Retrospective Cohort Study

INTERNATIONAL JOURNAL OF SURGERY

OPEN

Prognostic impact of increased lymph node yield in colorectal cancer patients with synchronous liver metastasis: a population-based retrospective study of the US database and a Chinese registry

Shuai Jiao, MD[a], Xu Guan, PhD[b,*], Weiyuan Zhang, MS[a], Ran Wei, MD[b], Guiyu Wang, PhD[b,*], Xishan Wang, PhD, MD[a,b,*]

Background: The National Quality Forum has endorsed at least 12 lymph node yield (LNY) as a surgical quality indicator in colorectal cancer (CRC), but the prognostic value of adequate lymphadenectomy has rarely been investigated for CRC patients with distant metastatic disease.

Methods: A total of 4575 CRC patients with synchronous liver metastasis who underwent primary tumor resection were identified from a Chinese registry and the Surveillance, Epidemiology, and End Results (SEER) database between 2010 and 2017. The Kaplan–Meier methods and Cox regression models were performed to assess the correlations between LNY and 3-year cancer-specific survival (CSS). Propensity score matching were used to confirmed the survival comparison between patients with less than 12 and of at least 12 LNY.

Results: The retrieval of at least 12 LNY was identified in most CRC patients (SEER database, 3380/3899, 86.7%; Chinese cohort, 565/676, 83.6%). In both the SEER database and the Chinese cohort, the patients with LNY $\geq$ 12 was significantly associated with better CSS compared with patients with LNY <12 before and after propensity score matching, with all *P*-value less than 0.05. After controlling for the confounders, multivariate analysis demonstrated that LNY was also an independent prognostic factor for patients with distant metastasis in both cohorts. In subgroup analysis, the CSS benefit for patients with LNY $\geq$ 12 was observed across most of the subgroups.

Conclusions: Clinical feasibility of the 12-node threshold as a guideline quality metric of cancer care for CRC patients is necessary, and an oncologically adequate lymphadenectomy is still a critical component of high-quality surgical standard in CRC patients with distant metastases.

Keywords: colorectal cancer, lymphadenectomy, prognosis, surgical quality

[a]*Department of Colorectal Surgery, The Second Affiliated Hospital of Harbin Medical University, Harbin and* [b]*Department of Colorectal Surgery, National Cancer Center/ Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China*

Shuai Jiao, Xu Guan and Weiyuan Zhang contributed equally to this study.

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

**Corresponding author. Address: Department of Colorectal Surgery, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100021, China. Tel.: +86 13141307719; fax: +86 010 67781331. E-mail address: drguanxu@163.com (X. Guan); Tel.: +86 13552367779; fax: +86 010 67781331. E-mail address: wxshan1208@126.com (X. Wang) and Department of Colorectal Surgery, The Second Affiliated Hospital of Harbin Medical University, Harbin 150086, China. Tel.: +86 13945133256; fax: +86 0451 86662962. Email address: guiywang@163.com (G. Wang).*

International Journal of Surgery (2023) 109:1932–1940

Received 23 September 2022; Accepted 13 January 2023

Supplemental Digital Content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's website, www.lww.com/international-journal-of-surgery.

Published online 11 April 2023

http://dx.doi.org/10.1097/JS9.0000000000000244

HIGHLIGHTS

- This is the first study addressing the implications of the 12 lymph node yield (LNY) quality indicator on survival for colorectal cancer (CRC) patients with distant metastasis based on two large population-based cohorts.
- An adequate lymphadenectomy with a 12-node threshold as a guideline quality is still a critical component of high-quality surgical standard in (CRC) patients with distant metastases.

Introduction

CRC is an important cause of cancer-related morbidity and mortality in our population[1]. Approximately 20% of CRC patients have synchronous distant metastases at the time of diagnosis, presenting with very low survival[2]. Despite advances in multimodal care have led to improved survival outcomes of CRC patients with distant metastases, surgical treatment is still one crucial procedure for them to prolong life or at least improve their quality of life.

Adequate lymphadenectomy, a proxy of quality surgery, remains a fundamental surgical principle in the resection for CRC and a principal determinant of cancer outcomes[3–5]. Moreover,

LNY is an objective quantifiable marker that reflect the adequacy of surgical care in routine clinical practice[6–8]. In 2007, after considering the recommendations of various professional committees on CRC, the National Quality Forum endorsed the harvest of at least 12 LNY as a standard quality indicator and a means of improving survival. Importantly, LNY removed surgically as well as assessed pathologically governs not only the accuracy of tumor staging but also therapeutic decision-making[9,10].

In CRC patients with distant metastatic disease, prognostic significance of adequate lymphadenectomy has rarely been investigated previously. With the use of LNY as a quality indicator of lymphadenectomy extension and a routine parameter of evaluation in early-stage CRC patients, we supposed that even in the setting of patients with distant metastatic disease, adequate resection of the primary tumor of CRC and lymphadenectomy should be practiced. To better address this issue, we performed analyses based on two international population-based databases (1) to investigate the relationship between LNY and survival outcomes and (2) to further confirm its utility of a 12-node threshold as a quality indicator of surgical management in CRC patients with distant metastatic disease.

Methods

Data sources

Data on CRC patients with synchronous liver metastasis (LM) were derived from the US Surveillance, Epidemiology, and End Results (SEER) and a Chinese registry (from two Chinese tertiary centers) between January 2010 and December 2017. Individual-level data on patients with incident CRC were consecutively collected in both registries. The primary tumor site was divided into three subsites according to the International Classification of Diseases for Oncology (ICD-O-3) topography codes: proximal colon (C18.0, C18.1, C18.2, C18.3, and C18.4), distal colon (C18.5, C18.6, C18.7) and rectum (C19.9 and C20.9). The synchronous LM were identified by imaging or histopathological examinations. Synchronous LM refers to liver lesions found within 6 months after the diagnosis of primary CRC. Patients were excluded if they did not undergo surgery for CRC, did not have data on the number of LNs retrieved and their survival status was unknown. This study was approved by the review boards (Approval No. 17-116/1439). This trial was retrospectively registered with the Clinical Trials. Unique Identifying Number (UIN) is "NCT05550701". This work has been reported in line with the STROCSS criteria, Supplemental Digital Content 1 (http://links.lww.com/JS9/A239).

