

Original Article

The Use of Ratio of Metastasis in Lymph Nodes as a Predictor of Overall Survival in Colorectal Cancer

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Key Words

Colorectal cancer;

Predictor;

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Purpose. The evaluated the use of lymph node ratio (LNR) as a prognostic predictor for patients with stage III colorectal cancer.

Materials and Methods. We retrospectively and consecutively reviewed the records of 109 colorectal cancer patients who had received curative resection at Veteran General Hospital Kaohsiung (VGHKS) between January 1998 to December 2002. Lymph node (LN) disease was diagnosed and staged into quartiles according criteria established by the American Joint Committee on Cancer. Survival was calculated by Kaplan-Meier analysis and was assessed by the log rank test. The lymph node ratio was calculated by dividing the number of disease positive lymph nodes with the total number of resected nodes, both variables previously reported to be of independent prognostic importance.

Result. Eight hundred eighty-four patients were diagnosed with colorectal cancer in our hospital between 1998 and 2002. We selected 109 patients with stage III disease. Seventy-three (67%) were men and 36 women (33%) with median age was 63 years (range 27 to 86). In each patient, a minimum of 10 LNs were harvested. We found a significant difference in overall survival among the four groups analyzed by LN ratio quartiles: group 1 had an LNR less than 0.25; group 2, 0.25-0.5; group 3, 0.5-0.75; and group 4, 0.75-1.0.) The 5-year survival rate of those in group 1 was 75% but for those in group 4, it was 23% ($P < 0.007$).

Conclusion. This study suggests that LNR can be used as a potent predictor of survival for patients with stage III colorectal carcinoma.

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Adenocarcinoma of the colon is the third leading cause of cancer death in Taiwan where curative resection remains the primary treatment for this disease. According to the American Joint Committee (AJCC) on Cancer's 2002 *Cancer Staging Manual*, the outcome of colon cancer can be strongly predicted by the total number of metastatic lymph nodes in found in a specimen.¹ However, although it is known

that the number of lymph nodes that a pathologist examines directly influences the accuracy of nodal staging,^{2,3} fewer than forty percent of patients with this disease in the United States receive adequate lymph node evaluation.⁴ Recently, studies have reported lymph node ratio (LNR), the ratio of metastatic lymph nodes to total resected lymph nodes, to be a more accurate predictor of survival than total number of meta-

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static LNs in other malignancies such as gastric and pancreatic cancer.^{5,6}

LNR has also been found by two recent studies to be a useful prognostic marker for patients with Stage III colorectal carcinoma.^{7,8} Since this method may be more accurate than total number of LNs in its prognosis, its use could help reduce mis-staging as well and inappropriate treatment. Since these studies are rather recent unconfirmed studies, we designed this investigation to further substantiate the usefulness of lymph node ratio as a prognostic predictor of survival in 109 patients with histopathologically confirmed stage III colorectal carcinoma by comparing LNR with survival.

Methods

Between 1998 and 2002, 884 patients were diagnosed with stage III colorectal cancer and received surgical resection for colorectal cancer at Veteran General Hospital Kaohsiung. In this study, which retrospectively reviewed the medical records of these patients, we excluded patients who were not found to have lymph node metastasis, those who had fewer than ten lymph nodes examined and those lost to follow up. We also excluded any of patients who had been found preoperatively to have Stage IV colorectal cancer by chest X-ray and abdominal CT scan. In total, we included 109 patients (73 men and 36 women). All patients received post-surgery chemotherapy. There was no difference in choice of regimen. All patients received postoperative surveillance and were staged using TNM classification as recommended by AJCC's *Cancer Staging Manual*, 6th ED. 2002. The

characteristics of the patients (age, sex, tumor location, tumor differentiation, and tumor stage) are summarized in Table 1. More than 95% of the patients received 5-FU and Leucovorin. (Table 2)

Using the number of lymph nodes reported to be studied and those reported to be metastatic in the reports, we calculated the lymph node ratio by dividing the number of metastatic lymph nodes by the total examined lymph nodes. Patients were divided into four LNR groups based of ratio quartiles: Group 1: LNR less than 0.25 (n = 62), Group 2: 0.25-0.5 (n = 21), Group 3: 0.5-0.75 (n = 11), Group 4: 0.75-1.0 (n = 15). Survival was calculated in months post-surgery. Any patient who had survived more than 80 months was classified as 80 months. After completion of post-surgical chemotherapy, patients were followed up every 3 months for 1 year. After that, they were followed up on an every-six-month basis. After 5 years, each

