Oncologic outcomes after minimally invasive segmentectomy or lobectomy in patients with hypermetabolic clinical stage IA1-2 non–small cell lung cancer

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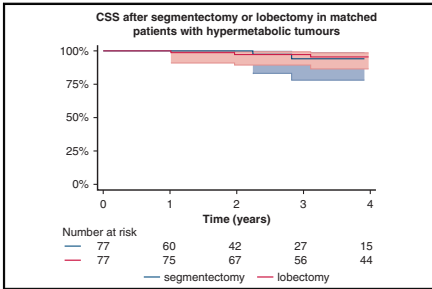
ABSTRACT

Objective: To evaluate the oncologic outcome of patients with hypermetabolic tumors resected by segmentectomy or lobectomy.

Methods: This was a retrospective analysis of all consecutive patients with peripheral clinical stage IA1-2 non–small cell lung cancer (January 2017-June 2023) who underwent resection by segmentectomy or lobectomy in a single center. A hypermetabolic tumor was defined as a tumor with a positron emission tomography (PET) maximum standardized uptake value >2.5. Propensity score case-matching analysis was used to generate 2 balanced groups of patients with hypermetabolic tumors operated by segmentectomy or lobectomy. Four-year overall survival (OS), event-free survival (EFS), and cancer-specific survival were compared between the matched groups.

Results: A total of 164 segmentectomies and 234 lobectomies were analyzed. There were 91 (55%) hypermetabolic tumors in the segmentectomy group versus 178 in the lobectomy group (76%), $P < .001$. The comparison of the matched groups with hypermetabolic tumors showed a better 4-year OS after lobectomy compared with segmentectomy (lobectomy 87%; 95% confidence interval [CI], 76-93; segmentectomy, 67%; 95% CI, 49-80; $P = .029$). The 4-year EFS appeared to have a better trend after lobectomy (77%; 95% CI, 65-85) compared with segmentectomy (58%; 95% CI, 39-72), $P = .088$. The 4-year cancer-specific survival, however, was similar between the matched groups (lobectomy, 95%; 95% CI, 86-98 vs segmentectomy, 94%; 95% CI, 78-99, $P = .79$).

Conclusions: Early-stage peripheral hypermetabolic tumors are associated with poorer oncologic outcomes compared with less PET-avid tumors. Despite poorer OS and EFS after segmentectomy likely caused by cancer-unrelated deaths, cancer-specific survival in this high-risk group was similar after lobectomy or segmentectomy. In well-selected patients, a high PET maximum standardized uptake value should not be considered a contraindication to segmentectomy. (JTCVS Open 2024;20:167-73)

CSS after segmentectomy or lobectomy in matched patients with hypermetabolic tumours

Number at risk
	77	60	42	27	15
	77	75	67	56	44

segmentectomy — lobectomy

Cancer-specific survival after segmentectomy or lobectomy for hypermetabolic tumors.

CENTRAL MESSAGE

A high PET SUVmax should not be regarded as an absolute contraindication to segmentectomy for peripheral clinical stage IA1-2 NSCLC.

PERSPECTIVE

Early-stage peripheral hypermetabolic tumors are associated with poorer oncologic outcomes compared with less PET-avid tumors. Despite poorer OS and EFS after segmentectomy likely caused by cancer-unrelated deaths, cancer-specific survival in this high-risk group was similar after lobectomy or segmentectomy. A high PET SUVmax should not be considered a contraindication to segmentectomy.

