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ORIGINAL ARTICLE

The re-evaluation of optimal lymph node yield in stage II right-sided colon cancer: is a minimum of 12 lymph nodes adequate?

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Abstract
Purpose Adequate lymphadenectomy is critical for accurate nodal staging and planning adjuvant therapy in colon cancer. However, the optimal lymph node (LN) yield for stage II right-sided colon cancer (RSCC) is still unclear. This population-based study aimed to determine the optimal LN yield associated with survival and LN positivity in patients with stage II RSCC.
Methods All patients with stage II–III RSCC were identified from the Surveillance, Epidemiology, and End Results database over a 10-year interval (2006–2015). The optimal threshold for LN yield was explored using an outcome-oriented approach based on survival and LN positivity.
Results The median number of LNs examined for all 17,385 patients with stage II RSCC was 17 (IQR 12–23). Nineteen LNs were determined as the optimal cut-off point to maximize survival benefit from lymphadenectomy. Increased LN yield was associated with a gradual increase in the risk of node positivity, with no change after 19 nodes. Compared with patients with 19 or more LNs examined, the group with fewer LNs had a significantly poor cancer-specific survival (< 12 nodes: hazard ratio (HR) 2.26, $P < 0.001$; 12–18 nodes: HR 1.58, $P < 0.001$) and overall survival (< 12 nodes: HR 1.80, $P < 0.001$; 12–18 nodes: HR 1.31, $P < 0.001$). Similar survival results were found in the validation cohort. Patients with older age, small tumor size, and appendix and transverse colon cancer were more likely to receive inadequate LN harvest.
Conclusion A minimum of 19 LNs is needed to be examined for optimal survival and adequate node staging in lymph node-negative RSCC.

Keywords Right-sided colon cancer · Lymph node yield · SEER database · Nodal staging · Survival

Introduction

The proximal colon is the most common location of colorectal cancer and approximately 41–67% of patients are diagnosed as right-sided colon cancer (RSCC) in the USA [1, 2]. RSCC harbors distinct clinical and biologic characteristics compared with left-sided colon cancer [2]. Radical surgery is the standard treatment for stage II RSCC, and the number of lymph nodes (LNs) harvested served as a benchmark for evaluating the quality of curative resection [3]. Adequate LN yield is critical for accurate nodal staging and optimal survival, which is emphasized in practice guidelines to guide decision-making about adjuvant therapy and postoperative surveillance for recurrence [4]. Recommended by the American Joint Committee on Cancer (AJCC), the pathological examination of at least 12 LNs in the surgical specimen has become the general consensus to identify node-negative patients in stage II colon cancer [5]. Indeed, a higher level of LN evaluation was advocated in several previous studies to further optimize nodal staging and long-

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term survival in patients with colon cancer, despite results from these studies show a great variation in the optimal LN yield [4, 6–13]. Indeed, there are some disparities for LN harvest and LN metastatic potential between the primary tumors in right-sided and left-sided lesions. Therefore, we believe that the optimal LN yield should be discriminately evaluated for stage II RSCC and left-sided colon cancer [7, 10, 13–18]. For patients who underwent right hemicolectomy, it is questionable whether a minimum of 12 LNs examined is adequate and the optimal LN yield is still controversial.

LN metastasis is significantly associated with poor prognosis, especially in patients diagnosed as RSCC [2]. However, the majority of previous studies evaluated the optimal LN yield based on its association with tumor outcomes and few studies explored the optimal number of LNs examined to detect node positivity [4, 7–13]. We performed an outcome-oriented approach for these two outcomes of interest, to comprehensively evaluate the optimal LN yield in patients with stage II RSCC. The aim of this study was to identify the optimal cut-off point that maximizes survival benefit and minimizes the risk of disease understaging.

Materials and methods

Cancer data were obtained from the Surveillance, Epidemiology, and End Results (SEER) program, which is a large population-based cancer registry sponsored by the National Cancer Institute (NCI). The SEER catchment area covers approximately 28% of the US population. SEER collects and updates de-identified data regarding cancer incidence, clinicopathological characteristics, treatment modalities, and survival from 18 participating population-based cancer registries annually [19]. This retrospective study used publicly available data from 2006 through 2015 from the SEER program (the SEER 18 Registries, April 2018 released) [20].

