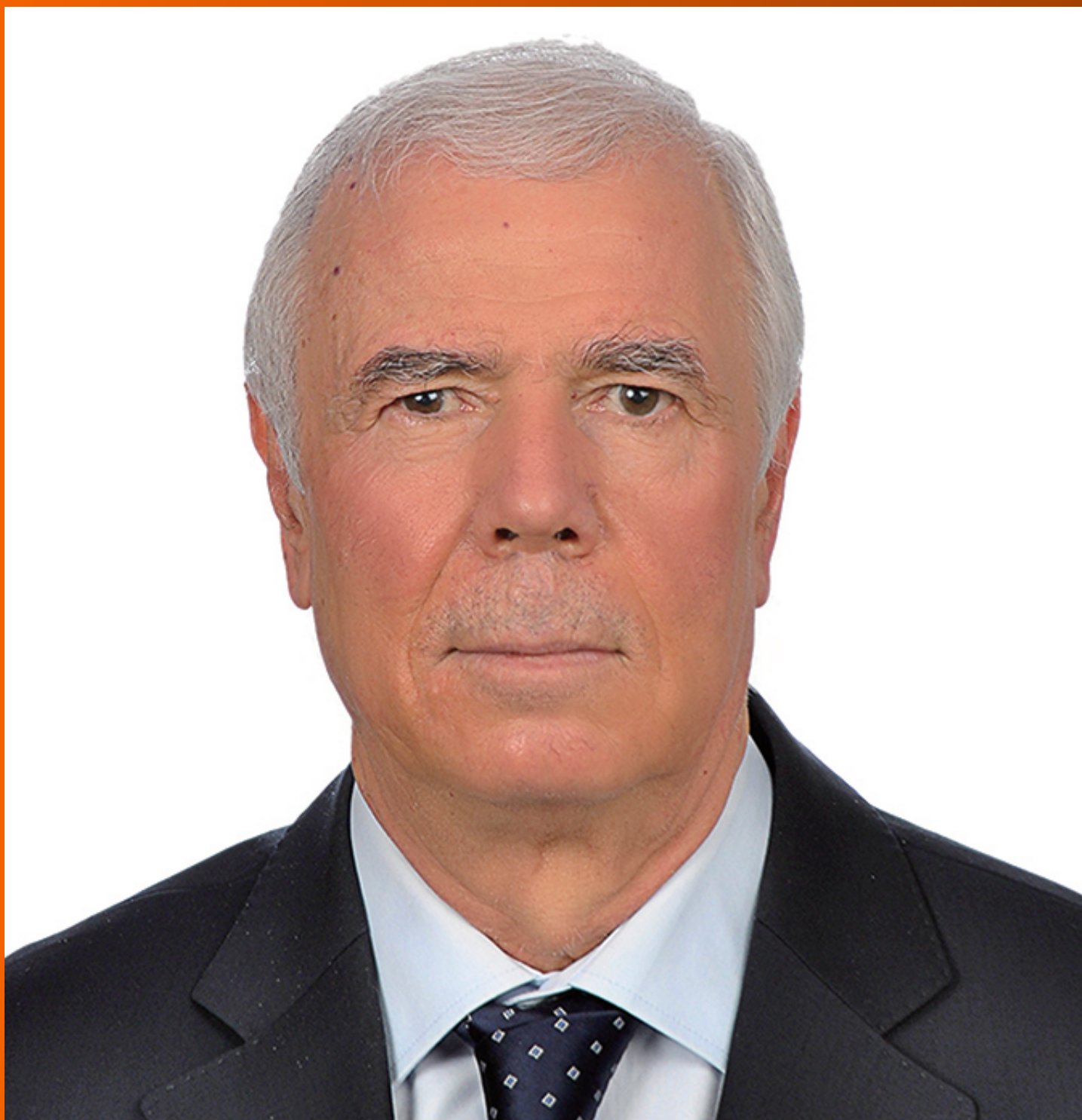


# World Journal of *Gastrointestinal Surgery*

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WJGS mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, etc.

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## Observational Study

# Long-term survival of patients with stage II and III gastric cancer who underwent gastrectomy with inadequate nodal assessment

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### Institutional review board

**statement:** This is a study using a population-based registry, so institutional review board was not

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## Abstract

### BACKGROUND

Gastric cancer is an aggressive disease with frequent lymph node (LN) involvement. The NCCN recommends a D2 lymphadenectomy and the harvesting of at least 16 LNs. This threshold has been the subject of great debate, not only for the extent of surgery but also for more appropriate staging. The reclassification of stage IIB through IIIC based on N3b nodal staging in the eighth edition of the American Joint Committee on Cancer (AJCC) staging system highlights the efforts to more accurately discriminate survival expectancy based on nodal number. Furthermore, studies have suggested that pathologic assessment of 30 or more LNs improve prognostic accuracy and is required for proper staging of gastric



applicable.

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cancer.

## AIM

To evaluate the long-term survival of advanced gastric cancer patients who deviated from expected survival curves because of inadequate nodal evaluation.

## METHODS

Eligible patients were identified from the Surveillance, Epidemiology, and End Results database. Those with stage II–III gastric cancer were considered for inclusion. Three groups were compared based on the number of analyzed LNs. They were inadequate LN assessment (ILA, < 16 LNs), adequate LN assessment (ALA, 16–29 LNs), and optimal LN assessment (OLA, ≥ 30 LNs). The main outcomes were overall survival (OS) and cancer-specific survival. Data were analyzed by the Kaplan-Meier product-limit method, log-rank test, hazard risk, and Cox proportional univariate and multivariate models. Propensity score matching (PSM) was used to compare the ALA and OLA groups.

## RESULTS

The analysis included 11607 patients. Most had advanced T stages (T3 = 48%; T4 = 42%). The pathological AJCC stage distribution was IIA = 22%, IIB = 18%, IIIA = 26%, IIIB = 22%, and IIIC = 12%. The overall sample divided by the study objective included ILA (50%), ALA (35%), and OLA (15%). Median OS was 24 mo for the ILA group, 29 mo for the ALA group, and 34 mo for the OLA group ( $P < 0.001$ ). Univariate analysis showed that the ALA and OLA groups had better OS than the ILA group [ALA hazard ratio (HR) = 0.84, 95% confidence interval (CI): 0.79–0.88,  $P < 0.001$  and OLA HR = 0.73, 95%CI: 0.68–0.79,  $P < 0.001$ ]. The OS outcome was confirmed by multivariate analysis (ALA HR = 0.68, 95%CI: 0.64–0.71,  $P < 0.001$  and OLA: HR = 0.48, 95%CI: 0.44–0.52,  $P < 0.001$ ). A 1:1 PSM analysis in 3428 patients found that the OLA group had better survival than the ALA group (OS: OLA median = 34 mo *vs* ALA median = 26 mo,  $P < 0.001$ , which was confirmed by univariate analysis (HR = 0.81, 95%CI: 0.75–0.89,  $P < 0.001$ ) and multivariate analysis: (HR = 0.71, 95%CI: 0.65–0.78,  $P < 0.001$ ).

## CONCLUSION

Proper nodal staging is a critical issue in gastric cancer. Assessment of an inadequate number of LNs places patients at high risk of adverse long-term survival outcomes.

**Key Words:** Gastric Cancer; Lymphadenectomy; Gastrectomy; Staging; N stage; Surveillance, Epidemiology, and End Results

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**Core Tip:** A large database was analyzed to investigate survival outcomes related to lymph node assessment in locally advanced gastric cancer patients with radical gastrectomy. Independent of TNM-stage, the group with assessment of < 16 lymph nodes (LNs) had significantly worse survival than two other groups, 16–29 LNs and ≥ 30 LNs. Stage migration because of inadequate specimen analysis and improper lymphadenectomy was the main root cause.

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## INTRODUCTION

Lymph node (LN) involvement in gastric cancer is one of the most significant prognostic factors for survival. Starting with the fifth edition of the Union for International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC) cancer staging manual, the N category has been evaluated based on the total number of metastatic LNs detected in a surgical specimen, independent of their retrieved locations[1]. Until recently, the N3 category required the identification of at least 15 positive LNs. However, the seventh edition revisions of nodal classification introduced the N3a (7–15 positive LNs) and N3b ( $\geq 16$  positive LNs) substages[2], with the updates having a significant impact on the eighth edition updates to stages IIB through IIIA-C[3]. Consequently, the current guidelines recommend the analysis of at least 16 LNs[4].

Despite the national guidelines, many studies particularly those from Western countries continue to show high rates of inadequate nodal assessment[5–7]. To mitigate the effects of stage migration and survival inaccuracies in patients with locally advanced gastric cancer, use of the ratio of positive to total LN has been proposed[8]. However, the utility of existing prognostic methods remains limited in patients with an insufficient total number of assessed LNs. This study aimed to evaluate the survival impact of inadequate LN assessment (ILA) in patients with advanced gastric cancer disease (stages II and III) compared with that of patients receiving adequate and optimal nodal evaluation ( $\geq 30$  LNs), as defined in the latest AJCC cancer staging manual[9].

