Impact of examined lymph node counts on survival of patients with stage IA non-small cell lung cancer undergoing sublobar resection

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Background: The correlation between the number of examined lymph nodes (ELNs) and lung cancer-specific survival (LCSS) of stage IA non-small cell lung cancer (NSCLC) patients, who underwent sublobar resection in which lymph node (LN) sampling was relatively restricted as compared with standard lobectomy remains unclear.

Methods: Patients from the Surveillance, Epidemiology, and End Results database with stage IA NSCLC who underwent sublobar resection were categorized based on ELN count (1–6 *vs.* ≥7; the cut point 7 was identified by Cox model).

Results: Collectively, 3,219 patients with a median follow-up time of 37 months were included in this study (G1: 1–6 ELN, n=2,410; G2: ≥7 ELN, n=809). The 5-year LCSS rate of the G1 and G2 cohorts were 75% and 83%, respectively. Cox analysis suggested that the LCSS of G1 cohort patients was lower as compared with the G2 cohort [hazard ratio (HR) =1.530; 95% confidence interval (CI): 1.240–1.988, P<0.001]. Propensity score analysis also showed decreased survival of the matched G1 cohort (HR =1.499; 95% CI: 1.176–1.911; P=0.001).

Conclusions: The data suggested the ELNs ≤6 were associated with poor prognoses. Adequate LN sampling is essential even for stage IA NSCLC patients undergoing sublobar resection.

Keywords: Lymph nodes; sublobar resection; stage IA; lung cancer; survival

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Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide, with non-small cell lung cancer (NSCLC) accounting for nearly 85% of all diagnosed cases (1,2). Approximately 25% of NSCLC patients are diagnosed in the early stages of the disease. Surgical resection is the best option for NSCLC patients. The 5-year overall survival (OS) rate of resected stage I NSCLC patients ranges from 55% to 80% (3,4).

For these patients, lymph node (LN) recurrence and metastasis may be the principal reason for unsatisfactory prognoses of NSCLC. Positive LN disease was undetected because of inadequate LN sampling and the shortage of LN dissection (5,6). Smeltzer *et al.* in 2016 reported that the intrapulmonary metastasis LN discarded inadvertently from lung cancer resection specimens was associated with reduced survival (7). The accuracy of node staging and the number of positive LN are a strong prognostic indicator (8-10). LN involvement is one of the most important determinants of prognosis and treatment strategy decisions (11,12).

Survival of stage IA NSCLC patients undergoing lobectomy could be improved by increasing the number of ELNs (13). However, these recommendations and potentially beneficial outcomes are based mainly on patients undergoing lobectomy, not sublobar resection. The current National Comprehensive Cancer Network (NCCN) guidelines recommend that sublobar resection should be based on sampling appropriate N1 and N2 LN stations, not on the number of ELN. The impact of ELNs on survival remains unclear and the evidence in the international guidelines for patients with stage IA NSCLC undergoing sublobar resection was based on very limited data.

In 2016, Speicher *et al.* reported better prognoses for stage IA NSCLC patients who underwent sublobar resection with nodal sampling (14). However, they did not elucidate the importance of the number of ELN. The significance of ELN count on survival of stage IA NSCLC patients undergoing sublobar resection has not yet been established. Herein, we investigated the correlation between the number of ELNs and LCSS in patients with stage IA NSCLC who underwent sublobar resection.

Methods

This study was approved by institutional board of the First Affiliated Hospital of Guangzhou Medical University.

The study used the Surveillance, Epidemiology, and End Results (SEER) database which includes patient demographics, cancer diagnoses and treatment related information, and cause of death. SEER is representative of the US population, with patient-level data abstracted from 18 geographically diverse populations that represent rural, urban, and regional populations (15). We identified patients aged ≥20 years who underwent sublobar (wedge or segmental) resection between the years 2000 and 2013 with the following criteria: (I) pathologically confirmed diagnosis of stage IA (T1N0M0) NSCLC (based on the 8th edition of the Union for International Cancer Control/American Joint Committee on Cancer Tumor, Node, and Metastasis (TNM) classification for lung cancer); (II) first primary NSCLC treated by sublobar resection; and (III) at least one LN examined. Patients with missing ELN count values and clinical features were excluded from the study.

The Cox proportional hazards regression model was used to determine the effect of ELN count on LCSS, which were adjusted for other significant prognostic factors (age at diagnosis, sex, race, histology, grade, tumor size, and surgery type). Patients were stratified based on the per ELN count, ranging from 1 to 12. Finally, a cut point of 7 was identified based on the maximum hazard ratio (HR) and the minimum P value, and the structural break points were considered the threshold of clinical impact (16). Complete analyses of the ELN count on LCSS are shown in *Table 1*. Patients were divided into 2 groups: G1 (1–6 ELNs) and G2 (≥7 ELNs).