Variable and outcome of interest

The primary outcome was cancer-specific survival (CSS), which was defined as the time interval from the synchronous LM diagnosis until cancer-specific death or the end of follow-up in the Chinese registry, and the CSS was defined using the SEER cause-of-death codes in the SEER registry[11]. The primary independent variable was the number of LNY evaluated. In addition, demographic and clinical information about patients (age, sex), lymph node ratio (LNR), the number of positive lymph nodes divided by the total LNY, tumor [primary tumor site, tumor grade, histology types, the American Joint Committee on Cancer (AJCC) TNM stage and preoperative carcinoembryonic antigen (CEA)], surgical strategy (only primary site resection, both primary site and metastasis resection), and outcome variables (follow-up time and survival status). The pathological tumor stage was characterized according to the seventh edition of the AJCC TNM staging system.

Statistical analysis

Patients were grouped by the suggested lymph node number of 12 according to the National Comprehensive Cancer Network (NCCN) guideline[6]. Descriptive statistics were presented as median [interquartile range (IQR)] and frequency (%) for continuous and categorical variables, respectively. Categorical variables were compared using the chi-square test. Survival analyses were performed using the Kaplan–Meier method and differences between groups were assessed with the log-rank test. Multivariate analysis was performed using the Cox proportional hazards regression model for calculating hazard ratio (HR) with its 95% CI. The baseline characteristics between the two groups were

Table 1

Clinicopathological characteristics of colorectal cancer patients in stage IV in SEER database and Chinese registry

	n (%)	
Characteristics	**SEER database**	**Chinese registry**
Total	3899	676
LNY [median (IQR)]	17 (13, 23)	18 (13, 26)
LNR [median (IQR)]	0.18 (0.05, 0.42)	0.11 (0, 0.29)
Age (years)		
≤60	1791 (45.9)	406 (60.1)
>60	2108 (54.1)	270 (39.9)
Sex		
Female	1704 (43.7)	235 (34.8)
Male	2195 (56.3)	441 (65.2)
Primary tumor site		
Proximal colon	1549 (39.7)	133 (19.7)
Distal colon	1947 (49.9)	294 (43.5)
Rectum	403 (10.3)	249 (36.8)
Grade		
Well/moderately	2863 (73.4)	493 (72.9)
Poorly/undifferentiated	1036 (26.6)	183 (27.1)
Histology type		
Adenocarcinoma	3627 (93.0)	660 (97.6)
Mucinous/signet	272 (7.0)	16 (2.4)
AJCC T stage		
T1–T2	145 (3.7)	40 (5.9)
T3–T4	3754 (96.3)	636 (94.1)
AJCC N stage		
N0	587 (15.1)	172 (25.4)
N1–N2	3312 (84.9)	504 (74.6)
AJCC M stage		
M1a	3256 (83.5)	608 (89.9)
M1b	643 (16.5)	68 (10.1)
Preoperative CEA		
Normal	574 (14.7)	129 (19.1)
High	2198 (56.4)	415 (61.4)
Unknown	1127 (28.9)	132 (19.5)
Metastasectomy		
No	2928 (75.1)	278 (41.1)
Yes	971 (24.9)	398 (58.9)

AJCC, American Joint Committee on Cancer; CEA, carcinoembryonic antigen; IQR, interquartile range; LNR, lymph node ratio; LNY, lymph node yield; SEER, Surveillance, Epidemiology, and End Results.

Table 2

Association between LNY and clinicopathological characteristics in colorectal cancer patients in stage IV in SEER database and Chinese registry

	SEER database						Chinese registry					
	Before PSM			After PSM			Before PSM			After PSM		
Characteristics	LNY <12	LNY ≥12	*P*	LNY <12	LNY ≥ 12	*P*	LNY <12	LNY ≥12	*P*	LNY <12	LNY ≥ 12	*P*
Number of patients	519	3380		519	1550		111	565		108	299	
Age (years)			0.060			0.957			0.697			0.715
≤60	218 (42.0)	1573 (46.5)		218 (42.0)	647 (41.7)		69 (62.2)	337 (59.6)		68 (63.0)	196 (65.6)	
Sex			0.976			0.836			0.649			0.513
Female	226 (43.5)	1478 (43.7)		226 (43.5)	685 (44.2)		36 (32.4)	199 (35.2)		35 (32.4)	85 (28.4)	
Primary tumor site			<0.001			0.826			0.001			0.436
Proximal colon	151 (29.1)	1398 (41.3)		151 (29.1)	457 (29.5)		8 (7.2)	125 (22.1)		8 (7.4)	32 (10.7)	
Distal colon	299 (57.6)	1648 (48.8)		299 (57.6)	903 (58.3)		56 (50.5)	238 (42.1)		55 (50.9)	134 (44.8)	
Rectum	69 (13.3)	334 (9.9)		69 (13.3)	190 (12.2)		47 (42.3)	202 (35.8)		45 (41.7)	133 (44.5)	
Grade			1.000			0.735			0.898			0.701
Well/moderately	381 (73.4)	2482 (73.4)		381 (73.4)	1,124 (72.5)		82 (73.9)	411 (72.7)		79 (73.1)	211 (70.6)	
Histology type			0.542			0.905			0.201			0.932
Adenocarcinoma	479 (92.3)	3148 (93.1)		479 (92.3)	1,435 (92.6)		106 (95.5)	554 (98.1)		105 (97.2)	293 (98.0)	
AJCC T stage			0.122			0.200			0.395			1.000
T3–T4	493 (95.0)	3261 (96.5)		493 (95.0)	1,494 (96.4)		102 (91.9)	534 (94.5)		101 (93.5)	279 (93.3)	
AJCC N stage			0.002			0.399			0.014			0.934
N1–N2	417 (80.3)	2895 (85.7)		417 (80.3)	1,273 (82.1)		72 (64.9)	432 (76.5)		70 (64.8)	197 (65.9)	
AJCC M stage			0.166			0.800			0.565			0.255
M1a	422 (81.3)	2834 (83.8)		422 (81.3)	1,270 (81.9)		102 (91.9)	506 (89.6)		100 (92.6)	287 (96.0)	
Preoperative CEA			0.015			0.427			0.020			0.896
Normal	57 (11.0)	517 (15.3)		57 (11.0)	142 (9.2)		14 (12.6)	115 (20.3)		14 (13.0)	42 (14.1)	
High	293 (56.5)	1905 (56.4)		293 (56.5)	910 (58.7)		66 (59.5)	349 (61.8)		65 (60.1)	183 (61.2)	
Unknown	169 (32.5)	958 (28.3)		169 (32.5)	498 (32.1)		31 (27.9)	101 (17.9)		29 (26.9)	74 (24.7)	
Metastasectomy			<0.001			0.573			0.148			0.938
Yes	94 (18.1)	877 (25.9)		94 (18.1)	262 (16.9)		58 (52.3)	340 (60.2)		57 (52.8)	161 (53.8)	

Values are represented as *n* (%).

