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Is segmentectomy potentially adequate for clinical stage IA3 non-small cell lung cancer

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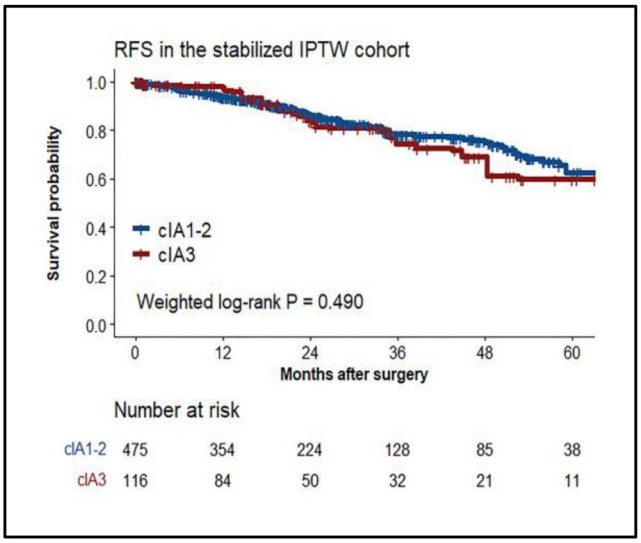
Is Segmentectomy Potentially Adequate for Clinical Stage IA3 Non-Small Cell Lung Cancer

Summary

This multicentre retrospective study included 589 patients who underwent segmentectomy for clinical stage IA1-3 NSCLC. We compared recurrence and death after segmentectomy between patients with clinical IA1-2 and IA3 NSCLC. Notably, we found no significant differences in these outcomes between the two groups.



Legend: IPTW: inverse probability of treatment weighting.

Abstract

OBJECTIVES: This study aims to identify the feasibility of segmentectomy for clinical stage IA3 (cIA3) vs cIA1-2 non-small cell lung cancer (NSCLC).

METHODS: We retrospectively analysed data of consecutive patients with segmentectomy for cIA NSCLC across three centres between January 2017 and December 2022. The stabilized inverse probability of treatment-weighting (IPTW) was employed to minimize potential confounding in baseline characteristics. Recurrence-free survival (RFS) differences were examined using Kaplan–Meier estimator with the log-rank test. The Cox regression model was applied to assess the average treatment effect (ATE) between two groups in RFS. Subgroup and sensitivity analyses were performed.

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RESULTS: Of a total of 589 patients who underwent segmentectomy, 478 presented with cIA1-2 NSCLC while 111 presented with cIA3 NSCLC. In comparison with cIA1-2 cases, the cIA3 cohort were significantly older with poorer lung function and more comorbidity. The cIA3 NSCLC presented significantly invasive characteristics, with extensive tissues dissected. After median follow-up of 24.0 (interquartile range 12.5–40.1) months, we did not observe significant difference in RFS (3-year 73.4% vs 78.5%, $P = 0.490$; ATE: 1.17) between the cIA3 vs cIA1-2 groups. These findings were corroborated following the stabilized IPTW. Preoperative characteristics in the cIA3 subgroup were not related to RFS. In the sensitivity analysis, no difference in RFS was found between the two groups stratified by peripheral and central localization.

CONCLUSIONS: In well-selected patients with cIA3 NSCLC, segmentectomy leads to no statistical difference in oncologic outcomes compared to those observed in earlier stages in a relatively short follow-up period.

Keywords: segmentectomy • non-small cell lung cancer • clinical stage IA3 • recurrence • survival

ABBREVIATIONS

c	Clinical stage
ESTS	European Society of Thoracic Surgeons
IPTW	Inverse probability of treatment-weighting
IQR	Interquartile range
MIS	Minimally invasive surgery
NCCN	National Comprehensive Cancer Network
NSCLC	Non-small cell lung cancer
PS	Propensity score
RFS	Recurrence-free survival

INTRODUCTION

Recent randomized controlled trials have indicated that segmentectomy is a viable alternative to lobectomy for peripheral clinical stage IA1-2 non-small cell lung cancer (cIA1-2 NSCLC) [1–3]. Meanwhile, the National Comprehensive Cancer Network (NCCN) guidelines have updated recommendations accordingly [4]. Prior segmentectomy was primarily employed for patients with compromised conditions, including those diagnosed with cIA3 NSCLC.

