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Original Article

Stage II colon cancer patients with no more than 6 lymph nodes harvested may be understaged and should be considered for adjuvant chemotherapy: a retrospective analysis of 87,090 patients in the SEER database

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Abstract: Background: We suspect that patients with stage II colon cancer with only a few lymph nodes harvested (LNH) may be understaged. Therefore, we hypothesize that stage II patients with a few LNH have a poorer cancer specific-survival (CSS) compared with N1a (stage III) patients with adequate LNH. Methods: We analyzed patients with stage II or N1a (stage III) colon cancer based on data from the US Surveillance, Epidemiology, and End Results (SEER) database. Survival was analyzed using the Kaplan-Meier method, and the log-rank test was performed to identify differences. A multivariate Cox proportional hazards model was used to analyze the risk factors. Results: In all, 87,090 patients (66,820 stage II patients and 20,270 N1a patients) from the SEER database were included in the analysis. We selected no more than 6 LNH to be "a few" LNH in stage II patients and at least 12 LNH as adequate LNH in N1a (stage III) patients. A Kaplan-Meier analysis suggested that stage II patients with ≤6 LNH had a poorer CSS than the N1a (stage III) patients with ≥12 LNH (P<0.001). A multivariate analysis showed that compared with stage II patients with ≤6 LNH, N1a (stage III) patients with ≥12 LNH were more likely to exhibit a better CSS (HR 0.839, 95% CI 0.793-0.887, P<0.001). Conclusions: Stage II colon cancer patients with no more than 6 lymph nodes harvested may be understaged and should be considered for adjuvant chemotherapy.

Keywords: Colon cancer, lymph node, stage II, stage migration

Introduction

Stage II colon cancer, which is a lymph node-negative disease, comprises one third of all colon cancer cases in western countries [1]. The lymph node status is still an important prognostic factor despite the node-negative diagnosis in this disease. The number of lymph nodes harvested (LNH) has been reported to be significantly associated with survival outcomes of patients with stage II disease [2-4]. Peeples et al. [2] found that in patients with stage II disease, the 5-year survival rates were 52% (1-11 lymph nodes), 63% (≥12 lymph nodes), 64% (≥18 lymph nodes), and 68% (≥24 lymph nodes) with P<0.01 for all groups. As recommended by the American National Comprehensive Cancer Network (NCCN) guidelines, at least 12 lymph nodes should be retrieved to adequately stage colon cancer patients [5, 6]. Okada et al. [7] reported that in patients with 12 or more retrieved lymph nodes, the overall survival rate was 84% at 5 years and 76% at 8 years, which was significantly better than the corresponding rates in patients with fewer than 12 retrieved lymph nodes (P=0.004). For stage II colon cancer patients with fewer than 12 lymph nodes harvested, the survival rates decreased as the number of LNH decreased [8-10].

Stage migration is used to describe the phenomenon of understaging, which occurs when an inadequate number of lymph nodes is examined in patients with colorectal cancer [11]. Some researchers have suggested that sometimes positive lymph nodes in a surgical specimen were missed, and as a result, such patients

Table 1. Demographics of patients with stage II and N1a (stage III) colon cancer [N (%)]

Characteristics	Total (N=87,090)	Stage II (N=66,820)	N1a (Stage III) (N=20,270)	*P* value
Sex				0.793
Male	40,158 (46.1)	30,795 (46.1)	9363 (46.2)	
Female	46,932 (53.9)	36,025 (53.9)	10,907 (53.8)	
Year of diagnosis				<0.001
1988-1995	16,257 (18.7)	12,803 (19.2)	3454 (17.0)	
1996-2003	30,980 (35.6)	23,952 (35.8)	7028 (34.7)	
2004-2011	39,853 (45.7)	30,065 (45.0)	9788 (48.3)	
Age at diagnosis (yr)				<0.001
≤60	20,889 (24.0)	15,240 (22.8)	5649 (27.9)	
>60	66,201 (76.0)	51,580 (77.2)	14,621 (72.1)	
Primary site				<0.001
Right colon	51,412 (59.0)	40,199 (60.2)	11,213 (55.3)	
Left colon	35,678 (41.0)	26,621 (39.8)	9057 (44.7)	
Race				<0.001
White	71,052 (81.6)	55,037 (82.4)	16,015 (79.0)	
Black	9287 (10.7)	6815 (10.2)	2472 (12.2)	
Other*	6751 (7.7)	4968 (7.4)	1783 (8.8)	
Pathology grade				<0.001
High	6601 (7.6)	5262 (7.8)	1339 (6.6)	
Moderate	64,882 (74.5)	50,166 (75.1)	14,716 (72.6)	
Poor	14,799 (17.0)	10,808 (16.2)	3991 (19.7)	
Undifferentiated	808 (0.9)	584 (0.9)	224 (1.1)	

