Original Article

Risk of recurrence in stage I adenocarcinoma of the lung: a multi-institutional study on synergism between type of surgery and type of nodal staging

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Background: In last years, an increasing interest emerges on the role of sub-lobar resection and lobe-specific lymph nodal dissection in the treatment of early-stage lung cancer. The aim of our study was to define the impact on cumulative incidence of recurrence (CIR) of type of surgical resection and type of nodal staging in this subset of patients. Furthermore, we evaluated the possible synergism between the different kinds of procedure.

Methods: An analysis of 969 consecutive stage I pulmonary adenocarcinoma patients, operated in six Thoracic Surgery Institutions between 2001 and 2013, was conducted. Type of surgical resection included lobectomy and sub-lobar resection; while pneumonectomy and bilobectomy were excluded from the analysis. Nodal staging procedures were classified in nodal sampling (NS), lobe-specific lymph node dissection (LS-ND) and systematic lymph node dissection (SND). Multivariable-adjusted comparisons for CIR was performed using Fine and Grey model, taking into account of death by any cause as competing event. In order to evaluate synergism between the different procedures, the test of interaction between type of surgical resection and type of nodal staging was carried out and results presented in a stratified way.

Results: Eight-hundred forty-six (87%) patients were submitted to lobectomy, while 123 (13%) to sub-lobar resection. Four-hundred fifty-five (47%) patients received SND, 98 (10%) LS-ND and 416 (43%) NS. Two-hundred forty-seven (26%) patients developed a local/distant recurrence with a 5-year CIR of 24.2%. Multivariable-adjusted comparisons showed an independent negative effect of sub-lobar resection (HR =1.52; 95% CI: 1.07–2.17), LS-ND (HR =1.74; 95% CI: 1.16–2.6) and NS (HR =1.49; 95% CI: 1.12–1.98) on CIR. Test of interaction showed a homogeneity of results among subgroups.

Conclusions: Patients affected by stage I pulmonary adenocarcinoma and submitted to lobectomy presented a significant lower recurrence rate than those submitted to sub-lobar resection. Moreover, SND presented an independent positive effect on recurrence development than other lymph node assessment strategy. Finally, lobectomy in combination with systematic lymph nodal resection showed the best results in term of CIR.

Keywords: Non-small cell lung cancer (NSCLC); lobectomy; lymphadenectomy; staging

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Introduction

Non-small cell lung cancer (NSCLC) confirmed to be a major public health issue worldwide (1). In this context, 20% of whole NSCLC were diagnosticated as early stage (2), while lung adenocarcinoma accounted 70% of all NSCLC cases (3).

Currently, lobectomy with radical lymph node dissection represent the standard of care for resectable NSCLC (4,5). Nonetheless, in last years, an increasing interest emerges on the role of sub-lobar resection in the treatment of stage I lung cancer. Undeniably, the possibility to perform parenchymal sparing resection (i.e., anatomical segmentectomy and wedge resection), primarily reserved to unfit patients, to the whole cases of early stage NSCLC fascinated numerous surgical groups over the years. However, the only randomized clinical trial comparing sub-lobar resection with lobectomy for clinical stage IA NSCLC demonstrated an inferior survival and a higher local recurrence rate in the limited resection group (5). Still, interest concerning convenience of limited lung resections in early stage NSCLC remains and numerous studies could be found in recent literature, assessing their equivalence with lobectomy in term of survival and recurrence rate (6-11).

On the other hand, lymph nodal status is one of the most important prognostic factors in the management of NSCLC (12). However, optimal lymph node assessment strategy is still matter of debate amongst surgical community. Indubitably, systematic nodal dissection (13), in respect of lymph nodal sampling (NS), provides a more accurate pathological staging and allows to sterilize unknown or microscopic neoplastic lymph node spreading (14). Nevertheless, new minimally invasive biopsy techniques (15,16) and high definition imaging rise doubts on unavoidability of such aggressive nodal assessment.