In the JCOG1211 trial, segmentectomy was suggested as an appropriate procedure for ground-glass-dominant NSCLC with tumour sizes $\leq$ 3 cm [5]. A recent survey conducted by the European Society of Thoracic Surgeons (ESTS) revealed that 41% of thoracic surgeons would prefer segmentectomy to lobectomy for cIA3 NSCLC [6]. It likely reflects the ongoing debate about recurrence and survival outcomes in cIA3 NSCLC when comparing segmentectomy with lobectomy [7–11]. To date, there is no procedure-specific evidence comparing segmentectomy for cIA3 NSCLC to those for cIA1-2 NSCLC.

Therefore, the objective of this multicentre study was to provide insight about the feasibility of segmentectomy for cIA3 NSCLC compared to cIA1-2 NSCLC.

METHODS

Ethical statement

The study was approved by the Regional Review Boards or the Ethics Committee of Denmark (R-22063267), the University Hospital of Lausanne (2024–00173) and Leeds Teaching Hospitals. The requirement for informed consent was waived. Furthermore, the collection and storage of data from research participants for multiple and indefinite use align with the requirements outlined in the WMA Declaration of Taipei.

Study design

This multicentre study was designed as a retrospective analysis on prospectively collected data of consecutive adult patients ($\geq$ 18 years old) undergoing segmentectomy for cIA1-3 NSCLC at three European hospitals from January 2017 to December 2022. The primary outcome was recurrence-free survival (RFS) comparing cIA3 to cIA1-2 NSCLC. Secondary outcomes included cumulative recurrence and death rates. The results were reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines (STROBE) [12].

Variables

The collected data included demographic and clinicopathological characteristics, as well as end-points observed during the follow-up period. The follow-up duration was calculated from the day of surgery to the day of last recording.

The intrapulmonary tumour locations were categorized as central, with NSCLC situated in the inner two-thirds of the lung parenchyma, and peripheral, where NSCLC was in the outer one-third of the parenchyma. Complex segmentectomy is characterized by the dissection of two or more intersegmental planes. RFS was calculated from the day of surgery to the day of recurrence or death with censoring patients without event at the last follow-up date.

Perioperative and follow-up procedure

All patients underwent a comprehensive preoperative assessment as details published in previous studies [13–15]. The segmentectomies were performed not as part of an intent-to-treat protocol. Operation was performed by open or minimally invasive surgery (MIS). The surgical approach and the way of lymphadenectomy were decided under the surgeon's preference considering the tumour location and health status of patients. Intraoperative frozen section analysis was not routine. The anatomical pulmonary segments containing the tumour were excised. The blood vessels and bronchus heading to the target segment were individually divided. Adjuvant chemotherapy following segmentectomy was administered to patients based on a multidisciplinary tumour board discussion.

The follow-up procedure involves computed tomography examinations at 3-month intervals for the initial 2 years,

subsequently transitioning to biannual assessments over the following 3 years.

Statistical analysis

The statistical analysis adhered to the recently published guidelines [16].

Missing data were identified in body mass index (0.3%), percentage of predicted forced expiratory volume in 1 second (0.3%), percentage of predicted diffusing capacity for carbon monoxide (1.9%), Eastern Cooperative Oncology Group performance score (9.3%), maximum standardized uptake values (4.9%) and margin distance (1.7%). To address these missing data, multiple imputations using chained equations were employed, creating 20 imputed datasets. These datasets were then analysed using multiple regression models, with pooled estimates subsequently obtained in accordance with Rubin's rule.