*Includes Native American, Asian, Pacific Islander and Unknown.

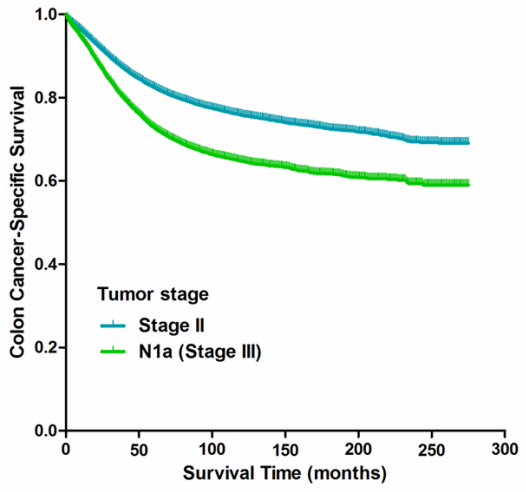

Figure 1. Kaplan-Meier curves for stage II and N1a (stage III) colon cancer patients.

were falsely identified as "node-negative" because of an inadequate number of lymph nodes harvested. These researchers have therefore called for an increased number of retrieved lymph nodes to decrease the risk of missing a metastatic node [5, 12-15]. Sarli et al. [16] reported that the 5-year survival rate for stage III colorectal cancer patients with only 1-3 positive lymph nodes (52.6%) was comparable with that of stage II patients who had nine or fewer lymph nodes retrieved (51.3%). Mario et al. [17] found that stage B patients with fewer than 7 lymph nodes examined had both a shorter overall survival (P< 001) and a shorter relapse-free survival (P=0.002) than the other stage B patients; they concluded that stage B patients with a small number of retrieved nodes may be understaged.

Accordingly, we hypothesized that patients with stage II colon cancer with a few LNH would be understaged. Colon cancer patients with lymph node metastasis (stage III) typically exhibit a poor survival [10, 18]. Cases with solitary lymph node metastasis (N1a) comprise a distinct subset of patients with stage III disease with a superior survival [19]. To address this hypothesis, colon cancer patients with stage II or N1a (stage III) disease from the Surveillance, Epidemiology, and End Results (SEER) database were analyzed, and the cancer specific-survival (CSS) of stage II patients with a few LNH was compared with that of N1a (stage III) patients with adequate LNH.

Methods

Patient selection

The SEER program (http://seer.cancer.gov/), sponsored by the National Cancer Institute, is a population-based cancer registry that collects and publishes cancer incidence and survival data. It comprises 18 population-based cancer registries that cover approximately 26% of the

Table 2. Univariate and multivariate survival analyses of patients with stage II and N1a (stage III) colon cancer

