Original Article

Selective versus systematic lymph node dissection (other than sampling) for clinical N2-negative non-small cell lung cancer: a meta-analysis of observational studies

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Background: The proper extent of lymph node dissection is still controversial. Hence, we compared the clinical efficacy between two strategies of lymph node dissection [selective lymph node dissection (SLND) and systematic lymph node dissection (LND)] for clinical N2-negative non-small cell lung cancer (NSCLC) patients.

Methods: After searching five databases, six cohort studies were eligible for this meta-analysis and the primary endpoint was overall survival (OS). In order to provide a comprehensive perspective, we estimated some perioperative outcomes as well. Either fixed effect or random effects model were properly selected to evaluate the data according to the heterogeneity of included studies.

Results: A total of 7,333 patients with clinical N2-negative NSCLC patients were analyzed for OS. The pooled results demonstrated that LND did not improve survival in OS [hazard ratio (HR) =1.05, 95% confidence interval (CI): 0.82–1.34, P=0.69] compared with SLND. In accordance with OS, there is no significant difference in DFS between LND and SLND (HR =0.98, 95% CI: 0.78–1.23, P=0.87). Moreover, SLND could significantly reduce the operative time [mean difference (MD) =–21.45, 95% CI: –29.53 to –13.36, P<0.001] and blood loss (MD =–28.88, 95% CI: –44.38 to –13.39, P<0.001). Both postoperative morbidity and recurrence showed no significant between two groups.

Conclusions: SLND is an alternative to LND for clinical N2-negative NSCLC patients, which may even provide clinical benefits. However, more randomized controlled trials (RCTs) are expected to determine whether SLND is valid and practical to become a standard procedure of surgical treatment for early-stage NSCLC patients.

Keywords: Carcinoma; non-small cell lung (NSCLC); surgical oncology; lymph node excision

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Introduction

Lung cancer is the most common cancer diagnosed and the leading cause of cancer-related deaths in China (1) and worldwide (2). The vast majority of cases are non-small cell lung cancer (NSCLC) where surgery plays a pivotal role among the associated therapeutic methods. As recommended by the guidelines (3,4), lobectomy with systematic lymph node dissection (LND) is regarded as

the standard surgical treatment for early-stage NSCLC, which meant to provide accurate staging (5,6) detect occult metastasis (7) and improve survival (5,8,9). With the general acceptance of lung-cancer screening and the development of radiographic techniques, an increasing number of early-stage NSCLC patients can now be diagnosed. Therefore, minimally invasive approaches should be considered, such as video-assisted thoracic surgery, parenchyma-preserving resection and selective lymph node dissection (SLND) (10). The first two approaches have been well documented in the literature (11,12) and widely accepted in clinical practice while SLND remains controversial. Randomized trials have not demonstrated that LND had more survival benefit than sampling (7,13) while SLND is a totally different approach. SLND means specific lymph node stations are selected to dissect (14) according to the location, but sampling only makes a specimen of the relevant lymph node stations. Hence, whether SLND is comparable to LND and whether LND is favorable to prognosis stays unsolved.

SLND is now frequently mentioned because it is considered able to reduce operative time, blood loss, hospital stay, postoperative morbidity and mortality (15). Nowadays, advanced radiographic techniques such as positron emission computed tomography-computed tomography (PET-CT) can detect metastatic lymph nodes and provide accurate clinical stage. Therefore, the advantage of LND in comprehensive staging is weakened. Several retrospective studies (16-21) have revealed the rules of lobe-specific lymphatic drainage pattern. Meanwhile, some authors have put forward a concept of regional lymph nodes (22-25), which is similar to the idea of sentinel lymph nodes. They supposed that if regional lymph nodes are proved tumor-free, the rest should be preserved. On the basis of such findings (16-25), SLND may be applicable for early-stage NSCLC patients to minimize surgical trauma and provide clinical benefits.

Methods

Search strategy

We searched several databases (PubMed, Cochrane Library, OVID, EBSCO and web of science) for pertinent literature from January 2006 to October 2016. In order to search comprehensively, we used the terms: (lung cancer OR lung carcinoma OR lung neoplasm OR nsclc OR NSCLC) AND (selective lymph node OR selected lymph node OR elective lymph node OR selective lymphadenectomy OR selected lymphadenectomy OR elective lymphadenectomy OR selective nodal OR selected nodal OR elective nodal OR selective mediastinal lymph node OR selected mediastinal lymph node OR elective mediastinal lymph node OR lobe specific) among title or abstract in each database. The specific process is available in the flow chart (*Figure 1*).

Inclusive criteria

Two reviewers screened the literature searched via the method above independently. Their judgments were based on the following inclusive criteria: (I) the comparison was between SLND and LND in surgical treatment of NSCLC; (II) all patients should be resectable clinical N2-negative NSCLC patients; (III) hazard ratio (HR) of overall survival (OS) could be calculated; (IV) the studies were published between 2006 and 2016.