The Kolmogorov–Smirnov test and the Shapiro–Wilk test identified all continuous variables as abnormal distribution. Continuous variables were presented as medians with interquartile ranges (IQRs), while categorical variables were presented as counts and proportions. The Mann–Whitney *U* test was applied to compare continuous outcomes. The Fisher's exact test was applied to compare categorical outcomes if $>$ 20% of expected cell counts were less than 5, otherwise, the chi-square test was applied. To mitigate potential selection bias between cIA1-2 and cIA3 groups across three centres, the stabilized inverse probability of treatment-weighting (IPTW) was utilized [17], which may result in a slight difference in the effective sample size compared to the original dataset. The propensity model incorporated all characteristics listed in Table 1, with scores (propensity score [PS]) calculated using a multivariate logistic regression model. For the stabilized IPTW, a pseudo-population was generated by weighting each patient based on their calculated PS. The specific calculations were as follows:

- Proportion exposed = number of cIA3 patients/number of all patients
- Weight for the exposed group = proportion exposed/PS
- Weight for the unexposed group = (1−proportion exposed)/(1−PS).

All covariates had standardized mean differences $<$ 0.10 and *P*-values $<$ 0.05, indicating satisfactory balance after stabilized IPTW. We conducted Kaplan–Meier estimator with the log-rank test to investigate RFS differences. Weights were applied for stabilized IPTW adjustments. The Cox regression model was applied to assess the average treatment effect between two groups in RFS, as well as to perform a subgroup analysis of preoperative associations within the cIA3 group related to RFS. A sensitivity analysis of the primary outcomes was conducted based on the peripheral and central lesions. Statistical significance was set at a $P < 0.05$. We used R Software (version 4.3.3, R Foundation for Statistical Computing, Vienna, Austria) for all analyses.

RESULTS

A total of 589 patients from three centres were included in the final analysis. Of these, 478 (81.2%) were diagnosed with cIA1-2

Table 1: Preoperative and intraoperative characteristics

Characteristics	The entire cohort				The stabilized IPTW cohort			
	cIA1-2[a] ($n = 478$)	cIA3[a] ($n = 111$)	SMD	*P*-value[b]	cIA1-2[a] ($n = 475$)	cIA3[a] ($n = 116$)	SMD	*P*-value[b]
Age (year)	69 (63, 75)	73 (66, 77)	0.304	**0.004**	70 (63, 75)	70 (60, 74)	0.058	0.844
Male	206 (43%)	55 (50%)	0.130	0.218	209 (44%)	48 (41%)	0.060	0.648
BMI (kg/m^2)	25.8 (22.7, 28.6)	25.3 (22.2, 28.7)	0.012	0.868	25.8 (22.7, 28.4)	25.9 (23.8, 28.4)	0.059	0.688
ECOG performance score $>$ 0	188 (39%)	47 (42%)	0.129	0.454	187 (39%)	43 (37%)	0.054	0.672
FEV1 (%pre)	86 (69, 100)	79 (60, 100)	0.211	**0.030**	85 (68, 100)	88 (65, 102)	0.099	0.573
DLCO (%pre)	70 (60, 85)	63 (50, 80)	0.328	**0.001**	69 (59, 83)	70 (54, 90)	0.055	0.761
CAD	86 (18%)	30 (27%)	0.218	**0.031**	89 (19%)	21 (18%)	0.027	0.820
CVD	52 (11%)	18 (16%)	0.156	0.117	54 (11%)	9 (8%)	0.100	0.203
CCI, score	3 (1, 5)	5 (2, 7)	0.534	**<0.001**	4 (1, 5)	3 (1, 5)	0.070	0.450
Peripheral lesion	380 (80%)	91 (82%)	0.063	0.556	379 (80%)	86 (74%)	0.098	0.381
Solid lesion	208 (44%)	69 (62%)	0.380	**<0.001**	222 (47%)	54 (47%)	0.003	0.981
SUVmax	3 (2, 6)	4 (3, 10)	0.379	**<0.001**	3 (2, 6)	4 (2, 7)	0.072	0.052
Upper lobe	278 (58%)	69 (62%)	0.082	0.440	279 (59%)	69 (59%)	0.012	0.930
Left side	241 (50%)	62 (56%)	0.109	0.302	245 (52%)	58 (50%)	0.039	0.766
MIS	469 (98%)	104 (94%)	0.225	**0.018**	464 (98%)	114 (98%)	0.007	0.936
Number of segments resected	1 (1, 2)	2 (1, 3)	0.352	**<0.001**	1 (1, 2)	1 (1, 2)	0.020	0.778
Complex segmentectomy	240 (50%)	47 (42%)	0.162	0.125	231 (49%)	58 (50%)	0.023	0.860
Total lymph nodes dissected	6 (4, 10)	7 (5, 11)	0.193	**0.009**	6 (4, 10)	6 (5, 10)	0.036	0.221
N1 stations dissected	1 (1, 2)	1 (1, 2)	0.027	0.699	1 (1, 2)	2 (1, 2)	0.099	0.209
N2 stations dissected	2 (2, 3)	2 (2, 3)	0.008	0.905	2 (2, 3)	2 (2, 3)	0.052	0.715