Variable	Univariate analysis		Multivariate analysis		
	5-year CSS	*P* value	HR	95% CI	*P* value
Sex		0.025			<0.001
Male	78.2%		1	Reference	
Female	78.8%		0.919	0.892-0.947	
Year of diagnosis		<0.001			<0.001
1988-1995	74.6%		1	Reference	
1996-2003	77.8%		0.884	0.852-0.918	
2004-2011	81.6%		0.740	0.710-0.771	
Race		<0.001			<0.001
White	78.7%		1	Reference	
Black	73.6%		1.345	1.285-1.409	
Other*	82.7%		0.792	0.745-0.843	
Age at diagnosis (yr)		<0.001			<0.001
≤60	86.0%		1	Reference	
>60	76.1%		1.941	1.864-2.022	
Primary site		<0.001			<0.001
Right colon	79.3%		1	Reference	
Left colon	77.5%		1.176	1.141-1.213	
Pathology grade		<0.001			<0.001
High	80.0%		1	Reference	
Moderate	79.4%		1.027	0.969-1.088	
Poor	74.9%		1.290	1.209-1.376	
Undifferentiated	77.1%		1.293	1.086-1.539	
Tumor stage		<0.001			<0.001
Stage II	80.7%		1	Reference	
N1a (Stage III)	71.5%		1.528	1.479-1.579	

LNH=Number of lymph nodes harvested, HR=Hazard ratio, CI=Confidence interval.
*Includes Native American, Asian, Pacific Islander and Unknown.

US population. We extracted cases of invasive colon cancer that presented from January 1988 to December 2011 from the SEER database (http://seer.cancer.gov, April 2013 release). Cases that met the following inclusion criteria were included: (1) adenocarcinoma of the colon; (2) AJCC stage II or stage III with solitary lymph node metastasis (N1a); (3) known depth of invasion and lymph node status; (4) colon cancer surgically resected with a pathology specimen; (5) pathologically confirmed diagnosis; (6) known survival time and cause of death; and (7) colon cancer as the first and only malignant tumor. Patients who underwent preoperative radiotherapy and those whose tumors were only locally excised were excluded. We received permission to access the data in the SEER database for research-only purposes. The Fudan University Shanghai Cancer Center Ethical Committee and Institutional Review Board reviewed and approved the research protocol.

Outcome measures

Data on the following variables were derived from the SEER database: sex, race, age at diagnosis (cutoff value of 60 years), year of diagnosis, primary site, pathology grade, number of primaries, histological type, number of lymph nodes harvested and number of positive lymph nodes (N0, N1, or N2), depth of local tumor invasion (T1, T2, T3, or T4), AJCC TNM stage, radiation sequence with surgery, follow-up time and SEER cause-specific death classification. All patients were restaged based on the AJCC Cancer Staging Manual (7th edition). CSS was the primary outcome for our study and was calculated from the time of diagnosis to the time of colon cancer-specific death. Deaths attributed to colon cancer were treated as events, and deaths from other causes or being alive at the last follow-up were treated as censored observations.

Statistical analysis

Groups based on tumor stage were compared in terms of patient demographics and pathologic features using chi-squared tests. Survival data are shown in Kaplan-Meier curves and were analyzed with log-rank tests. Multivariate Cox proportional hazards models were used to analyze risk factors for CSS. All computed *p* values were two-sided, and statistical significance was accepted at P<0.05. All analyses were performed using SPSS 20.0 for Windows.

Results

Stage II vs. N1a (stage III)

We included 87,090 patients (66,820 stage II patients and 20,270 N1a patients) in our study. Patient demographics and pathologic features