The results of the recent randomized clinical trials have established segmentectomy as a procedure at least noninferior to lobectomy to treat peripheral non–small cell lung cancers (NSCLCs) of 2 cm or smaller and without clinically involved lymph nodes.[1,2] However, there are still concerns in the thoracic community about a greater risk of

Abbreviations and Acronyms

CI	=	confidence interval
CT	=	computed tomography
C/T	=	consolidation to tumor
EFS	=	event-free survival
FDG	=	fluorodeoxyglucose
IQR	=	interquartile range
NSCLC	=	non–small cell lung cancer
OS	=	overall survival
PET	=	positron emission tomography
SUVmax	=	maximum standardized uptake value

locoregional recurrences after sublobar resections. When surveyed about the preferred extent of surgery in case they were diagnosed with an early-stage lung cancer, many surgeons would still choose a lobectomy.[3] It appears that other factors in addition to the crude clinical staging would be helpful to characterize the biology of the tumor and more safely select the most appropriate patients for segmentectomy. Certainly, one of these factors is the metabolism of the tumor measured through positron emission tomography (PET) scan maximum standardized uptake value (SUVmax). This may in fact represent a surrogate for tumor aggressiveness with hypermetabolic tumors, which has been shown in previous studies to be associated with invasive pathologic characteristics and poorer postoperative outcomes compared with tumors with lower SUVmax.[4-6] The current study was set to assess whether clinically staged IA1-2 tumors with high PET SUVmax are associated with different oncologic outcomes after segmentectomy or lobectomy.

PATIENTS AND METHODS

The Research and Innovation Department of Leeds Teaching Hospitals reviewed this study and considered it as service evaluation not requiring formal review by the research ethics committee and individual consent for this retrospective analysis was waived. This was a retrospective cohort analysis of patients undergoing lobectomy or segmentectomy at the Department of Thoracic Surgery, St James's University Hospital, Leeds, from January 2017 to June 2023. Our unit is a tertiary referral center. The study was written according to the Strengthening the Reporting of Observational Studies in Epidemiology checklist (www.strobe-statement. org). All consecutive patients submitted to minimally invasive (video-assisted thoracoscopic or robotic) anatomic segmentectomy or lobectomy for clinical stage IA1-2 NSCLC located in the outer third of the lung were included in the analysis. Clinical staging was based on the 8th edition of the tumor–node–metastasis staging system. Only patients with a proven NSCLC at definitive pathology were included in the analysis. For both lobectomy and segmentectomy, cases initiated minimally invasively and converted to open surgery were included in the analysis as per intention to treat.

It is important to note that the study period preceded the publication of the randomized trials and some of the surgeons were still reluctant to offer a sublobar resection to fit patients.[1] The choice of the procedure might have

reflected, therefore, the preference of the individual surgeon and their surgical expertise in this procedure.

As a rule, all patients with lung cancer were discussed at a multidisciplinary team meeting where the indication for surgery was agreed, and the operations were performed by 6 board-certified general thoracic surgeons. All patients were clinically staged using 18F-fluorodeoxyglucose (FDG)-PET/computed tomography (CT) and endobronchial ultrasound-esophageal ultrasound nodal sampling in case of suspected hilar or mediastinal enlarged or PET-avid lymph nodes. Patients with positive lymph nodes detected preoperatively through endobronchial ultrasound were not considered suitable for sublobar resections and were excluded from this study.

Segmentectomies were performed by the individual dissection and division of the segmental arteries, bronchus, and veins. Lymph node frozen section was occasionally performed in case of a highly suspicious nodal disease. A systematic lymph node dissection was routinely performed. The intersegmental planes were identified using the inflation-deflation technique and following the anatomic landmarks of the segment. They were divided using mechanical stapler devices.

Immediately after extubation, patients were monitored for few hours in a recovery unit and then transferred to a specialized thoracic ward. Perioperative management was standardized according to our enhanced recovery program,[7] focusing on as early as possible mobilization and feeding, postoperative physical rehabilitation under the supervision of specialized physiotherapists, opioid-sparing pain control, and use of digital chest-drainage systems.

For this study, cardiopulmonary complications occurring within 30 days from surgery or while the patient was still hospitalized were recorded. They were defined according to the joint Society of Thoracic Surgeons/European Society of Thoracic Surgeons definitions[8] and included respiratory failure requiring reintubation or a mechanical ventilation for longer than 24 hours, pneumonia, atelectasis requiring bronchoscopy, pulmonary embolism, atrial arrhythmia requiring pharmacologic or electrical cardioversion, acute myocardial ischemia, acute cardiac failure, stroke, and acute renal failure.