AJCC, American Joint Committee on Cancer; CEA, carcinoembryonic antigen; LNY, lymph node yield; PSM, propensity score matching; SEER, Surveillance, Epidemiology, and End Results.

matched by the propensity score matching (PSM) using the nearest-neighbor method with a caliper of 0.20 (ratio: 1:3) to reduce selection bias[12,13]. The balance in covariates was assessed by using the standardized mean difference (SMD) approach. If the SMD is greater than 10%, this is usually considered a meaningful imbalance in the factors between the two groups. A *P*-value less than 0.05 was considered statistically significant. All statistical analyses were performed using R software (version 4.0.4; http://www.r-project.org).

Results

Patient and tumor characteristics

A total of 3899 patients in the SEER database and 676 patients in the Chinese registry who met the eligibility criteria were included in this study. The baseline characteristics are shown in Table 1. Of these patients, the proportion of males was higher than that of in both the SEER cohort (56.3%) and the Chinese cohort (65.2%). Most resected primary tumors were located in the distal colon (SEER, 49.9%; Chinese registry, 43.5%), were of stage T3–T4 (SEER, 96.3%; Chinese registry, 94.1%), and were declared node-positive (SEER, 84.9%; Chinese registry, 74.6%). In addition, 24.9 and 58.9% of patients in SEER cohort and Chinese cohort underwent metastases resection respectively.

In terms of the count of LNY, the median LNY in surgical specimens was 17 (IQR: 12–23) and 18 (IQR: 13–26) in the SEER database and Chinses registry, respectively. The retrieval of at least 12 LNY was identified in most patients (SEER, 86.7%; Chinese registry, 83.6%). Also, the proportion of LNY ≥12 with respect to different tumor sites showed that the proximal colon was higher than the distal colon and rectum in both cohorts (Table 2). Similar results are observed for the mean and median of LNY (Supplementary Table 1, Supplemental Digital Content 2, http://links.lww.com/JS9/A240).

Baseline covariates after propensity score matching

We used the PSM to balance baseline covariates between subgroups of patients with LNY <12 and LNY ≥12. The baseline characteristics of eligible patients in the prematched and postmatched cohorts were listed in Table 2. In SEER and Chinese cohorts, 1550 patients in the LNY ≥12 subgroup were matched with 519 patients in the LNY <12 subgroup and 299 patients in the LNY ≥12 subgroup were matched with 108 patients in the LNY <12 subgroup, respectively. The matching process eliminated some significant differences that existed between two subgroups. After PSM adjustment, the SMD for all characteristics was less than 0.1, indicating that the population in the LNY <12 versus LNY ≥12 groups were subsequently comparable (Supplementary Fig. 1, Supplemental Digital Content 3, http://links.lww.com/JS9/A241).

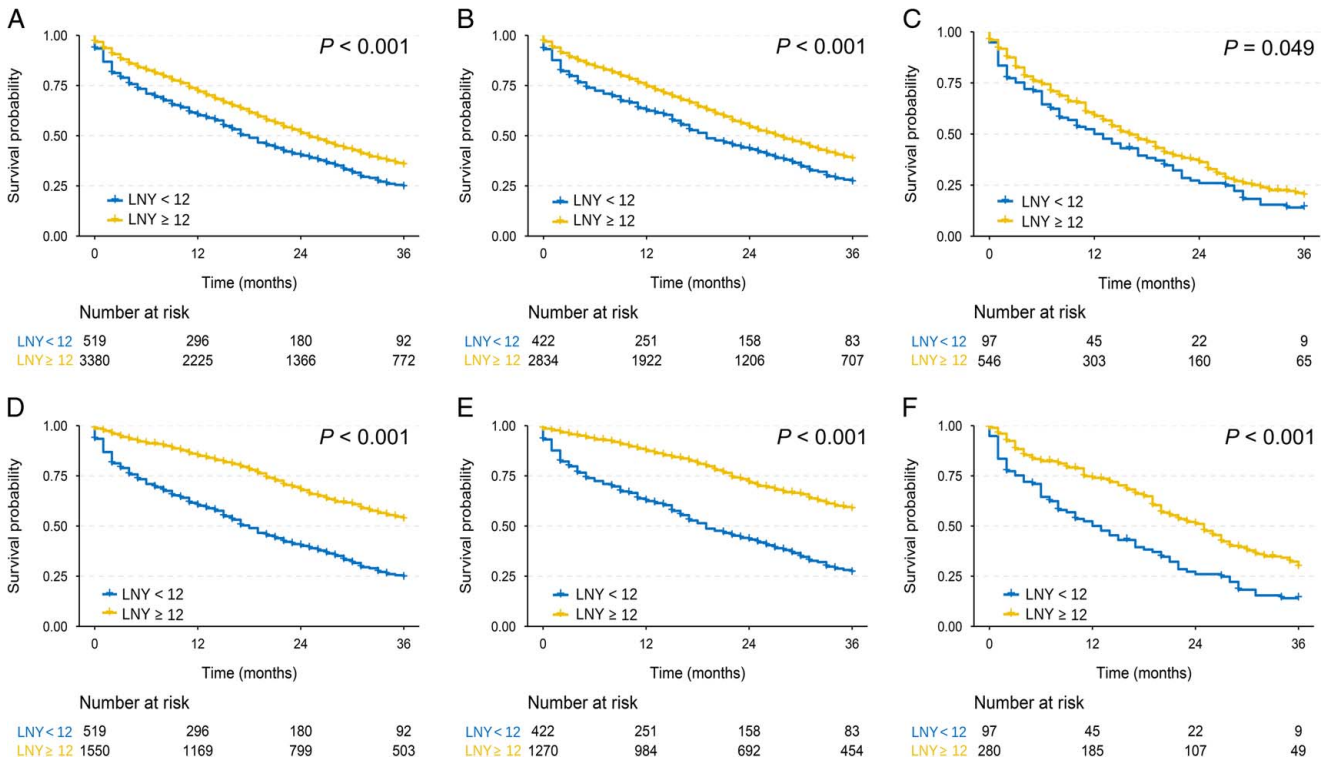

Figure 1. Cox adjusted survival curves stratified by the LNY among patients in the SEER database before and after PSM. (A) All patients in stage IV before PSM. (B) Patients in stage M1a before PSM. (C) Patients in stage M1b before PSM. (D) All patients in stage IV after PSM. (E) Patients in stage M1a after PSM. (F) Patients in stage M1b after PSM. LNY, lymph node yield; PSM, propensity score matching; SEER, Surveillance, Epidemiology, and End Results.