[a]Median (interquartile range); *n* (%).

[b]Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test.

BMI: body mass index; CAD: coronary artery disease; CCI: Charlson comorbidity index; CVD: cerebrovascular disease; DLCO: diffusing capacity of carbon monoxide; ECOG: Eastern Cooperative Oncology Group; FEV1: forced expiratory volume in 1 second; SMD: standardized mean difference; SUVmax: maximum standardized uptake values.

The bold *p*-values indicate statistically significant differences.

Table 2: Pathological and postoperative characteristics

Characteristics	The entire cohort			The stabilized IPTW cohort		
	cIA1-2[a] ($n = 478$)	cIA3[a] ($n = 111$)	*P*-value[b]	cIA1-2[a] ($n = 475$)	cIA3[a] ($n = 116$)	*P*-value[b]
Histology			0.275			0.397
Adenocarcinoma in situ	25 (5%)	1 (1%)		23 (5%)	2 (2%)	
MIA	6 (1%)	0 (0%)		5 (1%)	0 (0%)	
Invasive adenocarcinoma	369 (77%)	90 (81%)		364 (77%)	100 (86%)	
Squamous cell carcinoma	67 (14%)	18 (16%)		71 (15%)	13 (11%)	
Adenosquamous cell carcinoma	4 (1%)	0 (0%)		4 (1%)	0 (0%)	
Large cell carcinoma	5 (1%)	2 (1.8%)		5 (1%)	2 (2%)	
Others[c]	2 (0%)	0 (0%)		2 (0%)	0 (0%)	
Tumour size (mm)	14 (10, 18)	23 (21, 26)	**<0.001**	14 (10, 18)	23 (21, 25)	**<0.001**
Nodal upstaging			**0.010**			**0.009**
N1	10 (2%)	4 (4%)		9 (2%)	8 (7%)	
N2	6 (1%)	5 (5%)		6 (1%)	6 (5%)	
N1 + 2	3 (1%)	2 (2%)		3 (1%)	2 (2%)	
Margin distance (mm)	15 (6, 25)	10 (5, 25)	0.501	14 (6, 25)	10 (5, 20)	**0.031**
Residual tumour (R1)	3 (1%)	0 (0%)	>0.999	3 (1%)	0 (0%)	0.396
Pleural invasion	46 (10%)	31 (28%)	**<0.001**	47 (10%)	26 (23%)	**0.002**
Length of stay, day	4 (3–6)	4 (3–7)	0.104	4 (3–6)	4 (3–6)	0.231
Cardiopulmonary complications	83 (17%)	24 (22%)	0.295	87 (18%)	17 (14%)	0.370
Adjuvant therapy	34 (7%)	27 (24%)	**<0.001**	34 (7%)	27 (23%)	**<0.001**
Completion lobectomy	4 (1%)	2 (2%)	0.316	4 (1%)	3 (3%)	0.138

[a]Median (Interquartile range); *n* (%).