## MATERIALS AND METHODS

### *Patient source and definitions*

Eligible patients were identified in the Surveillance, Epidemiology, and End Results (SEER) database[10] and detailed data were retrieved with SEER\*Stat 8.3.5 software <https://seer.cancer.gov/seerstat/>. Patients 18 years of age or older with a diagnosis of stage II–III gastric cancer, according to the eighth edition of the AJCC cancer staging manual[9], were included in the study. Patients with cardiac tumors, without resective surgery, without available LN assessment information, and patients without follow-up duration data were excluded from the study. Tumor location was identified using the “primary site labeled” variable (C16.1: fundus of stomach; C16.2: body of stomach; C16.3: gastric antrum; C16.4: pylorus; C16.5: lesser curvature of stomach, NOS; C16.6: greater curvature of stomach, NOS; C16.8: overlapping lesion of stomach; and C16.9: stomach, NOS). Histology was evaluated by the International Classification of Disease for Oncology (ICD-O-3; M-8010/3–M-8015/3, M-8020/3–M-8022/3, M-8030/3–M-8035/3, M-8041/3, M-8043/3, M-8050/3–M-8052/3, M-8070/3–M-8078/3, M-8140/3–M-8145/3, M-8147/3, M-8210/3–M-8211/3, M-8214/3, M-8220/3, M-8221/3, M-8230/3, M-8231/3, M-8255/3, M-8260/3–M-8263/3, M-8310/3, M-8323/3, M-8480/3, M-8481/3, M-8490/3, M-8510/3, M-8560/3, M-8562/3, M-8570/3–M-8576/3, and M-8980/3–M-8982/3).

### *Decoding of treatment*

The study population was divided into three groups based on the number of retrieved and analyzed LNs, which were inadequate LN assessment (ILA),  $< 16$  LNs, adequate LN assessment (ALA), 16–29 LNs, and optimal LN assessment (OLA),  $\geq 30$  LNs. The type of gastrectomy was identified using cancer-specific codes (40–42, 50, 52, and 62 indicated total or near-total gastrectomy and 30–33, 51, 60, 61, and 63 indicated partial gastrectomy). “CHT recode” and “radiation recode” were used to determine whether single or combined treatments were administered. The “CS Tumor Size/Ext Eval (2004 +)” and “CS Reg Node Eval (2004 +)” codes were used to identify patients who received neoadjuvant treatment.

### *Statistical analysis*

Patient characteristics were summarized by descriptive statistics. The study groups were compared using Pearson’s chi square test or Student’s *t*-test, as appropriate. Overall survival (OS) was defined as the duration from the date of diagnosis to death or last follow-up, with no restriction on the cause of death. Cancer-specific survival (CSS) was defined as the duration from the date of diagnosis to death from gastric cancer other than other causes. Patients with a follow-up of less than 1 mo and patients without data on their alive or dead status were excluded from the survival analysis.

OS and CSS were calculated using the Kaplan-Meier product-limit method.

The log-rank test was used to assess potential differences between subgroups. The hazard ratio (HR) and its relative 95% confidence interval (CI) were estimated for each parameter of interest using the Cox proportional univariate model while adopting the most suitable prognostic category as the referent group. In addition, a multivariate Cox proportional hazard model was developed by stepwise regression (forward selection). The enter and remove limits were  $P = 0.05$  and  $P = 0.10$ , respectively. Significance was defined at the  $P < 0.05$  level.

To control for potential confounders that could affect the outcomes of interest, propensity score matching (PSM)[11,12] was employed to generate two treatment groups with a balanced distribution of baseline features. Propensity scores were obtained from logistic regression, and the dependent variable was the choice to undergo surgery. The retrieval of 16–29 LNs was the control. The selected covariates were diagnosis period, age at diagnosis, sex, race, primary site, eighth edition N, and T stage, histology, and grading. To ensure good matches, patients were matched 1:1 using the nearest neighbor method and a caliper distance of 0.25 of the standard deviation of the logit of the estimated propensity score. Balance between the two groups was assessed using the relative multivariate imbalance measure, L1, as proposed by Iacus *et al*[13,14]. All analyses were carried out with SPSS v. 21.0. The statistical methods were reviewed by one of the authors of this manuscript (Terrenato I).

## RESULTS

### **Baseline patient characteristics of the total sample population**

Based on the inclusion criteria, we studied 11,607 patients with stage II–III gastric carcinoma diagnosed between 2004 and 2015 (Table 1). There were 6697 men (58%) in the sample population, and the mean age at diagnosis was 69 years of age. In 4626 patients (40%), the tumor was located at the antrum/pylorus, and a poorly/undifferentiated adenocarcinoma was reported in 8524 patients (73%). Neoadjuvant chemotherapy was administered in 11% of cases, and a partial gastrectomy was performed in 72%. Most patients had advanced T stages (T3 = 5,569, 48%; T4a = 3,551, 31%; T4b = 1,254, 11%), while T1–T2 stages accounted for only 10% of the total sample. The patient distribution based on the N stages reported in the SEER registry was N0 = 2,863, 25%; N1 = 2,422, 21%; N2 = 2,757, 24%; N3a = 2,498, 21%; and N3b = 1,067, 9%. The patient distribution based on gastric cancer stage was IIA = 2,585, 22%; IIB = 2,129, 18%; IIIA = 3,049, 26%; IIIB = 2,511, 22%; and IIIC = 1,333, 12%.

### **Treatment groups**

Based on the overall number of retrieved LNs, patients were divided into three groups, ILA (< 16 LNs = 5806, 50%), ALA (16–29 LNs = 4085, 35%), and OLA, 30 + LNs = 1716, 15%). Clinicopathologic characteristics are reported in Table 2. In the last study period, a distribution trend for the total sample population was identified and determined to be in favor of the OLA group (30% vs 19% in the ILA and ALA groups, respectively). The median age was higher in the ILA group (71 years) than in the other two groups, 68 years in the ALA group and 65 years in the OLA group. No differences were found in the T1, T2, and T4b stage rates, and only slight differences were found in the T3 (50% vs 47% vs 46%) and T4a (29% vs 32% vs 33%) stage rates ( $P < 0.001$ ).

As expected, significant differences were identified for the N stage variable. In particular, most patients in the ILA group were classified in the N0 and N1 stages (31% and 26%, respectively). However, that was not the case in the ALA (19% and 16%, respectively) and OLA (15% and 13%, respectively) groups. Regarding staging, no patients in the ILA group were staged as N3b, and 16% were staged as N3a. The findings affected the attribution of the condensed stage. Most patients in the ILA group were in stage II or IIIA, while only 18% and 3% were in stages IIIB and IIIC, respectively. In contrast, 27% and 16% of the patients in the ALA group were in these stages, respectively, and 21% and 31% of the patients in the OLA group were in these stages, respectively ( $P < 0.001$ ). Differences were also seen in the treatments administered; most patients in the ILA group received a partial gastrectomy, and few received neoadjuvant therapy (7%).

### **Survival outcomes in the total sample population**

Figure 1 shows the survival curves of the overall sample. The median OS was 27 mo (95% CI: 26.1–27.9), and the median CSS was 33 mo (95% CI: 31.5–34.5). OS in each



**Table 1 Sample characteristics, *n* (%)**

Characteristic	<i>n</i> (%)
Year of diagnosis	
2004-2006	3142 (27)
2007-2009	3028 (26)
2010-2012	2850 (25)
2013-2015	2587 (22)
Age at diagnosis (yr)	
Median (range)	69 (12-99)
Sex	
Male	6697 (58)
Female	4910 (42)
Race	
White	7045 (61)
Black	2076 (18)
Asian/Pacific	2486 (21)
Marital status	
Single/divorced	2539 (22)
Married	6805 (58)
Widowed	1837 (16)
NA	426 (4)
Insurance status	
Insured	8033 (69)
Uninsured	432 (4)
NA	3142 (27)
Site of tumor	
Fundus/body	1866 (16)
Antrum/pylorus	4626 (40)
Overlapping lesion	1299 (11)
Stomach, NOS	3816 (33)
Tumor size (cm)	
≤ 5	5431 (47)
5.1-10	4203 (36)
≥ 10.1	1135 (10)
NA	838 (7)
Histology	
ADC, NOS	4481 (39)
Signet ring cell carcinoma	2726 (23)
ADC, intestinal type	1943 (17)
Carcinoma, diffuse type	958 (8)
ADC with mixed subtypes	424 (4)
Other	1075 (9)
Grade	

Well/moderately differentiated	2674 (23)
Poorly/undifferentiated	8524 (73)
NA	409 (4)
T stage, 8 <sup>th</sup> ed.	
T1	290 (2)
T2	943 (8)
T3	5569 (48)
T4a	3551 (31)
T4b	1254 (11)
N stage, 8 <sup>th</sup> ed.	
N0	2863 (25)
N1	2422 (21)
N2	2757 (24)
N3a	2498 (21)
N3b	1067 (9)
Stage, 8 <sup>th</sup> ed.	
IIA	2585 (22)
IIB	2129 (18)
IIIA	3049 (26)
IIIB	2511 (22)
IIIC	1333 (12)
Chemotherapy	
Yes	6473 (56)
No	5134 (44)
Neoadjuvant chemotherapy	
Yes	1255 (11)
No	10352 (89)
Radiotherapy	
Yes	4285 (37)
No	7322 (63)
Type of surgery	
Partial gastrectomy	8320 (72)
Total gastrectomy	3287 (28)
Number of retrieved lymphnodes	
< 16 LNs (ILA)	5806 (50)
16-29 LNs (ALA)	4085 (35)
≥ 30 LNs (OLA)	1716 (15)

ADC: Adenocarcinoma; ALA: Adequate lymph node assessment; ILA: Inadequate lymph node assessment; LN: Lymph node; NA: Not available, NOS: Not otherwise specified; OLA: Optimal lymph node assessment.

disease stage (Figure 1) was stage IIA = 69 mo (95%CI: 63.1–74.9), stage IIB = 42 mo (95%CI: 38.6–45.4), stage IIIA = 24 mo (95%CI: 22.5–25.5), stage IIIB = 17 mo (95%CI: 16.1–17.9), and stage IIIC = 13 mo (95%CI: 12.2–13.8). OS in each N stage was N0 = 51 mo (95%CI: 46.2–55.8), N1 = 36 mo (95%CI: 33.0–39.0), N2 = 27 mo (95%CI: 25.2–28.8), N3a = 17 mo (95%CI: 16.0–18.0), and N3b = 14 mo (95%CI: 13.1–14.9).