Study population

The study population included all patients who underwent radical surgical resection for primary stage II (T3-4N0M0) RSCC in 9 SEER cancer registries. Patients diagnosed as T3-4N1-2M0 RSCC were also enrolled into our study to evaluate the optimal LN yield for the detection of LN positivity. According to the International Classification of Disease for Oncology (ICD-O-3), patients with histological confirmation were identified by topography code (comprising of cecum, appendix, ascending colon, hepatic flexure, and transverse colon, C18.0 to C18.4) and histological type/behavior code (9140/3, 9480/3, and 9490/3). Tumor stage was restaged according to the 8th edition of the American Joint Committee on Cancer (AJCC) TNM staging system. The evaluation of T category, number of LNs examined, and LNs status was based on the pathological examination of surgical specimens. We analyzed age at diagnosis as a categorical variable (three categories: 50 years or younger, 51 to 70, and older than 70). Tumor size was dichotomized at 50 cm for simplicity. Patients with unclear information pertaining to tumor stage, number of LNs examined, or positive node count were excluded, as were those treated with local resection or total colectomy. To improve the predictive accuracy of survival models, patients with colon cancer that were not the first malignancy were also excluded in survival analyses. A population-based validation was performed to assess the reliability and reproducibility of the optimal LNs cut-off point in the other 9 SEER cancer registries (including Connecticut, Detroit, Atlanta, San Francisco-Oakland, Hawaii, Iowa, New Mexico, Seattle-Puget Sound, and Utah cancer registries).

Statistical analysis

We adopted an outcome-oriented approach to explore the optimal LN yield associated with the prognosis and LN positivity. Using varying thresholds for the number of LNs examined, the crude 5-year CSS rates were respectively calculated from Kaplan–Meier curves and standardized log-rank statistics were estimated using the log-rank test. According to the method previously described [21, 22], the optimal cut-off point of number of LNs examined was identified with the maximum value of absolute log-rank statistics. Multivariate Cox proportional hazards regression model was fitted to evaluate the association between LN harvest and cancer-specific survival. Additionally, a logistic regression model was also used to evaluate the association between LN harvest and relative risk of node positivity. Then, the corresponding covariate-adjusted hazard ratio (HR) and odds ratio (OR) were respectively estimated across the number of LNs examined to confirm the validity and feasibility of identified LN cut-off point.

After stratifying patients based on the identified cut-off point (value N), comparisons of clinicopathologic characteristics between patients from the two LN categories were performed. Factors associated with LN harvest were explored by bivariate logistic regression. Adequate LN yield in stage II colon cancer was defined as 12 or more nodes examined according to the recommendations of AJCC [5]. Accordingly, we further categorized patients based on the number of LNs examined in a narrower range (fewer than 12, 12 to (N-1), and N or more nodes). Subgroups were compared using Wilcoxon rank-sum test for continuous variables and using chi-squared test for categorical variables. The log-rank test was used to determine statistical differences between the survival curves of patients from different LN categories in both derivation and validation cohorts. Cox proportional hazard and logistic regression models adjusted for the novel LN categorization were fitted to validate the optimization of LN yield in terms of long-term survival and node positivity.

Survival time was quantified from the date of diagnosis to the date of cancer-specific death or total death. All statistical analyses were performed using SPSS statistical software version 22.0 (SPSS Inc., IBM Corporation, Chicago, IL, USA). All P values were calculated using two-tailed tests, and statistical significance was defined at two-sided P values < 0.05.

