

Lymph Node Size and Metastatic Infiltration in Colon Cancer

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Background: Detection of metastatic lymph nodes in colon cancer is essential for determining stage and adjuvant treatment modalities. Lymph node size has been used as one possible criterion for nodal metastasis. Although enlarged regional lymph nodes are generally interpreted as metastases, few data are available that correlate lymph node size with metastatic infiltration in colon cancer.

Methods: In a prospective morphometric study, the regional lymph nodes from 30 colon specimens from consecutive patients with primary colon cancer were analyzed. The lymph nodes were counted and the largest diameter of each lymph node was measured and analyzed for metastatic involvement by histological examination.

Results: A total of 698 lymph nodes were present in the 30 specimens examined for this study. A mean number of 23 (range, 19–39) lymph nodes was found in each specimen. Of these nodes, 566 (81%) were tumor-free and 132 (19%) contained metastases. The mean diameter of the lymph nodes free of metastases was 3.9 mm, whereas those infiltrated by metastases averaged 5.9 mm in diameter ($P < 0.0001$). Of the tumor-free lymph nodes, 528 (93%) measured < 5 mm in diameter, whereas 70 (53%) lymph nodes containing metastases measured < 5 mm in diameter.

Conclusions: Lymph node size is not a reliable indicator for lymph node metastasis in colon cancer. A careful histological search for small lymph node metastasis in the specimen should be undertaken to avoid false-negative node staging.

Key Word: Colon cancer - Lymph node metastasis - Lymph node size.

Lymph node metastasis remains an important prognostic factor in patients with primary colon cancer.¹ Detection of metastatic lymph nodes in colon cancer is essential for determining UICC stage and for indication of adjuvant therapy.² Lymph node size has been used as one possible clinical criterion for nodal metastasis. Although enlarged regional lymph nodes are generally interpreted as metastases, few data are available that correlate lymph node size with metastatic infiltration in colon cancer.³

In order to clarify whether lymph node size is correlated to metastatic infiltration, a morphometric study of the lymph nodes of colon specimens was performed after surgical resection for colon carcinoma.

PATIENTS AND METHODS

Patients

Specimens from 30 patients in whom a curative resection for colon cancer was performed between June 1, 1996 and June 30, 1997 were included in the study. The surgical procedure (no laparoscopic surgery) included the radical resection of the tumor-bearing colon with truncal ligation of its vessels and lymphadenectomy according to actual standards (Table 1).⁴ Seventeen specimens were obtained from male and 13 from female subjects. The age of the subjects ranged from 28–83 years, with a median of 55 years. None of the patients had been treated preoperatively with cytotoxic drugs or radiation.

Lymph Node Analysis

The specimens were removed en bloc and the lymph nodes were dissected from the specimens by two pathologists (TKZ and SEB) according to a standardized protocol. The specimens were fixed in 5% formaldehyde and embedded in paraffin. The nodes were counted and

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TABLE 1. Colon cancer: operations performed

Operation	No.	%
Right hemicolectomy	17	57
Left hemicolectomy	4	13
Radical sigmoid resection	8	27
Total colectomy	1	3
Total	30	100

the largest diameter of each node was measured with a slide gauge. A series of sections from six levels of each node were selected and stained with Hematoxylin and Eosin as well as with PAS. All dissected lymph nodes were analyzed microscopically for metastatic infiltration. Histological findings were classified according to the UICC-TNM-classification.⁵

To assess shrinkage due to fixation and staining, 48 lymph nodes from two colon specimens were measured before and after fixation and staining with hematoxylin and eosin.

Statistical Analysis

The relationship between lymph node size and the presence of metastases was evaluated statistically. Continuous variables were expressed as the mean \pm SD and were analyzed using the Student's *t*-test. Frequencies were analyzed using the χ^2 test; a *P* < .05 was considered significant.

RESULTS

Shrinkage Factor

The shrinkage factor during the laboratory preparation of nodes was calculated at 10%. There was no significant difference in shrinkage between metastatic and non-metastatic lymph nodes of any size.

Size of Lymph Node

In the 30 specimens, 698 lymph nodes were evaluated for size and for metastatic infiltration. An average of 23 lymph nodes per specimen was found (range, 19–39). Evidence of metastasis was found in 132 lymph nodes (19%), whereas 550 lymph nodes (81%) were free of tumor infiltration.

