

Original Article

# The Impact of Metastatic Ratio to Retrieved Regional Lymph Nodes on Overall Survival in Patients with Stage III Colorectal Cancer: Focus on Numbers of Lymph Node Retrieved Less Than 12

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**Purpose.** Colorectal cancer (CRC) is one of the most common causes of cancer death in Taiwan. According to current treatment guidelines, the number of metastatic lymph nodes is a prognostic factor of the disease. However, the relationship between the ratio of metastatic to examined lymph nodes and overall survival in stage III CRC patients is worth investigation, especially on numbers of retrieved lymph nodes less than 12.

**Methods.** From January 2004 to December 2010, four hundred and sixteen patients with stage III CRC were enrolled. All the patients received surgical intervention. According to the metastatic lymph node ratio (LNR), we divided all the included patients into four groups based on quartiles (LNR: < 0.1, 0.1 to 0.2, 0.2 to 0.4, and 0.4 to 1), and among those patients with 11 or less retrieved lymph nodes, we made two subgroups having a similar patient number depending on median of LNR. Then the correlation between LNR and overall survival was analyzed.

**Results.** The median and mean ages of the studied patients were 64 (range, 24-92) and  $63.47 \pm 13.39$  years, respectively. And the median number of examined lymph nodes was 13 (range, 1-68). The five-year overall survival rates of the four LNR groups were 69.7%, 64.5%, 62.0%, and 37.6%, respectively ( $p < 0.001$ ), while among patients with less than 12 harvested nodes, the higher LNR subgroup also showed a poorer prognosis.

**Conclusion.** For patients with stage III CRC, LNR might be considered as a crucial prognostic factor. Especially, while the number of retrieved nodes is under 12, high LNR patients might need a more intensive follow-up program compared to those with low LNR.

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## Key Words

Colorectal cancer;

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**M**alignant neoplasm of the colon and the rectum has become the cancer with the most reported incidents in Taiwan since 2009. Five-year overall survival rate of Taiwanese colorectal cancer (CRC) patients was 60.3% in 2009.<sup>1</sup> Up to the present time, radical surgery remains the major therapy for CRC. The current staging method used most frequently for CRC is tumor-node-metastasis (TNM) system of the American Joint Committee on Cancer (AJCC).<sup>2</sup> Because the status and increasing number of lymph node involvement is considered as a poor prognostic factor, adjuvant chemotherapy is recommended for patients with stage III colon cancer.<sup>3</sup> However, there is increasing concern about other metastatic lymph node status. For instance, a study by Johnson et al. concluded that increasing negative lymph node count is independently associated with long-term survival in stages IIIB and IIIC colon cancer.<sup>4</sup> The definition of metastatic lymph node ratio (LNR) is the ratio of involved lymph nodes to the total resected nodes. And in other human malignancies, such as the breast,<sup>5</sup> the stomach,<sup>6,7</sup> and the pancreas,<sup>8</sup> LNR has been reported to have significant impact on survival. For standard CRC surgery, the number of lymph node harvest is recommended to be at least 12.<sup>9</sup> However, nodal stage might be underestimated if the number of retrieved lymph nodes is less than 12.<sup>10</sup> Therefore the impact of LNR for stage III CRC patients is worthy of investigation, particularly in those with less than 12 evaluated nodes. Our aim was to evaluate the relationship between LNR and overall survival in stage III CRC in a single institute during a seven-year period, with a focus on lymph node retrieved number less than 12.

## Materials and Methods

### Patients

In the single medical center of southern Taiwan, all patients with malignant neoplasm of the colon and the rectum undergoing surgical resection were enrolled into a cancer registry database from our Cancer Center. After discharge from the hospital, all patients were routinely followed up according to a standard

protocol in our hospital. And if adjuvant chemotherapy was administered, the regime was fluoropyrimidine alone or in combination with oxaliplatin. And the follow-up time was continued till August 2012. We retrospectively inspected 426 cases with pathologic stage III CRC during the seven-year period (2004 to 2010), of which the complete medical record of these patients were available. Stage III CRC patients receiving neoadjuvant concurrent chemo-radiotherapy (CCRT) or neoadjuvant chemotherapy were excluded for the avoiding their effects on lymph nodes. Collected data included age, sex, location, TNM stage, retrieved lymph nodes, histology grade, and adjuvant therapy. 10 patients were not included because of unavailable records of number of lymph nodes. According to previous published work,<sup>11</sup> our 416 patients were divided into the following four groups based on quartiles: LNR less than 0.1 (n = 100), 0.1 to 0.2 (n = 114), 0.2 to 0.4 (n = 106), and 0.4 to 1.0 (n = 96). Finally, we focused on the group with less than 12 lymph nodes for further evaluation. Of these 177 patients with less than 12 lymph nodes, two subgroups were separated depending on median LNR (0.25).