PET Scan

Fasting for at least 4 hours before administration of intravenous injection of 74 to 370 MBq of FDG was advised for all patients. Low-dose non-enhanced CT images with 2- to 4-mm section thickness for attenuation correction and localization of lesions identified by PET were obtained from the head to the pelvic floor of each patient according to a standard protocol. Immediately after CT, PET was performed with an identical axial field of view for 2 to 4 minutes per table position, depending on the condition of the patient and the performance of the scanner. PET images were reviewed with standard iterative time-of-flight (SUV measurements) and Q CLEAR (600) reconstruction algorithms. The SUVmax values were determined by the attending radiologists.

Statistical Analysis

Follow-up information (including date and cause of death) was obtained by data retrieved from the hospital electronic clinical information system. All patients were followed up through October 2023. No patient was lost at follow-up. Overall survival (OS) was measured from the date of surgery to the date of death from any cause and censored at the date of last follow-up for survivors. Event-free survival (EFS) was measured from the date of surgery to the date of death from any cause or lung cancer recurrence, whichever occurred first, and censored at the date of last follow-up for survivors without recurrence.

Loco-regional recurrence was defined as recurrent disease in the lung, hilar nodes, or mediastinal nodes. All other recurrences were deemed to be systemic.

A threshold effect was sought using c statistic to find the best cut-off values of PET-SUVmax associated with any lung cancer recurrence after

segmentectomy. As a result, a hypermetabolic tumor was defined according to a PET-SUVmax greater than 2.5.

Patients with hypermetabolic tumors were compared with their counterparts with lower PET-SUVmax within each operation group. In addition, patients undergoing lobectomy and segmentectomy and with hypermetabolic tumors were compared.

To account for selection biases, a propensity score case-matching analysis was used to match pairs of patients with hypermetabolic tumors undergoing lobectomy or segmentectomy. To construct the propensity score, we used logistic regression including the following variables: age, sex, forced expiratory volume in 1 second, carbon monoxide lung diffusion capacity, body mass index, Eastern Cooperative Oncology Group performance status, presence of coronary artery disease, the PET SUVmax value, the radiologic size of the tumor, and the consolidation tumor ratio. A caliper of 0.05 was used, and a 1:1 matching with no replacement was applied.

The characteristics of the 2 matched groups were compared using standardized differences. The EFS and cancer-specific survival of the 2 matched groups were compared using the Kaplan-Meier estimation and log rank test. There were no missing data in this series, including follow-up information. Survival analysis was reported at 4-year follow-up. To compare survival up to 4 years, we truncated follow-up at this time point. All tests were performed using the Stata 15.0 statistical software (Stata Corp).

RESULTS

In total, 164 segmentectomies and 234 lobectomies were analyzed. The characteristics of all patients included in the study are shown in Table 1. Conversion rate was 3.6% (6/164) in the segmentectomy group and 6.0% (14/234) in the lobectomy group ($P = .35$). Median length of stay was 4 days after segmentectomies (interquartile range [IQR], 3-6) and 5 days (IQR, 3-6) after lobectomies ($P = .012$). Cardiopulmonary morbidity rate was 14% after segmentectomy and 17% after lobectomy ($P = .41$). Thirty-day mortality rate was 1.8% after segmentectomy (3/164) and 1.3% after lobectomy (3/234), $P = .69$. Median

follow-up was 1302 days (IQR, 710-1873). Four-year OS was 82% (95% confidence interval [CI], 71-89) after segmentectomy and 83% (95% CI, 77-88) after lobectomy, $P = .78$. Four-year EFS was 70% (95% CI, 57-79) after segmentectomy and 75% (95% CI, 68-80) after lobectomy, $P = .58$.

FDG-PET SUVmax Analysis

Median PET-SUVmax was 2.75 (IQR, 1.8-4.9) after segmentectomy and 4.2 (IQR, 2.7-7.2) after lobectomy, $P < .001$. There were 91 (55%) hypermetabolic tumors in the segmentectomy group versus 178 (76%) in the lobectomy group, $P < .001$.

