Upstaged from cT1a-c to pT2a lung cancer, related to visceral pleural invasion patients, after segmentectomy: Is it an indication to complete resection to lobectomy?

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Visual Abstract elements

Summary

In a retrospective study of 253 patients, we investigated if VPI upstaged (pT2a) patients, who underwent segmentectomy compared to those treated by lobectomy, had a worse prognosis.

5-year DFS and OS rates of VPI upstaged patients were similar in both segmentectomy and lobectomy groups. Segmentectomy did not impact recurrence nor survival.

VPI detection does not seem to be an indication of extending resection after segmentectomy.

Central image caption

- Visual abstract, summarizing the main aim, the main results, and the conclusion.
- A disease free-survival figure comparing visceral pleural invasion (VPI) upstaged pT2a patients who underwent lobectomy to those who were operated on by segmentectomy.

Abstract

OBJECTIVES

Segmentectomy may be indicated for T1a-cN0 non-small cell lung cancer. However, several patients are upstaged pT2a at final pathological examination due to visceral pleural invasion. As resection is usually not completed to lobectomy, this may raise issue of potential worse prognosis. The aim of this study is to compare prognosis of visceral pleural invasion upstaged cT1N0 patients operated on by segmentectomy or lobectomy.

METHODS

Data of patients from 3 centers were analyzed. This was a retrospective study, of patients operated on from April 2007 to December 2019. Survival and recurrence were assessed by Kaplan Meier method and cox regression analysis.

RESULTS

Lobectomy and segmentectomy were performed in 191 (75.4%) and in 62 (24.5%) patients, respectively. No difference in 5-year disease-free survival rate between lobectomy (70%) and segmentectomy (64.7%) was observed. There was no difference in locoregional recurrence, nor in ipsilateral pleural recurrence. The distant recurrence rate was higher (p= 0.027) in the segmentectomy group. Five-year overall survival rate was similar for both lobectomy (73 %) and segmentectomy (75.8%) groups. After propensity score matching, there was no difference in 5-year disease-free survival rate (p=0.27) between lobectomy (85 %) and segmentectomy (66.9 %), and in 5-year overall survival rate (p=0.42) between the 2 groups (lobectomy 76.3 % versus segmentectomy 80.1%). Segmentectomy was not impacting neither recurrence, nor survival.

CONCLUSIONS

Detection of visceral pleural invasion (pT2a upstage) on patient who underwent segmentectomy for cT1a-c non-small cell lung cancer does not seem to be an indication to extend resection to lobectomy.

Keywords: segmentectomy, visceral pleural invasion, early-stage lung cancer

ABBREVIATIONS

BMI	Body mass index
CALGB	Cancer and leukemia group B
CT	Computed tomography
DFS	Disease-free survival
DLCO	Diffusing capacity for carbon monoxide
FEV1	First second of forced expiratory volume
Fig	Figure
HR	Hazard ration
IASLC	International association for study of lung cancer
IQR	Interquartile range
JCOG	Japan clinical oncology group
MRI	Magnetic resonance imaging
NSCLC	Non-small cell lung cancer
OS	Overall survival
PET	Positron emission tomography
PL	Pleura
ppoFEV1	Predicted postoperative first second of forced expiratory volume
PS	Performance status
SMD	Standardized mean difference
SD	Standard deviation
STAS	Spread through air spaces
SUV max	Maximum standardized uptake value
TNM	Tumor node metastasis
UICC	Union for international cancer control
VPI	Visceral pleural Invasion
Vs	Versus

INTRODUCTION

Early-stage non-small cell lung cancer (NSCLC) are increasingly treated by segmentectomy (1–4). This trend is most likely going to increase after the publication of the JCOG 0802, a phase 3 clinical trial that showed that segmentectomy was non-inferior to lobectomy in patients with small-sized peripheral NSCLC (with consolidation-to-tumor ratio >0·5) (5). This study and the results of the CALGB 140503 (6), advocate segmentectomy as the surgical standard procedure for this population.

Nevertheless, visceral pleural invasion (VPI) as other pathological invasive characteristics such as lymphatic invasion, vascular invasion, lymph node metastasis and spread through air spaces (STAS) are correlated with a worse prognosis (7–10).