### Statistical analysis

All data were analyzed using the Statistical Package for the Social Sciences version 19.0 software (SPSS Inc., Chicago, IL, USA). The overall survival of each group was calculated using the Kaplan-Meier method, and the log rank test was applied to compare the differences. It was considered statistically significant if the *p* value was less than 0.05.

## Results

### Patient characteristics

Data of the four hundred and twenty-six patients with stage III CRC undergoing a radical resection during the seven years from 2004 to 2010 were available for review. Of these records, 10 were excluded because of missing data regarding the exact number of

lymph nodes removed. Table 1 shows demographic data of these patients. The mean and median ages of these patients were  $63.47 \pm 13.39$  and 64 years (range, 24-92), respectively. Regarding T status, 327 patients (78.8%) and 49 patients (11.81%) were categorized to T3 and T4 respectively. In nodal stage category, average evaluated node number was 14.7, ranging from 1 to 68. Two hundred and thirty-nine patients had 12 or more retrieved lymph nodes. Over two-thirds of the patients' primary site was the colon. Nine patients' histology grade was not identified properly, and 80% of the rest was moderately differentiated. All the included patients received regular follow-up till August 2012.

Base on the site of tumor, either the colon or the rectum, we could not find a prominently better prognosis on five-year overall survival (63.3% vs. 48.4%,  $p = 0.097$ ). In Fig. 1, we demonstrated that there was no statistical difference in overall survival between

**Table 1.** Demographic data of patients with stage III colorectal cancer

N	416
Mean age $\pm$ SD* (range) (years)	$63.47 \pm 13.39$
Median age (years)	64 (24~92)
Sex (male/female)	241/175
T stage	
T1 (%)	6 (1.45%)
T2 (%)	33 (7.95%)
T3 (%)	327 (78.80%)
T4 (%)	49 (11.81%)
N stage	
N1 (%)	283 (68.03%)
N2 (%)	133 (31.97%)
Mean number of retrieved nodes $\pm$ SD* (range)	$14.66 \pm 8.57$ (1~68)
Median number of retrieved nodes	13
Site	
Colon (%)	304 (73.08%)
Rectum (%)	112 (26.92%)
Histology grade	
WD** (%)	9 (2.21%)
MD** (%)	341 (83.78%)
PD** (%)	57 (14.00%)
Adjuvant chemotherapy or radiotherapy	
Yes (%)	381 (91.59%)
No (%)	35 (8.41%)

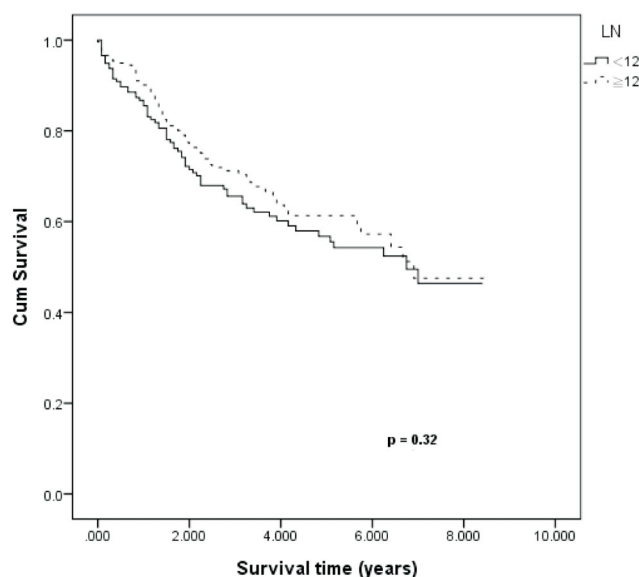
\* SD: standard deviation; \*\* WD: well differentiated; MD: moderately differentiated; PD: poorly differentiated; ^ CCRT: concurrent chemo-radiotherapy.

the patients with 12 or more retrieved nodes and the ones with less than 12 ( $p = 0.32$ ), though there was a slight increase of overall survival in patients with 12 or more retrieved nodes. Five-year overall survival rates of these patients were 61.3% and 56.8% respectively. According to a previous study by Berger et al.,<sup>11</sup> we divided all patients into four groups depended on quartiles (LNR:  $< 0.1$ ;  $0.1\sim 0.2$ ;  $0.2\sim 0.4$ ;  $0.4\sim 1$ ). On the Kaplan-Meier survival plot, the prognosis of higher LNR patients was significantly poorer than those with lower LNR (Fig. 2,  $p < 0.001$ ). Their respective five-year overall survival rates were shown in Table 2.