We performed propensity score matching (PSM) analysis to compare survival among the G1 and G2 cohorts. In each analysis, a propensity score for the G2 cohort was created using logistic regression based on potential confounding variables, including age, sex, race, tumor site, histology, grade, tumor size and surgery type. Patient characteristics were compared with t-tests for continuous variables and χ^2 tests for categorical variables. Survival was calculated from date of diagnosis until date of death or date of last follow-up (December 31, 2015). When analyzing the LCSS, deaths from other causes were censored at the date of death. LCSS were estimated by the Kaplan-Meier method and the log-rank test was used to assess differences.

Univariate and multivariate analyses were performed using Cox proportional hazards models to calculate adjusted HR and their 95% confidence interval (CI) relating to the variables as described. All data were analyzed using SPSS 22.0 or Prism 5.0 software. Results were considered to be statistically significant when $P<0.05$.

Table 1 The effect of examined lymph node (ELN) on lung cancer-specific survival as determined by the Cox proportional hazards regression model.

ELN group (Number of patients)	Hazard ratio	95% confidence interval	P value
1 (n=678) *vs.* 2–63 (n=2,541)	1.326	1.107–1.588	0.002
1–2 (n=1,236) *vs.* 3–63 (n=1,983)	1.340	1.139–1.576	<0.001
1–3 (n=1,676) *vs.* 4–63 (n=1,543)	1.397	1.183–1.650	<0.001
1–4 (n=1,986) *vs.* 5–63 (n=1,233)	1.355	1.137–1.615	0.001
1–5 (n=2,215) *vs.* 6–63 (n=1,004)	1.481	1.222–1.794	<0.001
1–6 (n=2,410) *vs.* 7–63 (n=809)	1.520	1.232–1.876	<0.001
1–7 (n=2,564) *vs.* 8–63 (n=655)	1.433	1.142–1.798	0.002
1–8 (n=2,669) *vs.* 9–63 (n=550)	1.304	1.031–1.649	0.027
1–9 (n=2,757) *vs.* 10–63 (n=462)	1.323	1.026–1.708	0.031
1–10 (n=2,829) *vs.* 11–63 (n=390)	1.212	0.926–1.587	0.162
1–11 (n=2,889) *vs.* 12–63 (n=330)	1.198	0.899–1.597	0.218
1–12 (n=2,938) *vs.* 13–63 (n=281)	1.241	0.906–1.700	0.179
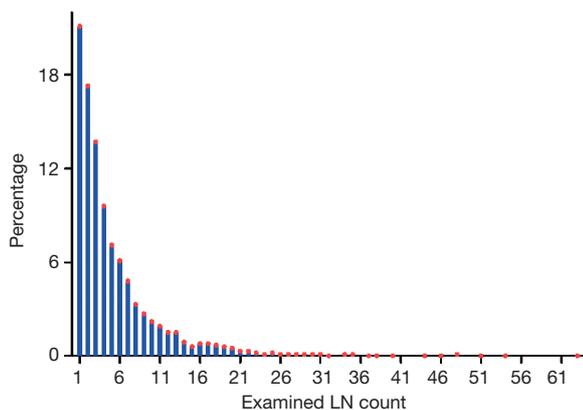
Figure 1 Distribution of the number of examined lymph nodes (ELNs) in the study cohort. Each red dots represents a number, and the height of bar represents the proportion of the whole.

Results

As a result of selection criteria, a total of 3,219 patients with pathologic stage IA (T1N0M0) NSCLC were included. The G1 cohort (2,410 patients) underwent sublobar resection with 1–6 ELNs. The median age within the cohort was 69 years (range, 20–92 years), and the median tumor size was 1.6 cm (range, 1–3.0 cm). The distribution of ELN number in this study cohort is shown in *Figure 1* (median, 3; interquartile range, 2–7). Patients with ≥7 ELNs were more likely to be younger (P=0.007), adenoid

differentiation (P<0.001), grade I–II disease (P=0.001) and to have a segmental resection (P=0.002), but there were no significant differences between the G1 and G2 cohorts in sex, race, tumor site and size (P>0.05 for all comparisons). However, after PSM, the differences between groups were well balanced (*Figures S1-S3*). The baseline characteristics of the full cohort and patients in the G1 and G2 cohorts are presented in *Table 2*.