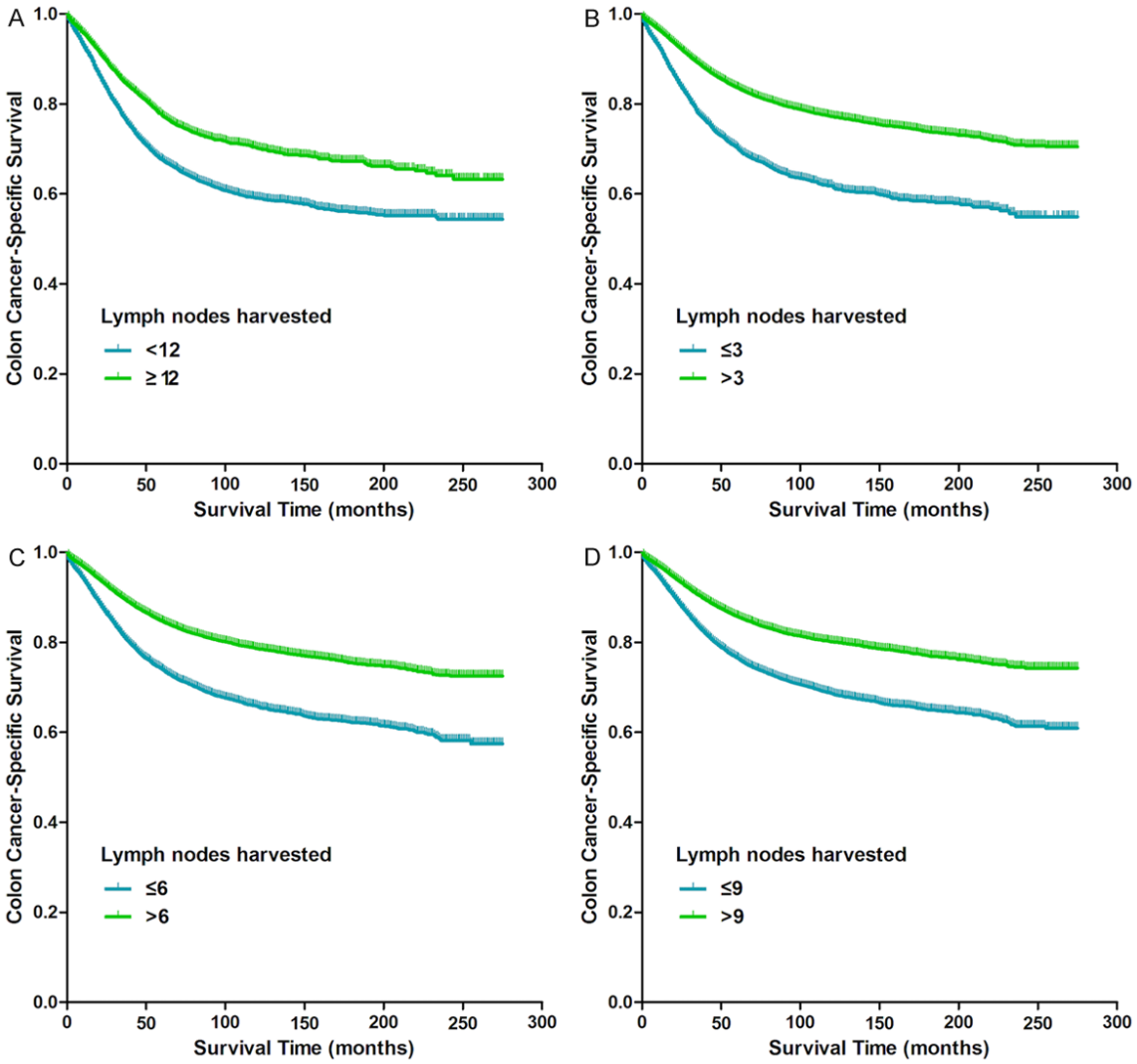

Figure 2. (A) Kaplan-Meier curves for N1a (stage III) colon cancer patients, stratified by 12 lymph nodes harvested. Kaplan-Meier curves for stage II colon cancer patients, stratified by (B) 3 lymph nodes harvested, (C) 6 lymph nodes harvested and (D) 9 lymph nodes harvested.

based on stage II and N1a (stage III) colon cancer are summarized in **Table 1**. The median follow-up time was 51 months (interquartile range, 20-93 months). Out of the included patients, 40,158 were males (46.1%) and 46,932 were females (53.9%). The data indicated that the patients were mainly Caucasian (81.6%), followed by African-American (10.7%). Significant differences were observed in the year of diagnosis (P<0.001), age at diagnosis (P<0.001), primary site (P<0.001), race (P<0.001) and pathology grade (P<0.001) between patients with stage II and N1a (stage III) colon cancer.