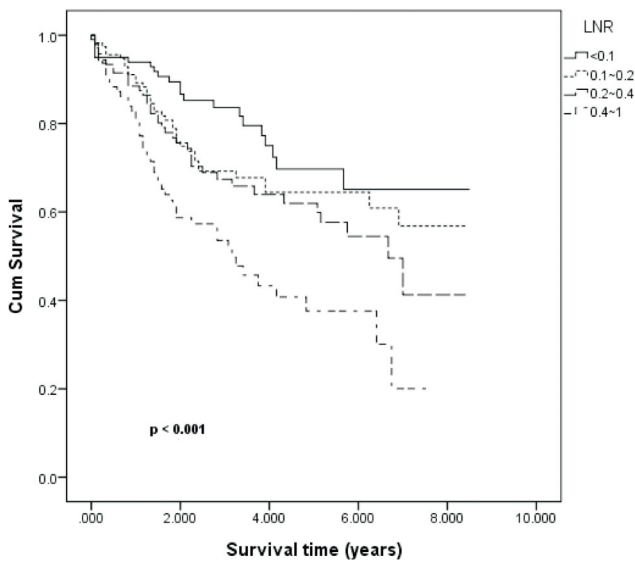
When we put a spotlight on those 177 patients with less than 12 retrieved regional lymph nodes, we analyzed the relationship between LNR and survival. The median number of LNR was 0.25; hence, we separated them into two subgroups to compare with each other. Fig. 3 demonstrated the Kaplan-Meier survival plot of those patients with LNR above or under 0.25. The five-year overall survival rates were 69.8% and 43.0%, respectively ( $p = 0.002$ ).

## Discussion

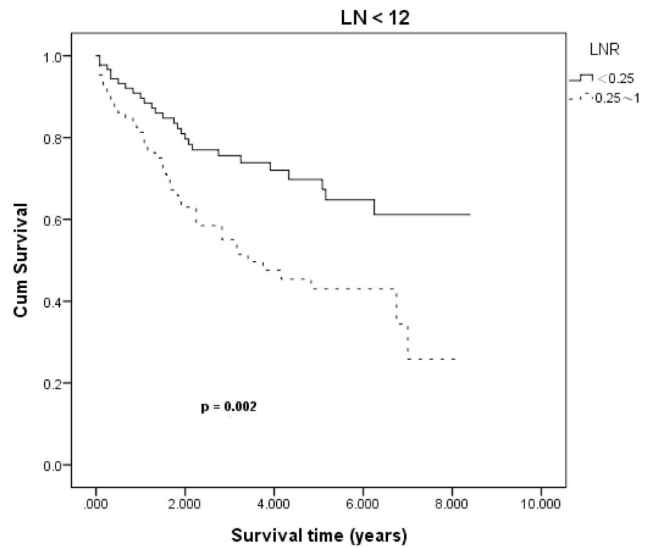
CRC has contributed to the leading malignancy in



**Fig. 1.** Overall survival of all patients according to total node number retrieved.



**Fig. 2.** Overall survival of all patients according to metastatic lymph node ratio.



**Fig. 3.** Overall survival of patients with less than 12 retrieved lymph nodes according to metastatic lymph node ratio.

**Table 2.** Five-year overall survival rate based on LNR\*

Group (LNR)	n	5-year survival rate (%)
1 (<math>< 0.1</math>)	100	69.7%
2 (0.1~0.2)	114	64.5%
3 (0.2~0.4)	106	62.0%
4 (0.4~1)	96	37.6%

\* LNR: metastatic lymph node ratio.

Taiwan since 2009. Among Taiwanese CRC patients, the median age of CRC was 67 years, and the incidence rate was 41.4 per one hundred thousand people in 2009.<sup>1</sup> In our data, the median age and five-year overall survival rate were 64 years and 59.3% in stage III CRC. Although some of these cases were transferred from other regional institutes on account of severity and complexity, we still had similar therapeutic results compared to the national database.<sup>1</sup>

