

Original Article

# Prognostic Value of the Total Number of Lymph Nodes Retrieved in Stage II and Stage III Colorectal Cancer

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**Key Words**

Colorectal cancer;  
Survival;  
Lymph node

**Purpose.** This study aimed to evaluate the prognostic value of the total number of lymph nodes retrieved from patients with stage II and III colorectal cancer at the Cathay General Hospital and to identify clinicopathological factors that affect the number of retrieved lymph nodes.

**Methods.** Data of patients with stage II and III colorectal cancer who underwent curative resection between 2007 and 2016 were retrospectively retrieved from the colorectal cancer registry database at Cathay General Hospital. Kaplan-Meier curves and log-rank tests were used to analyze overall survival to determine the prognostic value of the total number of retrieved lymph nodes. Clinicopathological factors that affected this number were analyzed using t-tests and analysis of variance. The effect of lymph node retrieval on survival was evaluated using the Cox proportional hazards model after adjusting for significant factors.

**Results.** A total of 746 stage II and III colorectal cancer patients received curative resection at the Cathay General Hospital from January 2007 to December 2016. Retrieval of  $\geq 17$  lymph nodes resulted in significantly improved overall survival. Young age, right-sided tumor, larger tumor size, advanced T status, and poorly differentiated tumors were factors that were significantly associated with higher lymph node number. Total lymph node retrieval therefore has pronounced prognostic value on overall survival after adjusting for significant factors.

**Conclusions.** We recommend that colorectal surgeons perform radical lymph node dissection with an effort to retrieve more lymph nodes and thus improve survival outcomes in patients with stage II and III colorectal cancer.

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Surgical resection is the most common method used to treat non-metastatic colorectal cancer (CRC). Adequate resection includes en bloc resection of the affected bowel segment with negative margins and regional lymph nodes to the extent of origin of blood supply.<sup>1</sup> The status of the lymph node is an important parameter used for staging CRC. The presence

of metastatic lymph nodes differentiates stage III from stage II. The use of adjuvant chemotherapy in stage III CRC patients is clearly established and has a proven survival benefit.<sup>2</sup> However, based on the available data, adjuvant chemotherapy cannot be used as standard therapy for all patients with stage II CRC who have undergone curative resection. Therefore,

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the appropriate administration of adjuvant chemotherapy is dependent on accurate cancer staging. Adequate lymphadenectomy and sufficient lymph node retrieval from the resected specimen are crucial to ensure accuracy in staging and to prevent under-staging.<sup>3</sup> Although the cut-off number of lymph nodes varies across studies, several authors have shown improved survival with an increase in the total number of lymph nodes retrieved.<sup>4-6</sup> The purpose of this study was to evaluate the prognostic value of the total number of retrieved lymph nodes in patients with stage II and III CRC at Cathay General Hospital (CGH) based on different cut-off numbers of lymph nodes and to identify clinicopathological factors that affect the number of lymph nodes retrieved.

## Materials and Methods

This retrospective study used the CGH colorectal cancer registry database. All patients with stage II and III CRC who had undergone curative resection between January 2007 and December 2016 were enrolled in this study. They were treated and followed until the end of December 2017. The mean follow-up time was 56 months ( $\pm 34.5$  months) from diagnosis. Patients with the following criteria were excluded from the study cohort: positive surgical margin, synchronous and metachronous cancer, carcinoid tumor, gastrointestinal stromal tumor, and patients who received neoadjuvant chemoradiotherapy. The clinicopathological data included age, sex, tumor location, tumor size, tumor grade, pathological stage, perineural invasion, and tumor margin. We categorized tumors located in the descending colon, sigmoid colon, rectosigmoid junction, and rectum as left-sided cancers, whereas those located along the line of the cecum to the splenic flexure were classified as right-sided cancers. Overall survival (OS) was defined as the time from the date of surgical resection to the date of death from any cause. OS was analyzed using the Kaplan-Meier method by arranging the cut-off numbers of retrieved lymph nodes in a serially ascending manner from 12 to 22 and compared using the log-rank test. The association between the mean numbers

of retrieved lymph nodes and clinicopathological characteristics was analyzed using Student's t-test or the analysis of variance (ANOVA) test. Multivariate analysis was performed using the Cox proportional-hazard model to examine the effect of lymph node retrieval on survival. All reported *p* values are two-tailed, with significance set at  $p \leq 0.05$ . All statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 20.0.