After segmentectomy, the 4-year OS and EFS of patients with hypermetabolic tumors was poorer compared with patients with less PET-avid tumors (OS, 71%; 95% CI, 53-83 vs 97%; 95% CI, 89-99, $P = .002$; EFS, 59%; 95% CI, 41-73 vs 78%; 95% CI, 60-89, $P = .003$) (Figure 1).

Propensity score analysis yielded 2 well-matched groups of 77 patients each with hypermetabolic tumors and operated on by segmentectomy or lobectomy. The characteristics of these matched groups are displayed in Table 2. After matching, the mean PET SUVmax, radiologic tumor size, and proportion of tumors with consolidation to tumor (C/T) ratio <0.5 in the 2 groups became similar and with a standardized difference, indicating a clinically irrelevant difference. It must be noted, however, that even after matching, the lobectomy group retained a greater proportion of patients with purely solid tumors (C/T ratio = 1) (60% vs
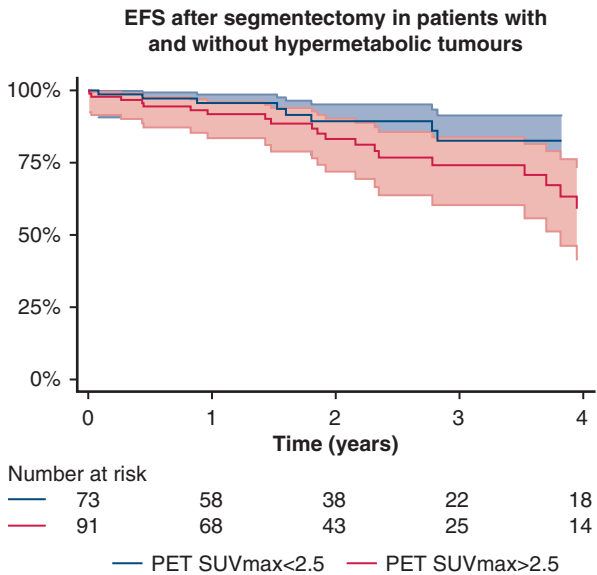
TABLE 1. Characteristics of all patients included in the study

	Segmentectomy (n = 164)	Lobectomy (n = 234)	P value
Age, y	70.1 (7.4)	69.0 (8.0)	.17
Sex male, n (%)	59 (36%)	101 (43%)	.15
BMI, kg/m^2	27.0 (5.0)	26.9 (5.1)	.52
PS >1, n (%)	10 (6.1%)	13 (5.6%)	.82
FEV1%	92.2 (20.9)	89.8 (20.2)	.29
DLCO%	77.1 (19.1)	75.0 (17.7)	.19
CAD, n (%)	17 (10%)	23 (9.8%)	.86
Tumor radiologic size, mm	15.2 (6.4)	17.3 (5.8)	<.001
C/T ratio <1	78 (48%)	59 (25%)	<.001
FDG-PET SUV max	3.5 (2.5)	5.5 (4.1)	<.001
cT1a, n (%)	76 (46%)	55 (24%)	<.001

Results are reported as means and standard deviations or count and percentages. *BMI*, Body mass index; *PS*, performance score; *FEV1*, forced expiratory volume in 1 second; *DLCO*, carbon monoxide lung diffusion capacity; *CAD*, coronary artery disease; *C/T ratio*, consolidation to tumor ratio; *FDG-PET SUV max*, fluorodeoxyglucose-positron emission tomography maximum standardized uptake value.

EFS after segmentectomy in patients with and without hypermetabolic tumours

Number at risk				
73	58	38	22	18
91	68	43	25	14

— PET SUVmax<2.5 — PET SUVmax>2.5

FIGURE 1. Event-free survival (*EFS*) after segmentectomy in patients with FDG-PET SUV max >2.5 and in those with lower SUV max value. *Shading* represents 95% confidence intervals. *FDG-PET SUV max*, Fluorodeoxyglucose-positron emission tomography maximum standardized uptake value.