The higher the number of nodes examined, the lower the risk of a missed nodal metastasis.<sup>12</sup> From recent literature, the number of resected lymph nodes has also determined the prognosis of many malignancies, such as breast cancer, bladder cancer, and lung cancer.<sup>13-15</sup> In CRC, a minimum of 12 lymph nodes harvest is recommended,<sup>9</sup> which is also considered an indicator of quality of care in colorectal surgery.<sup>16</sup> Furthermore, it was suggested that 13 or more lymph nodes have to be examined in T3 colon cancer.<sup>17</sup> For

patients with stages II and III colon cancer, the number of lymph nodes evaluated was positively associated with survival.<sup>18</sup> Many factors may contribute to evaluated lymph nodes number, including a more radical lymphadenectomy by the surgeon and a more careful examination by the pathologist, probably depending on local practice patterns.<sup>19</sup> In our registry data of stage III CRC, however, the overall survival rate of the patients with 12 or more retrieved nodes was not significantly superior to those with less than 12 nodes (61.3% vs. 56.8%,  $p = 0.32$ , Fig. 2). Since inadequate lymph node evaluation may cause a well-described phenomenon of stage migration, particularly in stages I or II colon cancers,<sup>10</sup> all our reviewed patients were categorized into stage III, therefore the possibility of stage migration was relatively low.

It has been well established that the numbers of involved lymph nodes impact survival of patients with CRC. However, there is increasing evidence in multiple anatomic sites that LNR has a crucial influence on survival.<sup>5-8</sup> To minimize the influence of case number difference, we used the quartile method to group enrolled patients. The median value of LNR was 0.2, and the lower and upper quartiles were 0.1 and 0.4 respectively. We can find that a higher LNR represented a poorer overall survival (69.7% vs. 64.5% vs. 62.0%

vs. 37.6%). Especially, the prognosis changed dramatically for the patients with LNR above 0.4. As the number of positive nodes increased, the LNR also went upward if the total nodes number remained unchanged. This could be one of the explanations for what we observed. In the general stage system for node-positive status, it will be labeled as N1 stage if metastatic nodes number is less than four, and the others are going to be N2 stage. So the stage migration probably occurred in patients with stage III CRC, especially if lymph nodes were not adequately evaluated.

In our database, 177 patients had less than 12 retrieved regional lymph nodes, which was considered a risk factor for an adverse outcome in early invasive colorectal carcinoma.<sup>20</sup> In view of this point, we also discussed the influence of LNR for these patients. We classified them into two subgroups based on median LNR. Similarly, the higher the LNR, the poorer the prognosis observed. Because LNR may correct the influence of nodal stage migration in stage III patients with inadequate lymph node harvest, the inclusion of LNR into the current staging system for these patients may enable clinicians to assess the prognosis of patients more precisely.

In conclusion, LNR is an important prognostic factor for stage III CRC. For some certain risky conditions, such as improper lymph node harvest, it is possible that LNR could guide us more cautiously. Further workup is therefore mandatory to develop a more accurate staging policy to subcategorize stage III CRC, especially for patients with inadequate lymph node retrieved.

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原 著

## 轉移淋巴結比率對第三期大腸直腸癌病人總體存活的影響：針對摘取淋巴結少於 12 顆者

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**目的** 在台灣，大腸直腸癌是最常見的癌症死因之一。根據現行的治療準則，淋巴結轉移的數量是該疾病的預後因子。然而，轉移淋巴結佔所有淋巴結的比率跟第三期大腸直腸癌總體存活的關係仍是值得探究的，尤其是針對摘取不到 12 顆淋巴結病人的探討。

**方法** 2004 年一月至 2010 年 12 月間，416 位第三期大腸直腸癌病人被納入研究。這些病人全都接受手術治療。根據轉移淋巴結比率，我們用四分位法把所有納入研究的患者分成四組 (轉移淋巴結比率：小於 0.1、0.1 至 0.2、0.2 至 0.4 及 0.4 至 1)。另外針對總摘取淋巴結數少於 12 顆者，再依據轉移淋巴結比率的中位數等分成兩組。然後分析轉移淋巴結比率與總體存活的關係。

**結果** 這些病人年齡的中位數與平均數分為是 64 歲 (介於 24 至 92 歲之間) 與  $63.47 \pm 13.39$  歲。總摘取淋巴結數的中位數為 13 顆 (介於 1 至 68 顆之間)。不論是否有足夠的淋巴結摘除，第三期大腸直腸癌的存活並無差異。四組不同轉移淋巴結比率的五年總體存活率分別為 69.7%、64.5%、62.0% 與 37.6% ( $p$  值小於 0.001)。至於在摘除不足 12 顆淋巴結的病患之中，較高的轉移淋巴結比率也存在較差的預後。

**結論** 對第三期大腸直腸癌的病人而言，應該考慮把轉移淋巴結比率列為重要的預後因子。尤其是摘取不足 12 顆淋巴結的病人，較高的轉移淋巴結比率或許比較低者需要更積極的追蹤計畫。

**關鍵詞** 大腸直腸癌、第三期、淋巴結轉移比率、預後。