Original Article

The Impact of Lymph Node Harvest and Lymph Node Ratio on Survival in Stage I-III Colon Cancer

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Key Words
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Purpose. Lymph node harvest (LNH) ≥ 12 has been endorsed as a quality measure for patient care by the Bureau of Health Promotion, Department of Health, R.O.C. The aim of this study is to evaluate the impact of LNH and node-positive ratio (LNR) on overall survival in stage I-III colon cancer because an inadequate harvest is common in stage I disease.
Methods. From January 1995 to December 2004, a total of 3564 stage I-III colon cancer patients who underwent curative surgery were identified. All patients were classified according to LNH as either adequate (≥ 12) or inadequate (< 12). The stage III cancer patients were categorized into 3 groups, LNR1 to 3, according to interval: < 0.4, 0.4 to 0.7, and > 0.7.
Results. The mean of LNH in the stage I group was 17.6 (1 to 96). When compared to stage II and III, the node harvest differences were -8.0 and -8.1, respectively ($p < 0.001$). In multivariate analysis, the TNM-stage and tumor location were the independent factors affecting LNH ($p < 0.001$). In univariate analysis, the LNH played a crucial role for 5-year overall survival (OS) in stage II ($p = 0.001$) and III disease ($p = 0.009$), but not in stage I ($p = 0.653$). In multivariate analysis, the LNH was replaced by LNR as an independent predictor in stage III colon cancer ($p < 0.001$).
Conclusion. The impact of LNH on survival was different in different stages of colon cancer. LNR was more crucial than LNH with regard to survival in stage III disease.
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Colon cancer staging is based on the invasion depth, the presence and number of lymph node metastases and distant metastasis. One of the important prognostic factors for patients with colon cancer is the presence of lymph node metastasis. According to the tumor-node-metastasis (TNM) staging system proposed by the American Joint Committee on Cancer (AJCC), the 5-year overall survival declines from 90% to less than 10% with increasing stage from I to IV. The decision to perform adjuvant chemotherapy, which has been shown to improve survival by approximately 30% for patients with node-positive disease,[1] is based on the status of lymph node metastasis. Therefore, the quality of surgical resection and accurate pathological staging play crucial roles in oncologic outcome and prognostic information. If at least

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12 lymph nodes have been harvested or examined and all have been found to be negative, a node-negative staging will be more than 90% accurate.[2] Many previously published studies have reported a recommended minimum number of lymph node harvest (LNH) between 6 and 17, including a recommendation from the College of American Pathologists for a minimum of 12 nodes examined.[3-8] Patients with stage I-III colon cancer may have better survival rates with an increased number of lymph nodes retrievals.[9-11] Therefore, the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) have recommended a minimum 12-node count as a quality indicator in colon cancer surgery.[12] The LNH is a really simple indicator and easily applied in clinical practice. The impact of tumor invasion depth, i.e., T-stage, on the number of nodes needed for adequate staging also needs further investigation, because nearly 40% of patients with stage I colon cancer have had LNH < 12 in our clinical practice. All of these patients were listed as negative or poor quality in our colon cancer surgery in Taiwan and other countries. The aim of this study was to evaluate the correlation between patients' survival rates and current guidelines for node harvest as proposed by the AJCC in different colon cancer stages because it has been treated equally as a quality indicator in management of colon cancer. We wound like to know what is the impact of LNH ≥ 12 on survival and whether it is equal for patients with stage I-III colon cancer and whether an LNH ≥ or < 12 should be treated equally without discrimination for different stages of disease.