Table 1. Demographics of study population

Characteristic	n	%
Sex		
Male	73	67
Female	36	33
Tumor grade		
Moderately differentiated	98	89.9
Poorly differentiated	11	10.1
Stage		
N1	57	52.3
N2	52	47.7
Location of tumor		
Ascending colon	16	14.7
Transverse colon	8	7.3
Descending colon	9	8.25
Sigmoid colon	25	22.9
Sigmoid-rectal junction	1	0.92
Rectum	50	45.93

Table 2. Treatment schema for our study

Surgery	R A	1. Leucovorin	20 mg/M ² IV push
	A S		450 mg/M ² IV push
	N S		Days 1-5: repeat at 4 weeks, 8 weeks, then every 5 weeks
	D I	2. Leucovorin 500 mg/M ² IV by infusion	For a total of 6 courses
	O G		500 mg/M ² IV push beginning 1 hour after leucovorin infusion starts.
	M N		Treatment repeated weekly × 6, followed by a 2-week break. Each 8-week cycle is repeated for a total of 4 courses (24 treatments total).
	L E	3. Levamisole	50 mg PO every 8 hours × 3 days repeated every 14 days for 1 year
	Y D		450 mg/M ² IV push × 5 days; on day 29 begin 450 mg/M ² IV push
			weekly × 48 weeks, for a total 1 year

patient was seen once a year. During the follow up visits, patients received CEA testing and serial CXR, if they desired a more thorough assessment. Patients received a CT scan once a year. Patients who survived less than five full years were not considered to have survived 5 years, and those who had survived more than 5 years were categorized into the 5-year group.

Kaplan-Meier curves and the log rank test were used to assess the five-year overall survival rates. All statistical operations were performed using SPSS (version 11.5). A p-value less than 0.05 was considered significant.

Results

Patients

As can be seen in Table 1, our sample consisted of 109 patients (73 men and 36 women) with a mean age of 63 years (range, 27-86 years) (Table 1). Fifty-seven patients (52.3%) were staged at N1 (1-3 positive nodes), and 52 (47.7%) at N2 (> 3 positive nodes), respectively. Most patients (89.9%) had moderately differentiated tumors. (Table 1)

Prediction of five-year survival rate

Although both TNM stage and tumor differentiation grade were found to significantly predict 5-year survival (data not shown) (both $P < 0.05$), We found that N2, those having more than three positive nodes ($n = 52$) had a much worse 5-year survival rate than N1, those having 1-3 positive nodes ($n = 57$) ($p < 0.005$). LNR was also found to significantly predict overall survival ($P < 0.007$) (Fig. 1). The 5-year survival groups 1, 2, 3 and 4 were 75%, 53%, 35%, 23%, respectively ($P < 0.007$). Of the four LNR groups, Group 4 (LNR 0.75-1.0) had a significantly worse overall five-year survival rate than the other groups (23%) ($P < 0.007$) (Fig. 1).

Discussion

This study confirmed previous findings that LNR

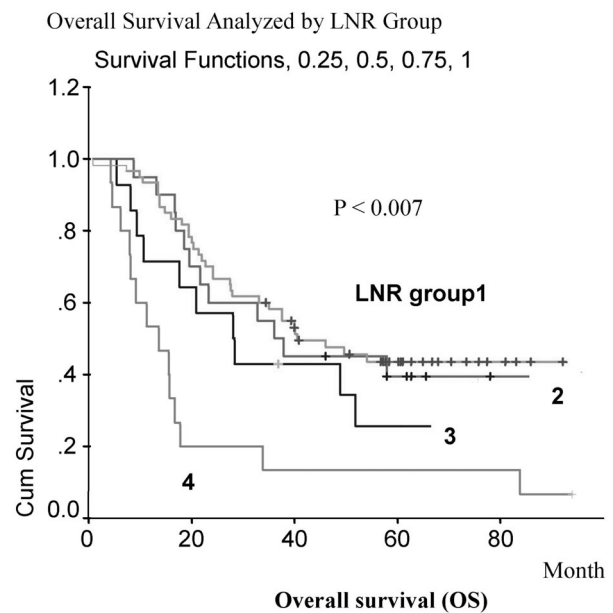


Fig. 1. Overall survival in LNR groups

can significantly predict overall 5-year survival in Stage III colorectal cancer patient.