**Table 2** Sample characteristics by the number of retrieved lymph nodes, *n* (%)

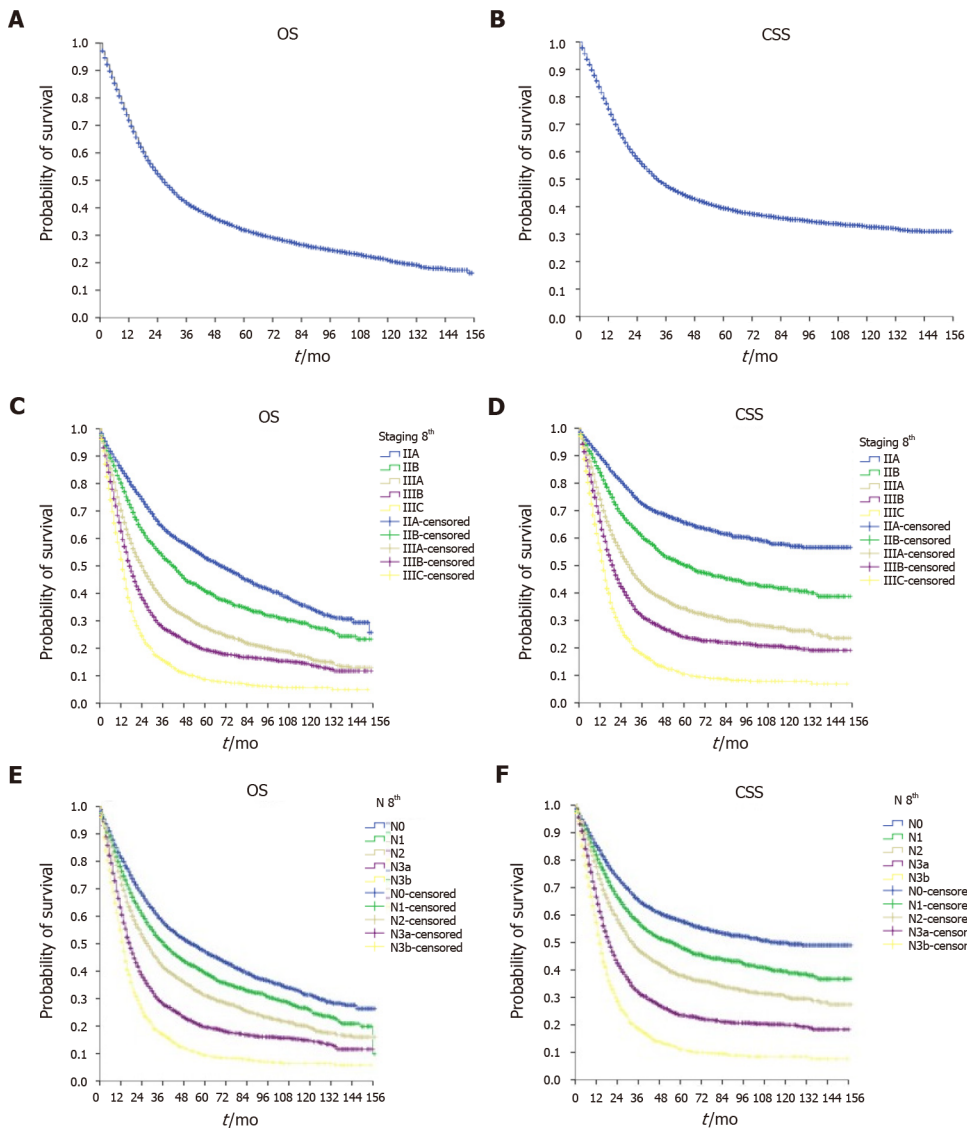
Characteristic	ILA	ALA	OLA	P value
	<i>n</i> = 5806	<i>n</i> = 4085	<i>n</i> = 1716	
Year of diagnosis				< 0.001
2004-2006	1861 (32)	947 (23)	334 (20)	
2007-2009	1563 (27)	1071 (26)	394 (23)	
2010-2012	1299 (22)	1080 (27)	471 (27)	
2013-2015	1083 (19)	987 (19)	517 (30)	
Age at diagnosis (yr)				< 0.001
Median (range)	71 (12-99)	68 (14-98)	65 (18-93)	
Sex				0.218
Male	3365 (58)	2318 (57)	1014 (59)	
Female	2441 (42)	1767 (43)	702 (41)	
Race				< 0.001
White	3695 (64)	2377 (58)	973 (57)	
Black	1061 (18)	747 (18)	268 (15)	
Asian/Pacific	1050 (18)	961 (24)	475 (28)	
Marital status				< 0.001
Single/divorced	1261 (22)	900 (22)	378 (22)	
Married	3282 (57)	2439 (60)	1084 (63)	
Widowed	1059 (18)	595 (15)	183 (11)	
NA	204 (3)	151 (4)	71 (4)	
Insurance status				< 0.001
Insured	3721 (64)	2998 (73)	68 (4)	
Uninsured	224 (4)	140 (4)	1314 (77)	
NA	1861 (32)	924 (23)	334 (20)	
Primary site				< 0.001
Fundus/body	835 (14)	696 (17)	335 (19)	
Antrum/pylorus	2562 (44)	1511 (37)	553 (32)	
Overlapping lesion	549 (10)	515 (13)	235 (14)	
Stomach, NOS	1860 (32)	1363 (33)	593 (35)	
Tumor size (cm)				< 0.001
≤ 5	2977 (51)	1808 (44)	646 (38)	
5.1-10	1906 (33)	1573 (39)	724 (42)	
≥ 10.1	438 (8)	448 (11)	249 (15)	
NA	485 (8)	256 (6)	97 (6)	
Hystology				< 0.001
ADC, NOS	2426 (42)	1517 (37)	538 (31)	
Signet ring cell carcinoma	1248 (22)	997 (24)	481 (28)	
ADC, intestinal type	928 (16)	702 (17)	313 (18)	
Carcinoma, diffuse type	422 (7)	360 (9)	176 (10)	
ADC with mixed subtypes	170 (3)	166 (4)	88 (5)	
Other	612 (10)	343 (9)	120 (7)	

Grade				< 0.001
Well/moderately differentiated	1493 (26)	862 (21)	319 (19)	
Poorly/undifferentiated	4072 (70)	3106 (76)	1346 (78)	
NA	241 (4)	117 (3)	51 (3)	
T stage, 8 <sup>th</sup> ed.				< 0.001
T1	111 (2)	131 (3)	48 (3)	
T2	490 (8)	321 (8)	132 (8)	
T3	2877 (50)	1897 (47)	795 (46)	
T4a	1658 (29)	1321 (32)	572 (33)	
T4b	670 (11)	415 (10)	169 (10)	
N stage, 8 <sup>th</sup> ed.				< 0.001
N0	1810 (31)	794 (19)	259 (15)	
N1	1528 (26)	671 (16)	223 (13)	
N2	1517 (26)	900 (22)	340 (20)	
N3a	951 (16)	1167 (29)	380 (22)	
N3b	0	553 (14)	514 (30)	
Stage, 8 <sup>th</sup> ed.				< 0.001
IIA	1557 (27)	775 (19)	253 (15)	
IIB	1293 (22)	621 (15)	215 (13)	
IIIA	1754 (30)	942 (23)	353 (20)	
IIIB	1055 (18)	1091 (27)	365 (21)	
IIIC	147 (3)	656 (16)	530 (31)	
Chemotherapy				< 0.001
Yes	2814 (48)	2490 (61)	1169 (68)	
No	2992 (52)	1595 (39)	547 (32)	
Neoadjuvant chemotherapy				< 0.001
Yes	408 (7)	536 (13)	311 (18)	
No	5398 (93)	3549 (87)	1405 (82)	
Radiotherapy				< 0.001
Yes	1993 (34)	1630 (40)	662 (39)	
No	3813 (66)	2455 (60)	1054 (61)	
Type of surgery				< 0.001
Partial gastrectomy	4623 (80)	2742 (67)	955 (56)	
Total gastrectomy	1183 (20)	1343 (33)	761 (44)	

ADC: Adenocarcinoma; NA: Not available; NOS: Not otherwise specified.