Accordingly, the aim of our study was to define impact on Cumulative incidence of recurrence (CIR) of type of surgical resection and type of nodal staging. Furthermore, we evaluated the possible synergism between the different kinds of procedure.

Methods

From 2001 to 2013, patients who underwent lung surgical resection with curative intent for stage I pulmonary adenocarcinoma in six thoracic surgery institutions (Appendix A) were retrospectively reviewed.

Extended resection (i.e., combined lung and chest wall/ diaphragm resections), pneumonectomy, bilobectomy or preoperative treatment regimen (e.g., chemotherapy, radiotherapy) represented the exclusion criteria from this study.

The preoperative assessment of patient encompassed chest radiographs; thoracic-, brain- and upper-abdominal computed tomography (CT) scans or whole-body 18-fluorodeoxyglucose positron emission tomography (PET), or both; fiber-optic bronchoscopy; electrocardiograms and lung function tests.

Surgical procedures were performed either through thoracotomy (muscle-sparing axillary or posterolateral) or video-assisted thoracic surgery (VATS).

Data variables and outcomes

The final data set for the analyses included the following data: age, gender, smoking habit, side of intervention, type of surgical resection, type of intraoperative lymph node assessment, pathological TNM (pTNM) stage (according to 7^{th} edition), vascular invasion, predominant histologic pattern and histologic grade and survival data.

Type of surgical resection were divided into lobectomy and sub-lobar resection (encompassed wedge and segmental resection).

Lymph node station were classified according to IASLC 8th edition lymph node map (12). Type of intraoperative lymph node assessment was classified as follow: (I) lymph NS consisted in the removal of one or more lymph nodes, guided by preoperative or intraoperative findings; (II) lobe-specific lymph node dissection (LS-ND), encompassed the resection of only stations which are considered as the natural drain for that lobe (Appendix B) (17,18); (III) systematic nodal dissection (SND), in which, according to ESTS (13), all mediastinal tissue containing lymph nodes is dissected and removed systematically within anatomical landmarks; the hilar and the intrapulmonary lymph nodes are dissected as well, and at least three mediastinal nodes are excised as a minimum requirement.

Surgery was defined as radical (R0) when a complete tumor resection was accomplished, and incomplete in case of microscopically (R1) or macroscopically (R2) residual disease.

Histological grading was categorized into well- (G1), moderately- (G2) and poorly differentiated (G3) carcinoma according to degree of architecture and cytological atypia.

The adenocarcinoma predominant patterns were determinate according to the criteria of the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society (IASLC/ATS/ERS) (19). The following predominant patterns were clustered in the "Common Variants" group in order to simplify the analysis: Solid, Micropapillary, Acinar and Papillary.

The study was approved by the IRB of each participating center.

Statistical analysis

Categorical data are presented as number (percentage, %), continuous data as median [interquartile range (IQR)]. Missing data in evaluated predictors were multiple-imputed and combined estimates were obtained from 5 imputed data sets. Associations between type of surgery, type of intraoperative lymph node assessment and clinicopathological characteristics were investigated with the use of the χ^2 test or Fisher's exact test, when appropriate (20).

Primary outcome was CIR, calculated from the date of intervention to the date of tumor distant or local relapse. CIR were estimated using the method proposes by Gooley *et al.* (21), taking into account death by any cause (except of cancer related death) as competing event. Differences in CIR between groups were investigated with Fine and Grey model, taking into account of death by any cause (except of cancer related death) as competing event. Univariable and Multivariable analysis were carried out. Multivariate adjusted analysis considers age, gender, smoking habit, side of intervention, pTNM stage, vascular invasion, predominant histologic pattern and histologic grade.

Moreover, we explored a potential synergism (the so called "effect modification") between surgical resection and intraoperative lymph node assessment in the determination of CIR. This potential synergism was evaluated from a statistical point of view by including and testing interaction terms between variables related to surgical resection and intraoperative lymph node assessment in the Fine & Gray model.