TMN staging, based on the counting of regional metastatic LN, has been thought to be the most significant predictor of long-term survival in colorectal cancer.⁵ And although it has been suggested the more lymph nodes involved in the determination, the more accurate the staging and prediction, there is much evidence indicating that the diagnostic and prognostic power of the number of metastatic LNs may be influenced by the total number of LNs examined.^{9,10} Staging plays a major role in the decision whether patients should be given adjuvant therapy or not after surgery. While it is clear that TNM Stage 4 patients (those with metastases to other organs) have a poorer prognosis for survival, there is great variation in survival among Stage III colorectal cancer patients. Therefore, prognostic predictions may need to be based on factors other than stage alone. Recently, LN ratio (the ratio of metastatic lymph to examined lymph nodes) has been reported to be an alternative means of predicting survival.^{7,8} This study confirms these findings. Lymph node ratio can provide information that could be used to better predict survival in patients with stage III disease. In our study, it was found to be highly significant ($P < 0.007$) (Fig. 1).

In a retrospective study of 265 patients with stage

III colon cancer data collected from 1999-2003, K. Derwinger et al.¹¹ found that LNR may be used effectively in the staging and prognosis of this disease. Studies evaluating the use LNR to stage gastric cancer found ratio-based nodal staging to be a better means of staging than that AJCC TNM staging, especially with respect to stage migration.^{5,12,13} It may, however, be limited by the number of LNs studied. For example, Berger et al.⁷ demonstrated that the LNR was not an important prognosis factor in patients in whom fewer than 10 LNs were recovered, and that if number was greater than 15, then evaluation of LNs could be performed accurately.

The pathologist plays an important role in counting the number of lymph nodes.¹⁴ Several studies have suggested that their preparation, method and analysis will affect the results. Both national and international standards require that the number of assessed lymph nodes needed for an adequate staging should be twelve. Although this quality factor should not to be neglected, there is great variation in how many lymph nodes different pathologists collect, and this difference may affect their assessments. In this study, for example we collected less than twelve.

One major limitation of this study may be the size of its sample, though this may be less of an issue if one realizes that both factors used to calculate LNR (number of disease-positive lymph nodes and the total number of harvest nodes) have been found by separate studies to be predictive of influence accuracy.¹⁵ Our findings were similar to the results of those two studies. Another possible limitation may be that we included patients in whom at least ten lymph nodes were examined by pathologists. Generally, at least 12 lymph nodes are examined.¹⁶ However, we found that if we used this method to select patients in an already small sample of patients, then study group might become too small to study. Despite this difference in number of lymph nodes examined, we still found a significant difference in survival in our Group 4 LNR patients. We believe that LN ratio can serve as an important variable in the prediction of 5-year survival in colorectal cancer, as has also been found by previous studies. This ratio may reflect tumor biology and the total cancer burden. Another study also testing quartile groupings has reported similar results, adding fur-

ther credence to the findings of this study.⁸

Conclusion

LNR can be used as an important prognostic predictor for stage III colorectal cancer. It may improve staging and decrease the possibility of stage migration.

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原 著

淋巴轉移數目對淋巴總數的比例 也許可成為大腸直腸癌的存活偵測因子

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目的 本篇研究的目的是在於評估淋巴結比率的重要性，它在第三期大腸直腸癌中是否可為預後偵測因子，我們假設淋巴結比率在第三期大腸直腸癌的存活率也許扮演重要的角色。

方法 此研究分析 1998 年 1 月至 2002 年 12 月共 109 位接受大腸直腸癌根治手術的患者 (男性共 73 位，女性共 36 位)。淋巴病變是依據美國癌症聯合會來分類，淋巴結比率用四分位法來計算分成四組。由 Kaplan-Meier 分析法和 log rank test 來計算存活率。患者年齡範圍從 27 歲到 86 歲 (平均 63 歲)。

結果 在 1998 年到 2002 年期間，在本院共計有 884 位大腸直腸癌患者。這篇研究中，選擇第三期的患者共有 109 位。73 位為男性 (佔 67%)，36 位女性 (佔 33%)。平均年齡 63 歲，且每位患者獲得的淋巴總數至少 10 顆。在淋巴結比率四分位的四個群組中，在整體存活有明顯的不同。根據我們的分析，第一組的五年整體存活率為 75%，而第四組五年整體存活率卻低於 23%。

結論 淋巴結比率合併了淋巴結轉移的數目和切除的淋巴總數，而上述兩者為獨立的預後重要因子。在第三期的大腸直腸癌患者，淋巴結比率也許可成為有利的預後偵測因子。

關鍵詞 大腸直腸癌、淋巴結比率、預後偵測因子。