These pathological factors could be found in small-sized NSCLC, and they are only asserted at final pathological examination.

VPI is the only pathological factor that upstages cT1 to pT2a, according to the 8th UICC TNM classification (11). Its incidence in early-stage NSCLC ranges between 10 % to 38%(2–4,10,12–15). Some patients with small-sized NSCLC that underwent segmentectomy are found with VPI. However, cT2a and pT2a NSCLC should theoretically be treated by lobectomy (16); this raises the issue of extending resection to lobectomy in patients who had a segmentectomy. We aimed at investigating in a standard practice outside of study protocol:

- If VPI upstaged cT1N0 patients had a worse prognosis when they were operated on by segmentectomy compared to patients operated on by lobectomy.
- If segmentectomy would negatively influence the long-term prognosis in VPI upstaged patients.

MATERIAL AND METHODS

Ethics Statement

The study was approved by the ethical committee for clinical research of the French society of thoracic and cardiovascular surgery (CERC-SFCTCV-2022-06-09_21777_SEAG).

Study cohort

We conducted a multicentric retrospective study. Data of patients operated on from April 2007 to December 2019 at Curie-Montsouris Thoracic Institute, Rouen University Hospital, and Rennes University Hospital were collected from the French national database, Epithor and from patients' records. Patients who underwent either

lobectomy or segmentectomy for early-stage NSCLC (cT1N0) with VPI at final pathological examination (pT2aN0M0, R0), were considered. All other pT2a upstaged patients' categories, for whatever reason, were excluded.

The following data were collected: type of operation (lobectomy or segmentectomy), clinical features (gender, age, body mass index, performance status, comorbidities, smocking history, clinical stage), morphological assessment (computed tomography, positron emission tomography, brain resonance imagery, 3D reconstruction for planned segmentectomies), first second of forced expiratory volume (FEV1), diffusing capacity for carbon monoxide (DLCO), intraoperative characteristics (duration of surgery), post-operative characteristics (final pathological examination, duration of pleural drainage, length of hospital stay, complications, adjuvant chemotherapy) and follow-up parameters (recurrence and survival). Ninety-days post-operative complications were assessed according to Clavien-Dindo classification, grade III or more were considered as major complications (17).

Segmentectomy was preferred to lobectomy mainly in cases of clinically less invasive pulmonary lesions or in patients with suboptimal respiratory function or presenting with major comorbidities. However, in our series, all patients who underwent segmentectomy would have supported a lobectomy.

Tumors were assessed using the 8th edition of the tumor, node, metastasis (TNM) classification. To assess pleural invasion, in pathological examination, the following stains were used: elastin at Curie-Montsouris Institute; routinely hematoxylin eosin safran and if more challenging cases orcein at Rouen University hospital and orcein at Rennes University Hospital.

Follow-up

Patients' records were discussed by the oncological multidisciplinary board with the result of final pathological examination. Patients were seen by surgeons at 30 postoperative days appointment. They were then regularly followed by their pneumologist or oncologist. They were generally checked up every 6 months for the first two years and then annually. The evaluation included physical examination, imaging (mostly chest-upper abdomen CT scan, sometimes PET scan or MRI if needed). Recurrence was classified as follow: loco regional recurrence (in the ipsilateral lung which included the resection margins of the lung or the bronchus, hilar lymph nodes, mediastinal lymph nodes, pleural invasion), distant recurrence (in contralateral lung parenchyma or extra thoracic metastasis).

Statistics

Statistical analysis were performed with IBM Corp, 2016. IBM SPSS statistics for windows, version 24.0. Armonk, New York and R software version 4.2.2. Numerical variables were expressed as median and interquartile range (IQR), mean and standard deviation (SD), categorical variables as number and percentage. We had a couple of missing data for the following variables: duration of operation, smoking package-year, and SUV max, they were addressed by exclusion. Disease-free survival (DFS) was defined as the time from the date of surgery until the date of recurrence, death, or last follow-up visit. Overall survival (OS) was defined as the time from the date of surgery until the date of death due to any cause or until the last follow-up visit.