Kaplan-Meier curves for patients with stage II and N1a (stage III) colon cancer are shown in **Figure 1**. As expected, N1a (stage III) patients had a poorer CSS than did stage II patients (P<0.001); the 5-year CSS rates of patients with stage II and N1a (stage III) colon cancer were 80.7% and 71.5%, respectively. A univariate analysis of all patients suggested that sex (P=0.025), year of diagnosis (P<0.001), race (P<0.001), age at diagnosis (P<0.001), primary site (P<0.001), pathology grade (P<0.001) and tumor stage (P<0.001) were risk factors for CSS. An analysis of the entire sample using a multivariate Cox proportional model identified the following independent prognostic factors: sex (P<0.001), year of diagnosis (P<0.001), race (P<0.001), age at diagnosis (P<0.001), primary site (P<0.001), pathology grade (P<0.001)

Table 3. Demographics of stage II colon cancer patients with no more than 6 LNH and N1a (stage III) colon cancer patients with at least 12 LNH [N (%)]

Characteristics	Total (N=24,602)	Stage II (LNH ≤6) (N=13,173)	N1a (Stage III) (LNH ≥12) (N=11,429)	*P* value
Sex				0.013
Male	11,370 (46.2)	6185 (47.0)	5185 (45.4)	
Female	13,232 (53.8)	6988 (53.0)	6244 (54.6)	
Year of diagnosis				<0.001
1988-1995	5506 (22.4)	4228 (32.1)	1278 (11.2)	
1996-2003	9147 (37.2)	6060 (46.0)	3087 (27.0)	
2004-2011	9949 (40.4)	2885 (21.9)	7064 (61.8)	
Age at diagnosis (yr)				<0.001
≤60	5707 (23.2)	2159 (16.4)	3548 (31.0)	
>60	18,895 (76.8)	11,014 (83.6)	7881 (69.0)	
Primary site				<0.001
Right colon	13,285 (54.0)	6165 (46.8)	7120 (62.3)	
Left colon	11,317 (46.0)	7008 (53.2)	4309 (37.7)	
Race				<0.001
White	20,001 (81.3)	11,010 (83.6)	8991 (78.7)	
Black	2657 (10.8)	1241 (9.4)	1416 (12.4)	
Other*	1944 (7.9)	922 (7.0)	1022 (8.9)	
Pathology grade				<0.001
High	1997 (8.1)	1277 (9.7)	720 (6.3)	
Moderate	18,144 (73.7)	9972 (75.7)	8172 (71.5)	
Poor	4245 (17.3)	1857 (14.1)	2388 (20.9)	
Undifferentiated	216 (0.9)	67 (0.5)	149 (1.3)	

LNH=Number of lymph nodes harvested. *Includes Native American, Asian, Pacific Islander and Unknown.

and tumor stage (P<0.001). Compared to stage II patients, N1a (stage III) patients were more likely to have a lower CSS (HR 1.528, 95% CI 1,479-1.579, P<0.001, **Table 2**).

Stage II (LNH ≤6) vs. N1a (LNH ≥12)

According to NCCN guidelines, we selected at least 12 LNH as an adequate number of lymph nodes harvested in N1a (stage III) patients. A Kaplan-Meier analysis showed that N1a (stage III) patients with <12 LNH had a poorer CSS than did patients with ≥12 LNH (P<0.001, **Figure 2A**), the 5-year CSS was 66.0% in patients with <12 LNH and 76.2% in those with ≥12 LNH. To select the cutoff for a few lymph nodes harvested in stage II patients, Kaplan-Meier analyses for stage II patients stratified by 3 LNH (P<0.001, **Figure 2B**), 6 LNH (P<0.001, **Figure 2C**) and 9 LNH (P<0.001, **Figure 2D**) were performed. The 5-year CSS was 67.2% in patients with ≤3 LNH, 71.3% in patients with ≤6 LNH and 74.0% in patients with ≤9 LNH. After a preliminary analysis, we selected no more than 6 LNH as "a few" lymph nodes harvested in stage II patients.

Patient demographics and pathologic features from stage II patients with ≤6 LNH and N1a (stage III) patients with ≥12 LNH are summarized in **Table 3**. Significant differences were observed in sex (P=0.013), year of diagnosis (P<0.001), age at diagnosis (P<0.001), primary site (P<0.001), race (P<0.001) and pathology grade (P<0.001) between stage II colon cancer patients with ≤6 LNH and N1a (stage III) colon cancer patients with ≥12 LNH.