Results

Determination of the optimal cut-off point of number of LNs examined

A total of 17,385 patients with pathologic stage II RSCC were included in the derivation cohort from 2006 to 2015. The median number of LNs examined in the surgical specimens was 17 (IQR 12–23) and the retrieval of at least 12 LNs was identified in most patients (85.3%). By varying thresholds for the number of LNs examined (range 2–40 nodes), the potential cut-off point with the maximum of standardized log-rank statistic occurred at 19 LNs (log-rank statistic 172.7, $P < 0.001$). The 5-year CSS rates of patients with N or more LNs examined progressively increased with the number of LN harvest, but reached a plateau after 19 LNs (Fig. 1). According to the number of LNs examined, patients were subdivided into 24 categories and HR for cancer-special survival was respectively calculated for each category (Table 1). Compared with patients with 30 or more nodes, patients with 18 or less nodes had a significantly increased risk of cancer-special mortality (all $P < 0.05$), which could disappear after the retrieval of at least 19 LNs (adjusted HR for 19 nodes vs. 30 or more nodes, 1.23; 95% CI, 0.93–1.64; $P = 0.153$) (Table 1). In terms of LN positivity, 31,621 patients with T3-4N0-2 RSCC were also subdivided into 13 categories to estimate OR for each category and identify the cut-off point at minimum risk of inaccurate nodal staging (Table 2). There was a gradual increase in the rate of node positivity if fewer than 18–19 nodes were examined (all $P < 0.05$). After the LN yield reaches 18–19 nodes, no changes in the node positivity rate could be observed despite a further increase in the LN harvest (adjusted OR for 18–19 nodes vs. 30 or more nodes, 0.96; 95% CI, 0.88–1.06; $P = 0.471$) (Table 2). Therefore, we identified 19 harvested LNs as an optimal cut-off point to maximize survival benefit and minimize the risk of pathological understaging. Patients were stratified by number of LNs examined as a high-risk group (less than 19 LNs, $n = 9697$, 55.7%) and a low-risk group (19 or more LNs, $n = 7688$, 44.3%). Approximately 73.6% of patients in the high-risk group reached the AJCC recommendation of at least 12 LNs examined (Table 3).

Factors associated with inadequate LN harvest

Demographics and tumor characteristics of patients in the low-risk and high-risk groups are listed in Table 3. Patients with older age (adjusted OR 2.59, $P < 0.001$), small tumor size (adjusted OR 1.57, $P < 0.001$), appendix cancer (adjusted OR 2.08, $P < 0.001$), or transverse colon cancer (adjusted OR 1.25, $P < 0.001$) were more likely to receive an inadequate LN harvest. A significantly decreased risk of inadequate lymphadenectomy could be observed in patients diagnosed in later years (2014–2015 period vs. 2006–2007 period: adjusted OR 0.58, $P < 0.001$). There were no significant differences between the two LN categories in terms of gender, race, T category, histological type, tumor grade, and preoperative CEA level.

The association among the LN harvest, survival, and node positivity

After further stratifying patients based on the number of LNs examined in a narrower range, univariable and multivariable

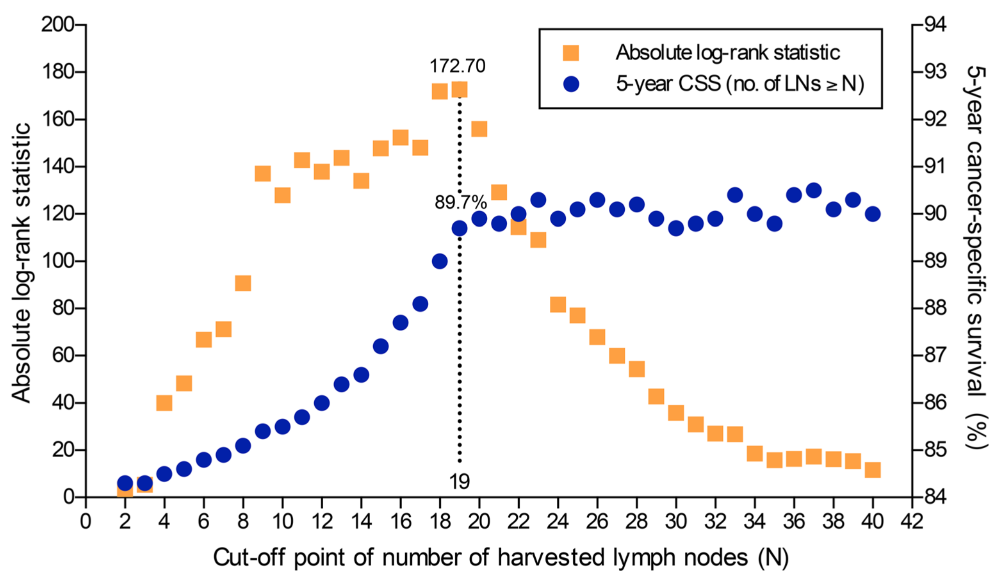

Fig. 1 Determination of the optimal lymph node yield associated with CSS. The dotted line that demarcates 19 LNs is the optimal cut-off point with the maximum value of absolute log-rank statistics (log-rank statistic, 172.7) and the 5-year CSS rate reached a plateau after 19 LNs (5-year CSS rate, 89.7%)