The 5-year LCSS rates of patients in the G1 and G2 cohorts were 75% and 83%, respectively. Cox analyses showed that the LCSS of patients in the G1 cohort was inferior as compared to the G2 cohort (HR =1.530; 95% CI: 1.240–1.988; P<0.001; *Figure 2A*). PSM analyses also showed decreased survival of the matched G1 cohort patients (HR =1.499; 95% CI: 1.176–1.911; P=0.001; *Figure 2B*).

Based on subset analysis of patients with wedge resection, the 5-year LCSS rates of the G1 and G2 cohorts were 74% and 81%, respectively. Survival of G1 cohort patients with wedge resection was poorer as compared to G2 (HR =1.433; 95% CI: 1.153–1.780; P=0.001). For patients with segmental resection, the 5-year LCSS rates of the G1 and G2 cohorts were 78% and 87%, respectively. Cox analysis showed decreased survival of G1 patients with segmental resection as compared to the G2 cohort (HR =1.514; 95% CI: 1.048–2.187; P=0.027). Results of PSM analysis were similar. The Kaplan-Meier plots for the subsets of patients with wedge and segmental resection are presented in *Figures 3,4*.

Table 2 The baseline characteristics of patients in the study cohort

Variable	All cohort (n=3,219)	No. of patients (%)		P value	P value*
		1-6 ELNs (n=2,410)	≥7 ELNs (n=809)		
Age at diagnosis, years				0.007	0.243
Median	69	69	68		
Range	20–92	20–92	29–92		
Sex, n (%)				0.341	0.683
Male	1,301 (40.4)	986 (40.9)	315 (38.9)		
Female	1,918 (59.6)	1,424 (59.1)	494 (61.1)		
Race, n (%)				0.840	0.121
White	2,805 (87.1)	2,099 (87.1)	706 (87.3)		
Black	271 (8.4)	206 (8.5)	65 (8.0)		
Other	143 (4.5)	105 (4.4)	38 (4.7)		
Tumor site, n (%)				0.255	0.990
Upper	2,013 (62.5)	1,502 (62.3)	511 (63.2)		
Middle	145 (4.5)	117 (4.9)	28 (3.5)		
Lower	1,061 (33.0)	791 (32.8)	270 (33.4)		
Histology, n (%)				<0.001	0.683
Adenocarcinoma	1,892 (58.8)	1,362 (56.5)	530 (65.5)		
Squamous cell	738 (22.9)	575 (23.9)	163 (20.1)		
Large cell	142 (4.4)	115 (4.8)	27 (3.3)		
Other	447 (13.9)	358 (14.9)	89 (11.1)		
Grade, n (%)				0.001	0.479
I	750 (23.3)	548 (22.7)	202 (25.0)		
II	1,244 (38.6)	890 (36.9)	354 (43.8)		
III	815 (25.3)	651 (27.0)	164 (20.3)		
IV	49 (1.5)	34 (1.4)	15 (1.9)		
Unknown	361 (11.2)	287 (11.9)	74 (9.1)		
Tumor size, cm				0.104	0.130
Median	1.6	1.6	1.6		
Range	1.0–3.0	1.0–3.0	2.0–3.0		
Surgery type, n (%)				0.002	0.053
Wedge	2,327 (72.3)	1,777 (73.7)	550 (68.0)		
Segmental	892 (27.7)	633 (26.3)	259 (32.0)		
Median follow-up, year				0.970	0.585
Median	37	38	37		
Range	1–120	1–120	1–120		