The overall survival (OS) was the secondary outcome and was defined as the time from the date of the intervention to the date of death by any cause. Survival function was estimated by Kaplan-Maier method.

All statistical analyses were performed using STATA (version 14) and R (version 3.1).

Results

According to the selection criteria, 969 patients with stage I adenocarcinoma of the lung were included in the final dataset (*Figure S1*). Population demographics and clinical, surgical and pathologic characteristics of the cohort were showed in *Table 1*.

Most of the patients are male (658, 68%) and smokers (599, 62%). Pathological stage Ia was more commonly observed (641, 66%), while the histological predominant pattern consisted of acinar adenocarcinoma (442, 46%), followed by the papillary (149, 15%), the solid (147, 15%), the lepidic (124, 12.8%) and the micropapillary (25, 3%).

Median follow-up was 63 months. A total of 686 (68%) were reported to be alive and 283 (32%) died during the follow-up period. Overall, the 5-year survival rate was 74.5% (95% CI: 71.3–77.3%) (*Figure 1*).

Clinicopathological variables and type of surgical resection

Table 1 shows the distribution of clinicopathological variables according to the type of surgical resection: Eight-hundred forty-six (87%) patients were submitted to lobectomy, while 123 (13%) to sub-lobar resection [72 (58%) segmentectomy, 51 (42%) wedge resection].

Patients submitted to lobectomy were predominantly younger (P=0.002). No difference between type of surgical resection was observed in regard to gender, smoking habit, pTNM stage, vascular invasion, predominant histological pattern and histological grade.

Clinicopathological variables and type of lymph node assessment

Table 1 shows the distribution of clinicopathological

Table 1 Patients characteristics

Characteristics	N non-missing	Overall (N=969)	1st comparison			2nd comparison			
			Lobectomy (N=846)	Sub-lobar resection (N=123)	P value*	SND (N=455)	LS-ND (N=98)	NS (N=416)	P value*
Age	969				0.002				0.009
≤70 years		597 [62]	537 [63]	60 [49]		297 [65]	48 [49]	252 [61]	
>70 years		372 [38]	309 [37]	63 [51]		158 [35]	50 [51]	164 [39]	
Gender	969				0.753				0.426
Female		311 [32]	270 [32]	41 [33]		154 [34]	27 [28]	130 [31]	
Male		658 [68]	576 [68]	82 [67]		301 [66]	71 [72]	286 [69]	
Smokers	969				0.547				0.043
No		370 [38]	320 [38]	50 [41]		180 [40]	26 [27]	164 [39]	
Yes		599 [62]	526 [62]	73 [59]		275 [60]	72 [73]	252 [61]	
pTNM stage	969				0.251				<0.001
Ia		641 [66]	554 [65]	87 [71]		271 [60]	71 [72]	299 [72]	
Ib		328 [34]	292 [35]	36 [29]		184 [40]	27 [28]	117 [28]	
Vascular invasion	815				0.08				<0.001
No		643 [79]	567 [80]	76 [72]		342 [78]	59 [65]	242 [85]	
Yes		172 [21]	143 [20]	29 [28]		98 [22]	32 [35]	42 [15]	
Histologic predominant pattern	959				0.196				0.127
Lepidic		124 [13]	102 [12]	22 [18]		54 [12]	17 [17]	53 [13]	
Common variants		762 [79]	671 [80]	91 [74]		365 [81]	79 [81]	318 [78]	
NOS—other variants		73 [8]	63 [8]	10 [8]		34 [8]	2 [2]	37 [9]	
Histologic grade	955				0.131				0.542
G1		202 [21]	170 [20]	32 [27]		90 [20]	17 [18]	95 [23]	
G2		484 [51]	422 [51]	62 [52]		238 [53]	51 [53]	195 [48]	
G3		269 [28]	243 [29]	26 [22]		124 [27]	29 [30]	116 [29]	

*, χ^2 test or Fisher's exact test. NS, lymph node sampling; LS-ND, lobe-specific lymph node dissection; SND, systematic nodal dissection.

variables according to the type of lymph nodal assessment: 455 (47%) patients received SND, 98 (10%) LS-ND and 416 (43%) NS.