### Survival by group

As shown in [Figure 2](#), the ILA group had the worst median OS (24, 95%CI: 22.9–25.1 mo) and median CSS (30, 95%CI: 28.4–31.6 mo) compared with the ALA group (median OS = 29, 95%CI: 27.2–30.8 mo and median CSS = 36, 95%CI: 32.9–39.1 mo,  $P < 0.001$ ) and the OLA group (median OS = 34, 95%CI: 30.0–38.0 mo and median CSS = 42, 95%CI: 35.9–48.1 mo,  $P < 0.001$ ). Of note, when comparing the ALA and OLA groups, the difference was significant for OS ( $P < 0.001$ ) but not for CSS ( $P < 0.078$ ). [Figures 3–5](#) show OS and CSS by the stage of disease and are arranged by study group. The actual survival curves for ILA group within stage IIA revealed significantly worse outcomes for ILA and ALA compared with OLA. The three substages of stage III in the



**Figure 1 Survival analysis of the entire sample.** A and B: Kaplan-Meier curves of overall survival (OS) (A) and cancer-specific survival (CSS) (B); C and D: Kaplan-Meier curves of OS (C) and CSS (D) of different stages; E and F: Kaplan-Meier curves of OS (E) and CSS (F) based of different N categories.

IIA group did not have the expected distribution, as found in the ALA and OLA groups.

The findings were confirmed after evaluating OS and CSS by the N stage (Figures 3-5). The OLA group had the best discrimination profile among the survival curves (Figure 5). In contrast, the IIA group did not have a survival curve for the N3b substage, and the difference between the N0 and N+ patients in that group was not as consistent as in the other two groups (Figure 3). Of note, the ALA group had an adequate patient distribution (Figure 4). However, the mean difference between the N3a and N3b substages was only 7 mo in the ALA group compared with 23 mo in the OLA group.

#### Univariate and multivariate analyses of the total population

As shown in Table 3, the Cox regression model univariate analysis clearly showed that the ALA and OLA groups had better OS (ALA HR = 0.84, 95%CI: 0.79–0.88,  $P < 0.001$  and OLA HR = 0.73, 95%CI: 0.68–0.79,  $P < 0.001$ ) and CSS (ALA HR = 0.85, 95%CI: 0.81–0.90,  $P < 0.001$  and OLA HR = 0.80, 95%CI: 0.74–0.86,  $P < 0.001$ ) than the IIA group. Other prognostic factors related to OS and CSS included age, race, site of tumor, histology, grade, T stage, N stage, stage of disease, type of gastrectomy, chemotherapy, neoadjuvant therapy, and radiotherapy. After adjusting for other variables in the multivariate Cox analysis (Table 3), the ALA and OLA groups still had significantly better OS (ALA HR = 0.68, 95%CI: 0.64–0.71,  $P < 0.001$  and OLA HR = 0.48, 95%CI: 0.44–0.52,  $P < 0.001$ ) and CSS (ALA HR = 0.64, 95%CI: 0.60–0.68,  $P < 0.001$ )

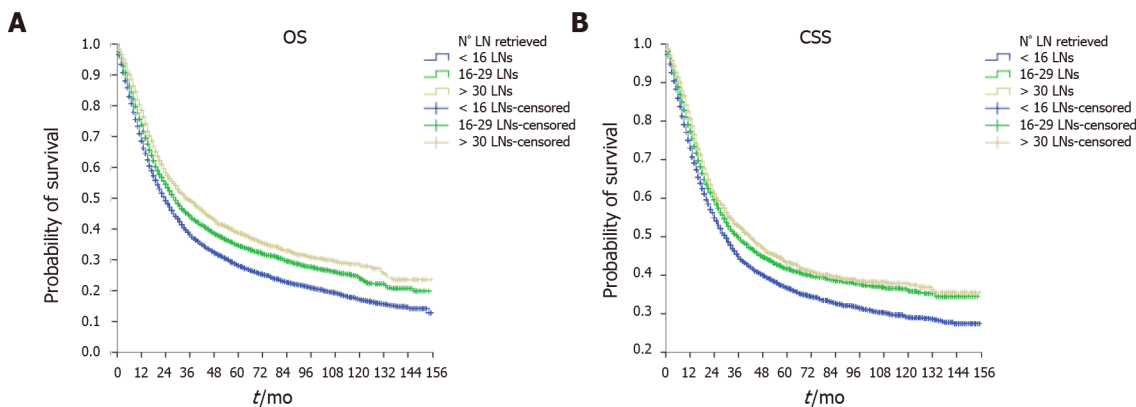


Table 3 Cox regression analysis of overall survival and cancer-specific survival

Variable	Overall survival				Cancer-specific survival			
	Univariable		Multivariable <sup>†</sup>		Univariable		Multivariable <sup>†</sup>	
	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value
Sex								
Male	Reference				Reference			
Female	1.03 (0.99-1.08)	0.171			1.07 (1.02-1.13)	0.006		
Age, yr								
< 70	Reference		Reference		Reference		Reference	
≥ 70	1.57 (1.50-1.64)	< 0.001	1.51 (1.43-1.59)	< 0.001	1.32 (1.26-1.39)	< 0.001	1.33 (1.26-1.41)	< 0.001
Race								
White	Reference				Reference		Reference	
Black	0.97 (0.91-1.03)	0.283	1.11 (1.05-1.18)	0.001	0.97 (0.90-1.03)	0.317	1.10 (1.03-1.18)	0.005
Asian/Pacific	0.80 (0.75-0.85)	< 0.001	0.82 (0.77-0.87)	< 0.001	0.82 (0.77-0.87)	< 0.001	0.83 (0.78-0.89)	< 0.001
Insurance status								
NA	Reference				Reference			
Insured	0.92 (0.88-0.97)	0.001			1.05 (0.91-1.21)	0.550		
Uninsured	0.96 (0.84-1.09)	0.501			0.95 (0.83-1.09)	0.459		
Site of tumor								
Fundus-body	Reference				Reference			
Antrum-pylorus	1.08 (1.01-1.15)	0.030			1.08 (0.99-1.16)	0.055		
Overlapping lesion of the stomach	1.30 (1.19-1.42)	< 0.001			1.35 (1.23-1.49)	< 0.001		
Stomach, NOS	1.05 (0.98-1.13)	0.167			1.04 (0.96-1.12)	0.373		
Histology								
ADC, NOS	Reference		Reference		Reference		Reference	
Signet ring cell carcinoma	1.16 (1.09-1.23)	< 0.001	1.14 (1.07-1.21)	< 0.001	1.28 (1.20-1.37)	< 0.001	1.16 (1.09-1.25)	< 0.001
ADC, intestinal type	0.87 (0.81-0.93)	< 0.001	0.98 (0.91-1.05)	0.547	0.79 (0.73-0.86)	< 0.001	0.93 (0.86-1.01)	0.086
Carcinoma, diffuse type	1.15 (1.06-1.26)	0.001	1.12 (1.03-1.23)	0.011	1.22 (1.11-1.34)	< 0.001	1.11 (1.00-1.22)	0.045
ADC with mixed subtypes	1.06 (0.94-1.20)	0.349	1.09 (0.96-1.24)	0.169	1.12 (0.98-1.28)	0.103	1.08 (0.94-1.24)	0.281
Other	0.92 (0.85-1.00)	0.062	0.97 (0.89-1.06)	0.543	0.95 (0.86-1.04)	< 0.001	1.01 (0.92-1.11)	0.862
T stage, 8 <sup>th</sup> ed.								
T1	Reference		Reference		Reference		Reference	
T2	1.13 (0.93-1.36)	0.217	1.08 (0.88-1.32)	0.455	1.12 (0.89-1.41)	0.322	1.01 (0.79-1.28)	0.963
T3	1.52 (1.28-1.80)	< 0.001	1.37 (1.09-1.73)	0.008	1.69 (1.37-2.07)	< 0.001	1.34 (1.02-1.76)	0.033
T4a	2.34 (1.98-2.78)	< 0.001	1.72 (1.33-2.22)	< 0.001	2.89 (2.35-3.55)	< 0.001	1.70 (1.27-2.28)	< 0.001
T4b	2.83 (2.37-3.38)	< 0.001	2.08 (1.48-2.93)	< 0.001	3.54 (2.86-4.39)	< 0.001	2.06 (1.40-3.01)	< 0.001
N stage, 8 <sup>th</sup> ed.								
N0	Reference		Reference		Reference		Reference	
N1	1.22 (1.14-1.31)	< 0.001	1.30 (1.16-1.46)	< 0.001	1.31 (1.21-1.43)	< 0.001	1.26 (1.10-1.43)	0.001
N2	1.49 (1.39-1.59)	< 0.001	1.49 (1.28-1.73)	< 0.001	1.70 (1.57-1.84)	< 0.001	1.44 (1.22-1.70)	< 0.001
N3a	2.05 (1.92-2.19)	< 0.001	2.10 (1.61-2.74)	< 0.001	2.51 (2.32-2.71)	< 0.001	2.06 (1.55-2.76)	< 0.001
N3b	2.90 (2.66-3.15)	< 0.001	3.22 (2.17-4.80)	< 0.001	3.68 (3.36-4.03)	< 0.001	3.29 (2.14-5.05)	< 0.001