Survival analyses

In the SEER cohort, both before and after PSM, survival analysis showed that patients with LNY ≥12 was significantly associated with better CSS (all log-rank $P < 0.001$) compared with patients with LNY <12. A consistent trend was observed when only patients with AJCC M1a or M1b stages were included in the analysis (Fig. 1). All of the clinicopathological and surgery-related variables were included in the univariate analysis. As shown in Table 3, LNY, LNR, age, sex, primary tumor site, grade, histology type, AJCC M stage, preoperative CEA, and metastasectomy were potential prognostic factors for CSS (all $P < 0.05$). Next, variables that tended to be significant ($P < 0.05$) in univariate analysis were included in a multivariate Cox proportional hazards regression model. After controlling for other prognostic factors, patients with LNY ≥12 were still associated with better CSS (HR =0.38; 95% CI, 0.33–0.44; $P < 0.001$), patients with higher LNR were still associated with worse CSS (HR = 2.26; 95% CI, 1.80–2.84; $P < 0.001$) and patients who underwent metastases resection were associated with decreased relative risk of death (HR = 0.56; 95% CI, 0.45–0.69; $P < 0.001$).

In the Chinese cohort, survival analysis also showed that patients with LNY ≥12 was significantly associated with better CSS (all log-rank $P < 0.001$) compared with patients with LNY <12 both before and after PSM. The same relationship was observed when only patients with AJCC M1a or M1b stages were included in the analysis (Fig. 2). Univariable Cox regression model suggested that LNY, LNR, grade, histology type, AJCC M stage, preoperative CEA, and metastasectomy were all associated with CSS (all $P < 0.05$). After controlling for other prognostic factors, the multivariate analysis further demonstrated that patients with LNY ≥12 were still associated with better CSS (HR = 0.61; 95% CI, 0.45–0.82; $P = 0.001$), patients with higher LNR were still associated with worse CSS (HR = 4.02; 95% CI, 2.11–7.66; $P < 0.001$) and patients who underwent metastases resection were still associated with decreased relative risk of death (HR = 0.44; 95% CI, 0.33–0.58; $P < 0.001$).

In addition, we used PSM to balance the baseline covariates between the LNY <12 and LNY ≥12 subgroups of overall patients in the two registries (Supplementary Table 2, Supplemental Digital Content 2, http://links.lww.com/JS9/A240) and also compared the CSS curves of the overall patients. Survival analysis also showed that patients with LNY ≥12 was significantly associated with better CSS (all log-rank $P < 0.05$) compared with patients with LNY <12 both before and after PSM. The same relationship was observed when only patients with AJCC M1a or M1b stages were included in the analysis (Supplementary Fig. 2, Supplemental Digital Content 4, http://links.lww.com/JS9/A242).

Subgroup survival analysis

In the SEER cohort, the CSS benefit for patients with LNY ≥12 was observed across most, but not all, subgroups (Fig. 3). In particular, patients with mucinous/signet histology and those with AJCC T1–T2 stage did not have a clear benefit. In the Chinese cohort, the results showed the CSS superiority of the patients with LNY ≥12 over the patients with LNY <12 in the majority of subgroups, except in the subgroups of patients

Table 3

Multivariate Cox analysis for cancer-specific survival in colorectal cancer patients in stage IV in SEER database and Chinese registry after propensity score matching

		SEER database				Chinese registry			
		Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
Variables	Category	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
LNY	≥12 vs. <12	0.40 (0.35–0.46)	<0.001	0.38 (0.33–0.44)	<0.001	0.54 (0.41–0.72)	<0.001	0.61 (0.45–0.82)	0.001
LNR	–	4.40 (3.56–5.45)	<0.001	2.26 (1.80–2.84)	<0.001	6.84 (4.17–11.23)	<0.001	4.02 (2.11–7.66)	<0.001
Age (years)	>60 vs. ≤60	1.89 (1.65–2.17)	<0.001	1.71 (1.49–1.97)	<0.001	1.24 (0.94–1.64)	0.141		
Sex	Male vs. female	0.87 (0.77–0.99)	0.036	0.86 (0.76–0.98)	0.025	1.02 (0.75–1.37)	0.934		
Primary tumor site	Distal vs. proximal colon	0.66 (0.57–0.76)	<0.001	0.81 (0.70–0.94)	0.004	0.66 (0.42–1.03)	0.072		
	Rectum vs. proximal colon	0.49 (0.39–0.62)	<0.001	0.72 (0.56–0.91)	0.007	0.71 (0.46–1.12)	0.144		
Grade	Poorly/undifferentiated vs. well/moderately	2.33 (2.04–2.66)	<0.001	2.10 (1.83–2.41)	<0.001	1.40 (1.05–1.87)	0.021	1.09 (0.80–1.50)	0.584
Histology type	Mucinous/signet vs. adenocarcinoma	1.90 (1.55–2.34)	<0.001	1.65 (1.34–2.04)	<0.001	4.46 (2.19–9.09)	<0.001	5.27 (2.46–11.32)	<0.001
AJCC T stage	T3–T4 vs. T1–T2	1.03 (0.74–1.43)	0.872			3.01 (1.34–6.78)	0.008	2.22 (0.98–5.03)	0.056
AJCC N stage	N1–N2 vs. N0	1.16 (0.98–1.37)	0.092			1.88 (1.37–2.58)	<0.001	1.11 (0.75–1.64)	0.618
AJCC M stage	M1b vs. M1a	1.92 (1.66–2.23)	<0.001	1.93 (1.66–2.24)	<0.001	1.91 (1.11–3.28)	0.021	1.28 (0.72–2.26)	0.403
Preoperative CEA	High vs. normal	1.82 (1.38–2.38)	<0.001	2.18 (1.66–2.87)	<0.001	1.75 (1.09–2.80)	0.023	1.57 (0.97–2.53)	0.068
Metastasectomy	Yes vs. no	0.49 (0.40–0.61)	<0.001	0.56 (0.45–0.69)	<0.001	0.38 (0.29–0.51)	<0.001	0.44 (0.33–0.58)	<0.001

AJCC, American Joint Committee on Cancer; CEA, carcinoembryonic antigen; HR, hazard ratio; LNR, lymph node ratio; LNY, lymph node yield; SEER, Surveillance, Epidemiology, and End Results.

with mucinous/signet histology, female, and those with AJCC T1–T2 stage (Fig. 4).