Data extraction

Two independent authors reviewed the full-text articles and extracted the data. Fundamental information of every study was summarized in accordance with the order: first author, year of publication, study design, population, lymphadenectomy strategy and clinical stage (*Table 1*). The primary endpoint was OS, and disease-free survival (DFS) was evaluated if available. In order to provide a comprehensive analysis of operative and postoperative conditions, we evaluated operative time, blood loss, postoperative morbidity and recurrence as well.

Quality assessment

The Newcastle-Ottawa Quality Assessment Scale was performed to estimate the bias risk for cohort studies in three aspects: selection, comparability and outcome. Maximum of 9 stars can be achieved regarded as minimum risk of bias and above 7 stars represents low risk of bias while below 4 stars means high risk of bias.

Data analysis

Survival (OS and DFS) was evaluated by HR, which was extracted along with associated 95% confidence interval (CI) if directly provided. The HR of the Hishida's study was extracted from Cox regression model. Otherwise, the survival data were extracted from the Kaplan-Meier curve (except for Hishida's study) by Engauge Digitizer software and HR was calculated by a specialized form designed by Tierney (31). For dichotomous data, risk ratio (RR)

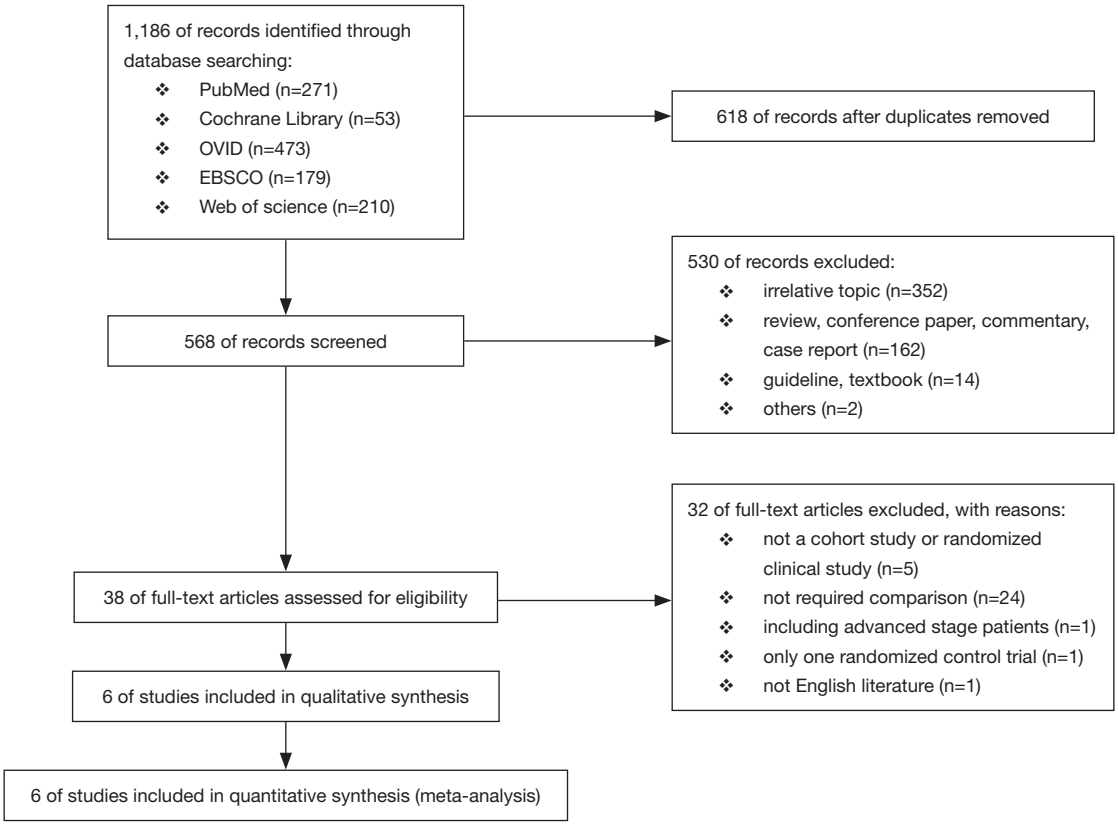

Figure 1 The flow chart of literature searching.

Table 1 Basic characteristics of included studies

Author	Year	Country	Study design	NOS score	Group		Clinical stage
					SLND	LND	
Adachi (26)[a]	2016	Japan	Retrospective	7 stars	49	49	Clinical T1a-2bN0-1M0
Hishida (27)	2016	Japan	Retrospective	5 stars	1268	4124	I–II
Jiang (28)	2013	China	Retrospective	5 stars	94	309	I
Maniwa (29)	2013	Japan	Retrospective	5 stars	129	206	Clinical or intraoperative N0
Okada (30)	2006	Japan	Retrospective	7 stars	377	358	I
Shapiro (10)	2013	America	Retrospective	5 stars	88	282	Clinical N0–N1

[a], a propensity score matching was performed. LND, systematic lymph node dissection; SLND, selective lymph node dissection; NOS, Newcastle-Ottawa quality assessment scale.

was calculated based on the number of events and total patients in each group. In addition, mean difference (MD) was calculated for continuous data derived from mean and standard deviation (SD) when presented in the article. If not, mean and SD were transformed from median and range by Hozo method (32).