Table 1 Association between cancer-specific survival and the lymph node yield in stage II RSCC ($n = 17,385$)

No. of LNs examined (N)	5-year CSS (LNs examined < N)	5-year CSS (LNs examined ≥ N)	HR (95% CI)*	P value
≤ 7	–	–	2.73 (2.18–3.41)	< 0.001
8	70.9%	85.1%	3.13 (2.33–4.21)	< 0.001
9	70.5%	85.4%	1.93 (1.35–2.77)	< 0.001
10	72.5%	85.5%	2.23 (1.67–2.98)	< 0.001
11	73.1%	85.7%	1.83 (1.36–2.45)	< 0.001
12	74.4%	86.0%	1.93 (1.52–2.46)	< 0.001
13	76.0%	86.4%	1.47 (1.14–1.91)	0.003
14	77.5%	86.6%	1.83 (1.44–2.32)	< 0.001
15	78.1%	87.2%	1.66 (1.29–2.13)	< 0.001
16	78.8%	87.7%	1.52 (1.18–1.96)	0.001
17	79.5%	88.1%	1.81 (1.41–2.32)	< 0.001
18	79.6%	89.0%	1.45 (1.11–1.89)	0.006
19	80.0%	89.7%	1.23 (0.93–1.64)	0.153
20	80.6%	89.9%	0.95 (0.69–1.30)	0.732
21	81.2%	89.8%	1.07 (0.77–1.50)	0.676
22	81.6%	90.0%	1.30 (0.95–1.78)	0.103
23	81.9%	90.3%	0.70 (0.47–1.06)	0.094
24	82.4%	89.9%	1.20 (0.85–1.68)	0.305
25	82.7%	90.1%	0.94 (0.62–1.41)	0.756
26	82.8%	90.3%	1.00 (0.66–1.52)	0.984
27	83.1%	90.1%	1.03 (0.67–1.58)	0.883
28	83.2%	90.2%	0.68 (0.39–1.20)	0.186
29	83.4%	89.9%	0.82 (0.48–1.43)	0.490
≥ 30	–	–	1.00 (reference)	

* Multivariate Cox regression model was adjusted for age at diagnosis, T stage, tumor grade, and preoperative CEA level

Table 2 Association between number of harvested LNs and relative risk of lymph node positivity in RSCC (T3-4N0-2M0, $n = 31,621$)

No. of harvested LNs (N)	Number (%)	OR (95% CI)*	P value
≤ 7	1577 (5.0)	0.64 (0.57–0.73)	< 0.001
8–9	1125 (3.6)	0.86 (0.75–0.99)	0.037
10–11	1680 (5.3%)	0.90 (0.80–1.02)	0.085
12–13	3533 (11.2%)	0.87 (0.79–0.95)	0.003
14–15	3978 (12.6%)	0.87 (0.79–0.95)	0.003
16–17	3659 (11.6%)	0.89 (0.81–0.98)	0.015
18–19	3201 (10.1%)	0.96 (0.88–1.06)	0.471
20–21	2730 (8.6%)	1.02 (0.93–1.13)	0.641
22–23	2209 (7.0%)	0.96 (0.86–1.07)	0.455
24–25	1748 (5.5%)	0.98 (0.87–1.10)	0.721
26–27	1317 (4.2%)	0.93 (0.82–1.06)	0.255
28–29	975 (3.1%)	0.89 (0.77–1.03)	0.123
≥ 30	3889 (12.3)	1.00 (reference)	

* Logistic regression model was adjusted for age at diagnosis, race, T stage, tumor grade, histological type, tumor size, and preoperative CEA level

analyses were conducted to confirm the association among LN harvest, survival, and node positivity in both derivation and validation cohorts. The 5-year CSS rates and overall survival (OS) rates of patients with 19 or more LNs examined were significantly higher (5-year CSS for < 12 vs. 12–18 vs. ≥ 19 nodes, 74.4% vs. 82.1% vs. 89.5%, $P < 0.001$; 5-year OS for < 12 vs. 12–18 vs. ≥ 19 nodes, 54.7% vs. 65.6% vs. 75.6%, $P < 0.001$). After the adjustment for relevant covariables, multivariable analysis revealed that a minimum of 19 LNs examined was associated with improved survival compared with those of 12–18 nodes (CSS: adjusted HR 1.58, $P < 0.001$; OS: adjusted HR 1.31, $P < 0.001$) and fewer than 12 nodes (CSS: adjusted HR 2.26, $P < 0.001$; OS: adjusted HR 1.80, $P < 0.001$) (Fig. 2). Similar survival benefits from 19 or more LN harvest were also found in the validation cohort (Fig. 2). Subgroup analyses were conducted in patients with older age, small tumor size, appendix cancer, and transverse colon cancer, who were more likely to receive an inadequate lymphadenectomy. An increased risk of cancer-special mortality could also be observed in patients with 12–18 nodes examined in these subgroups (Fig. S1).