In addition, we performed a separate analysis for the effect of LNY on prognosis at different primary tumor sites. In both registries, the CSS benefit for patients with LNY ≥12 was observed in the proximal and distal colon, but not in the rectum (Supplementary Fig. 3, Supplemental Digital Content 5, http://links.lww.com/JS9/A243).

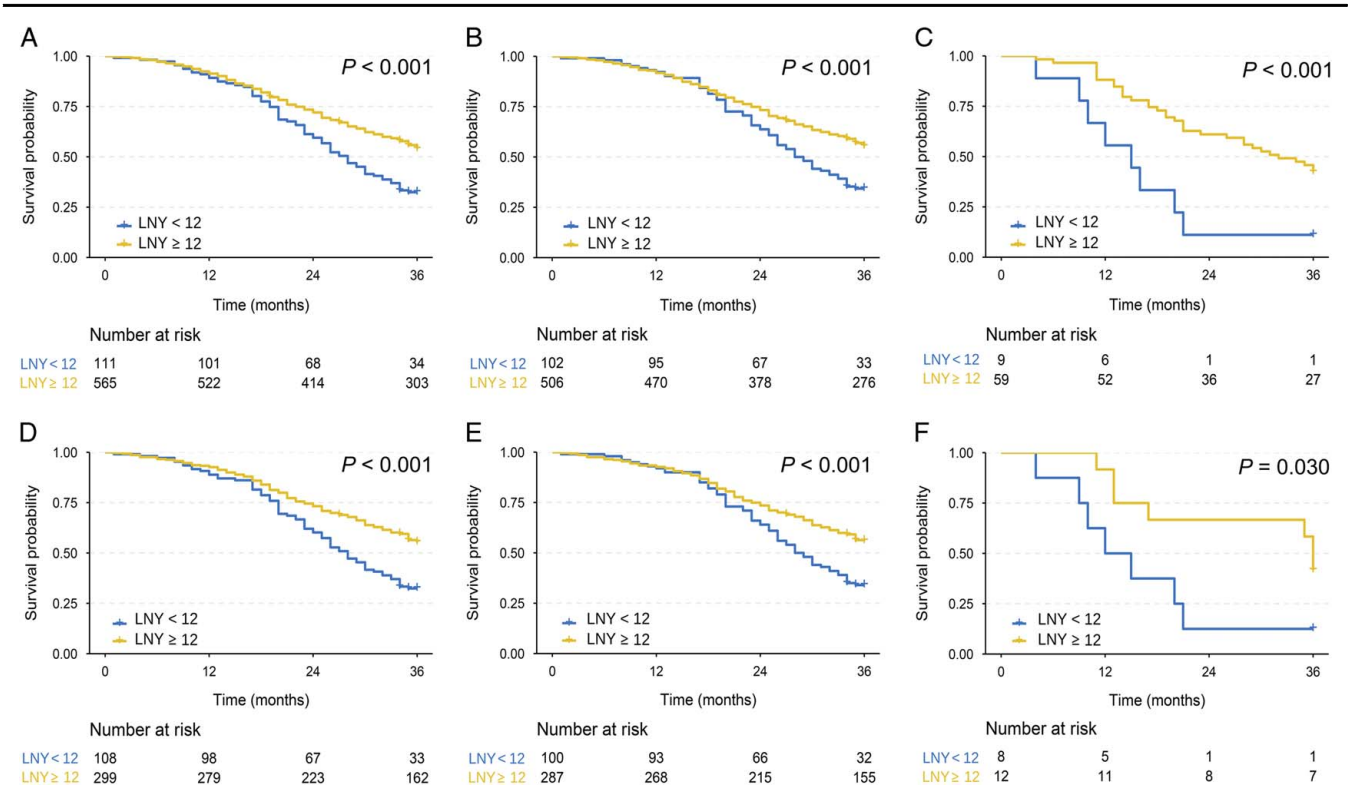

Figure 2. Cox adjusted survival curves stratified by the LNY among patients in the Chinese registry before and after PSM. (A) All patients in stage IV before PSM. (B) Patients in stage M1a before PSM. (C) Patients in stage M1b before PSM. (D) All patients in stage IV after PSM. (E) Patients in stage M1a after PSM. (F) Patients in stage M1b after PSM. LNY, lymph node yield; PSM, propensity score matching.