Patients submitted to SND were predominantly younger (P=0.009), non-smoker (P=0.043), with higher pTNM stage (P<0.001) and less frequently presented vascular invasion (P<0.001). No difference between the types of lymph nodal assessment was observed in regard to gender, predominant histological pattern and histological grade.

CIR analysis

Nine-hundred thirty-seven patients with stage I adenocarcinoma of the lung were included in the analyses (*Figure S1*).

Two-hundred forty-seven (26%) patients developed a local/distant recurrence with a 5-year CIR of 24.2% (95% CI: 21.3–27.1%) (*Figure 2*). In univariable analysis, lobectomy (20.5% *vs.* sub-lobar resection 38.1%; 20.5%, *vs.* LS-ND 37.8% *vs.* NS 24.9%; P=0.014) and SND (P=0.001)

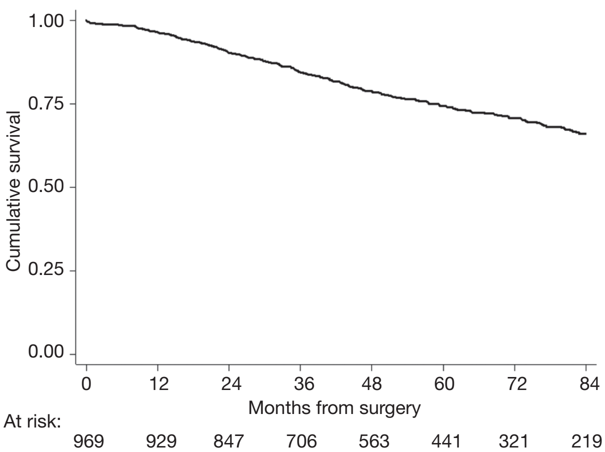


Figure 1 Overall survival.

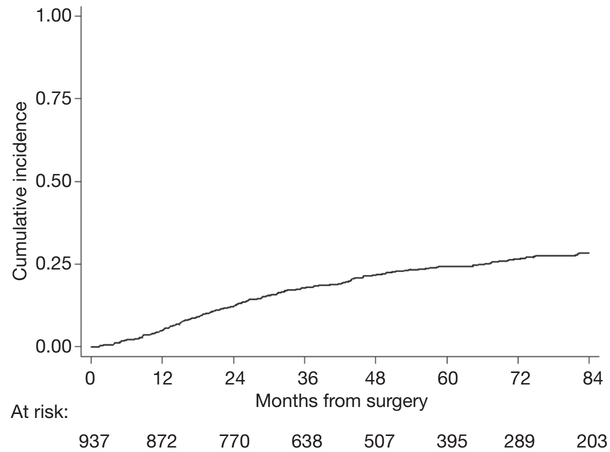


Figure 2 Cumulative incidence of recurrence.