TABLE 2. Unmatched and matched comparison of patients with hypermetabolic tumors in the 2 resection groups

	Unmatched groups			Matched groups		
Variables	Lobes, n = 178	Segments, n = 91	SD	Lobes, n = 178	Segments, n = 91	SD
Age	69.7 (7.4)	69.5 (7.4)	0.03	69.2 (7.3)	69.7 (7.4)	0.06
Sex male, n (%)	81 (46%)	30 (33%)	0.25	30	28	0.05
BMI, kg/m^2	27.1 (5.3)	27.2 (5.4)	0.02	26.8 (4.8)	27.3 (5.3)	0.11
PS >1, n (%)	11 (6.2%)	5 (5.5%)	0.03	6	4	0.10
FEV1%	89.7 (20.5)	89.3 (19.5)	0.02	88.5 (22.6)	89.4 (20.6)	0.04
DLCO%	73.8 (17.1)	73.0 (19.0)	0.04	72.9 (14.9)	72.1 (19.0)	0.05
CAD, n (%)	19 (11%)	13 (14%)	0.11	12	9	0.11
Tumor radiologic size, mm	18.0 (5.6)	14.9 (5.6)	0.53	16.2 (4.6)	15.6 (5.6)	0.12
C/T ratio <0.5	32 (18%)	33 (36%)	0.42	23 (30%)	28 (36%)	0.13
C/T ratio ≥0.5	146 (82%)	58 (64%)		54 (70%)	49 (64%)	
FDG-PET SUV max	6.8 (3.9)	5.2 (2.2)	0.44	5.8 (3.3)	5.4 (2.3)	0.14
cT1a, n (%)	30 (17%)	34 (37%)	0.47	20	23	0.08

Results are reported as means and standard deviations or count and percentages. *SD*, Standardized difference: differences of 0.2 or greater are considered clinically relevant; *BMI*, body mass index; *PS*, performance score; *FEV1*, forced expiratory volume in 1 second; *DLCO*, carbon monoxide lung diffusion capacity; *CAD*, coronary artery disease; *C/T ratio*, consolidation to tumor ratio; *FDG-PET SUV max*, fluorodeoxyglucose-positron emission tomography maximum standardized uptake value.

38% in patients who underwent segmentectomy). Conversely, the segmentectomy group had a greater proportion of patients with pure ground-glass opacity lesions (C/T ratio = 0) (13% vs 6.5% in patients who underwent lobectomy).

The comparison of the matched groups with hypermetabolic tumors showed a better 4-year OS after lobectomy compared with segmentectomy (lobectomy 87%; 95% CI, 76-93 and segmentectomy 67%; 95% CI, 49-80, $P = .029$). The power of the test to detect this OS difference was 82% with this sample size at a significance level of .05.

The 4-year EFS appeared to have a better trend after lobectomy (77%; 95% CI, 65-85) compared with segmentectomy (58%; 95% CI, 39-72) ($P = .088$) (Figure 2). The power of the test to detect this EFS difference was 70% with this sample size at a significance level of .05.

The 4-year cancer-specific survival, however, was similar between the matched groups (lobectomy, 95%; 95% CI, 86-98 vs segmentectomy, 94%; 95% CI, 78-99, $P = .79$) (Figure 3).

The occurrence of nodal upstaging in the matched patients with hypermetabolic tumors was not different after lobectomy compared with segmentectomy (10% vs 6.4%, $P = .56$). The incidence of locoregional recurrences in the matched patients with hypermetabolic tumors was not greater after segmentectomy (5.2%) compared with lobectomy (9.1%), $P = .53$. Similarly, the occurrence of distant recurrences in matched patients with hypermetabolic tumors was not greater after segmentectomy (2.6%) compared with lobectomy (5.2%), $P = .68$. Among the matched patients with unsuspected nodal disease found at definitive pathology, 5 of 5 (100%) received adjuvant systemic treatment after segmentectomy and 5 of 8 (63%) after lobectomy.