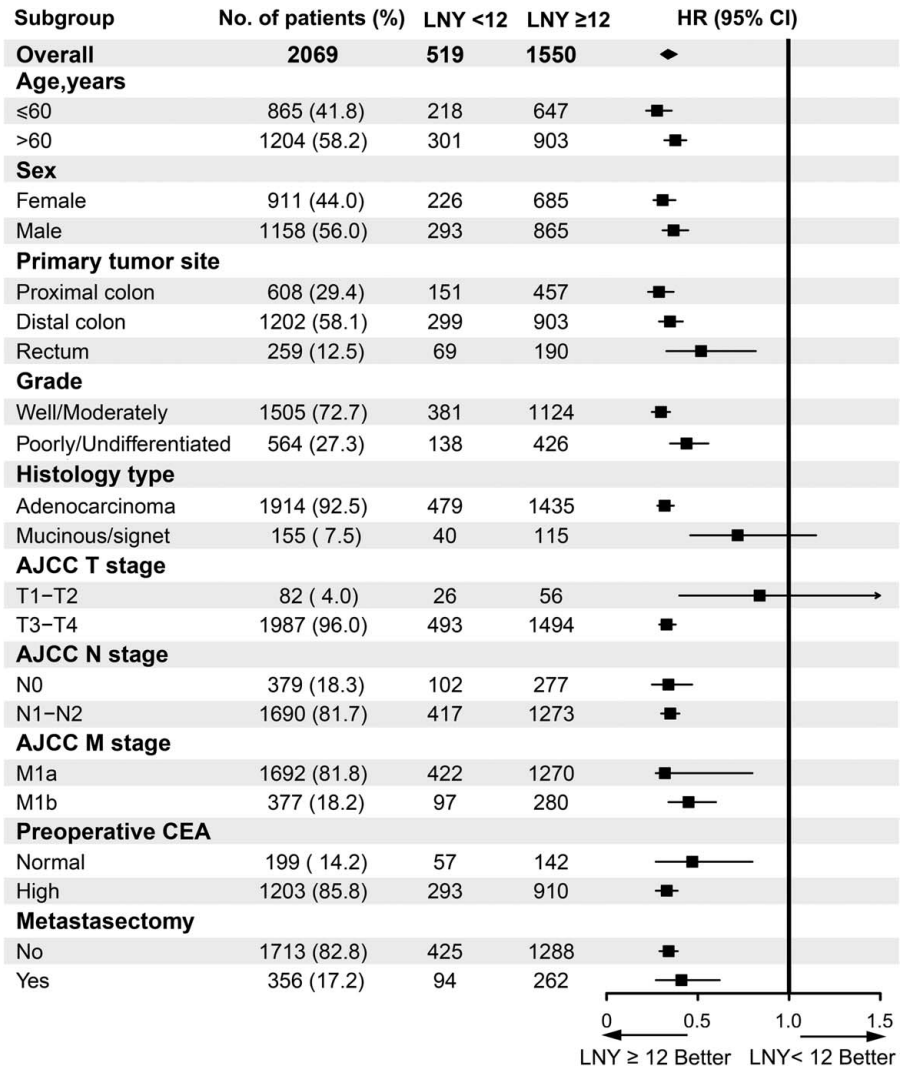

Figure 3. Subgroup analysis of survival in SEER database according to the LNY stratification. AJCC, American Joint Committee on Cancer; CEA, carcinoembryonic antigen; HR, hazard ratio; LNY, lymph node yield; SEER, Surveillance, Epidemiology, and End Results.

Discussion

In this international population-based study, we have explored practice outcomes related to LNY for CRC patients in stage IV treated with primary tumor resection and lymphadenectomy and to further validate its role of 12-node threshold as a quality indicator of surgical care. In our findings, patients in stage IV with more than 12 LNY exhibited significantly improved survival, indicating that the LNY considered as a powerful indicator for survival prediction and a quality indicator of surgical care in clinical practice. To our knowledge, this is the first study addressing the implications of the 12 LNY quality indicator on survival in patients with stage IV CRC based on two large cohorts.

Reassuringly, we found that most CRC patients had at least 12 LNY harvested at the time of primary tumor resection, which reflects an increased understanding of the importance of this metric as a critical principle of oncologic resection for CRC with efforts led by both surgeons and pathologists[8]. In concordant with the existing literature, our finding presented that resections of proximal colon tumors were more likely to reach a 12 LNY threshold compared with distal colon and rectum tumors, typically attributed to the longer size of right-sided specimens and thereby a higher LNY[14–16]. It is no surprise that more resected colorectal mesenteric tissue contribute to increased LNY, and variant lymphatic anatomy may also be another possible explanation[17]. In addition, the decrease in the number of LNY was due to the use of neoadjuvant chemoradiotherapy for rectal cancer patients[18–20].

For CRC patients in stage IV with resectable metastases, a 5-year overall survival of 60% can be achieved when surgery is feasible[21]. For those with initially non-resectable metastasis, current guides suggested that systemic chemotherapy should be administrated first to achieve secondary resection[22]. In this study, our analysis suggested that metastasectomy was an independent prognostic factor for survival, which was similar to the results of previous studies[23,24]. However, whether metastasectomy should be performed simultaneously with primary cancer

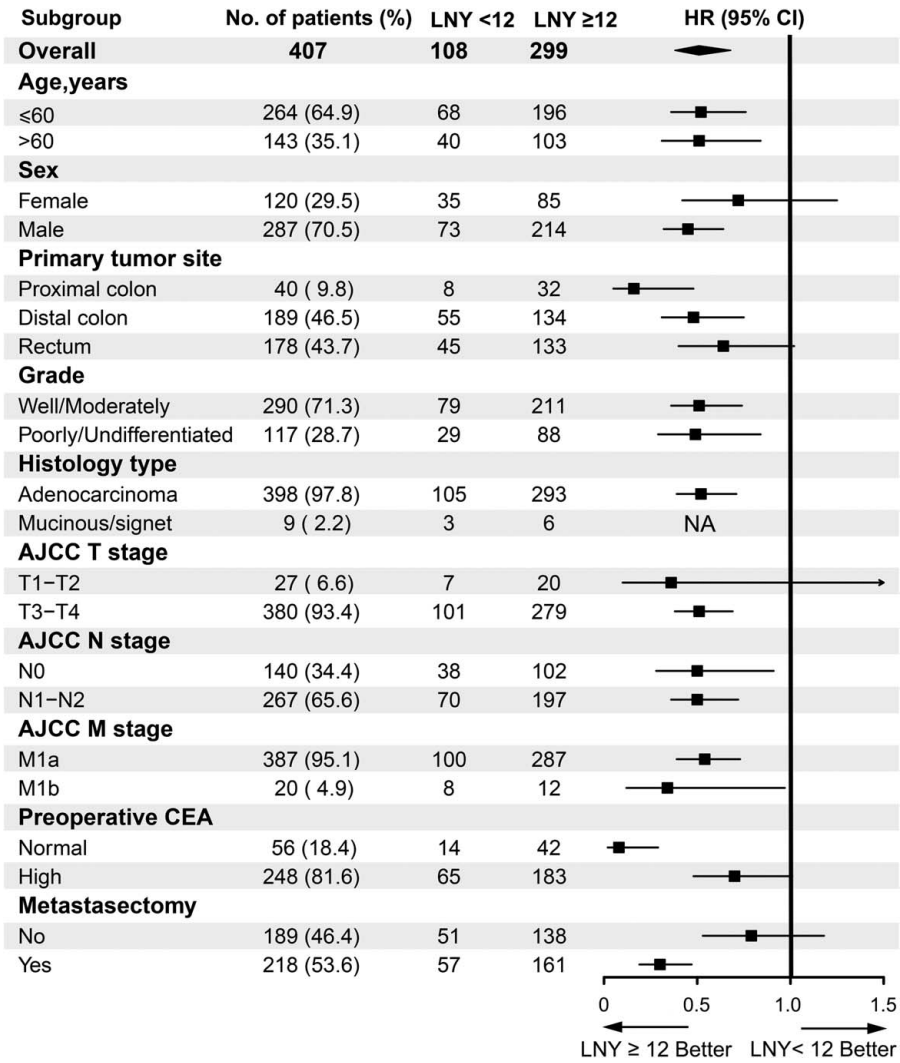

Figure 4. Subgroup analysis of survival in the Chinese registry according to the LNY stratification. AJCC, American Joint Committee on Cancer; CEA, carcinoembryonic antigen; HR, hazard ratio; LNY, lymph node yield; NA, not available.

or should be delayed remains controversial[25,26]. Thus, large-scale and multicenter prospective randomized studies are needed to compare both strategies in the future.