A Kaplan-Meier analysis suggested that stage II patients with ≤6 LNH had a poorer CSS than N1a (stage III) patients with ≥12 LNH (P<0.001), the 5-year CSS rates of stage II patients with ≤6 LNH and N1a (stage III) patients with ≥12 LNH were 71.3% and 76.2%, respectively (**Figure 3A**). Univariate analysis of all patients revealed the following risk factors: year of diagnosis (P<0.001), race (P<0.001), age at diagnosis (P<0.001), pathology grade (P<0.001) and

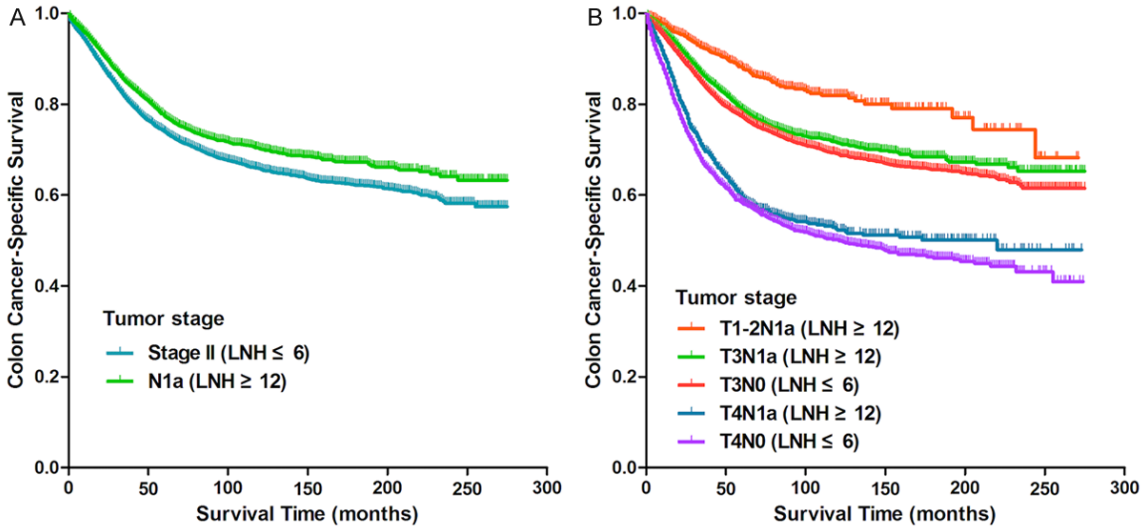

Figure 3. A: Kaplan-Meier curves for stage II (LNH ≤6) and N1a (LNH ≥12) colon cancer patients. B: Kaplan-Meier curves for the T1-2N1a (LNH ≥12), T3N1a (LNH ≥12), T4N1a (LNH ≥12), T3N0 (LNH ≤6) and T4N0 (LNH ≤6) subgroups of colon cancer patients.

tumor stage (P<0.001). Multivariate Cox proportional modeling identified the year of diagnosis (P<0.001), race (P<0.001), age at diagnosis (P<0.001), pathology grade (P<0.001) and tumor stage (P<0.001) as independent prognostic factors. Compared to stage II patients with ≤6 LNH, N1a (stage III) patients with ≥12 LNH were more likely to experience a greater CSS (HR 0.839, 95% CI 0.793-0.887, P<0.001, **Table 4**).