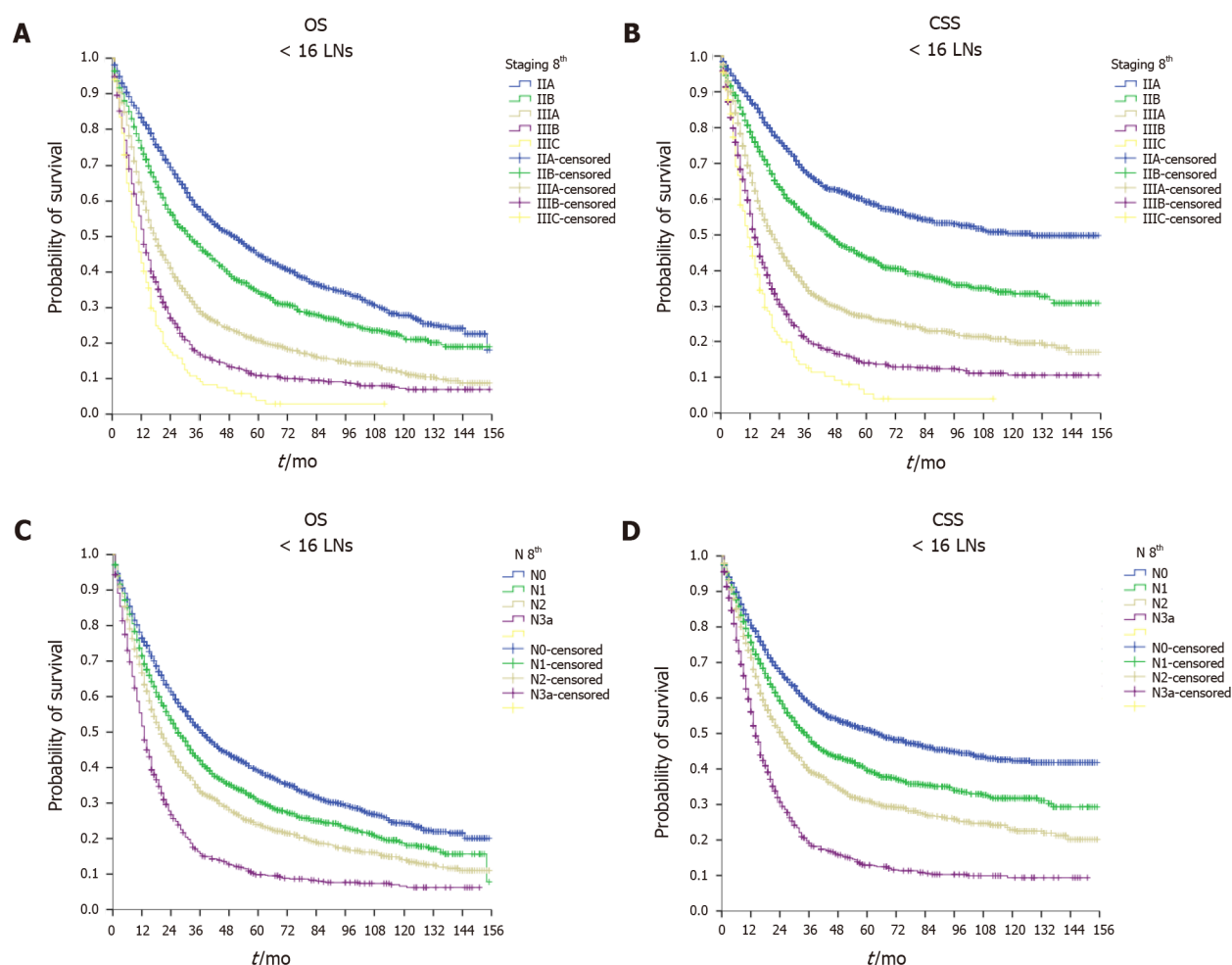
Stage, 8 <sup>th</sup> ed.							
IIA	Reference		Reference		Reference		Reference
IIB	1.34 (1.24-1.45) < 0.001		1.17 (1.05-1.31) 0.005		1.62 (1.47-1.78) < 0.001		1.38 (1.22-1.57) < 0.001
IIIA	1.96 (1.83-2.10) < 0.001		1.43 (1.21-1.70) < 0.001		2.53 (2.33-2.75) < 0.001		1.78 (1.48-2.15) < 0.001
IIIB	2.47 (2.30-2.66) < 0.001		1.44 (1.08-1.92) 0.012		3.38 (3.11-3.68) < 0.001		1.87 (1.37-2.55) < 0.001
IIIC	3.68 (3.39-3.99) < 0.001		1.59 (1.04-2.44) 0.034		5.19 (4.73-5.70) < 0.001		2.05 (1.29-3.26) 0.003
Grade							
Well/moderately differentiated	Reference		Reference		Reference		
Poorly/undifferentiated	1.35 (1.28-1.43) < 0.001		1.19 (1.12-1.26) < 0.001		1.59 (1.49-1.70) < 0.001		
Type of surgery							
Partial gastrectomy	Reference		Reference		Reference		Reference
Total gastrectomy	1.25 (1.19-1.32) < 0.001		1.23 (1.17-1.30) < 0.001		1.32 (1.25-1.40) < 0.001		1.22 (1.15-1.29) < 0.001
Chemotherapy							
No	Reference		Reference		Reference		Reference
Yes	0.62 (0.59-0.64) < 0.001		0.68 (0.64-0.72) < 0.001		0.71 (0.67-0.74) < 0.001		0.73 (0.68-0.78) < 0.001
Neoadjuvant chemotherapy							
No	Reference				Reference		
Yes	0.76 (0.71-0.83) < 0.001				0.82 (0.75-0.89) < 0.001		
Radiotherapy							
No	Reference		Reference		Reference		Reference
Yes	0.65 (0.62-0.68) < 0.001		0.77 (0.73-0.82) < 0.001		0.70 (0.66-0.73) < 0.001		0.75 (0.71-0.80) < 0.001
Number of retrieved lymph nodes							
ILA	Reference		Reference		Reference		Reference
ALA	0.84 (0.79-0.88) < 0.001		0.68 (0.64-0.71) < 0.001		0.85 (0.81-0.90) < 0.001		0.64 (0.60-0.68) < 0.001
OLA	0.73 (0.68-0.79) < 0.001		0.48 (0.44-0.52) < 0.001		0.80 (0.74-0.86) < 0.001		0.47 (0.43-0.51) < 0.001

<sup>1</sup>Forward selection model. ADC: Adenocarcinoma; ALA: Adequate lymph node assessment; CI: Confidence interval; HR: Hazard ratio; ILA: Inadequate lymph node assessment; OLA: Optimal lymph node assessment; NA: Not available; NOS: Not otherwise specified.



**Figure 2 Comparison of the survival of patients with inadequate (< 16), adequate (16-29), and optimal (> 30) lymph node assessment.** Kaplan-Meier curves of A: Overall survival; B: Cancer-specific survival.

and OLA HR = 0.47, 95%CI: 0.43–0.51,  $P < 0.001$ ) than the ILA group. Age, race, histology, T stage, N stage, stage of disease, type of gastrectomy, chemotherapy, and radiotherapy were confirmed as significant prognostic factors in the multivariate



**Figure 3 Analysis of survival of patients with inadequate lymph node assessment.** Kaplan-Meier curves of A: Overall survival (OS); B: Cancer-specific survival (CSS) based on stage; C and D: OS (C) and CSS (D) based on the N classification.

model for both OS and CSS.

### PSM

ALA and OLA were compared in 3428 PSM 1:1 patient pairs ( $n = 1,714$  per group) out of a total of 5801 patients. The L1 test measure was larger in the unmatched sample (0.989) than in the matched sample (0.964), indicating that the two groups were well-balanced across all considered variables. Successful matching (Table 4) was confirmed during the analysis because there were no differences between the two groups in the year of diagnosis, patient characteristics (age, sex, race, marital status, and insurance status), and tumor characteristics (site, grade, T stage, and N stage). As shown in Table 5, the OLA group had better OS and CSS than the ALA group (OLA median OS = 34 mo *vs* ALA median = 26 mo,  $P < 0.001$ , respectively; CSS: OLA median = 42 mo *vs* ALA median = 31 mo,  $P < 0.001$ , respectively). The Cox analysis conducted after PSM (Table 6) confirmed that OLA was associated with significantly improved OS (univariable HR = 0.81, 95%CI: 0.75–0.89,  $P < 0.001$  and multivariable HR = 0.71, 95%CI: 0.65–0.78,  $P < 0.001$ ) and CSS (univariable HR = 0.84, 95%CI: 0.76–0.92,  $P < 0.001$  and multivariable HR = 0.74, 95%CI: 0.67–0.82,  $P < 0.001$ ).