## Results

From January 2007 to December 2016, a total of 746 patients with stage II and stage III CRC underwent curative resection in our hospital. There were 380 men and 366 women (male:female ratio of 1.04:1). The mean age was 66.0 years, with a standard deviation of 13.7 years. A total of 313 patients had stage II disease and 433 patients had stage III disease. In the stage II group, 33.8% (179/313) of patients received adjuvant chemotherapy as compared to 66.2% (351/433) of patients with stage III CRC (Table 1). A total of 9 patients had local recurrence (1.2%) and 86 pa-

**Table 1.** Patient demographics (N = 746)

Variable	Number of patients (%)
Sex	
Male	380 (50.9%)
Female	366 (49.1%)
Age (years) mean $\pm$ SD	66.0 $\pm$ 13.7
Tumor location	
Cecum	41 (5.5%)
Ascending colon	127 (17.0%)
Hepatic flexure	16 (2.1%)
Transverse colon	61 (8.2%)
Splenic flexure	12 (1.6%)
Descending colon	70 (9.4%)
Sigmoid	204 (27.4%)
Rectosigmoid junction	57 (7.6%)
Rectum	158 (21.2%)
Pathological staging	
II	313 (42.0%)
III	433 (58.0%)
Chemotherapy	
II	179 (33.8%)
III	351 (66.2%)

tients had distant metastasis (11.5%) during the period of follow-up after the surgery (Table 2). When the impact of number of retrieved lymph nodes on OS was assessed, we found that OS was significantly improved when patients had 17 or more lymph nodes retrieved. The OS benefit was most significant when 22 or more lymph nodes were retrieved (81.9% for  $\geq 22$  lymph nodes versus 63.6% for  $< 22$  lymph nodes,  $p < 0.0001$ ) (Fig. 1 and Table 3). We then analyzed the association between clinicopathological factors and number of lymph nodes retrieved. Age ( $p < 0.001$ ), tumor location ( $p < 0.001$ ), tumor size ( $p < 0.001$ ), T status ( $p < 0.001$ ), N status ( $p = 0.018$ ), and tumor grade ( $p = 0.014$ ) were independently associated with the number of lymph nodes retrieved (Table 4). After adjusting for significant factors that affected the number of retrieved lymph nodes, the Cox proportional-hazard model showed that every unit increase in the total number of lymph nodes retrieved decreased the probability of death by 3% (HR = 0.970, 95% CI = 0.955-0.985;  $p < 0.001$ ) (Table 5).