The χ^2 test and I^2 data were calculated to estimate the heterogeneity among the trials. Once upon $P_{heterogeneity}<0.05$ or $I^2>50\%$ occurred, heterogeneity was considered existing and the data would be analyzed following a random effects

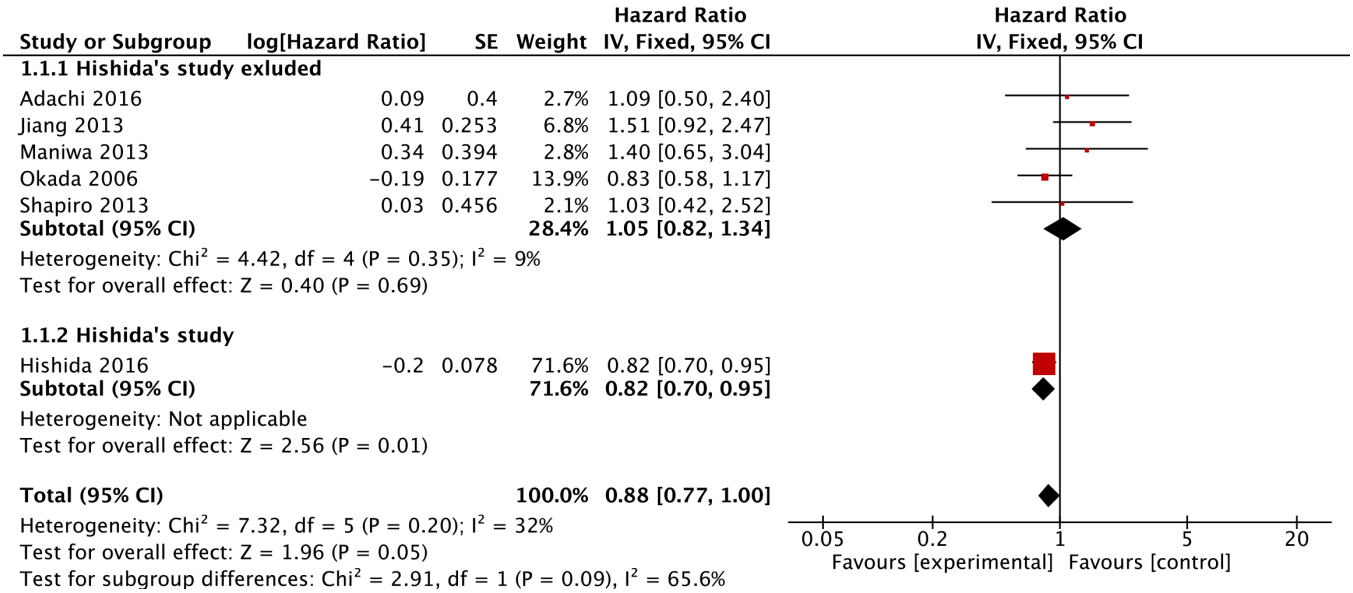

Figure 2 OS for the SLND versus LND with and without Hishida's study. OS, overall survival; SLND, selective lymph node dissection; LND, systematic lymph node dissection.

model. Otherwise, a fixed effect model would be employed. Moreover, publication bias was evaluated on the basis of funnel plot (*Figure S1*). P values above were two sided with 95% CI.

Results

Search results

A total of 1,186 potentially relevant articles were screened electronically, and the detailed reasons for exclusion were available in the flow chart (*Figure 1*). Six cohort studies were finally involved in this analysis. It is noteworthy that we excluded the only randomized controlled trial (RCT) we found in order to ensure the validity and reliability of our study. The basic characteristics of all studies are listed in *Table 1* and some other vital variables are listed in *Table S1*.

Study interpretation

In all, 7,333 patients with clinical N2-negative NSCLC were included in this analysis and divided into two groups according to different strategies of lymph node dissection. A total of 2,005 patients were in the SLND group while the remaining 5,328 patients belonged to the LND group.

In the LND group, mediastinal lymph node stations #2R, #4R, #7, #8 and #9 should be dissected for the right lobes and mediastinal lymph node stations #4L, #5, #6, #7, #8 and #9 dissection is required for the left lobes. On both sides, N1 nodes are dissected as part of lung resection. In the SLND group, similar protocols were performed and the details are presented in *Table S2*. The mediastinal lymph node map is based on the International Association for the Study of Lung Cancer (IASLC) node map in the seventh edition of the TNM classification (33).