[b]Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test.

[c]Mixed of squamous cell and large cell carcinoma.

The bold *p*-values indicate statistically significant differences.

NSCLC and 111 (18.8%) with cIA3 NSCLC (Supplementary Table S1). The stabilized IPTW analysis adjusted the groups to include 475 patients in the cIA1-2 group and 116 in the cIA3 group. The demographics and clinicopathological characteristics of all patients are detailed in Supplementary Tables S2 and S3.

Patients with cIA3 NSCLC were found to be older compared to those in the cIA1-2 stages, with poorer pulmonary function and more comorbidities. Radiologically, the cIA3 NSCLC predominantly exhibited a pure-solid appearance and increased metabolic activity. Segmentectomy performed on patients with cIA3 compared to cIA1-2 NSCLC involved more extensive resection in segments and lymph nodes. The stabilized IPTW method resulted in balanced baseline characteristics (Table 1). Overlap of the PSs has been shown in Supplementary Fig. S1.

In the terms of pathological characteristics, the cIA3 group presented with larger sizes, advanced pathological stages and higher rate of pleural invasion. No significant difference was investigated in the margin distance and residual tumours between the two groups. In postoperative outcomes, the median length of stay was identical for both cIA3 and cIA1-2 NSCLC groups at 4 days, with comparable cardiopulmonary complications. A significantly higher rate of adjuvant chemotherapy was observed in the cIA3 group in contrast to the cIA1-2 group. These characteristics mentioned above were identical to those observed after the stabilized IPTW, except the margin distance (Table 2).

The median follow-up period for this study was 24.0 (IQR 12.5–40.1) months. The RFS showed no significant differences between the two groups across various cohorts in both the entire and stabilized IPTW cohorts, with no statistically significant difference in the average treatment effect (Fig. 1). Similarly, cumulative recurrence and death rates also showed no significant differences (Supplementary Fig. S2).

In the subgroup analysis for cIA3 NSCLC, we did not find any significant preoperative risk factors for patients with 2–3 cm tumours to RFS (Supplementary Table S4). In the sensitivity analysis, we also did not find difference between two groups regardless of peripheral lesions (Supplementary Fig. S3).

DISCUSSION

This present study provides procedure-specific evidence for the feasibility of segmentectomy in cIA3 compared to cIA1-2 NSCLC. Despite more complex and invasive characteristics in patients and tumours in the cIA3 group, the recurrence and survival outcomes after segmentectomy were found to be comparable to those in patients with cIA1-2 NSCLC. These oncological results remained consistent even after balancing selection bias by the stabilized IPTW. Additionally, we did not identify any independent preoperative characteristics related to prognosis in cIA3 NSCLC after segmentectomy. However, cIA3 NSCLC, compared to cIA1-2 NSCLC, may elevate the potential risk of adverse oncological outcomes due to biological aggressiveness.

In previous studies comparing lobectomy to segmentectomy for cIA3 NSCLC, Kamigaichi *et al.* [10] observed a similar trend, with a total recurrence rate of 9.3% in cIA3 solid-dominant tumour after segmentectomy. The 3-year OS were at least 90.0% and the 3-year RFS exceeded 85.0%, which was supported by Hattori *et al.* [9]. These are generally higher than those found in our study. Nevertheless, Hattori *et al.* [7] found a higher 5-year cumulative recurrence rates in pure-solid cIA3 NSCLC after segmentectomy. Additionally, the survival curves from their study indicated approximately 75% for 3-year OS and about 70% for 3-year RFS, which are generally lower than those we observed. Similarly, Kamigaichi *et al.* [8] found increased recurrence rates for this group. However, the survival curves in 3-year OS and RFS appeared like our findings. These discrepancies might be