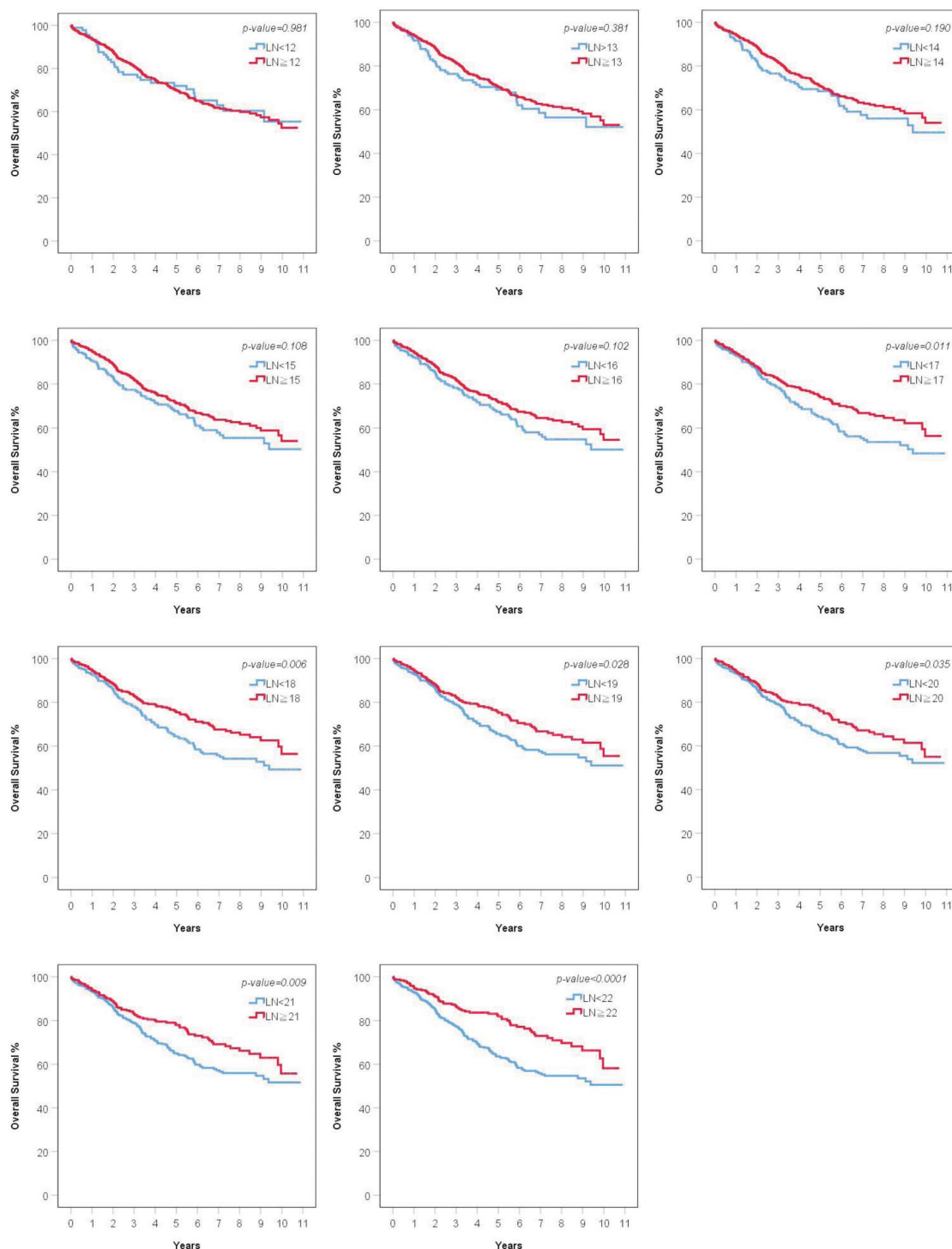
## Discussion

The prognosis of CRC is determined by the pathological stage after curative resection, which in turn is dependent on the status of lymph node retrieval. Aggressive lymph node dissection to retrieve adequate numbers of lymph nodes with en bloc resection of the tumor is one of the main goals of curative resection.<sup>1</sup> However, a study found that only 37% of patients with colon cancer received appropriate levels of lymph node evaluation. Inadequate lymph node retrieval may be due to multiple variables such as the experience and judgement of patients, surgeons, and pathologists.<sup>7</sup> In our study, a lymph node retrieval count of  $\geq 17$  resulted in significantly improved survival and lymph node retrieval count of  $> 22$  or more had the most significant survival benefit. A secondary analysis of patients from the Intergroup Trial INT-0089 showed that an increase in the number of lymph nodes examined was associated with increased survival for patients with both node-negative and node-positive disease.<sup>8</sup> In addition, results from population-based studies

**Table 2.** Patient with local recurrence or distant metastasis (N = 95)

Location	Number of patients
Local recurrence	9
Distant metastasis	86
Liver	23
Lung	25
Peritoneum	10
Bone	7
Distant LN	4
Abdominal wall	2
Ovary	2
Multiple sites	13

show an association between improvement in survival and examination of  $\geq 12$  lymph nodes.<sup>9</sup> One explanation for this finding is that patients who generate a greater immune response to their tumors have more identifiable mesenteric lymph nodes and improved survival over those who do not generate as strong an immune response.<sup>10</sup> Another explanation is that retrieving more lymph nodes allows for more accurate cancer staging and appropriate use of adjuvant chemotherapy for node-positive (stage III) patients.<sup>11</sup> Several studies found that the number of positive lymph nodes increase as the total number of lymph nodes retrieved increases.<sup>8</sup> However, the minimum number of lymph nodes required to improve survival and the optimal number of lymph nodes needed for accurate staging remains controversial, implying that many patients run the risk of being under-staged due to an inadequate number of retrieved lymph nodes. The National Comprehensive Cancer Network (NCCN) and American College of Pathologists (ACP) recommend analyzing a minimum of 12 lymph nodes for accurate staging. Although this number is widely accepted, it was not based on survival studies. In a systematic review of lymph node count, a wide range of cut points was reported in order to assess the number of nodes necessary to have an associated improvement in survival; the findings ranged from 6 nodes to 40 nodes.<sup>12</sup> Peebles et al. reported that 24 and 36 nodes for stages II and III cancers, respectively, as being significant numbers affecting survival.<sup>13</sup> Chandrasinghe et al. reported that a lymph node harvest of 14 or more nodes result in significantly improved survival of