Patients and Methods

From January 1995 to December 2004, a total of 3564 patients with histologically confirmed stage I to III colon cancer underwent elective radical resection for cancer cure at Chung Gung Memorial Hospital. This data permitted a retrospective analysis with a prospectively maintained data collection in a single institution. All patients underwent routine hemogram, carcinoembryonic antigen (CEA) tests, colonofiberoscopy, chest X-ray, abdominal computer tomography (CT) and/or ultrasound of the liver preoperatively. Post radical resection of colon cancer, all patients were followed up by physical examination, CEA follow-up every 3-6 months, regular chest X-ray, colonofiberoscopy every 1-3 years, abdominal ultrasound and/or CT of the chest and abdomen every year. In order to decrease variability in this study, all cases of rectal cancer, any malignancy other than colon adenocarcinoma, emergent surgery, surgery for recurrent adenocarcinoma, and metachronous colon cancer were excluded. Tumour location, histology and differentiation, surgical procedure, and the numbers of harvested and metastatic lymph nodes were evaluated for each patient. The surgical resection included resection of the affected segment of the colon and en block resection of associated draining lymph nodes to the original level of the primary blood supply to the colonic segment. The specimen was fixed in 10% formalin solution and then processed for paraffin block. Two pathologists identified the tumor and nodes by visual inspection and palpation. Immunohistochemistry stain and genetic methods were not routinely used. All patients with colon cancer were staged according to the AJCC's sixth edition TNM staging system. The number of LNH ≥ 12 was defined as an adequate lymphadenectomy based on AJCC guidelines. Adjuvant chemotherapy was performed for some patients who had stage II colon cancer with several risk factors (perforation, cancer obstruction and T4 stage in the TNM system) and for patients with stage III colon cancer if there was no contraindication. Adjuvant chemotherapy was one of the factors which affecting patient's survival rates. Therefore, subgroups classified by adjuvant chemotherapy in stage II colon cancer were analyzed in our study to understand the influence of node harvest. Recent studies have suggested that metastatic lymph node ratio (LNR) may decrease stage migration and is also a good prognostic factors in patients with stage III colon cancer.[13-15] The cutoff value of the LNR in colon cancer varies, with no definite consensus currently available. In our present study, patients with stage III colon cancer were categorized into ten groups by every 0.1 interval of LNR. The cutoff points 0.4 and 0.7 were chosen because there was no statistical difference in survival among

patients with an LNR ranging from 0.0 to 0.4 and patients with an LNR ranging from 0.4 to 0.7. Finally, the stage III colon cancer patients were categorized into LNR group 1 (LNR < 0.4), 2 (0.4 ≤ LNR < 0.7), and 3 (LNR ≥ 0.7). All patients in this study were followed-up until death or December 2009. The median follow-up period for surviving patients with regular follow-up program was 164 months and periods ranged between 9 and 180 months. The end-point of long-term outcome was 5-year overall survival (OS).

Statistical analysis

All analyses were performed using the Statistical Package for the Social Sciences, release 11.0 (SPSS Inc. Chicago, IL). Survival curves were produced using the Kaplan-Meier method and then compared utilizing the log-rank test. OS was calculated as the number of years from primary surgery to the date of death. The two arms were compared by Pearson chi-square test and independent-samples *t*-tests to detect any difference in proportions and means. A Cox hazard regression model was used for multivariate analysis. All *p* values were two-tailed and considered statistically significant if < 0.05.

Results

Clinicopathologic features in patients with stage I, II and III colon cancer

The study population consisted of 3564 patients (1855 men) with colon cancers from stage I to III. The mean age in our study was 62.8 (range, 20-100). Table 1 shows the differences in clinicopathologic features of the patients with stage I-III colon cancer. Compared with other groups, stage I patients were less likely to have proximal colon cancer (27.6%), less likely to have tumor size ≥ 5 cm and CEA level ≥ 5 ng/mL (p < 0.001). The mean and median numbers of LNH in stage I colon cancer were 17.6 and 14, lower than other stages. When stage II and III were compared with stage I colon cancer, the differences of node harvests were 8.0 and 8.1, respectively (p < 0.001). Only 59.1% of patients with stage I colon cancer had adequate LNH (node harvest or examined ≥ 12), which was also less than other stages (p < 0.001).

Analysis of various factors for adequate LNH

Table 2 outlines the possible factors affecting LNH based on uni- and multivariate analysis. 59.1%, 84.7% and 85.2% of patients with stage I, II and III colon cancer had adequate nodes harvested or examined in their colon cancer surgery. In univariate analysis by logistic regression model, patients with stage I colon cancer, distal colon cancer, better histology grade (well differentiated vs. poorly differentiated adenocarcinoma), age ≥ 50 years, and tumor size < 5 cm were less likely to make adequate LNH (p < 0.001). There was a trend to reach adequate nodes harvested or examined when patients had higher CEA levels (CEA ≥ 5 ng/mL). In multivariate analysis, the TNM stage and tumor location were the independent factors affecting LNH (p < 0.001).