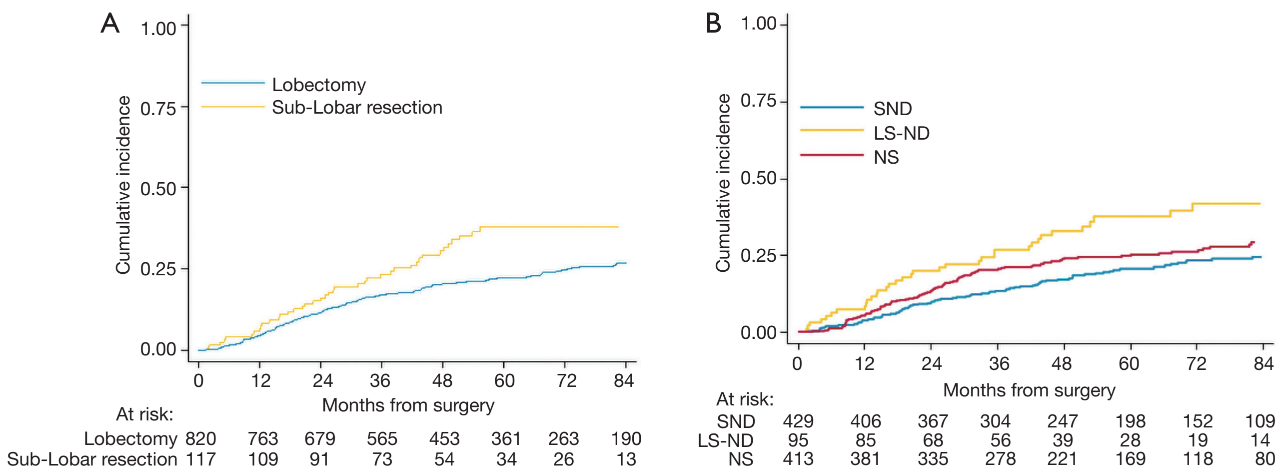


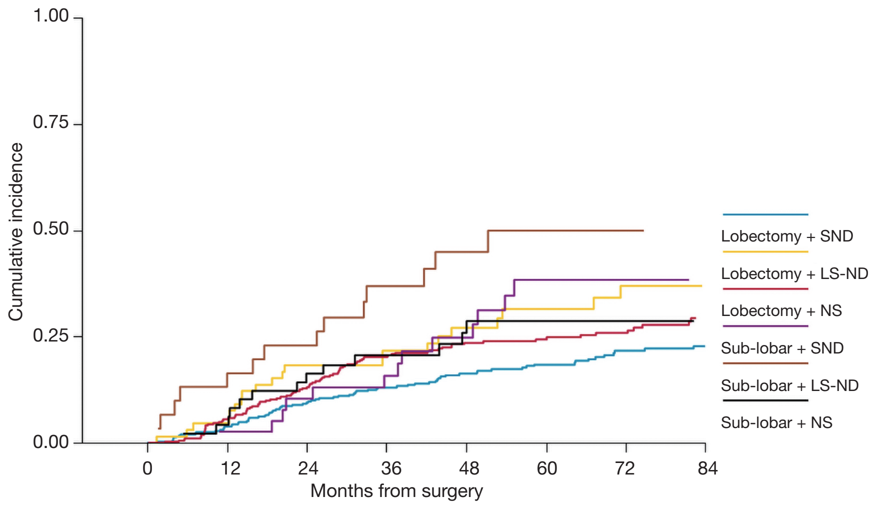
Figure 3 Cumulative incidence of recurrence. (A) According to type of surgical resection; (B) according to type of lymph node assessment. NS, lymph node sampling; LS-ND, lobe-specific lymph node dissection; SND, systematic nodal dissection.

were found to have a positive effect on survival (*Figure 3*). Combination of lobectomy plus SND showed the best recurrence rate pattern (P=0.01; *Figure 4*).

Multivariable-adjusted comparisons showed an independent negative effect of sub-lobar resection (HR =1.52; P=0.02; 95% CI: 1.07–2.17), LS-ND (HR =1.74; P=0.007; 95% CI: 1.16–2.6) and NS (HR =1.49; P=0.007; 95% CI: 1.12–1.98) on CIR. Test of interaction showed a homogeneity of results among subgroups (*Table 2*).

Discussion

The central point in performing more complex surgery is to offer an oncological advantage that balances the possible additional risks due to the procedure itself. Accordingly, lobectomy and systematic nodal dissection are currently the cornerstone in the treatment of surgically resectable NSCLC. Nevertheless, in last years, several studies questioned the established standard of care, highlighted the possibility to perform parenchymal preserving resection (6-11) and less aggressive nodal assessment strategy (18,22,23) in stage I NSCLC. Indeed, the results presented by these papers are variegate and often contradictory. Moreover, the influence of the combination between type of surgical resection and of nodal assessment was rarely explored.