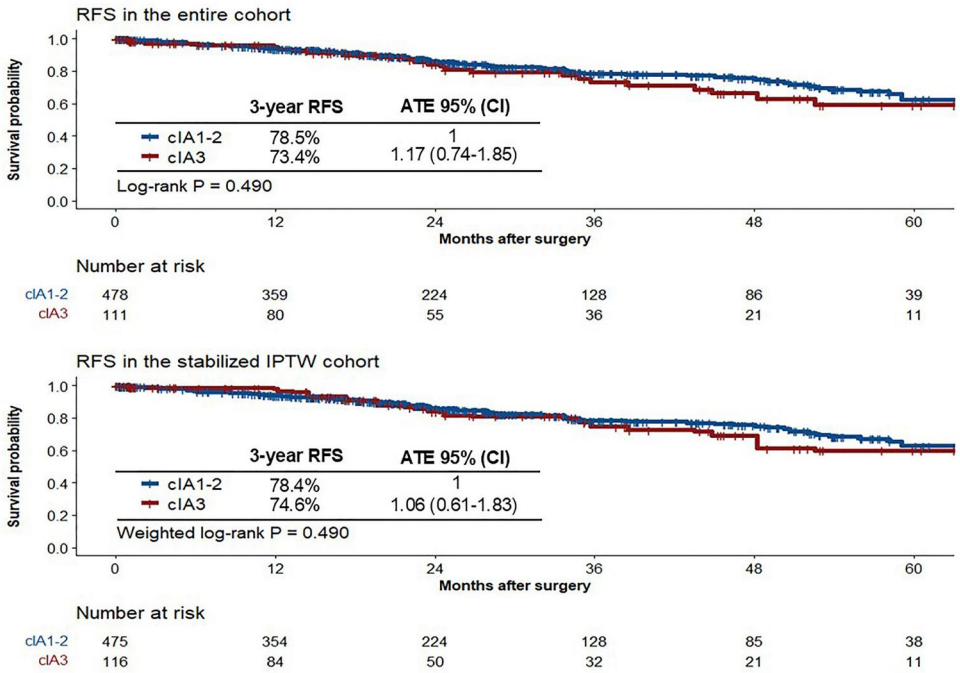

Figure 1: Recurrence-free survival (RFS) for clinical stage IA1-2 versus IA3 non-small cell lung cancer in the entire and stabilized inverse probability of treatment-weighting (IPTW) cohorts.

attributed to variations in the consolidation-to-tumour ratio. Furthermore, the lesion localization should also be considered.

Interestingly, despite more tumours in the cIA3 group exhibiting a pure solid appearance compared to those in the cIA1-2 group, as well as invasive tumour and lymph nodes, the recurrence and survival rates between the two groups showed no significant difference. Notably, we did not apply strict preoperative selection criteria for cIA3 NSCLC patients undergoing segmentectomy. Based on the subgroup and sensitivity analyses, we further identified that preoperative characteristics may not significantly impact outcomes in this study. However, the prognosis could be influenced by the relatively short follow-up period, because of an observed trend in RFS with a 5% difference between the groups. Longer follow-up and further studies involving broader patient populations are needed to validate these results. Additionally, the different proportions of adjuvant chemotherapy administered in each group may also have played a role in these observed prognoses.

In this study, the overwhelming preference (> 95%) for minimally invasive adenocarcinoma (MIA) for segmentectomy was in line with trends identified in the previous research [18]. While MIA may have a greater impact on perioperative outcomes compared to the extent of resection, there appears to be no significant difference in oncological outcomes between MIA and thoracotomy [19, 20].