*, P value was adjusted by propensity score matching analysis. ELN, examined lymph node.
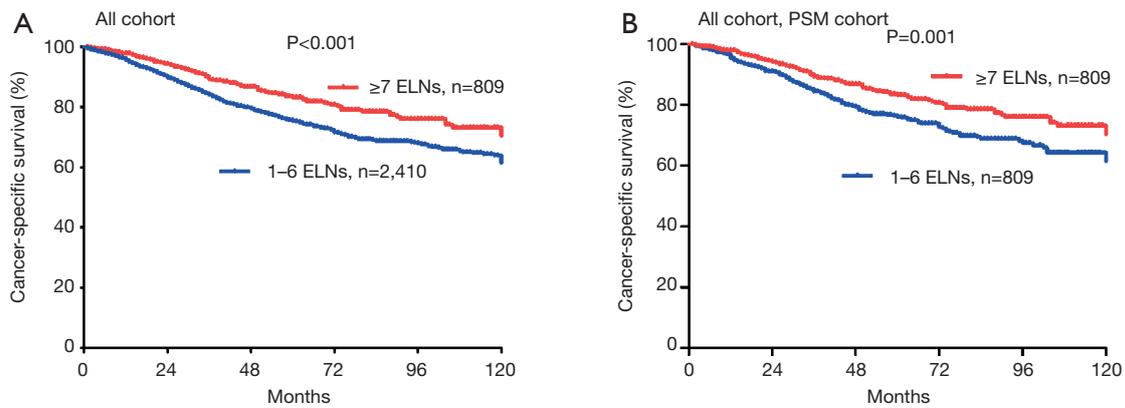
Figure 2 Kaplan-Meier plot for lung cancer-specific survival in the study cohort before (A) and after (B) propensity score matched.
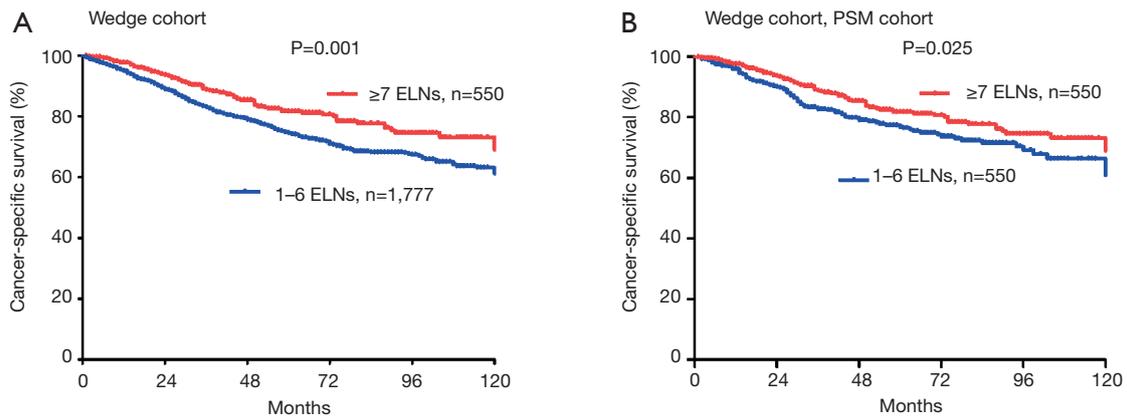
Figure 3 Kaplan-Meier plot for lung cancer-specific survival in patients with stage IA NSCLC undergoing wedge resection before (A) and after (B) propensity score matched.
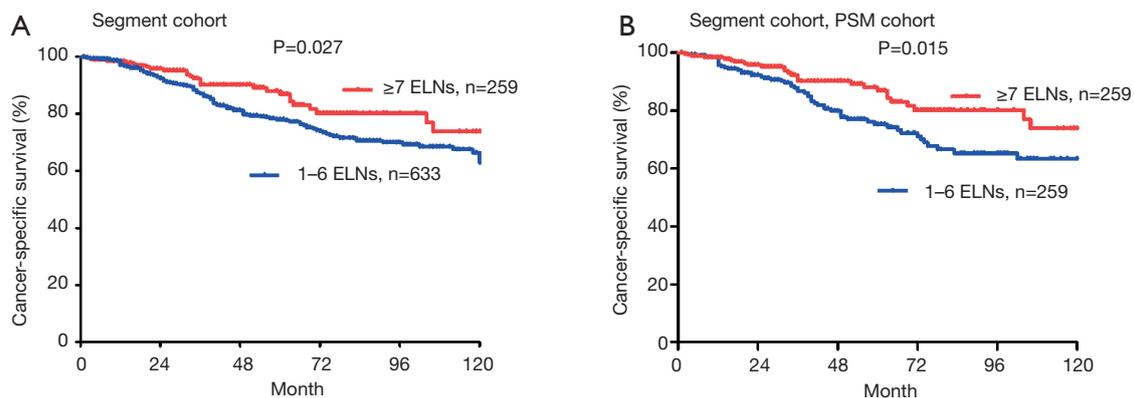
Figure 4 Kaplan-Meier plot for lung cancer-specific survival in patients with stage IA NSCLC undergoing segmental resection before (A) and after (B) propensity score matched.

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On univariate analysis, the Cox analyses indicated that 1–6 ELNs did not improve LCSS. Other adverse prognostic factors were older age, male sex, larger grade disease and wedge resection. Race and tumor site were not prognostic. Based on multivariate analysis of all patients, older age (HR =1.029; 95% CI: 1.019–1.038; P<0.001), and larger grade disease (HR =2.063; 95% CI: 1.564–2.720; P<0.001) had a negative impact on OS. Females (HR =0.677; 95% CI: 0.575–0.798; P<0.001), segmental resection (HR =0.768; 95% CI: 0.636–0.928; P=0.006) and ≥7 ELNs (HR =0.691; 95% CI: 0.559–0.855; P=0.001) were significantly associated with improved LCSS. The results of all univariate and multivariate analyses are listed in *Table 3*.