At risk:

	0	12	24	36	48	60	72	84
Lobectomy + SND	391	369	335	277	226	185	140	102
Lobectomy + LS-ND	65	59	48	43	31	22	17	14
Lobectomy + NS	364	335	296	245	196	154	106	74
Sub-lobar + SND	38	37	32	27	21	13	12	7
Sub-lobar + LS-ND	30	26	20	13	8	6	2	0
Sub-lobar + NS	49	46	39	33	25	15	12	6

Figure 4 Cumulative incidence of recurrence according to treatment combination. NS, lymph node sampling; LS-ND, lobe-specific lymph node dissection; SND, systematic nodal dissection.

Table 2 Multivariable-adjusted fine and grey model for cumulative incidence of recurrence (N=969)

Multivariable analysis*	Hazard ratio (95% CI)	P	Interaction P value
Sub-lobar resection *vs.* lobectomy		0.02	0.268
Overall	1.52 (1.07–2.17)		
SND	1.98 (1.14–3.42)		
LS-ND	1.87 (0.94–3.74)		
NS	1.08 (0.61–1.93)		
LS-ND *vs.* SND		0.007	0.903
Overall	1.74 (1.16–2.6)		
Lobectomy	1.66 (1.03–2.69)		
Sub-lobar resection	1.58 (0.75–3.32)		
NS *vs.* SND		0.007	0.131
Overall	1.49 (1.12–1.98)		
Lobectomy	1.61 (1.18–2.19)		
Sub-lobar resection	0.88 (0.43–1.82)		

*, take into account of age, gender, smoking habit, side of intervention, pTNM stage, vascular invasion, predominant histologic pattern and histologic grade. NS, lymph node sampling; LS-ND, lobe-specific lymph node dissection; SND, systematic nodal dissection.

The results of our study conducted on a cohort of 969 stage I adenocarcinoma of the lung suggest that (I) patients submitted to lobectomy presented a significant lower recurrence rate than those submitted to sub-lobar resection, (II) systematic lymph node dissection (SND) presented an independent positive effect on recurrence development than other lymph node assessment strategy, (III) lobectomy in combination with systematic lymph nodal resection showed the best results in term of CIR.

The benefit of lobectomy over sub-lobar resection was established by the results of the study of the Lung Cancer Study Group, that represent the only multicenter randomized clinical trial on this subject published so far (5). This study, conducted by Ginsberg and Rubinstein, demonstrated an increase in overall death rate, cancer related death and locoregional recurrence rate in sub-lobar resection group. Similar results were published by various authors (6,9,11,24,25). Still, interest concerning convenience of anatomical segmentectomy and wedge resection in early stage NSCLC remains; numerous studies were conducted, assessing to find sub-group of patients that may take advantage from these procedures. As matter of fact, several groups described the equivalence in term of clinical outcomes of lobectomy and lobectomy performed by VATS (26-28). Similarly, a number of papers showed no significant difference in survival for tumours ≤2 cm in size (6-11). Interestingly, numerous authors reported a significant reduction of dissected lymph nodes in the segmentectomy group than in the lobectomy group (24,28-30).

Our results showed an independent significant advantage of lobectomy on respect of sub-lobar resection in term of recurrence rate. Moreover, this benefit remains independently from the type of lymph nodal assessment performed. Hopefully, the ongoing multicenter randomized studies currently conducted by Cancer and Leukemia Group B (CALGB 140503) and Japan Clinical Oncology Group (JCOG0802/WJOG4607L) (31-33) will solve this issue. Till then, sub-lobar resections, as alternative to lobectomy, should be proposed only in selected patients (34).