## DISCUSSION

In this study evaluating the impact of nodal assessment in patients who underwent resection for locally advanced gastric cancer in the United States between 2004 and 2015, we found significant discrepancies between expected and actual survival differences in stage II and III gastric cancer patients who had a minimum of 30 LNs assessed compared with those who had <16 or 16–29 LNs. The adverse impact of insufficient nodal analysis was found to be significant in both II and III stage disease.

Table 4 Propensity score matching subgroups

Characteristic	ALA, n = 1714	OLA, n = 1714	P value
Year of diagnosis			0.978
2004-2006	339 (20)	334 (19)	
2007-2009	385 (23)	394 (23)	
2010-2012	468 (27)	471 (28)	
2013-2015	522 (30)	515 (30)	
Age at diagnosis (yr)			0.861
Median (range)	66 (14-98)	66 (18-93)	
Sex			0.945
Male	1011 (59)	1013 (59)	
Female	703 (41)	701 (41)	
Race			0.181
White	972 (57)	973 (57)	
Black	303 (18)	268 (16)	
Asian/Pacific	439 (25)	473 (28)	
Marital status			0.234
Single/divorced	389 (23)	378 (22)	
Married	1035 (60)	1082 (63)	
Widowed	218 (13)	183 (71)	
NA	72 (4)	71 (4)	
Insurance status			0.958
Insured	1305 (76)	1312 (77)	
Uninsured	339 (20)	334 (19)	
NA	70 (4)	68 (4)	
Primary site			0.926
Fundus/body	327 (19)	333 (19)	
Antrum/pylorus	571 (33)	553 (32)	
Overlapping lesion	235 (14)	235 (14)	
Stomach, NOS	581 (34)	593 (35)	
Tumor size (cm)			0.016
≤ 5	737 (43)	645 (38)	
5.1-10	663 (39)	724 (42)	
≥ 10.1	222 (13)	248 (15)	
NA	92 (5)	97 (6)	
Hystology			0.046
ADC, NOS	557 (32)	538 (31)	
Signet ring cell carcinoma	492 (29)	480 (28)	
ADC, Intestinal type	289 (17)	313 (18)	
Carcinoma, diffuse type	177 (10)	175 (10)	
ADC with mixed subtypes	69 (4)	88 (5)	
Other	130 (8)	110 (7)	
Grade			0.892

Well/moderately differentiated	310 (18)	319 (19)	
Poorly/undifferentiated	1351 (79)	1345 (79)	
NA	53 (3)	50 (3)	
T stage, 8 <sup>th</sup> ed.			0.553
T1	59 (3)	48 (3)	
T2	137 (8)	132 (8)	
T3	769 (45)	793 (46)	
T4a	597 (35)	572 (33)	
T4b	152 (9)	169 (10)	
N stage, 8 <sup>th</sup> ed.			0.659
N0	250 (15)	259 (15)	
N1	252 (15)	223 (13)	
N2	342 (20)	340 (20)	
N3a	380 (22)	380 (22)	
N3b	490 (29)	512 (30)	
Stage, 8 <sup>th</sup> ed.			0.808
IIA	263 (15)	253 (15)	
IIB	226 (13)	215 (13)	
IIIA	351 (21)	353 (21)	
IIIB	377 (22)	365 (21)	
IIIC	497 (29)	528 (30)	
Chemotherapy			0.025
Yes	1105 (65)	1167 (32)	
No	609 (35)	1167 (68)	
Neoadjuvant chemotherapy			< 0.001
Yes	225 (13)	310 (18)	
No	1499 (87)	1404 (82)	
Radiotherapy			0.051
Yes	718 (42)	662 (39)	
No	996 (58)	1052 (61)	
Type of surgery			< 0.001
Partial gastrectomy	1099 (64)	955 (56)	
Total gastrectomy	615 (36)	759 (44)	

ADC: Adenocarcinoma; ALA: Adequate lymph node assessment; NOS: Not otherwise specified; OLA: Optimal lymph node assessment.

The results suggest that proper assessment of nodal status requires at least 16 LNs, and optimally 30 LNs. Optimization of gastric cancer care across Eastern and Western countries continues to make substantial progress. The updated eighth edition of the TNM-staging system incorporated survival data from additional Eastern nations to provide a more accurate prognosis of all patients diagnosed with gastric cancer worldwide. One of the most important unresolved issues is understanding the true impact of surgical resection and extent of nodal assessment[15,16].

Gastrectomy, including LN dissection, has a major role in optimizing the treatment strategy for locally advanced gastric cancer. Improper LN dissection not only increases the risk of residual tumor and disease recurrence, but also compromises the patient's stage attribution[17] and more important may affect the choice of adjuvant therapies. The AJCC cancer staging system has been developed over the years to improve



Table 5 Kaplan-Meier estimates in propensity score matching subgroups

	Median OS, mo(95%CI)	P value	Median CSS, mo(95%CI)	P value
ALA	26 (23.5-28.4)	< 0.001	31 (27.3-34.7)	< 0.001
OLA	34 (30.0-38.0)		42 (35.9-48.1)	

ALA: Adequate lymph node assessment; CI: confidence interval; CSS: Cancer-specific survival; OLA: Optimal lymph node assessment; OS: Overall survival.

pathology assessment, facilitate comparisons, and increase compliance among centers. Nodal status is a relevant prognostic factor, and assessing an adequate number of LNs enables proper staging and, consequently leads to optimal treatment management[18, 19].

Significant variation has been seen in different series across the East and West[7]. Asian countries generally have a median number of harvested LNs that is three or four times higher than those in other regions. The variation affects staging accuracy and long-term patient survival. Meanwhile, insufficient LN assessment is often apparent in the current literature[20]. For example, in his review of 15 studies, which included 27,942 patients, Khanjani *et al*[5] showed that only 52.2% of the patients received an adequate nodal evaluation, given the AJCC's current recommendation to assess at least 16 LNs[9].

In this study, we focused on patients whose staging was expected to have the greatest impact on their treatment pathway, namely patients with potentially curable advanced disease that was formally classified as stage II or III. This issue is particularly relevant in Western countries, where most patients are belatedly diagnosed with gastric cancer because of a lack of screening programs and where gastric cancer treatments vary greatly by center. As the SEER database is one of the largest cancer databases in the West, it is particularly representative of the current management of patients with gastric cancer. We selected 11,607 patients who had undergone radical gastrectomy. In total, 50% of the patients did not reach the AJCC criteria for correct staging (< 16 LNs). Moreover, only 15% had an analysis of  $\geq 30$  LNs, which is considered the optimal assessment of N status. However, if we only considered the last study period, awareness of the complexity of disease treatment, and the development of referral centers seemed to result in more attention and more patients with correct management. For example, in the last study period, 30% of the overall sample population was in the OLA group.

For pathological staging, two factors are interrelated the depth of tumor invasion of the gastric wall (T stage) and the number of positive nodes among all retrieved nodes (N stage). T stage evaluation is not subject to significant surgical or pathological issues, but N stage evaluation is strongly influenced by surgical skill and pathologist interpretation. Regarding the latter, a difference in the analysis can be easily detected if the specimen is sent to the pathologist in a single piece or already divided by LN stations by the surgeon. Therefore, an inadequate assessment reflects a process bug that is generated at some point between the surgical procedure and the final specimen analysis. There is a need for a dedicated multidisciplinary team to manage gastric cancer patients. Interestingly, in our analysis, no significant differences between the three study groups were seen in the T stage distribution, meaning that the number of retrieved LNs was not influenced by the primary site extension.

As expected, we found a large disparity in patients classified as N0 and N1 in the ILA and OLA groups, with 30% *vs* 15% N0 and 26% *vs* 13% N1, respectively. If an inadequate number of nodes is assessed, a patient may be inappropriately considered node negative or assigned to a lower N stage. Consequently, the patient is assigned to a lower overall stage. Moreover, while the current recommendation to analyze at least 16 LN allows for N3b substage classification, which requires  $\geq 16$  positive LNs, the likelihood that a patient would be classified as N3b with only 16 analyzed nodes is extremely low. Therefore, a larger number of nodes is needed for this evaluation[21]. Based on this classification requirement, the N3b substage could not be assessed in the ILA group. However, 30% of patients in the OLA group were in that substage. The N3a and N2 categories can also be influenced by the overall number of analyzed nodes, and patients can therefore be subject to a stage migration effect. As a consequence, patients in the ILA group were formally assigned to the earlier II and IIIA stages, and very few patients fell within the more advanced stages. There was a 10-fold difference in the percentage of patients in the IIIC category in the ILA and OLA

**Table 6 Overall survival Cox regression results for overall survival and cancer-specific survival after propensity score matching**