OS

HRs were calculated from all six studies with 7,333 patients, and we regarded one of them (Hishida's study) as a subgroup because of the sensitivity analysis. The influence of Hishida's study on the pooled result could not be ignored (P value from 0.69 to 0.05), while the other studies did not have strong effects on the pooled result (Adachi's study, P value from 0.04 to 0.05; Jiang's study, P value from 0.01 to 0.05; Maniwa's study, P value from 0.03 to 0.05; Okada's study, P value from 0.09 to 0.05; Shapiro's study, P value from 0.05 to 0.05). As shown in the forest plot, LND did not improve OS compared with SLND, no matter Hishida's study was included (HR =0.88, 95% CI: 0.77–1.00, P=0.05, *Figure 2*) or not (HR =1.05, 95% CI: 0.82–1.34, P=0.69, *Figure 2*).

Table 2 Summary of operative and postoperative-associated outcomes

Outcome	No. of studies	SLND	LND	HR/MD/RR	95% CI	P value	Heterogeneity (P, I^2)	Meta-analysis model
Disease-free survival	3	594	846	0.98	0.78–1.23	0.87	0.38, 0%	Fixed
Operative time (min)	3	272	564	–21.45	–29.53 to –13.36	<0.001	0.15, 48%	Fixed
Blood loss (g)	3	272	564	–28.88	–44.38 to –13.39	<0.001	0.28, 22%	Fixed
Postoperative morbidity	4	1,868	4,997	0.82	0.61–1.11	0.21	0.08, 56%	Random
Total recurrence	6	2,005	5,328	0.84	0.73–0.92	<0.001	0.45, 0%	Fixed
Total recurrence (Hishida's study excluded)	5	737	1,204	0.89	0.76–1.05	0.17	0.43, 0%	Fixed
Local recurrence	6	2,005	5,328	0.81	0.67–0.98	0.03	0.83, 0%	Fixed
Local recurrence (Hishida's study excluded)	5	737	1,204	0.85	0.62–1.16	0.31	0.75, 0%	Fixed

HR hazard ratio, LND systematic lymph node dissection, MD mean difference, RR risk ratio, SLND selective lymph node dissection.

DFS

Data of 1,440 patients (594 in SLND group, 846 in LND group) from three studies were available to calculate HRs for DFS. In accordance with OS, there is no significant difference in DFS between LND and SLND (HR =0.98, 95% CI: 0.78–1.23, P=0.87, *Table 2*, *Figure S2*).

Operation associated outcomes

Three studies with 836 patients (272 in SLND, 564 in LND) were available to estimate operative time (min) and blood loss (g) by MD. In comparison with LND, SLND significantly reduced the operative time (MD =–21.45, 95% CI: –29.53 to –13.36], P<0.001, *Table 2*, *Figure S3*) and blood loss (MD =–28.88, 95% CI: –44.38 to –13.39, P<0.001, *Table 2*, *Figure S4*).

Postoperative morbidity

A total of 1,868 patients in SLND and 4,997 patients in LND were included to evaluate postoperative morbidity in terms of RR. The pooled results did not show significant difference (RR =0.82, 95% CI: 0.61–1.11, P=0.21, *Table 2*, *Figure S5*).

Recurrence

The data of recurrence were reported by six studies. After sensitivity analysis in total recurrence (Adachi's study, P value from <0.001 to <0.001; Jiang's study, P value from <0.001 to <0.001; Maniwa's study, P value from <0.001 to <0.001; Okada's study, P value from 0.02 to <0.001; Shapiro's study, P value from <0.001 to <0.001, Hishida's study, P value from 0.17 to <0.001) and local recurrence (Adachi's study, P value from 0.02 to 0.03; Jiang's study, P value from 0.02 to 0.03; Maniwa's study, P value from 0.03 to 0.03; Okada's study, P value from 0.06 to 0.03; Shapiro's study, P value from 0.05 to 0.03, Hishida's study, P value from 0.31 to 0.03), we set Hishida's study as a subgroup. When Hishida's study was included, both total recurrence (RR =0.84, 95% CI: 0.77–0.92, P<0.001, *Table 2*, *Figure S6*) and local recurrence (RR =0.81, 95% CI: 0.67–0.98, P=0.03, *Table 2*, *Figure S7*) showed significant difference under the comparison between SLND and LND. However, if Hishida's study spared, there was no statistical difference (*Table 2*).

Discussion

During the process of literature search, only one published meta-analysis (34) has been found comparing the clinical outcomes between SLND and LND, but only three cohort studies were included (other than sampling). Besides, survival was the only analyzed outcome while the associated preoperative and postoperative outcomes were also included in our study.

Our meta-analysis demonstrated that SLND did not have negative influence on OS or DFS compared with LND. Instead, it would minimize the surgical trauma and has the potential to improve postoperative quality of life. On one

hand, shorter operative time and less blood loss could be achieved in SLND, so that patients will suffer less from anesthesia and ischemia. On the other hand, the trend that SLND could decrease the postoperative morbidity should be noticed, which might contribute to quick recovery, shorter hospital stays and lower postoperative mortality rate. Moreover, although pooled results of recurrence were ambiguous because of the Hishida's study, there was no evidence to suspect that SLND would increase the possibility of recurrence. Besides these clinical conclusions, it is also a strong support and encouragement for RCTs.