Discussion

Results of this study suggest that stage IA NSCLC patients who underwent sublobar resection with ≤6 ELNs were associated with a poorer LCSS as compared to patients with ≥7 ELNs. We obtained consistent results in the subset analysis for patients with wedge and segmental resection. These results were confirmed by the Cox model and PSM analyses.

It is assumed that more ELNs provide a better opportunity to identify positive LNs; that is, a larger number of ELNs may reduce the risk of undetected positive LNs and may allow for improved outcomes. These findings may be attributed to more thorough examinations, the removal of potential remnants, and proper delivery of adjuvant chemotherapy to improve long-term survival.

There are limited data in the existing NCCN guidelines that address the impact of ELN counts on patients undergoing segmental or wedge resection; thus, surgical sampling of ELN counts of surgical specimens are not uniformly performed. The number of ELNs dissected by sublobar resection often varies between surgeons and pathologists. Therefore, survival of most patients with an inadequate ELN count is poor. Our results suggested that stage IA NSCLC patients undergoing sublobar resection with ≥7 ELNs correlated with improved prognoses. Previous studies suggested that the ELNs combined with tumor size or the ratios of positive LNs could be an independent prognostic factor and a reasonable stratification criterion in patients with pathologic node-negative NSCLC (17,18).

Stiles *et al*. in 2017 reported that LN removal decreased locoregional recurrence (P=0.024) and increased the 5-year survival rate (P=0.025), and LN sampling did not add to

morbidity and did not increase the length of stay (19). Varlotto *et al*. in 2009 showed that patients with dissected lymph nodes were associated with an increase in the 5-year OS rate (from 42% to 58%) and in DFS (from 58% to 73%) as compared to patients with no lymphadenectomy (20). Additionally, several previous studies support the viewpoint that the number of counted ELNs is beneficial for patients with declared node-negative disease (5,6,13,16,18,21,22).

However, other groups believe that recommending an optimal number of nodes is not an appropriate prognostic factor for stage I NSCLC patients (23,24). Altorki *et al*. found that LN sampling was more commonly performed on patients undergoing segmental resection as compared to patients undergoing wedge resection, with more stations sampled and more nodes resected in segmental resection patients. There were no differences between wedge and segmental resection in local recurrence (P=0.680) or 5-year disease-free survival (DFS: 51% *vs*. 53%, P=0.700) (25). Additionally, the results of the ACOSOG Z0030 trial showed that if systematic and thorough resection sampling of the mediastinal and hilar nodes is negative, mediastinal LN dissection does not improve survival of patients with early NSCLC (26). Izbicki *et al*. also reported that radical systematic mediastinal LN dissection did not influence the DFS or OS for NSCLC patients without overt LN involvement (27).

This study has some limitations. Bias is inevitable due to the retrospective nature. Some important information is missing, such as the access to perform limited resection (open or VATS) and the surgical technique of participating surgeons. We were not able to investigate other important points such as the impact of the number of LNs in the N1 and N2 (hilar and mediastinal) stations on our data analysis. In addition, two possible causes could have resulted in a miscount of ELN: underestimation as a result of the difficulty in separating each LN in the dissected tissues, and overestimation because of fragmentation of nodal tissue during the removal of LN. The SEER does not provide information on clinical stage, performance status, smoking, preoperative cardiopulmonary function, postoperative complications, or length of stay.

Conclusions

In summary, our data indicates that ≤6 ELNs was associated with poor prognosis of patients with pathological stage IA NSCLC undergoing sublobar resection. Adequate LN examination is essential even in patients with pathological

Table 3 Univariate and multivariate analysis on lung cancer-specific survival of the study cohort

Covariate	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Age at diagnosis	1.032 (1.023–1.041)	<0.001	1.029 (1.019–1.038)	<0.001
Sex				
Male	1		1	
Female	0.595 (0.506–0.699)	<0.001	0.677 (0.575–0.798)	<0.001
Race				
White	1		–	–
Black	0.950 (0.707–1.277)	0.734	–	–
Other	0.857 (0.542–1.355)	0.509	–	–
Tumor site				
Upper	1		–	–
Middle	0.577 (0.350–1.951)	0.131	–	–
Lower	1.017 (0.857–1.208)	0.845	–	–
Histology				
Adenocarcinoma	1		1	
Squamous cell	1.515 (1.258–1.825)	<0.001	1.105 (0.834–1.235)	0.885
Large cell	1.325 (0.930–1.888)	0.119	1.178 (0.804–1.726)	0.400
Other	0.836 (0.645–1.083)	0.175	0.945 (0.715–1.248)	0.689
Grade				
I	1		1	
II	2.236 (1.706–2.932)	<0.001	2.063 (1.564–2.720)	<0.001
III	3.020 (2.297–3.970)	<0.001	2.608 (1.956–3.476)	<0.001
IV	1.824 (0.939–3.546)	0.076	1.408 (1.695–2.849)	0.032
Tumor size	1.051 (1.038–1.065)	<0.001	1.035 (1.021–1.049)	<0.001
Surgery type				
Wedge	1		1	
Segmental	0.824 (0.684–0.993)	0.042	0.768 (0.636–0.928)	0.006
No. of nodes examined				
1–6 ELNs	1		1	
≥7 ELNs	0.654 (0.530–0.807)	<0.001	0.691 (0.559–0.855)	0.001