On the other hand, the IASLC staging project in the proposals for the revision of the N Descriptor in the 8th Edition of the TNM for Lung Cancer stated that "Nodal status is considered to be one of the most reliable indicators of the prognosis in patients with lung cancer and thus is indispensable in determining the optimal therapeutic options" (12). Undoubtable, systematic nodal dissection provides a higher accurate pathological staging accuracy, in reason to the higher number of lymph nodes resected (35). Moreover, systematic nodal dissection could consent the therapeutic excision of a minimal or unknown disease in mediastinal lymph nodes. However, new minimally invasive biopsy techniques (15,16) and high definition imaging rise doubts on unavoidability of such aggressive nodal assessment. Nevertheless, several studies reported an unexpected high occurrence of a node-positive occult disease in primary and secondary lung tumors (36-39) probably due to microscopic lymph nodal involvement. Contrariwise, this happened in less than 4% of cases ACOSOG Z0030 trial (23); in this study, systematic nodal dissection showed no survival benefit of over nodal sampling (NS). However, in this trial, all patients were submitted to NS and frozen section with the exclusion from the randomization for all patients with positive nodes; consequently, study conclusions could influenced be by this process. In addition, in recent years, some authors proposed a new strategy of nodal assessment, consisting in the resection of only stations which are considered as the natural drain for that lobe (17,18). Several studies compared the oncological results of this strategy with the ones of the systematic nodal dissection, mostly showing an equivalence in term of survival and recurrence rates.

Our analysis showed an independent benefit of systematic nodal dissection over both NS and lobe-specific nodal dissection. Furthermore, this benefit persists independently from the type of surgical resection performed. Accordingly, a recent metanalysis encompassed more than 1,900 patients, reported an improved OS in systematic nodal dissection group than in NS group (18).

Our study presents some limitations. First, the retrospective nature of the analysis relatively limits the strength of the results, and this should be considered by the readers when conferring clinical value to the reported evidence. Moreover, data collection from different centers represents an additional significant limitation; indeed, despite the centers do not substantially differ in the strategy of care adopted in current clinical practice, a series of confounding variables are unavoidable, and this bias potentially limiting the impact of our results. Concerning the type of surgical resection, we encompassed wedge and segmental resection as "sub-lobar resection". On one hand this represents a statistical simplification and divers Authors have recently reported different recurrence rates between the two procedures; on the other hand, considering that lobectomy is still the gold standard even in node-negative NSCLC measuring less than 3 cm, the distinction between lobar and sub-lobar resection has a certain validity although it involves a consistent degree of approximation.

Conclusions

In the present series, lobectomy and SND confirmed to be the optimal strategy to achieve a favorable prognosis in stage I adenocarcinoma of the lung. The real value of sublobar resection and less aggressive nodal staging should be assessed by ongoing randomized clinical trial before being integrated in clinical practice.

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None.

Footnote

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

Ethical Statement: The study was approved by the IRB of each participating center.

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Supplementary

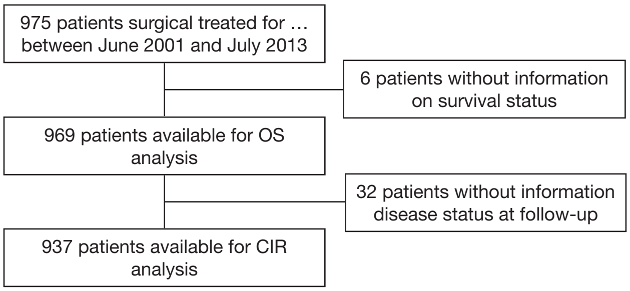

Figure S1 Study flow diagram of the patient population.

Appendix A

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Appendix B

Lobe-specific lymph node dissection encompassed the follow lymph node station according to IASCLC lymph node map (12):

- Right upper lobar tumour: Stations 2, 4R and 7;
- Left upper lobar tumour: Stations 5, 6 and 7;
- Right and left middle or lower lobar tumour: Stations 7 and 9.