Our study has provided possible answers to some questions. Still, several problems remain unsolved. Whether SLND can reduce the postoperative mortality rate or shorten the hospital stay are not clear. In order to provide unambiguous answers, multi-institutional RCTs are expected to carry out in the future. Hence, it is crucial to formulate the specific definition and standard protocol of SLND because a conservative or radical option may reduce the efficacy of a clinical trial or cause adverse effect on patients. Moreover, although pathological types were comparable in each research included in our study, histological subtypes and intraoperative frozen section analysis should be taken into account in decisions on strategies of lymph node dissection. With the rapid development of radiographic field, some advanced techniques such as PET-CT should be performed before the surgery to provide accurate clinical stage. Meanwhile, the inclusion criteria of patients need to be cautiously considered.

Several limitations need to be acknowledged in our study. First and foremost, all the studies analyzed were cohort studies where selection bias and attrition bias were inevitable. For example, the patients' selection and surgical approach were not randomized in each research included. And we suppose it is the reason why SLND showed decreased possibility of recurrence when Hishida's study included. In fact, one eligible RCT (35), which indicates that the efficacy was similar in the SLND and LND group, has been screened out. Because we believe that it is inappropriate to combine an RCT with other retrospective studies and in order to ensure the validity and reliability of our study, we have to exclude it. In addition, most of the studies were carried out in Asia. Although the protocols of SLND were similar in different groups, no uniform criteria were formulated and the conversion from SLND group to LND group was not clearly described as well.

In conclusion, our meta-analysis indicated that SLND is an alternative to LND for clinical N2-negative NSCLC patients, which may even provide clinical benefits. However, more RCTs are expected to determine whether SLND is valid and practical to become a standard procedure of surgical treatment for early-stage NSCLC patients.

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None.

Footnote

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

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Supplementary

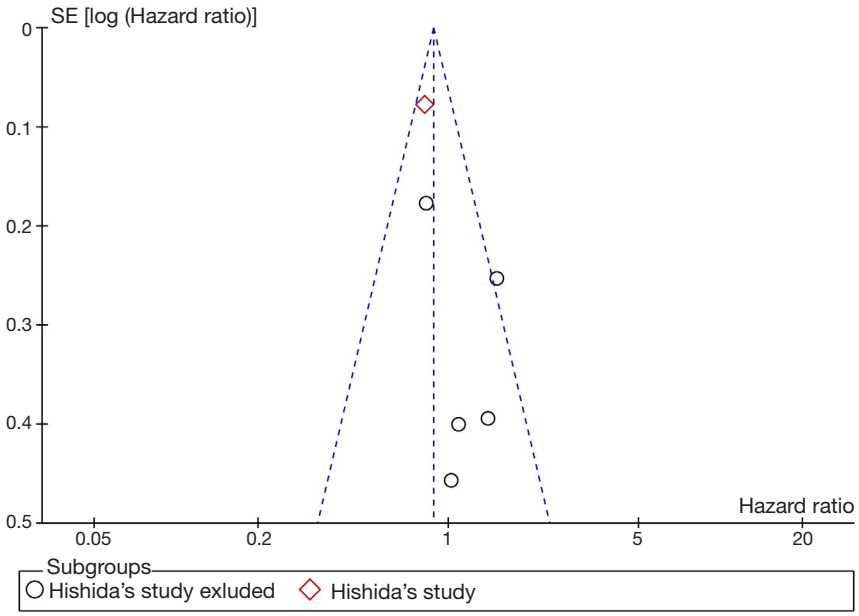

Figure S1 Funnel plot of overall survival for the SLND versus LND group. SLND, selective lymph node dissection, LND, systematic lymph node dissection.