DISCUSSION
Background and Rationale

Whether a segmentectomy is an oncologically safe operation for tumors that are biologically more aggressive remains a matter of debate. FDG-PET SUVmax represents a surrogate for cancer aggressiveness. Previous studies have shown that tumors with high PET SUVmax display features of invasiveness and portend a poorer prognosis.[4-6] Two recent randomized trials[1,2] did not report the PET-SUVmax value distribution in the randomized groups, nor did they use this parameter in sensitivity analyses.

Despite previous reports showing reassuringly similar longitudinal outcomes after segmentectomies and
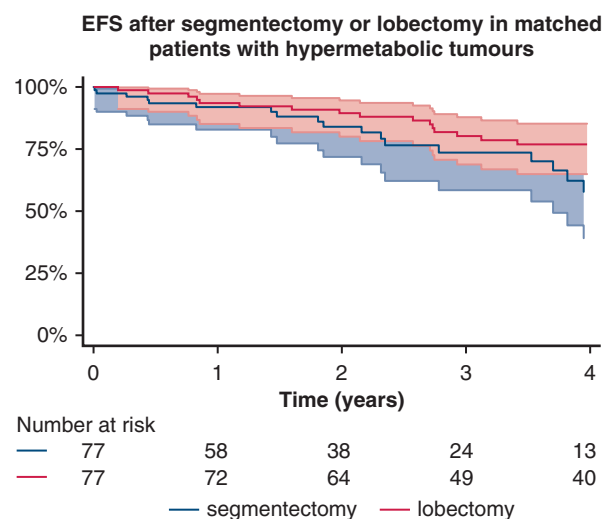
FIGURE 2. Event-free survival (*EFS*) after segmentectomy or lobectomy in matched patients with hypermetabolic tumors. *Shading* represents 95% confidence intervals.

CSS after segmentectomy or lobectomy in matched patients with hypermetabolic tumours
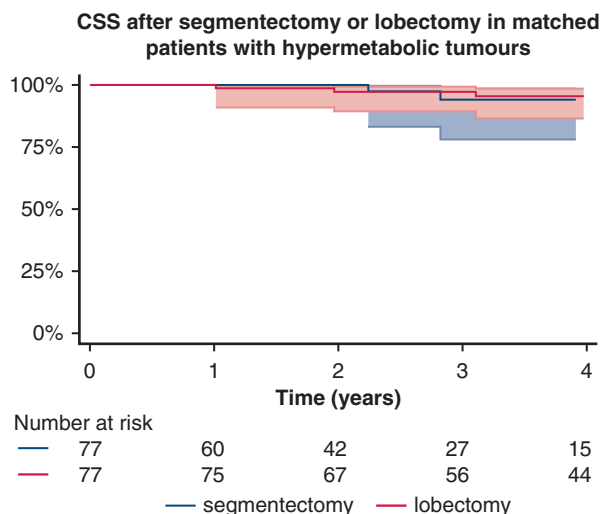
FIGURE 3. Cancer-specific survival (*CSS*) after segmentectomy or lobectomy in matched patients with hypermetabolic tumors. *Shading* represents 95% confidence intervals.

lobectomies in patients with high FDG-PET SUVmax,[9-12] concern remains in clinical practice whether to offer sublobar resections in this greater risk group of patients.

For this reason, we retrospectively analyzed our series of patients operated for clinically staged IA1-2 NSCLC and compared the outcome observed after segmentectomy or lobectomy in patients with a hypermetabolic tumor at PET-SUVmax.

Main Findings

We found that patients presenting with hypermetabolic tumors had a poorer OS and EFS than those with less PET-avid tumors. This finding corroborates previous studies showing a greater aggressiveness of tumors with a greater PET SUVmax value[2-4] and support the rationale to investigate whether there are differences of prognosis within this category between different extents of resection.

After matching, we found that patients with hypermetabolic tumors had a worse OS and EFS after segmentectomy compared with lobectomy. Cancer-specific survival, however, was similar between the 2 groups, suggesting that most of the deaths in the segmentectomy group occurred for causes other than cancer recurrence.