Variable	Overall survival				Cancer-specific survival			
	Univariable		Multivariable <sup>†</sup>		Univariable		Multivariable <sup>†</sup>	
	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value
Sex								
Male	Reference				Reference			
Female	0.98 (0.90-1.07)	0.662			1.03 (0.94-1.14)	0.517		
Age								
< 70	Reference				Reference			
≥ 70	1.56 (1.43-1.71)	< 0.001			1.35 (1.23-1.49)	< 0.001		
Race								
White	Reference				Reference		Reference	
Black	0.96 (0.85-1.08)	0.528	1.10 (0.97-1.24)	0.147	0.94 (0.83-1.08)	0.383	1.08 (0.94-1.23)	0.274
Asian/pacific	0.80 (0.72-0.89)	< 0.001	0.84 (0.75-0.93)	0.001	0.81 (0.72-0.90)	< 0.001	0.87 (0.77-0.97)	0.014
Insurance status								
NA	Reference				Reference			
Insured	0.87 (0.79-0.97)	0.009			0.87 (0.78-0.97)	0.013		
Uninsured	0.99 (0.78-1.27)	0.972			0.96 (0.74-1.25)	0.754		
Site of tumor								
Fundus-body	Reference				Reference			
Antrum-pylorus	1.07 (0.95-1.22)	0.275			1.11 (0.97-1.27)	0.140		
Overlapping lesion of the stomach	1.33 (1.15-1.55)	< 0.001			1.39 (1.18-1.64)	< 0.001		
Stomach, NOS	1.04 (0.92-1.18)	0.516			1.03 (0.90-1.19)	0.631		
Histology								
ADC, NOS	Reference				Reference		Reference	
Signet ring cell carcinoma	1.26 (1.13-1.41)	< 0.001			1.37 (1.22-1.54)	< 0.001	1.22 (1.08-1.38)	0.001
ADC, intestinal type	0.89 (0.79-1.03)	0.114			0.81 (0.70-0.95)	0.008	0.91 (0.78-1.06)	0.238
Carcinoma, diffuse type	1.23 (1.06-1.44)	0.008			1.29 (1.09-1.52)	0.003	1.18 (0.99-1.40)	0.054
ADC with mixed subtypes	1.15 (0.93-1.43)	0.193			1.28 (1.02-1.60)	0.032	1.13 (0.89-1.42)	0.318
Other	0.93 (0.77-1.13)	0.472			0.99 (0.81-1.21)	0.913	1.15 (0.93-1.41)	0.199
T stage, 8 <sup>th</sup> ed								
T1	Reference				Reference			
T2	1.18 (0.83-1.67)	0.356			1.43 (0.91-2.24)	0.121		
T3	1.85 (1.37-2.51)	< 0.001			2.60 (1.74-3.87)	< 0.001		
T4a	2.84 (2.10-3.86)	< 0.001			4.28 (2.87-6.39)	< 0.001		
T4b	3.44 (2.49-4.75)	< 0.001			5.13 (3.39-7.77)	< 0.001		
N stage, 8 <sup>th</sup> ed								
N0	Reference				Reference			
N1	1.09 (0.89-1.34)	0.380			1.08 (0.86-1.36)	0.518		
N2	1.56 (1.31-1.87)	< 0.001			1.63 (1.33-1.99)	< 0.001		
N3a	2.28 (1.93-2.69)	< 0.001			2.61 (2.16-3.16)	< 0.001		
N3b	4.58 (3.91-5.37)	< 0.001			5.50 (4.59-6.58)	< 0.001		

Stage, 8 <sup>th</sup> ed							
IIA	Reference		Reference		Reference		Reference
IIB	1.38 (1.12-1.70) 0.003		1.47 (1.18-1.81) < 0.001		1.70 (1.33-2.18) < 0.001		1.77 (1.38-2.29) < 0.001
IIIA	1.96 (1.63-2.35) < 0.001		2.21 (1.83-2.66) < 0.001		2.39 (1.92-2.98) < 0.001		2.66 (2.12-3.32) < 0.001
IIIB	2.85 (2.39-3.40) < 0.001		3.31 (2.76-3.96) < 0.001		3.75 (3.04-6.64) < 0.001		4.22 (3.40-5.23) < 0.001
IIIC	5.73 (4.85-6.77) < 0.001		6.32 (5.31-7.52) < 0.001		8.06 (6.58-9.88) < 0.001		8.58 (6.97-10.57) < 0.001
Grade							
Well/moderately differentiated	Reference		Reference		Reference		
Poorly/undifferentiated	1.52 (1.35-1.72) < 0.001		1.19 (1.05-1.35) 0.007		1.70 (1.49-1.96) < 0.001		
Type of surgery							
Partial gastrectomy	Reference		Reference		Reference		Reference
Total gastrectomy	1.40 (1.29-1.53) < 0.001		1.28 (1.17-1.40) < 0.001		1.43 (1.31-1.58) < 0.001		1.24 (1.13-1.37) < 0.001
Chemotherapy							
No	Reference		Reference		Reference		Reference
Yes	0.56 (0.51-0.61) < 0.001		0.63 (0.56-0.70) < 0.001		0.61 (0.55-0.67) < 0.001		0.66 (0.89-0.74) < 0.001
Neoadjuvant chemotherapy							
No	Reference		Reference		Reference		Reference
Yes	0.71 (0.62-0.81) < 0.001		1.48 (1.35-1.63) < 0.001		0.76 (0.66-0.87) < 0.001		1.33 (1.20-1.48) < 0.001
Radiotherapy							
No	Reference		Reference		Reference		Reference
Yes	0.64 (0.59-0.70) < 0.001		0.77 (0.69-0.86) < 0.001		0.67 (0.61-0.73) < 0.001		0.76 (0.68-0.85) < 0.001
Number of retrieved lymph nodes							
ALA	Reference		Reference		Reference		Reference
OLA	0.81 (0.75-0.89) < 0.001		0.71 (0.65-0.78) < 0.001		0.84 (0.76-0.92) < 0.001		0.74 (0.67-0.82) < 0.001

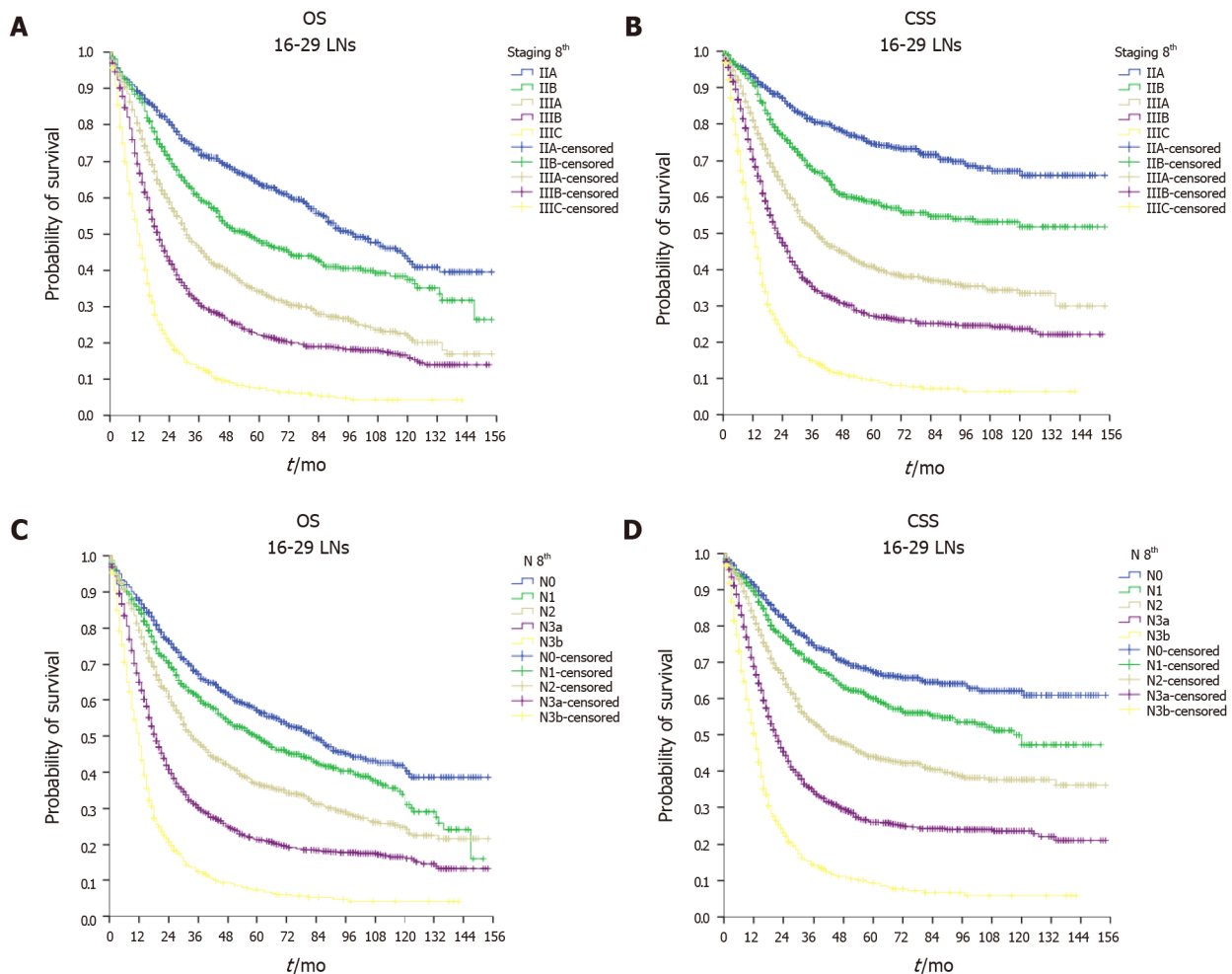
<sup>1</sup>Forward selection model. ADC: Adenocarcinoma; ALA: Adequate lymph node assessment; ILA: Inadequate lymph node assessment; NA: Not available, NOS: Not otherwise specified; OLA: Optimal lymph node assessment.

groups (3% *vs* 31%, respectively).