Survival analyses stratified by LNH in stage I-III colon cancer

As shown in Fig. 1, no statistical difference was observed for 5-year OS in patients with stage I colon cancer when stratified by LNH (p = 0.653). However, the LNH played a crucial role for 5-year OS in stage II (p = 0.001) and III disease (p = 0.009). In our study, 74.7% of stage III colon cancer patients received adjuvant chemotherapy. Chemotherapy was also performed for patients who had stage II colon cancer with risk factors. In order to draw proper conclusions about patients at stage II, knowledge regarding whether adjuvant chemotherapy was equally distributed between both subgroups (LNH ≥ 12 and LNH < 12) is important. In the stage II colon cancer group, 290 of 1332 patients with adequate LNH (21.8%) and 53 of 255 patients with inadequate LNH (20.8%) had received adjuvant chemotherapy, (p = 0.295, data not shown; 83 patients with missing data in adjuvant chemotherapy). When patients with stage II colon cancer were classified by adjuvant chemotherapy, the LNH

Table 1. Percentage of patients within stage I-III category

	Stage I (n = 450)	Stage II (n = 1670)	Stage III (n = 1444)	*p* value
Age at diagnosis (yr)				0.022
< 50	15.3%	16.6%	19.4%	
50-75	69.6%	64.1%	61.8%	
> 75	15.1%	19.3%	18.8%	
Gender				0.472
Male	54.7%	51.9%	51.4%	
Tumor locations				< 0.001
Proximal colon	27.6%	42.9%	37.4%	
Tumor size				< 0.001
WID ≥ 5 cm	9.6%	49.6%	34.8%	
LEN ≥ 5 cm	8.7%	40.1%	29.4%	
Histology grade				< 0.001
WD	44.5%	16%	10.7%	
MD	53.7%	77.1%	81.5%	
PD	1.8%	6.9%	7.8%	
CEA level				< 0.001
≥ 5 ng/mL	12.6%	36.2%	43.4%	
ELN, mean/median (min, max)	17.6/14 (1, 96)	25.6/22 (1, 168)	25.8/22 (2, 147)	< 0.001
≥ 12 nodes harvest	59.1%	84.7%	85.2%	< 0.001
Difference of node harvest	Reference	8.0	8.1	< 0.001
Adjuvant C/T	No data	21.6%	74.7%	

Table 2. Uni- and multivariate for adequate lymph node recovery (≥ 12 LNs) by binary logistic regression model

Variable	Category	OR, UV	*p* value & 95% CI	OR, MV	*p* value & 95% CI
Stage	I	Reference		Reference	
	II	3.821	$p < 0.001$, 3.035-4.810	2.371	$p < 0.001$, 1.818-3.092
	III	3.998	$p < 0.001$, 3.152-5.070	2.899	$p < 0.001$, 2.210-3.803
Tumor location	Proximal	3.558	$p < 0.001$, 2.873-4.405	3.175	$p < 0.001$, 2.528-3.986
	Distal	Reference		Reference	
CEA (ng/mL)	< 5	0.823	$p = 0.038$, 0.685-0.989	1.022	$p = 0.828$, 0.836-1.250
	≥ 5	Reference		Reference	
Histology grade	WD	0.329	$p < 0.001$, 0.214-0.507	0.782	$p = 0.316$, 0.484-1.264
	MD	0.678	$p = 0.061$, 0.451-1.018	1.289	$p = 0.265$, 0.825-2.015
	PD	Reference		Reference	
WID (cm)	< 5	0.407	$p < 0.001$, 0.334-0.496	0.789	$p = 0.055$, 0.619-1.055
	≥ 5	Reference		Reference	
LEN (cm)	< 5	0.342	$p < 0.001$, 0.273-0.428	0.481	$p < 0.001$, 0.369-0.628
	≥ 5	Reference		Reference	
Age	< 50	Reference		Reference	
	50-75	0.519	$p < 0.001$, 0.396-0.680	0.566	$p < 0.001$, 0.424-0.756
	> 75	0.436	$p < 0.001$, 0.320-0.595	0.421	$p < 0.001$, 0.302-0.589