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stage IA NSCLC.

Acknowledgements

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This study was approved by institutional board of the First Affiliated Hospital of Guangzhou Medical University.

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Sample sizes

Subsamples	All		Matched		Unmatched		Discarded	
	Control	Treated	Control	Treated	Control	Treated	Control	Treated
(all cases)	2,410	809	809	809	1,601	0	0	0

Relative multivariate imbalance L1
(Iacus, King, & Porro, 2010)

	Before matching	After matching
(all cases)	0.931	0.862

Distribution of propensity scores
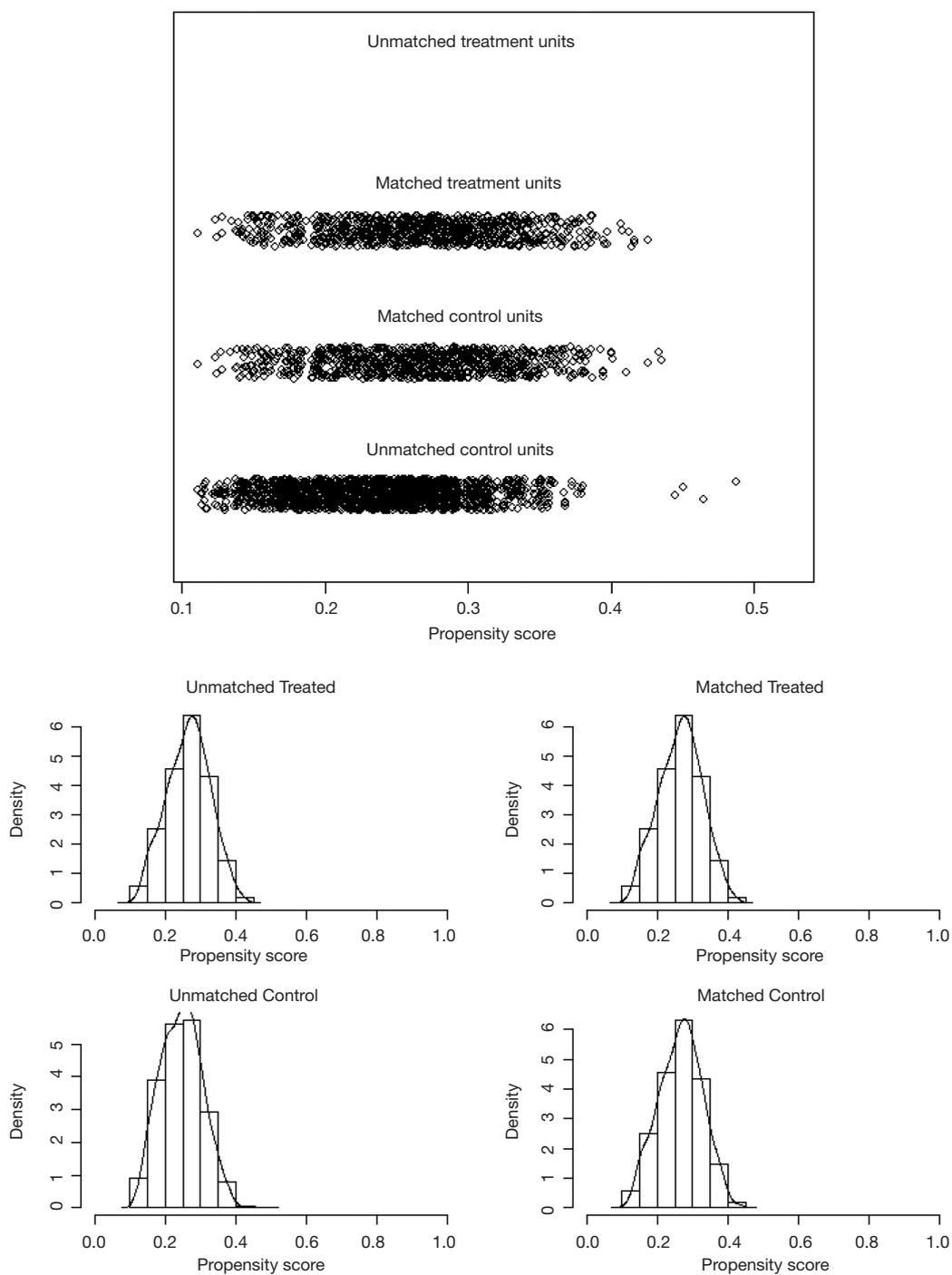
Figure S1 The charts of propensity score matching in the all study cohort.