Three main questions can be answered by the present study: (1) Does this have an overall impact on long-term survival? (2) How beneficial is the correct staging of patients? and (3) Given the same stage conditions and patient characteristics, is there a survival difference between ALA and OLA? The answer to the first question is yes. The ILA group had the worst OS (median = 24 mo) and CSS (median = 30 mo) compared with the ALA (median OS = 29 mo, median CSS = 36 mo,  $P < 0.001$ ) and OLA (median OS = 34 mo, median CSS = 42 mo,  $P < 0.001$ ) groups. Our findings clearly show that the stage-specific survival curves of the ILA group do not follow the expected trend. In particular, there were 49-month and 81-month mean differences between patients in stage IIA in the ILA group and in the ALA and OLA groups, respectively. Regarding the second question, correct staging requires the efforts of surgeons and pathologists. Of course, several other factors may influence survival in this context. Therefore, we included patient and tumor characteristics and treatment variables in the Cox regression analysis. The multivariate model confirmed that the ALA and OLA groups significantly improved OS (ALA HR = 0.68 and OLA HR = 0.48,  $P < 0.001$ ) and CSS (ALA HR = 0.64 and OLA HR = 0.47,  $P < 0.001$ ). Regarding the third question, PSM in the ALA and OLA groups (3428 matched patients) demonstrated that optimal assessment was key for better survival (univariable OS HR = 0.81,  $P < 0.001$ ; multivariable HR = 0.71,  $P < 0.001$ ).

### Limitations and strengths

This study evaluated patients included in a population registry who were selected by both direct and indirect variables related to a code system. One major study limitation

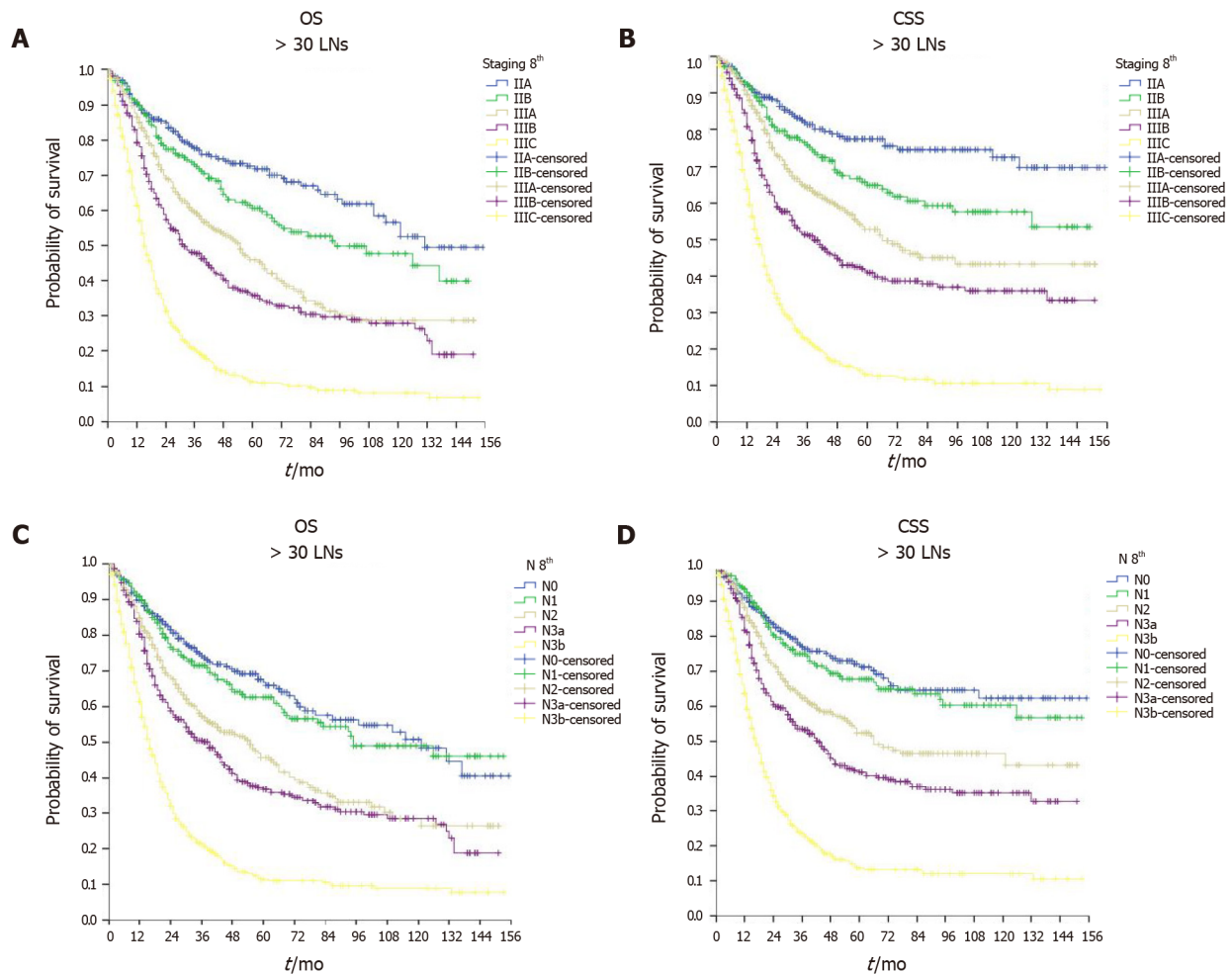


**Figure 4 Analysis of survival of patients with lymph node assessment group.** Kaplan-Meier curves of A: Overall survival (OS); B: Cancer-specific survival (CSS) based on stages; C and D: OS (C) and CSS (D) based on the N classification.

was the use of a population registry based on a coding system of direct and indirect variables, which reduced the availability of more detailed information of the patient characteristics and treatment details. For example, the extent of lymphadenectomy performed or the type of neoadjuvant and adjuvant chemotherapy regimens were not known. In particular, standard D2 LN dissection may not have been performed in the elderly or in high-risk patients who were included in the analysis. As a result, it is presumed that the prognosis in these categories was poor independent of the inadequate staging effect. Despite the limitations, the strength of the study is the large sample of patients analyzed, which allowed statistical rigor. Moreover, the SEER database contains rigorous, standardized information and the guarantee of a high-quality data collection process.

## CONCLUSION

Inadequate staging is an important issue in gastric cancer management that adversely impacts the survival of a large proportion of patients undergoing radical resection. Our study findings demonstrate that analyzing < 16 LNs is insufficient for accurate staging and prognostically misleading. In contrast, analyzing 16–29 LNs improves the accuracy of staging, and evaluation of ≥ 30 LNs offers the most consistent chance of correctly classifying patients into the appropriate N3 substages. Therefore, surgeons and pathologists should make concerted efforts to analyze as many LNs as possible beyond the current NCCN recommendations. That may require a D2 lymphadenectomy as recommended by experienced surgeons in patients without restrictive surgical risk. Moreover a more thorough reassessment of the surgical specimen may be required if an inadequate number of LNs is initially found after a radical gastrectomy. Most important, all patients with inadequate LNA should be considered at high risk



**Figure 5 Analysis of survival of patients with optimal lymph node assessment.** Kaplan-Meier curves of A: Overall survival (OS); B: Cancer-specific survival (CSS) based on stage; C: OS; D: CSS based on the N category.

for stage migration and can expect a survival rate significantly worse than their formally assigned TNM-stage.

## ARTICLE HIGHLIGHTS

### Research background

Lymphadenectomy in gastric cancer remains a relevant issue because of its impact on survival. The SEER database is one of the largest Western cancer databases. Patients were assigned to three groups depending on the number of analyzed lymph nodes (LNs) to evaluate survival differences and the stage migration effect.

### Research motivation

Gastric cancer should be treated in dedicated centers to offer the patient both optimal surgery and a correct pathological assessment and to avoid improper staging.

### Research objectives

We aimed to analyze the survival of patients with inadequate numbers of assessed LNs and to quantify the effect *vs* correctly staged patients, based on the stage definitions in the AJCC staging manual.

### Research methods

Eligible gastric cancer patients were identified in the SEER database and assigned of three groups, inadequate LN assessment (< 16 LNs), adequate LN assessment (16-29 LNs), and optimal LN assessment ( $\geq 30$  LNs).



### Research results

The ILA group had the worst survival. The finding was confirmed in by univariate and multivariate analysis. OLA gave the best chance of both correct staging and proper surgery performed as demonstrated after propensity score matching.

### Research conclusions

Inadequate staging led to a significant reduction in the expected survival associated with the formally attributed stage. An analysis of at least > 16 LNs should be offered to all patients treated with curative intent.

### Research perspectives

The role of referral centers for gastric cancer should be strengthened to obtain optimal treatment and accurate patient staging.

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