We further divided stage II patients with ≤6 LNH into the T3N0 (LNH ≤6) and T4N0 (LNH ≤6) subgroups, while we divided N1a (stage III) patients with ≥12 LNH into the T1-2N1a (LNH ≥12), T3N1a (LNH ≥12) and T4N1a (LNH ≥12) subgroups based on T stage. The Kaplan-Meier curves for these subgroups are shown in **Figure 3B**. The 5-year CSS rates of the T1-2N1a (LNH ≥12), T3N1a (LNH ≥12), T3N0 (LNH ≤6), T4N1a (LNH ≥12) and T4N0 (LNH ≤6) subgroups were 88.0%, 77.7%, 74.9%, 57.8% and 54.6%, respectively (P<0.001). A multivariate analysis of the entire sample showed that compared with T3N0 (LNH ≤6) patients, T3N1a (LNH ≥12) patients were more likely to experience a greater CSS (HR 0.893, 95% CI 0.836-0.954, P=0.001, **Table 5**). Relative to T4N0 (LNH ≤6) patients, T4N1a (LNH ≥12) patients were more likely to have a higher CSS (HR 0.898, 95% CI 0.809-0.997, P=0.044). This indicated that our results are applicable to these subgroups of patients with stage II colon cancer.

Discussion

Lymph node status, determining postoperative therapeutic course and planning follow-up, has been established as an important prognostic factor in colorectal cancer. The evaluation of no fewer than 12 lymph nodes is recommended by the NCCN Guidelines for accurate staging of colon cancer patients. In stage II colon cancer patients, survival rates decreased as the number of LNH decreased. Law et al. [20] found that in stage II colon cancer patients, the actuarial 5-year overall survival was 62% in patients with ≤6 nodes retrieved and 86% in patients with >6 nodes retrieved (P=0.03). Duraker et al. [21] reported that node-negative patients with colorectal cancer who have 1-7 lymph node(s) or 8-11 lymph nodes retrieved exhibited a poorer CSS than patients with 12 or more lymph nodes retrieved (P=0.006 or P=0.037). In general, patients with stage II colon cancer demonstrated a better survival compared with those with stage III disease. Sarli et al. [16] found that patients with stage III colorectal cancer (42.9%) had a lower 5-year survival rate than those with stage II disease (61.1%).

The results from the current study indicated that stage II colon cancer patients with no more than 6 LNH had a poorer CSS than N1a (stage III) patients with at least 12 LNH. Our results are also applicable to the subgroups of stage II colon cancer patients. Our findings suggested

Table 4. Univariate and multivariate survival analyses of stage II colon cancer patients with no more than 6 LNH and N1a (stage III) colon cancer patients with at least 12 LNH

Variable	Univariate analysis		Multivariate analysis		
	5-year CSS	*P* value	HR	95% CI	*P* value
Sex		0.360			NI
Male	73.3%				
Female	73.7%				
Year of diagnosis		<0.001			<0.001
1988-1995	69.9%		1	Reference	
1996-2003	72.7%		0.931	0.876-0.990	
2004-2011	77.4%		0.826	0.768-0.889	
Race		<0.001			<0.001
White	74.0%		1	Reference	
Black	67.3%		1.431	1.326-1.545	
Other*	77.0%		0.891	0.805-0.987	
Age at diagnosis (yr)		<0.001			<0.001
≤60	81.5%		1	Reference	
>60	71.1%		1.649	1.541-1.765	
Primary site		0.987			NI
Right colon	73.3%				
Left colon	73.8%				
Pathology grade		<0.001			<0.001
High	75.7%		1	Reference	
Moderate	74.7%		1.098	0.998-1.209	
Poor	68.3%		1.451	1.303-1.616	
Undifferentiated	74.2%		1.271	0.926-1.744	
Tumor stage		<0.001			<0.001
Stage II (LNH ≤6)	71.3%		1	Reference	
N1a (LNH ≥12)	76.2%		0.839	0.793-0.887	

LNH=Number of lymph nodes harvested, HR=Hazard ratio, CI=Confidence interval.
*Includes Native American, Asian, Pacific Islander and Unknown.