Sample sizes

Subsamples	All		Matched		Unmatched		Discarded	
	Control	Treated	Control	Treated	Control	Treated	Control	Treated
(all cases)	1,777	550	550	550	1,227	0	0	0

Relative multivariate imbalance L1
(Iacus, King, & Porro, 2010)

	Before matching	After matching
(all cases)	0.921	0.840

Distribution of propensity scores
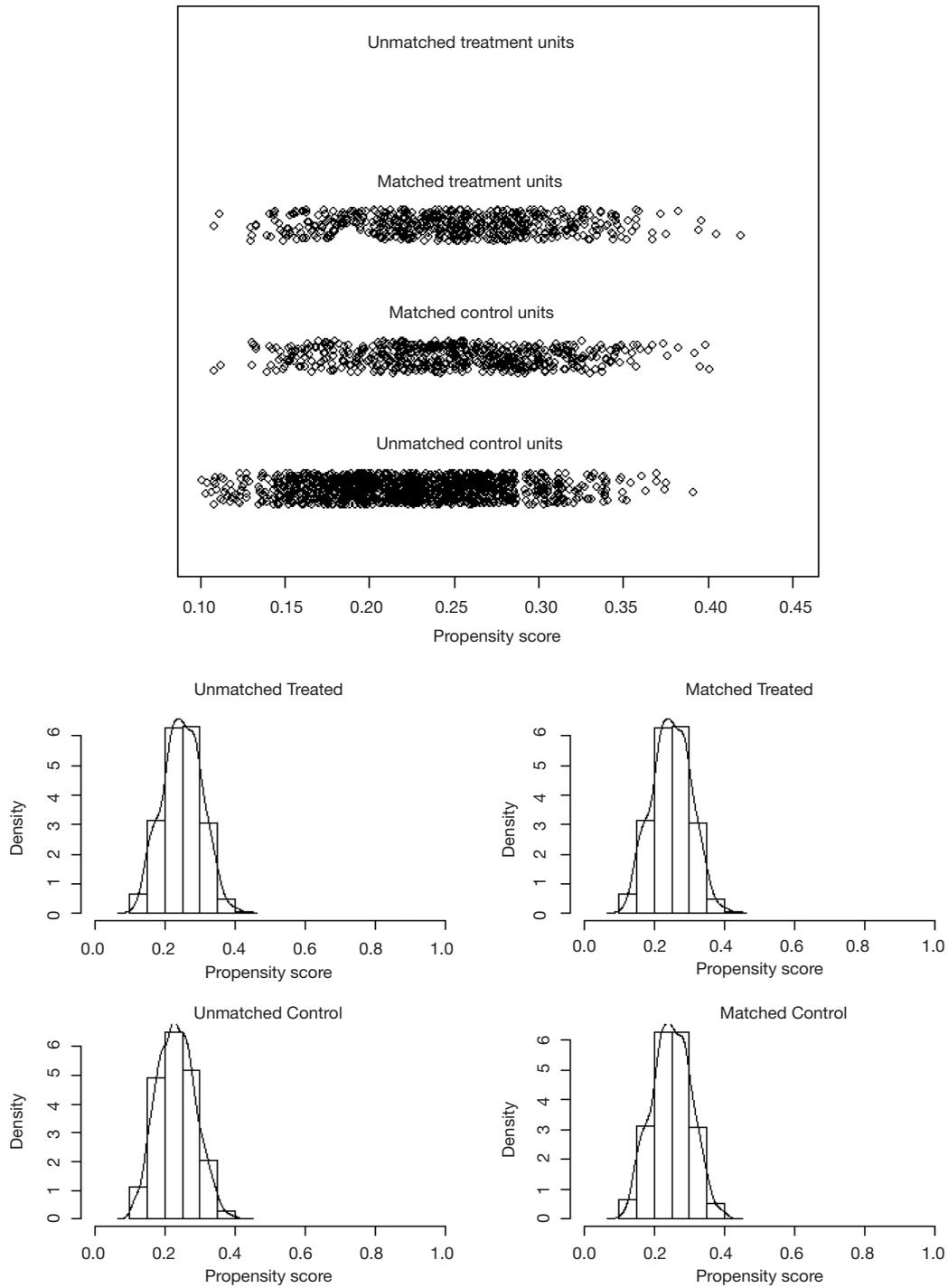
Figure S2 The charts of propensity score matching in the wedge cohort.