According to our findings, the total number of lymph nodes dissected in the cIA3 group was higher than in the cIA1-2 group, which might increase discovery of nodal metastasis in the cIA3 group. However, a recent study showed that the total number of lymph nodes dissected may not influence recurrence and survival rates [21]. Another previous study supported this view and also demonstrated that the extent of dissection did have an impact [22]. Moreover, selective or systemic lymphadenectomy in early-stage NSCLC remains controversial.

The NCCN guidelines specify a minimum margin distance of 2 cm [4], while the more recent ESTS guidelines for the treatment of ground-glass opacities suggest a minimum of 1 cm [23]. In the present study, the cIA1-2 group showed a median margin distance of approximately 1.5 cm, while the cIA3 group had a median of 1 cm. The differences in margin distance were not statistically significant. However, after stabilized IPTW adjustment, the difference in margin distance became statistically significant. Here we did not specify how the margin distance was assessed and instead relied on data extracted from the individual database. This approach may introduce reporting bias and limit the depth of further discussion. To achieve sufficient margin distances during segmentectomy, preoperative three-dimensional reconstruction and intraoperative indocyanine green can be employed. Furthermore, considering that three patients had positive microscopic margins following tumour resection, the intraoperative frozen section may be a valuable consideration.

The perioperative outcomes following segmentectomy in this study were similar to or better than those reported in previous studies [24]. These outcomes could result from the enhanced recovery after surgery settings, as these three institutions are core contributors to the relevant guidelines authored by the ESTS [25].

Several limitations should be considered when interpreting the results of this study. First, this study involved a retrospective analysis of prospectively collected data from patients at three institutions across three countries, which potentially introduced heterogeneity in patient backgrounds. Thus, we employed the stabilized IPTW. However, stabilized IPTW does not account for biases related to the treatment allocation process or time-dependent confounding that may affect patient outcomes. Second, the possibility of type II errors cannot be entirely ruled out. Third, the criteria of selecting cIA3 patients for segmentectomy may limit the generalizability of our findings to the average cIA3 population. Importantly, our study may not be sufficiently

powered to support recommendations for the treatment of centrally located cIA3 cases. Fourth, this present study focused on comparing outcomes between cIA3 and cIA1-2 NSCLC within the context of segmentectomy, which may limit the robustness of the findings.

CONCLUSION

Despite more comorbidity observed in patients with cIA3 NSCLC compared to cIA1-2, there was no difference in RFS. This suggests that segmentectomy might be a viable option in properly selected patients with cIA3 NSCLC in a relative short follow-up period. Future studies, like the WJOG16923L trial, are essential to validate these findings and further inform clinical practice regarding the treatment of cIA3 NSCLC through segmentectomy.

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SUPPLEMENTARY MATERIAL

Supplementary material is available at *ICVTS* online.

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CONFLICT OF INTEREST

R.H.P. reports speaker fee from Medtronic, Medela, AstraZeneca and AMBU and advisory board member for AstraZeneca, MSD, BMS and Roche. A.B. reports speaker and advisory board fees for Astra Zeneca, BMS, MSD, Ethicon, Medtronic, Medela and Roche. M.G. reports speaker fee from Ethicon and Medtronic. The other authors have no conflict of interest to report.

DATA AVAILABILITY

The full setup raw data is available upon request.

Author contributions

Lin Huang: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Resources; Software; Visualization; Writing—original draft; Writing—review & editing. **Alessandro Brunelli:** Conceptualization; Data curation; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Writing—original draft; Writing—review & editing. **Demetrios Stefanou:** Data curation; Investigation; Writing—original draft; Writing—review & editing. **Edoardo Zanfrini:** Data curation; Investigation; Writing—original draft; Writing—review & editing. **Abid Donlagic:** Data curation; Investigation; Writing—original draft; Writing—review & editing. **Michel Gonzalez:** Conceptualization; Data curation; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Writing—original draft; Writing—review & editing. **René Horsleben Petersen:** Conceptualization; Data curation; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Writing—original draft; Writing—review & editing

Reviewer information

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