Table S1 Some other vital variables of included studies

Author	Adachi (26)			Hishida (27)			Jiang (28)			Maniwa (29)			Okada (30)			Shapiro (10)		
	SLND	LND	P value	SLND	LND	P value	SLND	LND	P value	SLND	LND	P value	SLND	LND	P value	SLND	LND	P value
Age[a]	69 [50–80]	67 [39–82]	0.746	66.1±9.6	65.8±9.3	0.330	61.2 [30–80]	58.7 [26–84]	0.053	70 [43–89]	64 [20–81]	<0.0001	65 [20–83]	65 [30–85]	0.822	70.0 (63.5–78.0)	68.4 (60.9–75.5)	0.11
Gender			1.000			0.325			0.284			0.71			0.166			0.91
Male	30 (61.2%)	30 (62.2%)		780 (61.5%)	2,471 (59.9%)		59 (62.8 %)	173 (56.0 %)		55 (56.1%)	115 (55.8%)		234 (62.1%)	240 (67.0%)		39	123	
Female	19 (38.8%)	19 (38.8%)		488 (38.5%)	1,653 (40.1%)		35 (37.2 %)	136 (44.0 %)		43 (43.9%)	95 (44.2%)		143 (37.9%)	118 (33.0%)		49	159	
Histology			0.576			0.941[b]			0.191						0.118			0.72
Adeno-carcinoma	34 (69.4%)	36 (73.5%)		944 (74.4%)	3,074 (74.4%)		55 (58.5 %)	211 (68.3 %)		65 (66.3%)	158 (76.7%)	0.15	274 (72.7%)	233 (65.1%)		63 (71.6%)	211 (74.8%)	
Squamous cell carcinoma	13 (26.5%)	9 (18.4%)		242 (19.1%)	818 (19.9%)		26 (27.7 %)	67 (21.7 %)		20 (20.4%)	26 (12.6%)	0.083	82 (21.8%)	108 (30.2%)		18 (20.5%)	47 (16.7%)	
Others	2 (4.1%)	4 (8.1%)		82 (6.5%)	232 (5.7%)		13 (13.8 %)	31 (10.0 %)		13 (13.3%)	22 (10.7%)	0.51	21 (5.7%)	17 (4.8%)		7 (7.9%)	24 (8.5%)	
Pathological N status			0.825						0.909						0.719			0.20
pN0	38 (77.5%)	40 (81.6%)		NA	NA		67 (71.3 %)	221 (71.5 %)		86 (87.6%)	173 (84.0%)	0.38	354 (93.9%)	336 (93.9%)		69 (78.4%)	241 (85.5%)	
pN1	7 (14.3%)	5 (10.2%)		NA	NA		10 (10.6 %)	29 (9.4 %)		8 (8.2%)	17 (8.3%)	0.98	21 (5.6%)	19 (5.3%)		10 (11.4%)	26 (9.2%)	
pN2	4 (8.2%)	4 (8.2%)		NA	NA		17 (18.1 %)	59 (19.1 %)		4 (4.1%)	16 (7.7%)	0.21	2 (0.5%)	3 (0.8%)		9 (10.2%)	15 (5.3%)	
Follow up period[c] (month)	66 [1–97]	69 [6–69]	0.712	NA	NA		34.6±17.2	35.8±13.7		60 [36–110]			62 [28–98]	111 [67–207]		20.4 (12.3–33.1)	27.0 (12.4–50.5)	0.06

[a], medium, range/medium, IQR/mean + SD/mean, range; [b], adenocarcinoma *vs.* squamous cell + others; [c], medium, range/medium, IQR/mean ± SD. SLND, selective lymph node dissection, LND, systematic lymph node dissection; IQR, interquartile range; SD; standard deviation.

Table S2 Different protocols of selective lymph node dissection[a]

Author	Location of tumor					
	RUL	RML	RLL	LUD	LLD	LLL
Adachi (26)	#2R #4R	Excluded	#7 #8 #9	#4L #5 #6		#7 #8 #9
Hishida (27)	#2R #4R	Excluded	#7 #8 #9	#4L #5 #6		#7 #8 #9
Jiang (28)	#2R #4R	Unknown	#7 #8 #9	#5 #6		#7 #8 #9
Maniwa (29)[c]	#2R #4R	Unknown	#7 #8 #9	#4L #5 #6		#7 #8 #9
Okada (30)[c]	#2R #4R	Excluded	#7 #8 #9	#4L #5 #6		#7 #8 #9
Shapiro (10)[b]	#2R (#4R)	#7	#7 (#8 or #9)	#5 #6		#7 (#8 or #9)

[a], N1 nodes were dissected as a part of lung resection; [b], lymph node before the bracket was constantly dissected while those enclosed in the bracket were removed only if suspicious of metastases; [c], intraoperative frozen section analysis was performed. LUD, left upper division; LLD, left lingular division; LLL, left lower lobe; RUL, right upper lobe; RML right middle lobe; RLL, right lower lobe.

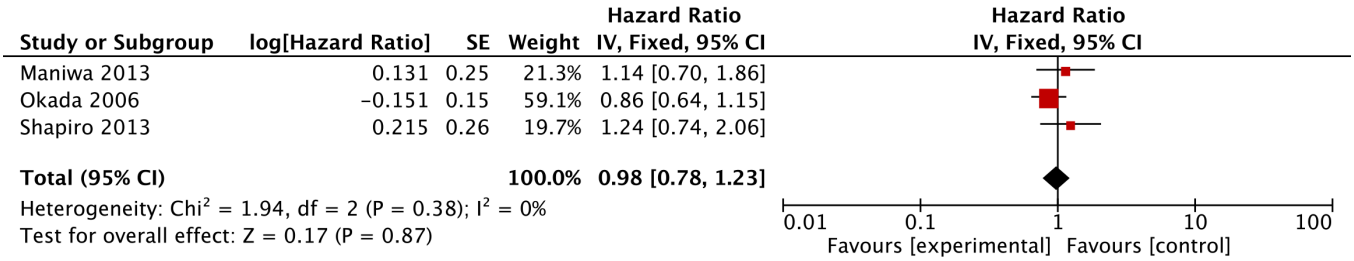

Figure S2 Forest plot of disease-free survival for the SLND versus LND group. SLND, selective lymph node dissection, LND, systematic lymph node dissection.