In terms of node positivity, more positive LNs could be detected after a minimum of 19 LN harvest. Patients with 19 or more LNs examined had higher rates of LN metastases and N2 stage than those with fewer than 19 nodes (Table 4). Compared with a minimum of 19 LN harvest, the fewer LNs examined (< 12 nodes: adjusted OR 0.84, $P < 0.001$; 12–18 nodes: adjusted OR 0.93, $P = 0.003$) were associated with a decreased risk of node positivity. The consistent findings were also recognized in the validation cohort (Table 4).

Discussion

Lymph node–negative RSCC is associated with better survival than those in left-sided colon, while the cancer-specific mortality is significantly increased in RSCC after LN metastasis [2]. Therefore, an adequate LN examination is essential to accurately evaluate the LN status and avoid understaging in patients with RSCC. We designed this largest population-based study, to explore the optimal LN yield in stage II RSCC associated with the prognosis and LN positivity. A minimum of 12 LN harvest recommended by the AJCC seemed to be insufficient. Our data determined 19 LNs as the optimal cut-off point for improved CSS and accurate nodal staging. Patients with older age, small tumor size, appendix, and transverse colon cancer were more likely to receive an inadequate pathologic examination of the surgical specimen.

Adequate lymphadenectomy has been suggested for colon cancer to improve survival in many previous studies [3, 7, 12,

Table 3 Clinicopathologic characteristics of patients stratified by number of LNs examined and factors associated with inadequate lymph node harvest ($n = 17,385$)

Variable[*]	LNs examined < 19 ($n = 9697$) (%)	LNs examined ≥ 19 ($n = 7688$) (%)	P value[#]	OR (95% CI)	P value
Age (years)			< 0.001		
≤ 50	472 (4.9)	570 (9.8)		1.00 (reference)	
51–70	3057 (31.5)	2982 (38.8)		1.57 (1.38–1.79)	< 0.001
> 70	6168 (63.6)	3956 (51.5)		2.41 (2.13–2.73)	< 0.001
Gender			0.313		
Male	4527 (46.2)	3530 (45.6)		–	
Female	5170 (53.8)	4158 (54.4)			
Race ($n = 17,355$)			0.311		
White	8297 (85.7)	6535 (85.2)		–	
Nonwhite	1384 (14.3)	1139 (14.8)			
T stage			0.067		
T3	8339 (86.0)	6685 (87.0)		–	
T4	1358 (14.0)	1003 (13.0)			
Tumor grade ($n = 17,096$)			0.033		
Well/moderately	7619 (80.0)	5961 (79.4)		1.00 (reference)	
Poorly	1902 (20.0)	1614 (20.6)		0.94 (0.87–1.02)	0.116
Histology			0.005		
Adenocarcinoma	8250 (85.1)	6413 (83.4)		1.00 (reference)	
Mucinous carcinoma	1331 (13.7)	1189 (15.5)		0.93 (0.85–1.02)	0.111
Signet ring cell	116 (1.2)	86 (1.1)		1.13 (0.85–1.51)	0.411
Tumor size (mm) ($n = 16,894$)			< 0.001		
≤ 50	5712 (60.8)	3643 (48.6)		1.60 (1.50–1.70)	< 0.001
> 50	3689 (39.2)	3850 (51.4)		1.00 (reference)	
Preoperative CEA level ($n = 10,098$)			0.069		
Elevated	2090 (38.1)	1680 (36.4)		–	
Normal	3390 (61.9)	2938 (63.6)			
Year of diagnosis			< 0.001		
2006–2007	2358 (24.3)	1347 (17.5)		1.00 (reference)	
2008–2009	1983 (20.4)	1519 (19.8)		0.75 (0.68–0.83)	< 0.001
2010–2011	1885 (19.4)	1545 (20.1)		0.70 (0.63–0.77)	< 0.001
2012–2013	1781 (18.4)	1628 (21.2)		0.63 (0.58–0.70)	< 0.001
2014–2015	1690 (17.4)	1649 (21.4)		0.60 (0.54–0.66)	< 0.001
No. of LNs examined (current guideline)			–	–	
LNs < 12	2558 (26.4)	0 (0.0)			
LNs ≥ 12	7139 (73.6)	7688 (100.0)			