Sample sizes

Subsamples	All		Matched		Unmatched		Discarded	
	Control	Treated	Control	Treated	Control	Treated	Control	Treated
(all cases)	633	259	259	259	374	0	0	0

Relative multivariate imbalance L1
(Iacus, King, & Porro, 2010)

	Before matching	After matching
(all cases)	0.897	0.865

Distribution of propensity scores
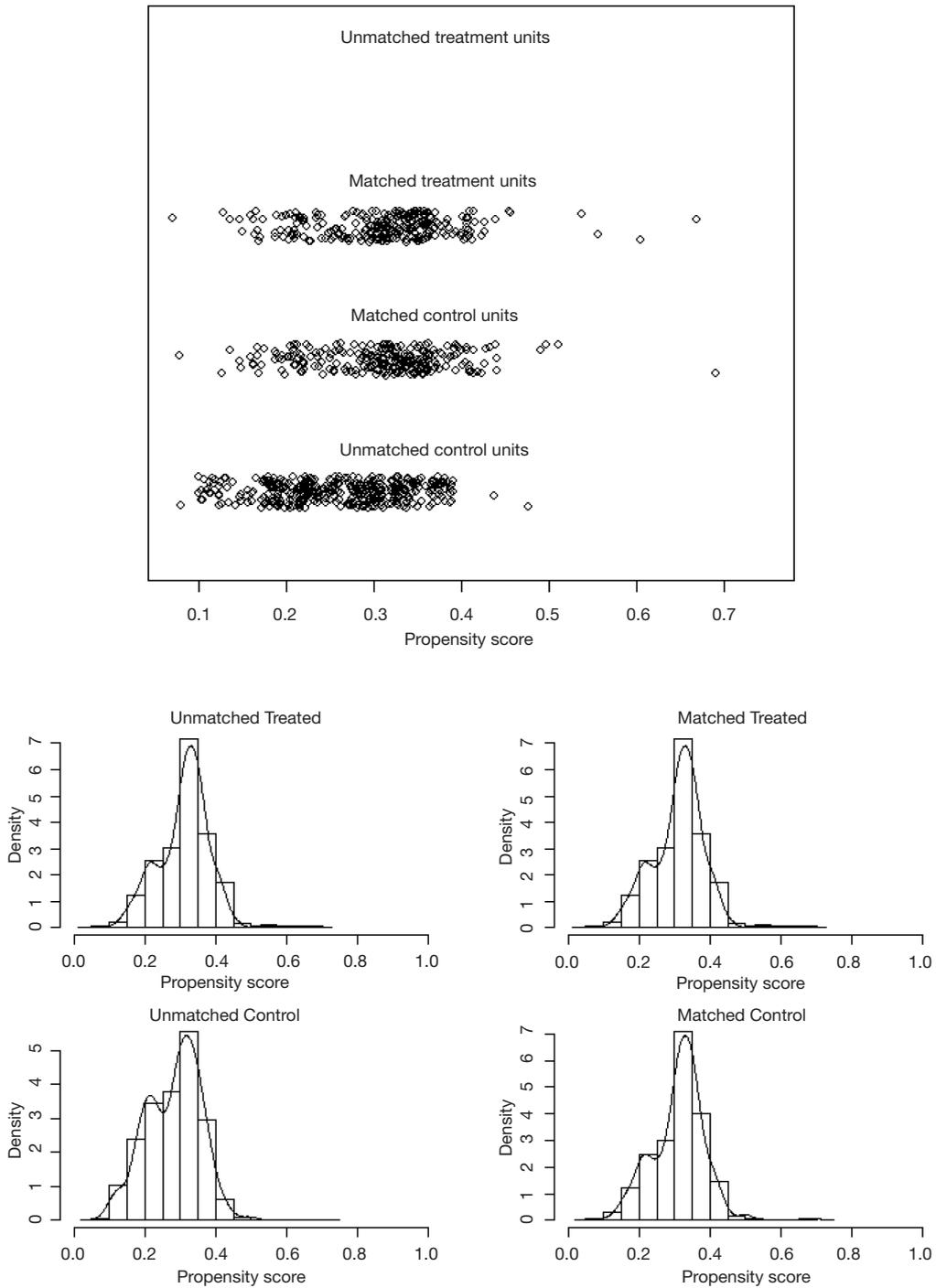
Figure S3 The charts of propensity score matching in the segment cohort.