still served as a prognostic factor for 5-year OS (Fig. 2). Multivariate analysis by time-dependent Cox regression was used to further identify the confounding factors that might influence the long term OS. Table 3 shows the result of multivariate analysis for OS in different stage colon cancer (from stage I to III). The CEA level was a significant predictor from stage I to III disease. Other than age, it was the best prognostic predictor in stage I disease ($p = 0.020$). In multivariate analysis, LNH ≥ 12 was a positive predictor only for

stage II disease ($p = 0.022$), although it was a significant predictor in stage II and III colon cancer in the survival curve by Kaplan-Meier method and the log-rank test (Figs. 1 and 2).

Survival according to LNR in patients with stage III colon cancer

In patients with stage III colon cancer, a higher LNR was significantly associated with reduced OS; when patients with stage III colon cancer were stratified with ELN, the LNR groups 1 (LNR < 0.4), 2 (0.4 ≤ LNR < 0.7), and 3 (LNR ≥ 0.7) had 64%, 57% and 33%, respectively, of 5-year OS if they had ELN < 12 and the LNR groups 1, 2, and 3 had 68%, 45% and 0%, respectively, of 5-year OS if they had ELN ≥ 12 (Fig. 3, $p = 0.044$ and $p < 0.001$, respectively). The survival rate of stage III colon cancer patients with LNH ≥ 12 was significantly worse for those with higher LNR strata. In the LNH ≥ 12 subgroup, patients with LNR ≥ 0.7 all died owing to distant metastasis or local recurrence within 5 years. The LNR was also confirmed in multivariate analysis (Table 3) to show increased hazard ratio for OS in patients in LNR group 2 (HR 1.808, CI 1.367-2.391) and 3 (HR 4.197, CI 2.578-6.833). The ELN ≥ 12 played no more crucial role if the confounding factor, LNR, was included in multivariate analysis for OS in stage III colon cancer.

Discussion

The examination of 12 lymph nodes for adequate staging of colorectal cancer is being considered as a quality measure. The minimum versus the optimal number of nodes should be factored to assess the confidence of staging. Joseph et al. previously estimated the probability of correctly determining lymph node status.[16] The number of LNH required to accurately predict node negative was 36 and 39 to reach 50%

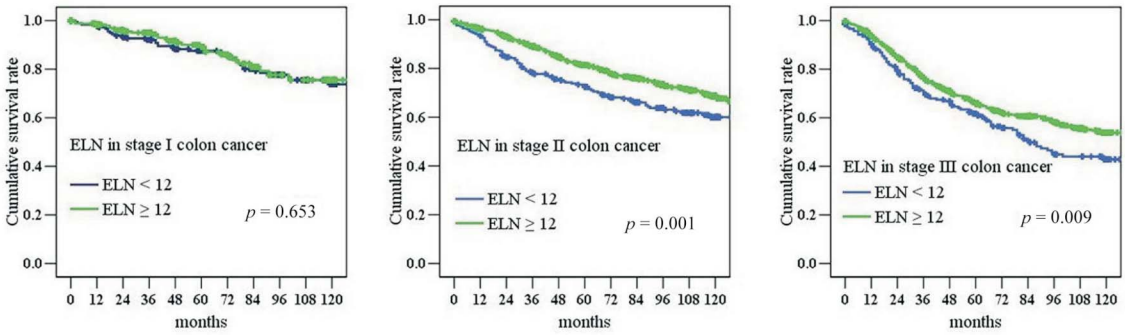

Fig. 1. No statistical difference was observed for 5-year OS in patients with stage I colon cancer when stratified by LNH ($p = 0.653$). However, the LNH played a crucial role for 5-year OS in stage II ($p = 0.001$) and III disease ($p = 0.009$).