Despite the fact we used propensity score matching and the most-used fitness parameters appeared balanced, we cannot rule out that unaccounted underlying comorbidities or frailty played a role in selecting the patients for segmentectomy instead of lobectomy. The retrospective nature of the study prevents us from eliminating this bias.

The similar cancer-specific survival was also found in previous investigations. Handa and colleagues[9] found similar cancer-specific survival and recurrence-free interval

in 55 pairs of propensity score–matched patients with hypermetabolic tumors (PET SUVmax of or greater than 2.5 g/dL) undergoing complex segmentectomy or location-adjusted lobectomies.

Similar results were found by Kamel and colleagues[10] in a series of 46 segmentectomies for hypermetabolic tumors (PET SUVmax >3 g/dL) compared with lobectomies. Tsutani and colleagues[11] found that in a Cox regression analysis PET SUVmax, but not the extent of operation, was associated with recurrence-free survival.

Finally, using a visual evaluation of positron emission tomography, Kagimoto and colleagues[12] also found a poorer prognosis in patients operated for tumors with a greater FDG accumulation but no differences between those undergoing lobectomy or segmentectomy.

These studies included patients with tumors up to 3 cm. In our study, we included only patients with stage IA1-2 NSCLC, in line with the recent randomized controlled trials and most current indications for segmentectomy. In addition, our series reflects the practice of a center from Europe, whereas previous investigation included mainly patients from Asia and one from North America. In our opinion, it is important to report findings from diverse geographic areas, as previous trials have reported strikingly different survival rates in different continents after both lobectomies and segmentectomies for stage IA1-2.[1,2]

Another interesting finding in our study was the fact that within the group of patients with hypermetabolic tumors, we found a greater trend (albeit not statistically significant) of recurrences after lobectomy. This appears in contrast with the results found in a previous trial.[1] We believe that despite our best efforts to minimize the selection bias using propensity score analysis, tumors operated by lobectomy were likely more aggressive, and this could explain this finding. For instance, despite matching, patients undergoing lobectomy had a larger proportion of purely solid tumors compared with those undergoing segmentectomy.

Limitations

This study should be interpreted considering some limitations. This is a retrospective analysis. Despite the careful selection of peripheral tumors with a radiologic size smaller than 2 cm, inherent selection biases remain, as shown by the fact patients in the lobectomy group had larger and more frequently solid tumors with greater FDG-PET SUVmax. This study reflects the real-world scenario in which all patients with a clinical stage IA are discussed in a multidisciplinary setting and multiple factors are considered to decide the most appropriate treatment, including the extent of resection.