[*] Patients with unknown value or missing data in the above categories (race, tumor grade, tumor size, and preoperative CEA level) were excluded

[#] Pearson chi-squared test

13, 23, 24], even in node-negative patients [9–11, 15, 18, 25, 26]. Ideally, all LNs should be retrieved from the surgical specimen to assure the accuracy of nodal staging [4]. Nevertheless, it is impractical to achieve in the most patients because of the high cost and low efficacy in this ideal approach. A "ceiling effect" may exist in the LN yield, although the optimal number of LNs examined has not yet been definitely determined [27]. Despite that a minimum of 12 LNs examined is recommended by the AJCC as the standard for nodal staging, several investigators suggested that a greater number of LNs should be examined to identify node-negative tumors and avoid missing the opportunity of adjuvant chemotherapy [8, 11, 13, 24, 25]. Most studies evaluated the optimal LN yield to improve survival outcomes and reported inconsistent results ranging from 6 to 24 LNs [4, 6–13, 28]. Few studies have attempted to explore the optimal LN yield with consideration of the primary tumor location. Guan et al. suggested that a minimum of 15 LNs examined might be recommended instead of 12 LNs in patients with stage I–III RSCC [17]. Consistent with previous studies, we demonstrated that the increased LN yield was significantly associated with higher rates of CSS and node positivity. However, the