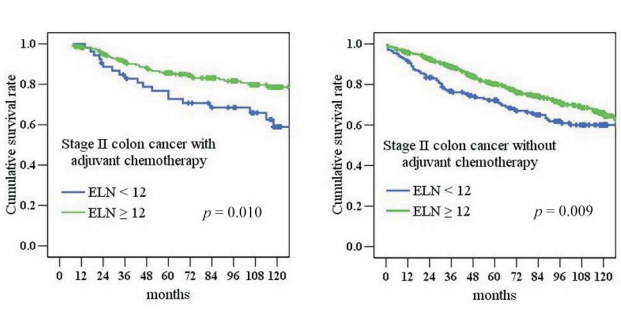

Fig. 2. When patients with stage II colon cancer were classified by adjuvant chemotherapy, the LNH still served as a prognostic factor for 5-year OS.

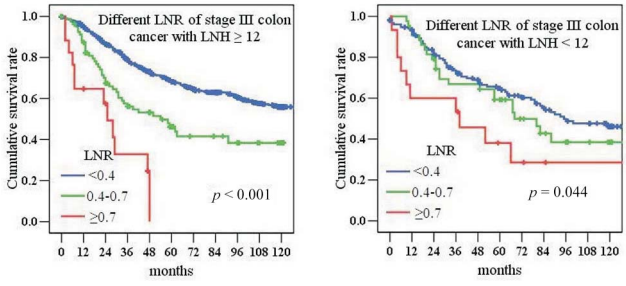

Fig. 3. In stage III colon cancer, a higher LNR was significantly associated with reduced OS, in both groups of LNH ≥ 12 and LNH < 12 ($p = 0.044$ and $p < 0.001$, respectively).

Table 3. Cox multivariate models for overall survival in stage I-III colon cancer

Stage	Category		HR	95% CI	*p* value
Stage I	CEA	< 5	0.495	0.274-0.896	0.020
(n = 450)		≥ 5	Reference		
	Histology grade	WD	2.042	0.269-15.516	0.822
		MD	2.477	0.330-18.598	0.378
		PD	Reference		
	ELN	≥ 12	0.849	0.500-1.440	0.543
		< 12	Reference		
	Gender	Female	0.779	0.464-1.307	0.344
		Male	Reference		
	Age (ys)	< 50	0.053	0.012-0.228	< 0.001
		50-75	0.235	0.135-0.410	< 0.001
		> 75	Reference		
Stage II	CEA	< 5	0.599	0.483-0.742	< 0.001
(n = 1670)		≥ 5	Reference		
	Histology grade	WD	0.687	0.424-1.112	0.126
		MD	0.624	0.406-0.960	0.032
		PD	Reference		
	ELN	≥ 12	0.749	0.585-0.960	0.022
		< 12	Reference		
	Gender	Female	0.740	0.596-0.919	0.006
		Male	Reference		
	Age (ys)	< 50	0.225	0.149-0.340	< 0.001
		50-75	0.369	0.291-0.467	< 0.001
		> 75	Reference		
	Adjuvant C/T	Yes	0.845	0.627-1.139	0.269
		No	Reference		
Stage III	CEA	< 5	0.561	0.463-0.679	< 0.001
(n = 1444)		≥ 5	Reference		
	Histology grade	WD	0.576	0.378-0.878	0.010
		MD	0.640	0.460-0.890	0.008
		PD	Reference		
	ELN	= 12	1.086	0.849-1.388	0.511
		< 12	Reference		
	LNR	LNR < 0.4	Reference		
		0.4 ≤ LNR < 0.7	1.808	1.367-2.391	< 0.001
		LNR ≥ 0.7	4.197	2.578-6.833	< 0.001
	Gender	Female	0.955	0.792-1.152	0.630
		Male	Reference		
	Age (ys)	< 50	0.493	0.359-0.677	< 0.001
		50-75	0.585	0.465-0.736	< 0.001
		> 75	Reference		
	Adjuvant C/T	Yes	0.556	0.453-0.684	< 0.001
		No	Reference		