There are many reasons to explain that patients with distant metastasis influence the retrieval of LNY at the time of primary tumor resection. Surgeons may adjust the planned lymphadenectomy because of the patient healthy status and complexity in practice. Increased technical difficulty regarding surgery for patients in stage IV is often expressed by surgeons, particularly the elderly who are considered to be high-risk operative candidates secondary to any life-threatening comorbidities, which then alter to perform less extensive mesenteric resections. Our results also demonstrated that patients in stage IV with LNY ≥ 12 had better survival, predicting a better prognostic correlation with appropriate lymphadenectomy. Thus, an oncologically adequate lymphadenectomy is still a critical component of high-quality surgical care even in CRC patients with stage IV disease.

Whether the total LNY should be used as an ideal quality measure for CRC had been immensely investigated. Evidence suggested that non-metastatic CRC patients, particularly in stage II disease, with a reduced LNY had a worse prognosis[27]. Accurate determination of nodal status is crucial to accomplish adequate staging and an inadequate LNY assessed may result in stage migration, with attendant prognostic and possibly therapeutic impacts. Meanwhile, studies have consistently shown that increased LNY is associated with improvement in survival[28–30], even in rectal cancer patients treated with neoadjuvant chemoradiotherapy[20]. The main mechanism underlying the association between a higher LNY and better survival remains unknown. Some researchers contended that there were two aspects of cancer immunity exerted by tumor-draining lymph nodes, namely antitumor immunity and tolerance for cancer, and that the balance of cancer immunity inclines toward tolerance as cancer advances[31]. Therefore, resection of regional lymph nodes, despite them not being metastatic nodes, may reset this 'cancer-friendly' immunological balance, resulting in an improvement of patient prognosis.

In addition to these literatures, several studies suggested that the number of lymph nodes present in a given patient reflects, at least in part, the underlying tumor–host interaction. Tumor

factors may stimulate reactive lymph nodes to grow, making them more visible to be detected by surgeons and pathologists, and tumor antigens may stimulate germinal centers resulting in an increase in the number of lymph nodes[32]. This also partly explains our previous findings that why lymph nodes were more likely to be detected in younger patients compared with older patients because increasing age is associated with a decline in immune competence[15]. LNY may therefore be a marker for tumor–host immunologic interactions, which may ultimately predict disease progression. Further studies exploring the mechanism underlying the relationship between LNY and cancer immunity may identify novel therapeutic targets and should be pursued.

There are some limitations in our study. First, the present study had its selection bias due to its retrospective nature. Second, similar to other national databases, the present cohort cannot provide more detailed information on the individual surgeon, pathologist, and hospital-related factors which also can affect surgical outcomes and LNY[33]. Third, recurrence would more likely be one primary endpoint in this study, but SEER lacked the recurrence data and thus could not be analyzed, CSS instead. Most notably, information regarding the use of chemotherapy was not available to the authors, raising additional concerns related to the possible impact of neoadjuvant and adjuvant therapy on survival. Although alternative statistical strategy applied to the present study, such as PSM, may have helped minimize confounding, these limitations should be kept in mind while interpreting our study. Indeed, very few quality indicators are 'perfect,' the aim of our study remains to better elucidate an already set benchmark, especially when it is used as a standard for surgical quality assessment across CRC patients in stage IV.

Conclusions

Adequate LNY (12-node threshold) was achieved in the majority of primary tumor resections for CRC patients in stage IV, and the 12-node threshold was predictive of CSS for patients with distant metastases. Therefore, we support the clinical feasibility of the 12-node threshold as both a guideline quality metric of cancer care for CRC patients in stage IV. Meanwhile, institutions should continue to promote safe, high-quality, surgical care by experienced teams, with the goal of appropriate lymphadenectomy as part of comprehensive multidisciplinary cancer management.

Ethical approval

This study was approved by the Ethics Committee of the National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College (Approval No. 17-116/1439)

Sources of funding

This study was supported by the Sanming Project of Medicine in Shenzhen (Grant Number: No. SZSM201911012), the National Natural Science Foundation of China (Grant Number: 82100598), the National Key R&D Program for Young Scientists (Grant Number: 2022YFC2505700).

Author contribution

S.J.: data curation, study concept and design, statistical analysis, drafting of the manuscript. X.G.: conceptualization, funding acquisition, acquisition or interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content. R.W.: data curation, statistical analysis, drafting of the manuscript. W.Z.: data curation, formal analysis, statistical analysis. G.W.: conceptualization, formal analysis, critical revision of the manuscript for important intellectual content. X.W.: conceptualization, funding acquisition, critical revision of the manuscript for important intellectual content, technical support, and administrative support.

Conflicts of interest disclosure

The authors declare that they have no financial conflict of interest with regard to the content of this report.

Research registration unique identifying number (UIN)

1. Name of the registry: https://register.clinicaltrials.gov/
2. Unique Identifying number or registration ID: Unique Identifying number: NCT05550701
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://clinicaltrials.gov/ct2/show/NCT05550701

Guarantors

Xu Guan and Xishan Wang.

Provenance and peer review

None.

Acknowledgements

The authors thank the staff in Surveillance, Epidemiology, and End Results Program (SEER) for their kind work in data collection and delivery.