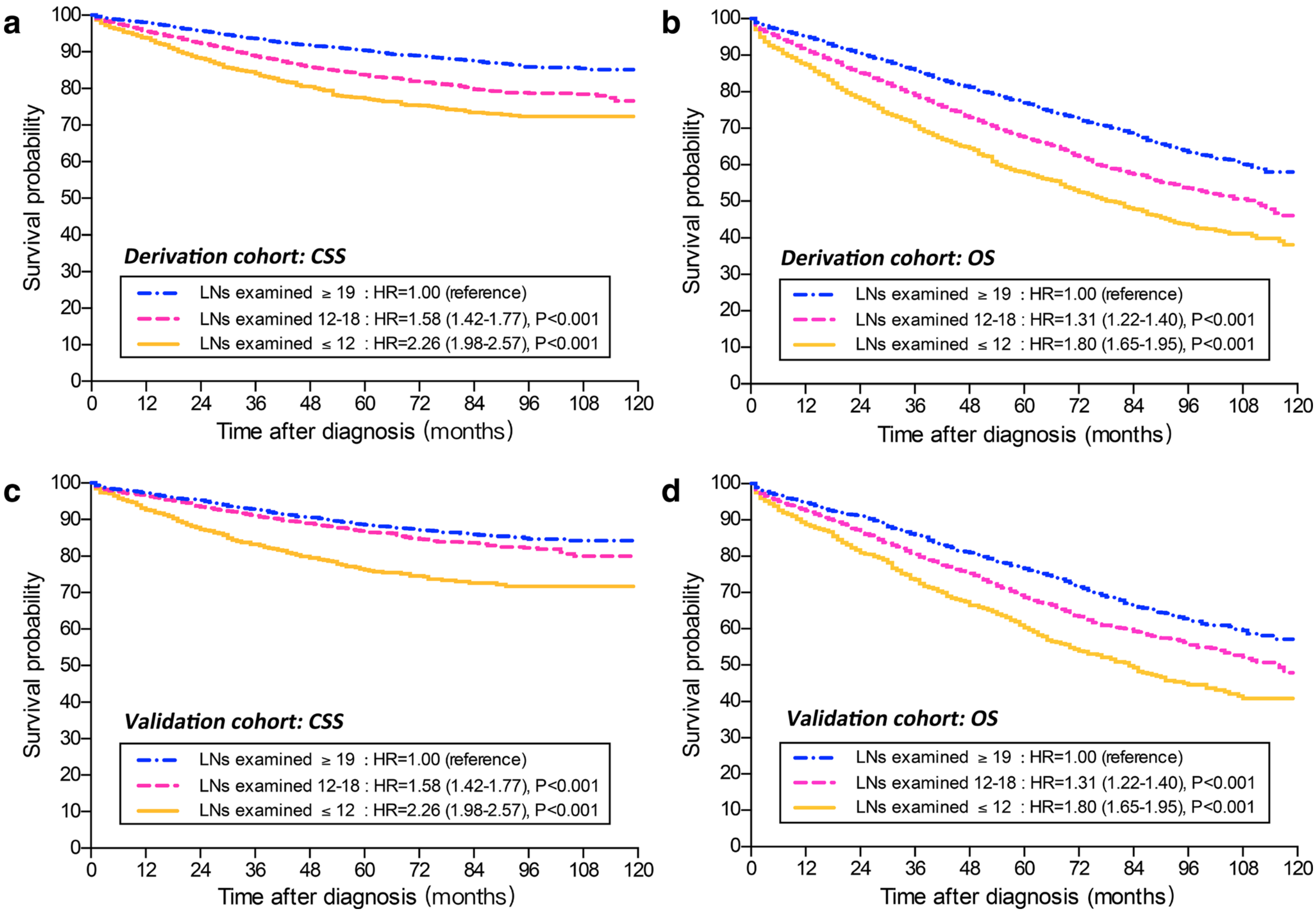

Fig. 2 Kaplan–Meier survival curves for patients with stage II RSCC according to number of LNs examined (< 12 vs. 12–18 vs. ≥ 19 nodes). **a** CSS in derivation cohort. **b** OS in derivation cohort. **c** CSS in validation cohort. **d** OS in validation cohort

5-year CSS and LN positivity rates remained constant after 19 nodes in stage II RSCC. Therefore, we suggest that a minimum of 19 LNs examined is necessary to consider a tumor as node-negative. A risk of disease understaging should not be neglected in patients with 12–18 LNs examined, who are always considered with a better survival according to the clinical practice guideline and are, subsequently, not recommended to receive an adjuvant chemotherapy.

The potential reasons for survival benefits gained from an increased LN yield were multifactorial, including accurate nodal staging, enhanced antitumor immune response, improved quality of curative resection and pathological examination, and tumor biological behavior (i.e., MSI status) [4, 6, 14, 23, 29–31]. Patients with LN metastasis might be erroneously identified as node-negative by improper LN harvest. Adequate nodal evaluation could lead to stage migration and therefore gain survival benefits derived from accurate staging and adjuvant chemotherapy [6, 14]. Our data demonstrated a pathological examination of at least 19 LNs minimized the risk of nodal understaging, which might be the underlying mechanism for optimal survival in patients with 19 or more harvested LNs. However, this prevailing hypothesis based on stage migration has been questioned by several recent studies [29, 32]. They reported that the proportion node positivity remained constant in colon cancer, despite the increasing LN yield observed over time. But in stage II RSCC, it was evident that patients diagnosed in later years were slightly more likely to have more positive LNs to be examined (2014–2015 period vs. 2006–2007 period: adjusted OR 1.08, 95% CI 1.00–1.16) with a steep increase in LN yield (Table 3).

Another possible explanation for the association between LN yield and survival is the enhanced antitumor immune response, which has been proposed as a surrogate marker for better survival [33]. A stronger host immune response could be manifested as reactive enlargement of LNs, leading to make them easier to find [15, 23, 34]. As constant with previous results, age at diagnosis and tumor size were found to affect the LN yield in the present study [16, 18, 31, 35–37]. Older patients and those with small tumor size were less likely to receive adequate LN evaluation. The adaptive immune response within the regional LN basin may be less vigorous in patients with older age or small tumor size [38, 39]. We speculated that aging and initially small tumor burden might elicit a diminished antigenic immune response, modifying the LN

Table 4 Number of LNs in relationship to lymph node status and relative risk of lymph node positivity in RSCC (T3-4N0-2M0, *n* = 31,621)

