Number Versus Distribution in Classifying Regional Lymph Node Metastases from Colon Cancer

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BACKGROUND: Metastasis to regional lymph nodes from colon cancer is an important prognostic factor. In the TNM classification, node metastases are classified into three grades based on the number of metastatic nodes. In the *Japanese General Rules for Clinical and Pathologic Studies on Cancer of the Colon, Rectum, and Anus* (JGR), node metastases are classified into four grades based on the distribution of metastatic nodes.

STUDY DESIGN: Based on the findings of node metastases in 164 patients with colon cancer obtained by the clearing method, node classifications by the JGR and TNM classifications were compared.

RESULTS: The case distribution by the JGR grading was 41.5% in n (−), 29.3% in n1 (+), 18.3% in n2 (+), and 11.0% in n3 (+) disease. In the TNM classification, the distribution was 23.8% in pN1 and 34.8% in pN2 disease. The 5-year survival rate by the JGR was 98.4% in n (−), 74.3% in n1 (+), 51.2% in n2 (+), and 30.0% in n3 (+) disease; in TNM classification, this rate was 76.0% in pN1 and 45.0% in pN2 disease.

CONCLUSIONS: In the classification of regional node metastases from colon cancer, the JGR classification showed a wider range in distribution and 5-year survival rate compared with the TNM system. (J Am Coll Surg 2005;201:217–222. © 2005 by the American College of Surgeons)

Metastasis to regional lymph nodes from colon cancer is an important prognostic factor.[1-10] Internationally, the treatment and prognosis of colon cancer have been based on the node classification by the tumor-node-metastasis (TNM) method;[11] in Japan, the *Japanese General Rules for Clinical and Pathologic Studies on Cancer of the Colon, Rectum, and Anus* (JGR)[12] have been used. Because these staging systems use different approaches to classify regional nodes, international comparisons of therapies and prognosis of colon cancer are difficult to undertake. In the TNM classification, node metastases are classified into three grades, from pN0 to pN2, based on the number of metastatic nodes. In the JGR, node metastases are classified into four levels: n (−), n1 (+), n2 (+), and n3 (+), based on the distribution of metastatic nodes. We have previously reported that the clearing method makes it possible to identify lymph nodes smaller than 4 mm in diameter that would be undetected by the conventional manual method.[13] In this study, node classifications by number and by distribution were compared based on the observation of node metastases using the clearing method.

METHODS

The study included 164 patients with colon cancer who had undergone surgical treatment between August 1979 and July 1989 (Table 1). The number of patients classified by pathologic tumor category in the TNM classification is shown in Table 2. Dissected nodes were examined by the clearing method described in our previous report.[13] The specimens resected en bloc were extended to the original size and shape, fixed in formalin solution containing methylene blue, dehydrated with alcohol, defatted with acetone, and cleared with xylene. Nodes were extracted using transillumination and histologically examined for metastases. A lymph node map that included the site of the primary lesion, vascular distribution, and sites of extracted nodes was produced.

Regional nodes were classified according to the JGR into three groups: pericolic nodes along the marginal

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Abbreviations and Acronyms

IMA = inferior mesenteric artery
JGR = Japanese General Rules for Clinical and Pathologic Studies on Cancer of the Colon, Rectum, and Anus
LCA = left colic artery

arteries; intermediate nodes along the ileocolic, right colic, middle colic, left colic, sigmoid, and inferior mesenteric artery (IMA) from the origin of the last sigmoid artery to the origin of the left colic artery (LCA); and the main nodes along the IMA from the origin of LCA to the origin of IMA, and along the superior mesenteric artery (Fig. 1). When no regional node metastasis was found, the patient was assigned to n (−). Metastasis to pericolic nodes within 5 cm from the margin of the tumor was graded as n1 (+); spread to pericolic nodes between 5 cm and 10 cm from the tumor margin or intermediate nodes was graded as n2 (+); and spread to the main nodes was graded as n3 (+) (Fig. 2). In the TNM classification, regional node metastases are classified into three pN categories (pN0 to pN2) based on the number of metastatic nodes (Table 3). The Kaplan-Meier method was used to calculate survival rate, and the Wilcoxon and Cox-Mantel tests were used to test for statistical significance, considered to exist at $p < 0.05$.

RESULTS

The mean number of examined nodes per patient was 76.2 (12,496 nodes in 164 patients). The metastatic rate (the number of patients with node metastases divided by the total number of patients) was 58.5% (96 of 164), and the metastatic incidence (the number of nodes with metastases divided by the total number of examined nodes) was 5.8% (724 of 12,496). The distribution of the patients by the JGR was 41.5% for n (−), 29.3% for n1 (+), 18.3% for n2 (+), and 11.0% for n3 (+) disease. By the TNM classification, the distribution of the patients was 23.8% for pN1 and 34.8% for pN2 disease (Table 4).

Table 1. Site of Primary Tumor

Tumor site	n
Cecum	12
Ascending	24
Transverse	24
Descending	16
Sigmoid	88
Total	164

Table 2. Extent of Primary Tumor

Extent of tumor	n
pT1	18
pT2	30
pT3	98
pT4	18
Total	164

pT, pathologic tumor.

The 5-year survival rates after curative resection were 98.4% for n (−), 74.3% for n1 (+), 51.2% for n2 (+), and 30.0% for n3 (+) disease in the JGR system (Fig. 3). By the TNM classification, the 5-year survival rates after curative resection were 76.0% for pN1 and 45.0% for pN2 disease (Fig. 4).

DISCUSSION

The greater the number of metastatic nodes and the larger the distribution area of metastases, the worse the prognosis.[1-5,10,14,15] According to the TNM classification (4th ed., 1992,[16]), node metastases are classified first by number and then by distribution of metastatic nodes (pN1, metastasis in 1 to 3 pericolic nodes; pN2, metastasis in 4 or more pericolic nodes; pN3, metastasis in any node along the course of a named vascular trunk, metastasis to an apical node, or both). But the number of patients classified as pN3 has been found to be greater than the number of patients classified as pN2,[5,10,14,15] and no significant difference between survival rates for pN2 patients and pN3 patients has been found.[4,5,10,15] So distribution ("pericolic" and pN3) was deleted from the fifth edition of the TNM classification (1997).[17] This has simplified the classification in the present sixth edition (2002)[11] by considering only the number of metastatic nodes (pN1, metastasis in 1 to 3 regional nodes; pN2, metastasis in 4 or more regional nodes). Imbalances in both patient distribution and survival rates were noted in the current version of the TNM classification (6th ed., 2002).

For example, Tang and colleagues[4] showed a 5-year survival rate of 67% for the pN1 group, which was significantly higher than the 36% in the pN2 group, even though both groups had the same number of patients (269 patients). Sternberg and associates[18] reported that 5-year disease-free survival rate for the pN1 group (122 patients) was 60%, which was not significantly different