probability in T1/2 proximal and distal colon cancer, and the number to accurately predict node negative was significant fewer in T3 and T4 lesions, according to their study (29 and 23 to reach 50% probability in T3 proximal and distal colon cancer; less than 10 to reach 50% probability in T4 colon cancer). Generally, the number of LNH over 35 is not frequently seen by a surgeon or pathologist; Chen previously reported that the resection of at least 15 nodes was associated with prolonged survival in all stage categories examined. However, they also agreed that surgeons and pathologists in their study did not generally succeed in meet-

ing minimum nodal staging requirements.[10] More lymph node count is usually associated with higher disease stage.[17] In the study by Joseph et al., more nodes were needed in T1/2 colon cancer to accurately predict node negative but it was more difficult in T1/2 than in T3/4. Our present study compared the impact of LNH ≥ 12 on survival from stage I to III colon cancer and analyzed the factors related to nodes harvested and examined. Multivariate analysis of our study (Table 2) revealed that tumor location, colon cancer stage and size (length) were independent factors affecting nodes harvested. Patients with stage I colon cancer had smaller tumor size and more frequency of distal colon cancer; they were also less likely to have high CEA level (≥ 5 ng/mL) and to make adequate LNH. Our results were similar to the conclusions in many studies. Previous studies have reported that lymph node count or harvest is positively associated with specimen length, right side colon location, large tumor size, and higher disease stage.[18-20] The surgeon's decision is one of the factors influencing LNH because limited resection may be performed for an early colon cancer. Kobayashi et al presented the conclusion for optimal lymph node dissection in clinical T1 and T2 colorectal cancer.[21] Paracolorectal lymph node dissection may be optimal for patients with clinical T1 node negative colorectal cancer, because over 98% of clinical T1 colorectal cancer patients had node negative or limited paracolorectal lymph node metastasis. Dissection of the regional nodes along the named vessels may be optimal for patients with clinical T2 and node negative status.

The observed difference in survival rates for patients with node negative colon cancer is likely related to inadequate adjuvant chemotherapy following understaging. In specimens with inadequate LNH, lymph node metastases may be overlooked and the stage falsely classified as stage I or II disease. When a larger number of nodes are examined, the risk of missing a positive node may be decreased. This has been proven in a series of 35,787 cases of stage II colon cancer from the National Cancer Data Base, in which the 5-year survival rate for stage II colon cancer varied from 64%, if only one or two lymph nodes were examined, to 86% if more than 25 lymph nodes were examined.[22] In the Kaplan-Meier method and log-rank test, our present study showed that the LNH ≥ 12 played a crucial role for OS in stage II and III disease; when patients with stage II colon cancer were stratified by adjuvant chemotherapy, the LNH still served as a prognostic factor for OS in our study. About 80% of patients with stage II colon cancer did not receive the adjuvant chemotherapy in our present study and the observed difference in survival could have resulted from stage migration and undertreatment. No statistical difference was observed with regard to OS in patients with stage I colon cancer classified as LNH ≥ 12. We should consider the possibility of stage migration in stage I colon cancer (T1 and 2) similar to stage II disease (T3 and 4). Controversy persists over the minimum number of lymph nodes required to stage early colon cancer. Maggard et al.[23] discussed the impact of LNH in patients with stage I colon cancer. Among patients with T1 and T2 node-negative colon cancers, better survival outcomes were observed in patients with ≥ 4 and ≥ 10 nodes harvested (both of $p = 0.008$). Metze et al.[24] provided an argument against the conclusion by Maggard et al. They thought that the probability of diagnosing the presence of at least one LN metastasis decreased continuously when fewer nodes are harvested. When 4 and 10 nodes were harvested in T1 and T2 node-negative colon cancers, the mean probability of diagnosing at least one lymph node metastasis is 26.5% and 74% in T1 and T2 lesions. Based on current guidelines of AJCC and the simulation study by Metze et al., the mean percentage of correct node staging is near 70% in the T1 stage and 80% in T2 colon if LNH ≥ 12 exists. An LNH ≥ 12 really generates a less understaging condition in stage I colon cancer. In other words, advanced T-stage has a strong correlation with the lymph node metastasis. The risk of lymph node metastasis in T1 and T2 colorectal cancer is relatively low, and approximately 13% of T1 and 14.5% of T2 tumors have node-positive disease.[25,26] In our present study, 17.2% of T1 and T2 patients had lymph node metastases, accounting for 6.5% of stage III colon cancer. The benefit of examining greater numbers of nodes may lessen in stage I colon cancer due to the low rate of lymph node metastases; otherwise, increasing the number of lymph no-