that stage II patients with no more than 6 LNH may be understaged. These results can be explained by the stage migration phenomenon, which occurs primarily for the following two reasons: inadequate lymph node dissection and inadequate lymph nodes retrieved [11, 22, 23]. For stage II colon cancer, the NCCN Guidelines recommend that the pathologist reevaluate specimen and submit additional tissue with potential lymph nodes if fewer than 12 nodes were initially identified [6, 24, 25]. In a study of 83 patients with colorectal cancer with an inadequate lymph node yield, an additional metastatic node was identified in 4 patients after reevaluation, and 1 patient experienced a stage migration in terms of TNM stage [26]. Therefore, the retrieval of more lymph nodes can provide an adequate assessment of the tumor stage and can minimize stage misclassification. Shanmugam et al. [27] reported that in patients with stage III colon cancer with more than 12 nodes retrieved, every six additional lymph nodes harvested would result in the identification of an additional metastatic lymph node. Peeples et al. [2] even proposed a much larger lymph node harvest number than recommended to minimize stage migration and improve survival in stage II and stage III colorectal cancer, which were 24 and 36 respectively.

Adjuvant chemotherapy is a standard component of treatment for stage III colon cancer, while its use in the treatment of stage II colon cancer is still a matter of debate [28, 29]. The NCCN Guidelines recommend that patients with stage II colon cancer who have high-risk factors, including poor histological differentiation, intestinal obstruction or perforation, elevated levels of preoperative carcinoembryonic antigen (CEA), T4 stage, inadequate nodal resection (<12 nodes), or the presence of lymphovascular or perineural invasion [30, 31], be considered for adjuvant chemotherapy [28, 32]. Earle et al. [33] analyzed several high-risk factors and found that fewer than 12 lymph nodes retrieved in a surgical specimen was a strong predictor of whether adjuvant chemotherapy was given to patients with stage II colon cancer (P=0.008). Zhou et al. [34] analyzed 443 patients with stage II colorectal cancer and found that patients with inadequate lymph nodes harvested achieved better 5-year survival rates with adjuvant chemotherapy than with surgery alone (P<0.05). Based on our results, patients with stage II colon cancer with no more than 6 LNH may be understaged. The trend in stage migration from

Table 5. Multivariate survival analyses of stage II colon cancer patients with no more than 6 LNH and N1a (stage III) colon cancer patients with at least 12 LNH

Variable	Multivariate analysis*		Multivariate analysis*	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
T1-2N1a (LNH ≥12)	0.511 (0.438-0.595)	<0.001	0.254 (0.217-0.299)	<0.001
T3N1a (LNH ≥12)	0.893 (0.836-0.954)	0.001	0.445 (0.410-0.484)	<0.001
T3N0 (LNH ≤6)	Reference		0.498 (0.463-0.536)	<0.001
T4N1a (LNH ≥12)	1.803 (1.645-1.975)	<0.001	0.898 (0.809-0.997)	0.044
T4N0 (LNH ≤6)	2.007 (1.866-2.158)	<0.001	Reference	

LNH=Number of lymph nodes harvested, HR=Hazard ratio, CI=Confidence interval. *Adjusted for sex, year of diagnosis, age at diagnosis, race, primary site and pathology grade as covariates.

stage II toward stage III led us to recommend adjuvant chemotherapy for patients with stage II colon cancer who had no more than 6 LNH.

To the best of our knowledge, this is the first study designed to compare the CSS of stage II patients with a few LNH with that of N1a (stage III) patients with adequate LNH. The large sample size of 87,090 patients from the SEER database ensures adequate power in the results, and therefore, our findings are likely to be reliable. However, our study still has several limitations. The SEER database does not include information regarding comorbidities, intestinal obstruction or penetration, status of surgical margins or pathology techniques, and such clinicopathological information may be a valuable addition to our analysis. In addition, data on adjuvant chemotherapy is also not available in the SEER database, yet the application of adjuvant chemotherapy may influence the prognosis of stage II colon cancer patients and our results. Because we only included and analyzed patients with adenocarcinoma of the colon, our findings may not be applicable to other histological types of colon.

Conclusions

In conclusion, stage II colon cancer patients with no more than 6 retrieved lymph nodes may be understaged and should be considered for adjuvant chemotherapy. Further studies about the effect of adjuvant chemotherapy on stage II colon cancer patients with a small number of retrieved lymph nodes are expected.

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Disclosure of conflict of interest

None.

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