Of the 30 patients, 12 were classified as pN0 and 18 patients as pN+; of the latter, 7 (39%) were classified as pN1 and 11 (61%) as pN2, according to the 1997 TNM-classification.⁵

The average size of the tumor-free lymph nodes was 3.8 ± 2.3 mm, whereas lymph nodes with metastatic infiltration averaged 5.9 ± 3.4 mm; the difference is statistically significant (*P* < .0001). Of the total lymph

nodes examined, 528 (75.6%) were 5 mm or less in diameter (Table 2); in these, metastasis was found in 70 (13.3%) lymph nodes, whereas 458 (86.7%) were tumor-free. Considering all lymph nodes < 10 mm in diameter (671 or 96.1%), 121 (18%) showed evidence of metastasis, whereas 550 (82%) were tumor-free. Of the total lymph nodes analyzed, 27 (3.9%) lymph nodes measured ≥ 10 mm in diameter; of these 11 (40.7%) contained metastases, whereas 16 (59.3%) were tumor-free.

Lymph nodes measuring 10 mm or greater exhibited a significantly higher rate of metastases than lymph nodes measuring < 10 mm (*P* < .0001). Of the 12 patients without lymph node metastases, 4 (33.3%) had at least one lymph node that measured 10 mm or greater in diameter. Of the 18 patients with lymph node metastases, 7 (38.9%) had at least one lymph node measuring 10 mm or greater in diameter. There was no difference in the findings between N1 and N2 patients (*P* > .05).

DISCUSSION

A standardized lymphadenectomy procedure for lymph node dissection is required for the evaluation of the lymph node status in patients with colon carcinomas, because the accuracy of the N-staging is in direct correlation to the number of lymph nodes dissected.⁶

To establish whether a correlation exists between lymph node size and metastatic infiltration we have dissected and analyzed 23 lymph nodes per patient, which exceeds by far the UICC standard requirement of a minimum of 12 lymph nodes for colon pN staging.⁵

Lymph node size has been used as one possible criterion for nodal metastasis; however, macroscopic evaluation of lymph nodes often can lead to erroneous conclusions. In a morphological study of gastrointestinal carcinoma specimens, 904 lymph nodes were macroscopically determined to be tumor-free based on size, color, and consistency, but 208 (23.0%) of these were found to contain metastases when examined histologically.⁶ Of the other 298 lymph nodes suspected to contain

TABLE 2. Colon cancer: size of lymph nodes and presence or absence of metastasis in 30 patients

Size of lymph node (mm)	No. of nodes	No. of positive nodes	No. of negative nodes
<3 mm	169	15 (8.9%)	154 (91.1%)
3–5 mm	359	55 (15.3%)	304 (84.7%)
6–9 mm	143	51 (35.7%)	92 (64.3%)
10–20 mm	27	11 (40.7%)	16 (59.3%)
Total	698	132 (18.9%)	566 (81.1%)

metastatic spread, 134 (45%) were found to be tumor-free.⁶

In our study, 53% (70) of the metastatic lymph nodes measured 5mm or less in diameter. Comparable to our results, Herrera-Ornales et al. demonstrated that in colon cancer, 65% of metastatic nodes were 5 mm or less in diameter.³ The lack of correlation between lymph node size and metastatic infiltration has been reported in studies of other solid tumors. In a Japanese study of esophageal carcinomas, 36% of the metastatic lymph nodes measured < 5 mm in diameter.⁷ Noda et al. demonstrated that in gastric cancer, 38% of metastatic nodes were 5 mm or less in diameter⁸ and in studies of rectal carcinoma, 50% to 64% of metastatic lymph nodes were 5mm or less in size.^{9,10} The available imaging techniques (CT, MRI) are only able to assess lymph nodes that are ≥ 5 mm in diameter.^{3,6}

Despite a significant difference in diameter of metastatic (5.9 mm) and non metastatic (3.9 mm) nodes, the accurate evaluation of lymph node metastasis in colon cancer cannot be determined by nodal size. Therefore, preoperative classification of N-category cannot be evaluated by measuring nodal size in imaging procedures alone.¹¹

Lymph node size is not a reliable indicator for lymph node metastasis in colon cancer. These data suggest that a careful histological search for small lymph node metastases should be undertaken to avoid false-negative lymph node staging. The results presented here make it clear that to provide a reliable pathological staging of

colon cancer, a standardized systematic lymphadenectomy⁴ is necessary whereas lymph node sampling based on lymph node size alone is not sufficient.

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