References

[1] Siegel RL, Miller KD, Fuchs HE, *et al*. Cancer statistics, 2021. CA Cancer J Clin 2021;71:7–33.
[2] Zhang GQ, Taylor JP, Stem M, *et al*. Aggressive multimodal treatment and metastatic colorectal cancer survival. J Am Coll Surg 2020;230:689–98.
[3] Nelson H, Petrelli N, Carlin A, *et al*. Guidelines 2000 for colon and rectal cancer surgery. J Natl Cancer Inst 2001;93:583–96.
[4] Shinagawa T, Tanaka T, Nozawa H, *et al*. Comparison of the guidelines for colorectal cancer in Japan, the USA and Europe. Ann Gastroenterol Surg 2018;2:6–12.
[5] West NP, Kobayashi H, Takahashi K, *et al*. Understanding optimal colonic cancer surgery: comparison of Japanese D3 resection and European complete mesocolic excision with central vascular ligation. J Clin Oncol 2012;30:1763–9.
[6] Chang GJ, Rodriguez-Bigas MA, Skibber JM, *et al*. Lymph node evaluation and survival after curative resection of colon cancer: systematic review. J Natl Cancer Inst 2007;99:433–41.

[7] Wong JH, Lum SS, Morgan JW. Lymph node counts as an indicator of quality at the hospital level in colorectal surgery. J Am Coll Surg 2011;213:226–30.
[8] Won DD, Choi SB, Lee YS, *et al*. The positive impact of surgical quality control on adequate lymph node harvest by standardized laparoscopic surgery and national quality assessment program in colorectal cancer. Int J Colorectal Dis 2017;32:975–82.
[9] Tran C, Howlett C, Driman DK. Evaluating the impact of lymph node resampling on colorectal cancer nodal stage. Histopathology 2020;77: 974–83.
[10] Bilchik A, Nissan A, Wainberg Z, *et al*. Surgical quality and nodal ultrastaging is associated with long-term disease-free survival in early colorectal cancer: an analysis of 2 international multicenter prospective trials. Ann Surg 2010;252:467–74; discussion 474–6.
[11] Doll KM, Rademaker A, Sosa JA. Practical guide to surgical data sets: Surveillance, Epidemiology, and End Results (SEER) Database. JAMA Surg 2018;153:588–9.
[12] Kuss O, Blettner M, Börgermann J. Propensity score: an alternative method of analyzing treatment effects. Dtsch Arztebl Int 2016;113:597–603.
[13] Thomas L, Li F, Pencina M. Using propensity score methods to create target populations in observational clinical research. JAMA 2020;323:466–7.
[14] Nedrebø BS, Søreide K, Nesbakken A, *et al*. Risk factors associated with poor lymph node harvest after colon cancer surgery in a national cohort. Colorectal Dis 2013;15:e301–8.
[15] Guan X, Chen W, Li S, *et al*. Alterations of lymph nodes evaluation after colon cancer resection: patient and tumor heterogeneity should be taken into consideration. Oncotarget 2016;7:62664–75.
[16] Moro-Valdezate D, Pla-Martí V, Martín-Arévalo J, *et al*. Factors related to lymph node harvest: does a recovery of more than 12 improve the outcome of colorectal cancer? Colorectal Dis 2013;15:1257–66.
[17] Ye K, Lin J, Sun Y, *et al*. Variation and treatment of vessels in laparoscopic right hemicolectomy. Surg Endosc 2018;32:1583–4.
[18] Mekenkamp LJ, van Krieken JH, Marijnen CA, *et al*. Lymph node retrieval in rectal cancer is dependent on many factors – the role of the tumor, the patient, the surgeon, the radiotherapist, and the pathologist. Am J Surg Pathol 2009;33:1547–53.
[19] Raoof M, Nelson RA, Nfonsam VN, *et al*. Prognostic significance of lymph node yield in ypN0 rectal cancer. Br J Surg 2016;103:1731–7.
[20] Wang Y, Zhou M, Yang J, *et al*. Increased lymph node yield indicates improved survival in locally advanced rectal cancer treated with neoadjuvant chemoradiotherapy. Cancer Med 2019;8:4615–25.
[21] van Amerongen MJ, van der Stok EP, Fütterer JJ, *et al*. Short term and long term results of patients with colorectal liver metastases undergoing surgery with or without radiofrequency ablation. Eur J Surg Oncol 2016;42:523–30.
[22] Wilke H, Stahl M. Colorectal cancer and metastasectomy: treatment of advanced disease. Ann Oncol 2000;11(suppl 3):45–9.
[23] Arhin ND, Shen C, Bailey CE, *et al*. Surgical resection and survival outcomes in metastatic young adult colorectal cancer patients. Cancer Med 2021;10:4269–81.
[24] Morris E, Treasure T. Surgical management and outcomes of colorectal cancer liver metastases. Cancer Epidemiol 2018;52:160–1.
[25] Boudjema K, Locher C, Sabbagh C, *et al*. Simultaneous versus delayed resection for initially resectable synchronous colorectal cancer liver metastases: a prospective, open-label, randomized, controlled trial. Ann Surg 2021;273:49–56.
[26] Gavriilidis P, Sutcliffe RP, Hodson J, *et al*. Simultaneous versus delayed hepatectomy for synchronous colorectal liver metastases: a systematic review and meta-analysis. HPB (Oxford) 2018;20:11–9.
[27] Foo CC, Ku C, Wei R, *et al*. How does lymph node yield affect survival outcomes of stage I and II colon cancer? World J Surg Oncol 2020;18:22.
[28] Backes Y, Elias SG, Bhoelan BS, *et al*. The prognostic value of lymph node yield in the earliest stage of colorectal cancer: a multicenter cohort study. BMC Med 2017;15:129.
[29] Vather R, Sammour T, Kahokehr A, *et al*. Lymph node evaluation and long-term survival in stage II and stage III colon cancer: a national study. Ann Surg Oncol 2009;16:585–93.
[30] Del Paggio JC, Peng Y, Wei X, *et al*. Population-based study to re-evaluate optimal lymph node yield in colonic cancer. Br J Surg 2017;104: 1087–96.
[31] Battaglia A, Buzzonetti A, Baranello C, *et al*. Metastatic tumour cells favour the generation of a tolerogenic milieu in tumour draining lymph node in patients with early cervical cancer. Cancer Immunol Immunother 2009;58:1363–73.
[32] Wright FC, Law CH, Last L, *et al*. Lymph node retrieval and assessment in stage II colorectal cancer: a population-based study. Ann Surg Oncol 2003;10:903–9.
[33] Becerra AZ, Aquina CT, Berho M, *et al*. Surgeon-, pathologist-, and hospital-level variation in suboptimal lymph node examination after colectomy: Compartmentalizing quality improvement strategies. Surgery 2017;161:1299–306.