To minimize selection bias in the context of a retrospective analysis, we used propensity score analysis. However, this method is not equal to randomization and cannot eliminate the unbalance caused by unaccounted or unrecorded
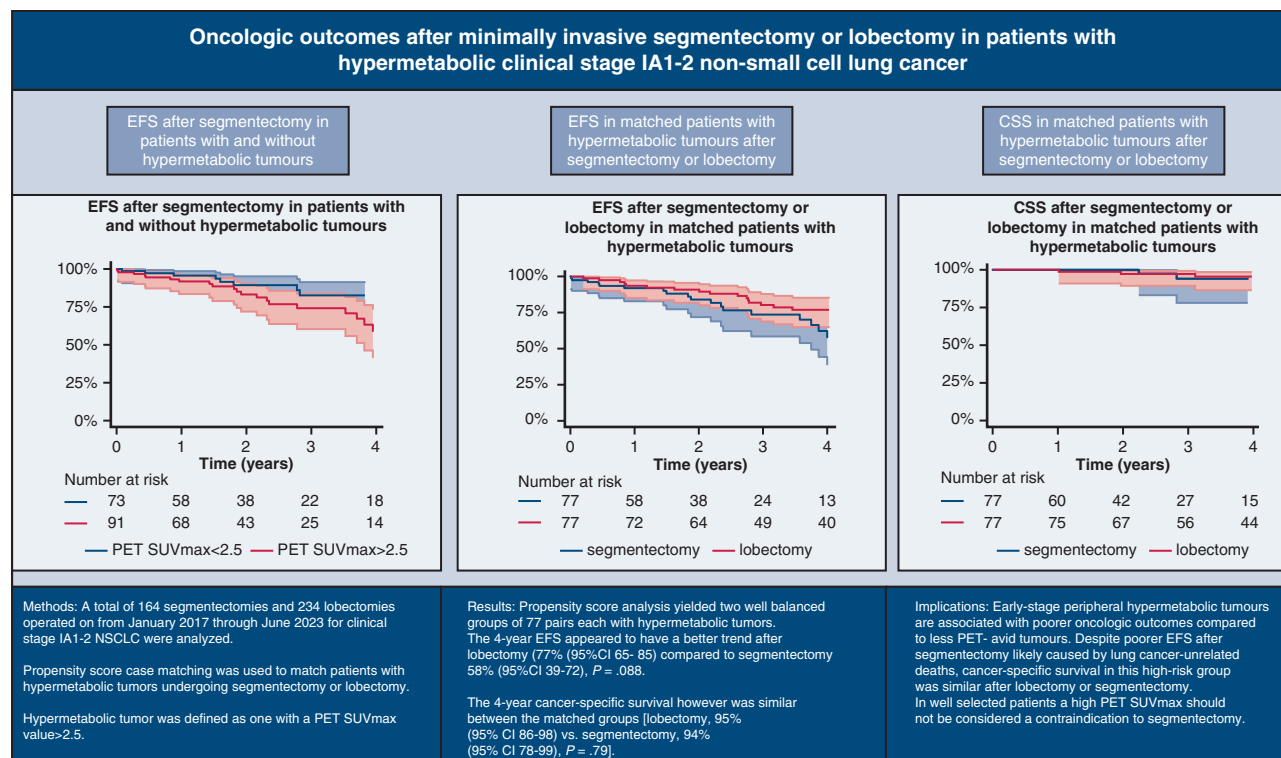
FIGURE 4. Oncologic outcome after minimally invasive lung resection in patients with hypermetabolic early stage non-small cell lung cancer. *EFS*, Event-free survival; *CSS*, cancer-specific survival; *NSCLC*, non–small cell lung cancer; *PET*, positron emission tomography; *SUVmax*, maximum standardized uptake value.

factors. For instance, patients who underwent lobectomy in this series appear to have biologically more aggressive tumors. The fact that cancer-specific survival was similar between the 2 operations may imply that lobectomy is a superior oncologic operation under these circumstances. At variance with the randomized trials, we also included patients with a C/T ratio <0.5, reflecting an increasingly common situation because of the implementation of the lung cancer screening program, which in our region started in November 2018.

The individual surgeon's experience with the procedure likely played a role in selecting the type of resection. This series spans back to 2017, when the results from the phase 3 trials were still not known and some of the surgeons in our units still preferred to offer lobectomy to patients with stage I NSCLC.

Finally, it is not our policy to systematically perform frozen section examination of the segmental or hilar nodes unless there is a strong suspicion during operation. In case of unexpected positive N1 or N2 disease at the definitive pathologic report, these patients are offered adjuvant systemic treatment in our setting. Whether the finding of a 5.4% nodal upstaging in patients undergoing segmentectomy for hypermetabolic tumors would warrant a more cost-effective use of frozen section in this group will be the subject of future discussion within the team.

CONCLUSIONS

Early-stage peripheral hypermetabolic tumors are associated with poorer oncologic outcomes compared with less PET-avid tumors, regardless of the extent of surgery. Despite a poorer OS and EFS after segmentectomy, cancer-specific survival was similar between the 2 groups and recurrence rates were not greater after segmentectomy. Considering the aforementioned limitations, our findings do not seem to support the use of PET-SUVmax as a criterion to exclude patients from segmentectomy (see Figure 4 for a graphical abstract of the study).

Conflict of Interest Statement

Dr Brunelli received consultancy fees for speaker honoraria and advisory board roles with Astra Zeneca, BMS, Ethicon, MSD, and Roche. All other authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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