des over a certain point may offer a survival benefit to the majority of patients with stage II colon cancer. Studies of survival in various stages of colon cancer (most of the data were stage II) have generally concluded that below a certain point, the LNH is a poor prognostic indicator. The number of nodes examined varied from 7 to 30 nodes to achieve a significant influence on survival.[16,27,28] Our study demonstrated that the current guidelines by AJCC, LNH ≥ 12, could be an adequate predictor for survival in stage II colon cancer but the impact of LNH ≥ 12 was not equal to stage I or III colon cancer in multivariate analysis.

Similar to previous reports, we found that an LNH ≥ 12 had statistical significance with regard to survival rates of stage III colon cancer by the Kaplan-Meier method and log-rank test. However, an LNH ≥ 12 was not an independent predictor for survival when the LNR was a confounding factor. In multivariate analysis for overall survival, CEA level, adjuvant chemotherapy, LNR, age, histology grade were the confounding factors influencing long term survival in stage III colon cancer in our present study. LNR was a prognostic factor for both patients with LNH < 12 and LNH ≥ 12. The survival of those with stage III colon cancer and LNH ≥ 12 was worse on univariate analysis in the higher LNR strata than for those with LNH < 12. The value of LNR could be maximized when adequate nodal sampling was achieved. In our study, the LNR appeared to stratify prognosis best in patients with LNH ≥ 12 (Table 4). Our result was similar to the findings of Chen et al.,[29] who previously described that a "denominator effect" could be inplicated in the different node sampling group for survival of stage III colon cancer. In their results, when the LNRs were 25-49%, 50-99% and 100%, the median survival rate was worse in those with LNH ≥ 12 than those with LNH < 12. A "small denominator effect" in LNH < 12 group would result in an artificial inflation of the LNR. Conversely, a "large denominator effect" in the LNH ≥ 12 group may be staged as N2 or more progressive lymph node metastases. Our data also complemented the conclusions of previous published studies. Lee and colleagues demonstrated that LNR is an independent predictor of survival.[14] Berger et al. revealed that LNR was a significant predictor among patients with 10 to 15 and 15 or more nodes harvested,

Table 4. Cox Multivariate models for overall survival in stage III colon cancer stratified by node harvest

Category	LNH ≥ 12, HR (95% CI)	*p* value	LNH <12, HR (95% CI)	*p* value
CEA				
< 5	0.564 (0.456-0.698)	< 0.001	0.567 (0.366-0.880)	0.011
≥ 5	Reference		Reference	
Histology grade				
WD	0.589 (0.366-0.948)	0.029	0.530 (0.210-1.339)	0.179
MD	0.634 (0.438-0.917)	0.015	0.670 (0.320-1.405)	0.290
PD	Reference		Reference	
LNR				
LNR < 0.4	Reference		Reference	
0.4 ≤ LNR < 0.7	2.067 (1.485-2.878)	< 0.001	1.359 (0.814-2.268)	0.241
LNR ≥ 0.7	5.456 (2.862-10.401)	< 0.001	3.349 (1.556-7.207)	0.002
Gender				
Female	1.014 (0.821-1.252)	0.897	0.730 (0.471-1.131)	0.159
Male	Reference		Reference	
Age (ys)				
< 50	0.494 (0.349-0.698)	< 0.001	0.423 (0.180-0.996)	0.049
50-75	0.568 (0.438-0.736)	< 0.001	0.650 (0.391-1.079)	0.096
> 75	Reference		Reference	
Adjuvant C/T				
Yes	0.533 (0.423-0.671)	< 0.001	0.566 (0.345-0.928)	0.024
No	Reference		Reference	

but not for those with less than 10 nodes harvested.[13] The cutoff value of LNR varied significantly in various studies, and our classification was similar to a study by Rosenberg et al.,[30] who suggested LNR cutoffs of 17%, 41% and 69% with excellent significance. Generally, the LNR has been accepted as a prognostic factor to estimate prognosis independent of total number of nodes examined in stage III colon cancer. LNR also appears to be equal or better than AJCC N stage and total nodes harvested in stage III colon adenocarcinoma.