No. of harvested LNs	No. of positive LNs (T3-4N1-2M0, mean)	Positive LNs (%)	N2 stage (%)	OR* (95% CI)	*P* value
Derivation cohort (*n* = 31,621)					
< 12	2.83	41.6	11.7	0.84 (0.78–0.90)	< 0.001
12–18	3.67	44.4	16.5	0.93 (0.88–0.97)	0.003
≥ 19	4.73	46.6	19.4	1.00 (reference)	
P value	< 0.001#	< 0.001†	< 0.001†	–	
Validation cohort (*n* = 19,405)					
< 12	2.73	41.7	11.6	0.84 (0.76–0.93)	0.001
12–18	3.68	43.8	16.4	0.92 (0.86–0.98)	0.008
≥ 19	4.58	46.0	18.6	1.00 (reference)	
P value	< 0.001#	0.002†	< 0.001†	–	

* Logistic regression model was adjusted for age at diagnosis, race, T stage, tumor grade, histological type, tumor size, and preoperative CEA level

\# Wilcoxon rank-sum test

† Pearson chi-squared test

size and therefore increasing the difficulty of LN harvest in the mesentery. For patients with old age and small tumor size, we believed that more LNs were still merited to examine because of its association with improvement of 15.7% and 12.3% in cancer-specific survival (5-year CSS for < 12 vs. ≥ 19 nodes: old age, 69.3% vs. 85.0%; small tumor size, 77.6% vs. 89.9%). However, surgeons may perform less extended lymphadenectomy on patients with older age or small tumor size [40]. Actually, this operation could lead to inadequate LN harvest and consequently affect the evaluation of nodal status and immune response; therefore, it should not be advocated.

The LN yield has been served as a benchmark for evaluating the quality of curative resection and pathological examination, the extended mesocolic excision and high quality of mesocolic dissection would increase the number of LNs examined [14, 31, 41]. The change in surgical techniques is most pronounced for patients with RSCC, and the implementation of complete mesocolic excision (CME) has been proposed to improve oncological outcomes [42]. Compared with conventional colonic resection, increased LN yield was performed in the CME surgery [43, 44]. For patients with appendix and transverse colon cancer, more extended lymphadenectomy has been suggested to improve survival [36, 45], whereas we found that appendix or transverse colon cancer was more likely to be associated with fewer LNs examined. It is necessary to comply with the principle of CME with central vascular ligation (CVL) to reach an adequate LN harvest in tumors located in the appendix and transverse colon. The skills of the pathologist and pathology techniques for harvesting LNs have been confirmed to influence the LN harvest [4, 14, 46]. Careful gross examination is necessary according to the recommendation from the College of American Pathologists [14]. The quality of surgical resection and pathological examination is the fundamental of adequate LN harvest. Standard surgical technology and careful gross pathological examination are suggested to harvest at least 19 LNs. Thereafter, the nodal status and host immune response to the primary tumor can be accurately evaluated, which will guide the follow-up treatment plans.

There are several certain limitations meriting comment in the current study. First, the SEER database does not collect information reflecting the hospital volume (i.e., surgeon volume and experience of the pathologist) and others may improve the quality of curative resection (i.e., advanced surgical and pathology techniques: CME, laparoscope, fat clearance, and so on), which have been confirmed to be associated with the LN harvest [25]. Therefore, these hospital-related factors could not be adjusted in our study. Second, no information regarding the application and administration of adjuvant chemotherapy was available. This may affect the survival differences among patients with different levels of LN evaluation. Moreover, the indications for adjuvant chemotherapy based on the LN yield could not be evaluated in our study.

Conclusions

Our population-based study provides the best evidence demonstrating the significant association between the LN yield and oncological outcomes in stage II RSCC when there is a lack of prospective studies. A pathological examination of at least 19 LNs could maximize survival benefit from LN harvest and minimize the risk of nodal understaging. Accordingly, we suggested that a minimum of 19 LNs need to be harvested to label a tumor as node-negative. Older age, small tumor size, appendix, and transverse colon cancer were considered as potential risk factors for an inadequate LN harvest. Only approximately 44.3% of stage II RSCC patients have undergone adequate lymphadenectomy in the USA in the last decade. More extensive resection (i.e., CME with CVL) and careful gross examination should be recommended to accurately evaluate the nodal status and immune response in stage II RSCC patients, especially in those with older age, small tumor size, appendix, and transverse colon cancer.

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Author contributions All authors meet the ICMJE authorship criteria and contributed substantially to the manuscript. X Zhu, HX Ju, and YB Cai designed the study conception. YB Cai, GP Cheng, and XG Lu finished the analysis and interpretation of data. YB Cai and X Zhu drafted the work.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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