**Fig. 1.** Overall survival (OS) for stages II and III CRC based on serial ascending cut-off number of lymph nodes retrieved. Survival was significantly improved when the cut-off number for retrieved lymph nodes was 17 or more.

stage II and III CRC patients.<sup>14</sup>

The number of lymph nodes retrieved is also affected by many clinicopathological factors. In our

study, young age (< 50 years), right-sided tumor, larger tumor size (≥ 5 cm), advanced T status, and poorly differentiated tumors were the clinicopathological

**Table 3.** Comparison of OS based on ascending cut-off number of lymph nodes

Lymph nodes retrieved	Number of patients	5-year overall survival (%)	<i>p</i> value
LN < 12 vs. LN ≥ 12	89 and 657	71.9 and 69.8	0.981
LN < 13 vs. LN ≥ 13	133 and 613	69.2 and 70.3	0.381
LN < 14 vs. LN ≥ 14	177 and 569	68.5 and 70.7	0.190
LN < 15 vs. LN ≥ 15	234 and 512	67.8 and 71.2	0.108
LN < 16 vs. LN ≥ 16	282 and 464	67.5 and 71.7	0.102
LN < 17 vs. LN ≥ 17	338 and 408	65.2 and 73.9	0.011*
LN < 18 vs. LN ≥ 18	377 and 369	64.5 and 75.4	0.006**
LN < 19 vs. LN ≥ 19	416 and 330	65.6 and 75.2	0.028*
LN < 20 vs. LN ≥ 20	449 and 297	65.8 and 75.9	0.035*
LN < 21 vs. LN ≥ 21	472 and 274	64.9 and 77.9	0.009**
LN < 22 vs. LN ≥ 22	503 and 243	63.6 and 81.9	< 0.0001***

\* *p* value < 0.05; \*\* *p* value < 0.01; \*\*\* *p* value < 0.001. LN, lymph node; OS, overall survival.

**Table 4.** The association between the mean numbers of lymph nodes retrieved and patient clinicopathological characteristics

Variable	Number (%)	Lymph nodes retrieved		<i>p</i> value
		Mean	SD	
Sex				0.348
Male	380 (50.9%)	19.9	10.4	
Female	366 (49.1%)	20.7	12.5	
Age, years				< 0.001***
< 50	86 (11.5%)	23.9	13.0	
50-65	273 (36.6%)	21.8	13.0	
> 65	387 (51.9%)	18.5	9.3	
Tumor location				< 0.001***
Right-sided	257 (34.5%)	23.8	13.4	
Left-sided	489 (65.5%)	18.5	9.7	
Tumor size				< 0.001***
< 5 cm	444 (59.8%)	18.0	10.1	
≥ 5 cm	298 (40.2%)	23.9	12.3	
T status				< 0.001***
pT1	14 (1.9%)	11.00	4.591	
pT2	44 (5.9%)	14.61	5.516	
pT3	565 (75.8%)	20.96	12.111	
pT4	122 (16.4%)	20.40	8.985	
N status				0.018*
pN0	313 (42.0%)	20.97	11.929	
pN1	263 (35.3%)	18.73	11.181	
pN2	170 (22.8%)	21.51	10.538	
Tumor grade				0.014*
Well differentiated	216 (29.0%)	21.56	12.704	
Moderately differentiated	449 (60.3%)	19.35	10.765	
Poorly differentiated	79 (10.6%)	22.48	10.8	
Perineural invasion				0.554
Yes	365 (50.8%)	20.44	10.762	
No	354 (49.2%)	19.95	11.657	
Stage				0.176
II	313 (42.0%)	20.97	11.929	
III	433 (58.0%)	19.82	11.004	

\* *p* value < 0.05; \*\* *p* value < 0.01; \*\*\* *p* value < 0.001.