Although the data collection was performed in a single center, this study still had several limitations. The case number was not large if it was compared with many other reports with data collection from Surveillance, Epidemiology, and End Results (SEER). We all know that the node harvest following colon cancer resection is dependent not only on the surgical resection, but also on the recovery from specimen. One report showed no difference in lymph node harvest between specialist colorectal surgeons; however, there was a significant difference between reporting pathologists ($p < 0.001$).[17] The influence of different pathologists and surgeons were a possible source of bias in our study, but this may be reduced since all patients were treated in a single center and under similar treatment criteria.

Conclusion

Our work demonstrated a strong relationship between survival rates and LNH for patients with stage II colon cancer. LNH ≥ 12 was an independent predictor for survival in this group, but not for stage I and III colon cancer. The overall survival in curative colon cancer surgery is not equally influenced by the total number of lymph node harvest (LNH). Minimal influence of LNH in stage I colon cancer is found. Lymph node ratio is a prognostic factor stronger than LHN for overall survival in curative resected stage III colon cancer. A cancer resection should be performed routinely for all colon cancer patients, but stage I colon cancer patients with less than 12 nodes harvested should not be classified with a negative predictor and receive inadequate treatment quality. More clinical practice and research may be needed for proving predictors in stage I colon cancer.

What is New in this Paper?

In this single institution study, we confirm that the overall survival in curative colon cancer surgery is not equally influenced by the total number of lymph node harvest (LNH). Minimal influence of LNH in stage I colon cancer is found. Lymph node ratio is a prognostic factor stronger than LHN for overall survival in curative resected stage III colon cancer.

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原　著

淋巴結摘取數目及轉移淋巴結比率對第一至三期結腸惡性腫瘤病患的影響

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目的　淋巴結摘取數目 ≥ 12 已被衛生署國民健康局視為治療大腸癌病患品質的指標之一。然而在第一期患者，臨床上淋巴結摘取數目經常無法達到標準，本研究的目的在於評估淋巴結摘取數目及轉移淋巴結比率對第一至三期結腸惡性腫瘤病患的存活影響。

方法　從 1995 年 1 月至 2004 年 12 月間，共 3564 病患因第一至第三期結腸癌接受根治性手術。第一至三期病患依淋巴結摘取數目 (≥ 12 或 < 12) 及第三期病患依轉移淋巴結比率 (< 0.4, 0.4 至 0.7, 及 ≥ 0.7) 進行存活影響分析。

結果　第二及第三期患者的平均淋巴結摘取數目與第一期患者 (平均為 17.6，範圍 1 至 96) 比較，差異為 8.0 與 8.1 (p < 0.001)。在多變數分析中，TNM 分期與腫瘤位置是影響淋巴結摘取數目是否 ≥ 12 的獨立因子 (p < 0.001)。在單變數分析中，淋巴結摘取數目 ≥ 12 對第二期與第三期結腸癌患者的 5 年存活率具有決定性的影響 (p = 0.001 與 p = 0.009)；淋巴結摘取數目 ≥ 12 與否對第一期病患則不具影響力 (p = 0.653)。在多變數分析中，淋巴結摘取數目對第三期結腸癌患者 5 年存活率的影響則被轉移淋巴結比率所取代 (p < 0.001)。

結論　淋巴結摘取數目 ≥ 12 對 5 年存活率的影響在不同期別的結腸癌有不同的影響力。在第三期結腸癌患者，轉移淋巴結比率比淋巴結摘取數目更具有決定性的影響。

關鍵詞　淋巴結摘取、淋巴轉移比率、存活率、第一至第三期結腸惡性腫瘤。