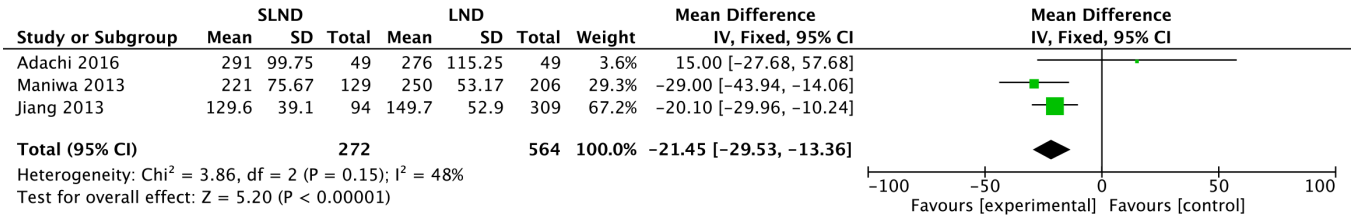

Figure S3 Forest plot of operative time for the SLND versus LND group. SLND, selective lymph node dissection, LND, systematic lymph node dissection.

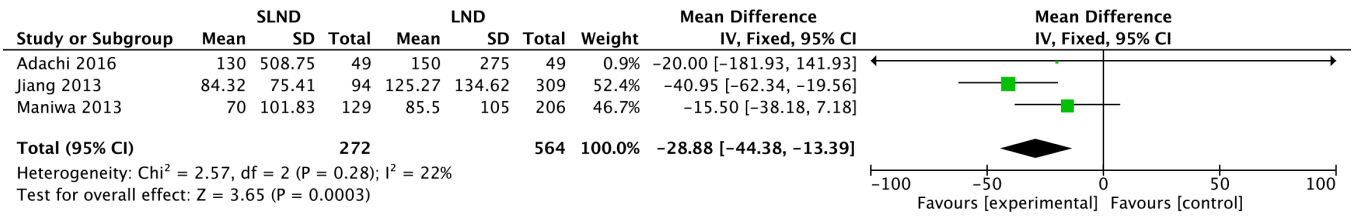

Figure S4 Forest plot of blood loss for the SLND versus LND group. SLND, selective lymph node dissection, LND, systematic lymph node dissection.

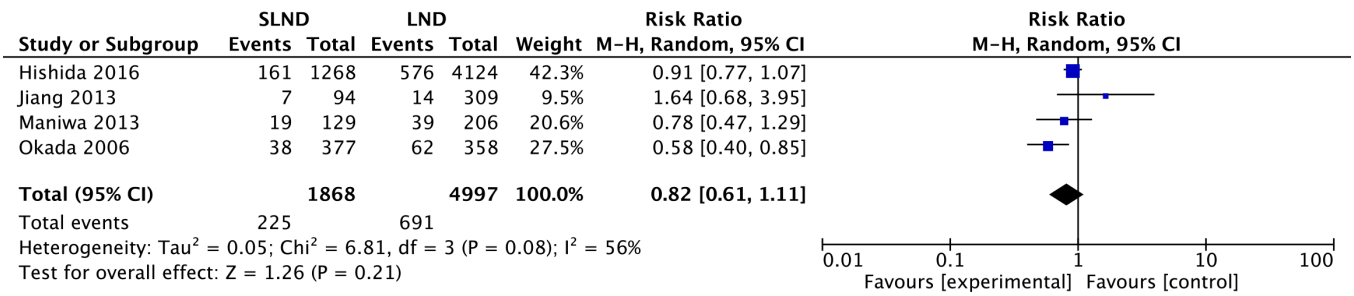

Figure S5 Forest plot of postoperative morbidity for the SLND versus LND group. SLND, selective lymph node dissection, LND, systematic lymph node dissection.