**Table 5.** The effect of lymph node retrieval on survival using Cox proportional-hazard model

Variable	Hazard ratio	95% CI	<i>p</i> value
Age (years)			
< 50			
50-65	1.113	0.636-1.949	0.707
> 65	3.273	1.934-5.541	< 0.001***
Tumor location			
Left-sided			
Right-sided	0.966	0.719-1.298	0.818
Tumor grade			
Well differentiated			
Moderately differentiated	0.879	0.652-1.185	0.398
Poorly differentiated	1.729	1.143-2.616	0.009**
Tumor size			
< 5 cm			
≥ 5 cm	1.56	1.186-2.052	< 0.001***
T status			
pT1			
pT2	3.039	0.388-23.787	0.290
pT3	5.236	0.717-38.210	0.103
pT4	9.422	1.274-69.675	0.028**
N status			
pN0			
pN1	1.429	1.030-1.981	0.032*
pN2	3.101	2.207-4.358	< 0.001***
Lymph nodes retrieved	0.970	0.955-0.985	< 0.001***

\* *p* value < 0.05; \*\* *p* value < 0.01; \*\*\* *p* value < 0.001.

CI, confidence interval.

factors that were significantly associated with higher lymph node number. Older age has been reported in several studies to be associated with a significant reduction in the number of retrieved lymph nodes. Although the reason remains unclear, it is probable that the size of the lymph nodes decreases with age, as a consequence of which the nodes became more difficult to identify and harvest.<sup>7</sup> It has also been observed that young patients are more likely to undergo more radical lymphadenectomy than older patients.<sup>1</sup> Regarding tumor size, some studies have reported that larger tumors induce more immunological reactions and increase the number of lymph nodes retrieved.<sup>15</sup> Furthermore, T-classification and higher tumor stage were significantly associated with a higher lymph node count. In both the above aspects, our results are supported by previous reports.<sup>1,16</sup> Furthermore, in accordance with our findings, it has been

observed that right-sided tumors have a higher number of retrieved lymph nodes than left-sided tumors. The right-sided colon tends to have a larger and wider mesentery than the left-sided colon. It was seen that the length of the specimen in the right-sided colon was usually longer than that in the left-sided-colon, which had an influence on the number of lymph nodes retrieved.<sup>11,15,17</sup>

There were a few limitations to our study. First, this was a retrospective study without randomization. Second, not all patients received adjuvant chemotherapy, and the impact of adjuvant chemotherapy on OS was not analyzed. Third, the primary outcome of the analysis was OS, not disease-free survival. Finally, stage II and stage III cancer were not separately evaluated.

## Conclusion

Retrieval of ≥ 17 lymph nodes resulted in significantly improved OS in patients with stage II and III CRC in our institution. Young age, right-sided tumor, larger tumor size, advanced T status, and poorly differentiated tumor were the clinicopathological factors that were significantly associated with higher lymph node number. Lymph node retrieval had significant prognostic value on hazard ratio after adjusting for significant factors. We recommend that surgeons perform adequate radical lymph node dissection, such as D3 dissection or complete mesocolic excision, with an effort to improve survival outcomes in patients with stage II and III CRC.

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原 著

## 淋巴結摘除數量對第二期與第三期大腸直腸癌 預後的價值

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**目的** 評估淋巴結摘除數量對第二期與第三期大腸直腸癌患者預後的價值，並確認會影響淋巴結摘除數量的因素。

**方法** 收錄了在 2007 年 1 月到 2016 年 12 月期間，第二期與第三期大腸直腸癌在國泰綜合醫院有接受根治性切除手術的患者，分析其淋巴結摘除數量對總體存活率的預後價值。接著分析影響淋巴結摘除數量的因素，最後在控制顯著因素後利用多變數迴歸分析淋巴結摘除數量是否仍對存活率產生影響。

**結果** 共計 746 位大腸直腸癌患者接受根治性手術，當淋巴結摘除數量超過 17 顆時五年整體存活率會有顯著提升。年輕，右側腫瘤，腫瘤尺寸較大，侵犯深度較深，腫瘤分化差都是淋巴結摘除數量較多的顯著相關因子。當控制顯著因子後，淋巴結摘除數量仍然對整體存活率有顯著性的影響。

**結論** 對於第二期與第三期大腸直腸癌的患者，外科醫師應盡力地施行根治性淋巴結廓清來摘取更多的淋巴結來提升病患的整體存活率。

**關鍵詞** 大腸直腸癌、存活率、淋巴結。