatic lymph nodes were 5 mm or less (2). Hida et al. have reported a 32% incidence of metastatic lymph nodes <4 mm detected when the fat-clearance technique was used versus a 15% incidence when manual examination was performed (4). In squamous cell carcinoma of the anal canal, Wade et al. reported a 44% incidence of involved lymph nodes <5 mm (13). Furthermore, if we accept that manual clearance will detect lymph nodes that are 5 mm or greater, then 25 of 77 our patients (32%) would have been understaged. This has significant implications concerning preoperative rectal ultrasound, and the decision for adjuvant therapy. Our data imply that in terms of preoperative staging of patients the size of the lymph nodes noted in the physical examination, transrectal ultrasound, computerized axial tomography, or magnetic resonance imaging is irrelevant to whether these nodes contain tumor or not. In our series of 32 lymph nodes 1 cm or greater, only 9 (28%) were metastatic whereas 78 of 253 lymph nodes (31%) 5 mm or less were involved by tumor. Thus, the lymph nodes have to be pathologically examined because the majority whether large or small are not involved with tumor. Similarly, we believe that when the lymph node clearing technique is used, there is accurate pathological staging of patients for inclusion in adjuvant clinical trials.

The major question is whether the size of the involved lymph node and the total number of lymph nodes cleared have an effect on disease-free and overall survival. To attempt to answer this question, a multivariate analysis was performed using the largest positive node as a parameter. There was no relationship between overall survival and size of the largest metastatic node by itself or after adjusting for other parameters. Subsequently we arbitrarily divided our patients into those with metastatic lymph nodes >5 mm and those with involved nodes ≤5 mm. There was no statistically significant difference in overall and disease-free survival whether the involved lymph nodes were <5 mm or >5 mm.

The multivariate analysis did demonstrate that the total number of metastatic lymph nodes and distal margins of resection were statistically significant variables in terms of overall survival. Distal margins of resection but not number of metastatic lymph nodes was statistically significant in terms of disease-free survival. The results on the distal margin of resection can be explained by the fact that the multivariate analysis was fitted with all the patients and the effect of the distal margins of resection among rectal cancer patients was so strong (data not shown) that the effect among all patients remained significant.

We have demonstrated that the majority of metastatic lymph nodes detected after curative colorectal resection are ≤5 mm in size. In addition, 25 patients (32%) would have been understaged, assuming that manual clearing techniques will not detect lymph nodes 4 mm or smaller. Based on our results, the size of metastatic lymph nodes does not affect disease-free survival or survival after potentially curative surgery in colorectal. We advocate the use of the lymph node clearing technique because a significant number of patients will be understaged with manual clearing techniques and lose the opportunity for adjuvant therapy.

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