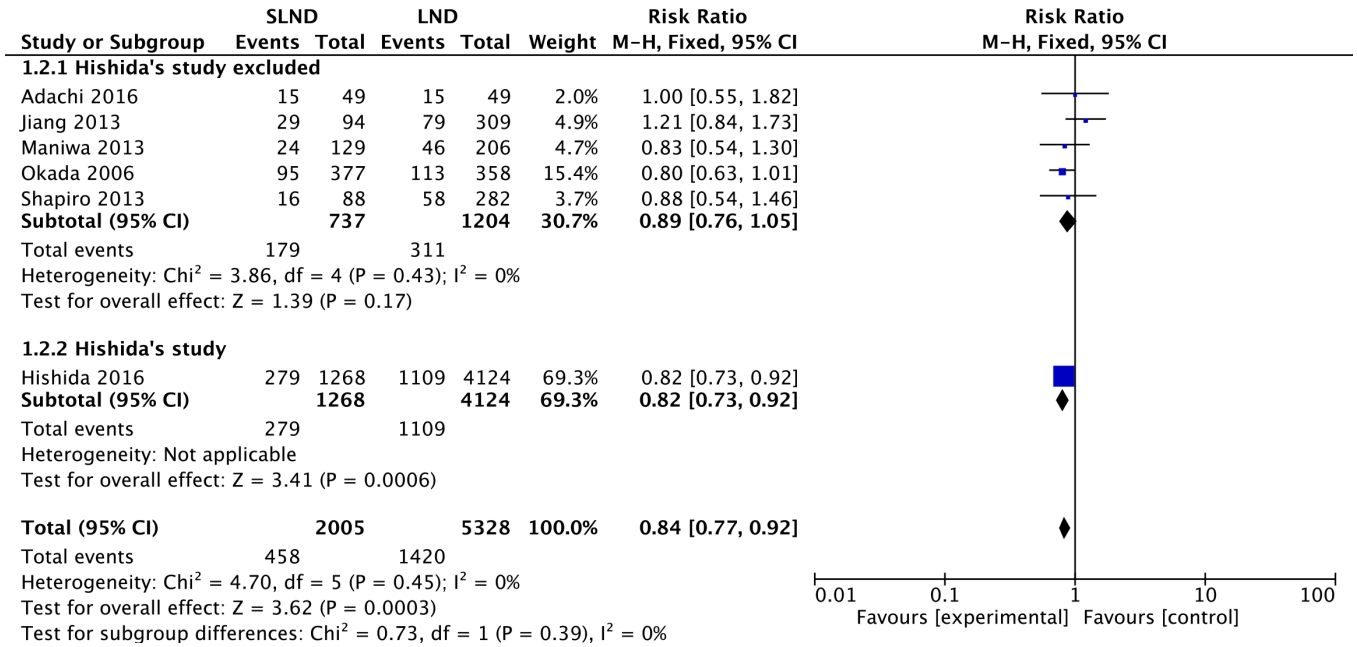

Figure S6 Forest plot of recurrence for the SLND versus LND group with and without Hishida's study. SLND, selective lymph node dissection, LND, systematic lymph node dissection.

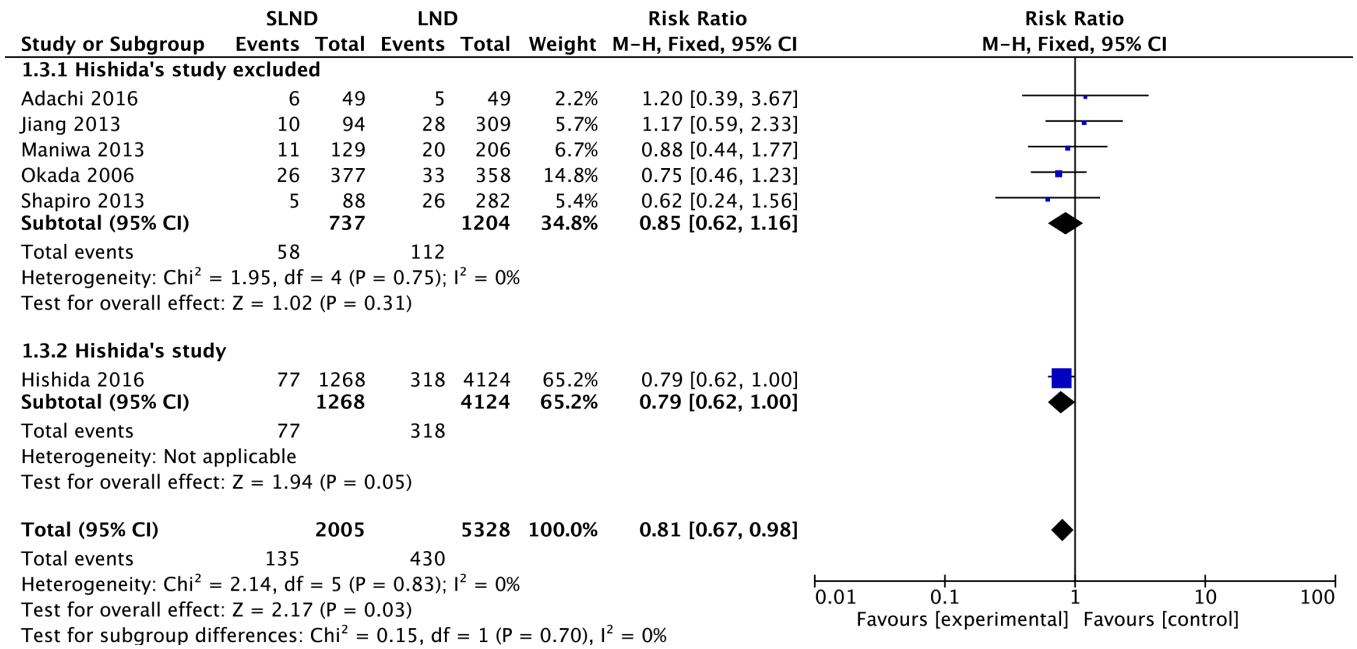

Figure S7 Forest plot of local recurrence for the SLND versus LND group with and without Hishida's study. SLND, selective lymph node dissection, LND, systematic lymph node dissection.