Chi-squared test and Fischer's test were used to compare categorical variables, Levene's test analyzed equality of variances, Student's T-test and Mann-Whitney test were used to compare numerical variables. Analysis of follow-up data were performed by the Kaplan–Meier method, and groups were compared with log-rank test.

Univariable analysis were performed for each variable with recurrence and survival. The following variables were included in the univariable analysis: age, sex, BMI, ppoFEV1, PS, history of smoking, comorbidity, previous lung cancer surgery, clinical stage, histology, surgical approach, type of operation, length of stay, adjuvant chemotherapy, postoperative complications. Significant ($p<0.05$) univariable variables were investigated in multivariable analysis using the stepwise Cox regression. We performed propensity score matching 1 by 1 with caliper width of 0.2 of standard deviation; we included age, sex, clinical stage, and previous lung cancer surgery. A stratified cox regression analysis using propensity score matching were performed.

RESULTS

Characteristics of patients

Of 3659 patients operated on from April 2007 to December 2019, 253 patients were upstaged from cT1N0 to pT2aN0, because of VPI. The median age was 65 years (IQR: 58-71.5), most patients were male 61.3% (155 of 253). There was no significant difference for age, sex, pack-year smoking, comorbidities, tumor histology, adjuvant chemotherapy between lobectomy and segmentectomy groups. Previous lung cancer surgery ($p<0.001$), ppoFEV1 ($p=0.009$) and clinical stage ($p= 0.001$) especially stage IA1($p=0.002$) and stage IA3 ($p=0.001$) were significantly different between both arms. Adenocarcinoma was the most prevalent histology (211 patients, 83 %) (Table 1).

After propensity score matching patients were grouped n=50 in each team (Table 2).

Perioperative results

Complications occurred in 105 patients (41.5%) over the 90 postoperative days. Thirty-four patients (13.4%) had a major complication. Ninety-days complications rate was not statistically different between lobectomy and segmentectomy groups.

However, length of stay was statistically (p=0.013) shorter in the segmentectomy group, median= 5 days (IQR 4- 6) than in the lobectomy group: median = 6 days (IQR 4-9).

Survival

The median follow-up was 41 months (IQR 24 – 65.5), it was 38 months (IQR 25 - 68) for lobectomy and 43.5 months (IQR 23 – 61.75) for segmentectomy. 84 (33.2%) patients had an oncological event (either a recurrence or a second primary lung cancer).

There was no statistical difference in five-year DFS rate (p=0.37) between lobectomy 70 % (95% CI: 60.8 – 77.5 %) and segmentectomy 64.8% (95%CI: 47.2 % - 77.8 %) groups

After propensity score matching the 5-year DFS (p=0.27) rate was similar between lobectomy 85 % (74.6% - 96.9%) and segmentectomy 66.9% (51.3% - 87.2%). (Fig.1)

Age (p=0.04), performance status (p<0.001), previous lung cancer surgery (p=0.05), clinical stage (p=0.04), adenocarcinoma histology (p=0.007), were statistically influencing recurrence in univariable analysis. The type of operation was not influencing recurrence (p=0.74), in univariable analysis even in the matched dataset. After multivariable analysis only performance status (p<0.001, HR=2.41) and age (p=0.031, HR=1.03) were statistically influencing recurrence.

After stratified cox regression analysis using propensity score matching, only PS was statistically influencing recurrence (p< 0.001, HR= 4.24).

The locoregional recurrence rate (p=0.84), ipsilateral pleural recurrence rate (p= 0.92) and brain recurrence rate (p= 0.68) were similar in the 2 arms. However, distant recurrence rate was statistically different between 2 groups (p= 0.027) (Table 3).

The five-year overall survival (OS) rate was similar (p= 0.93) between the groups: segmentectomy 75.8 % (95%CI: 59.3 % - 86.4 %) *vs* lobectomy 73 % (95%CI: 64.4 % -79.9 %)

After propensity score matching the 5-year overall survival rate (p=0.42) was similar between lobectomy 76.3% (95% CI: 64.4% - 90.5%) and segmentectomy 80.1% (67.2% - 95.5%) (Fig.2).

The following variables were statistically influencing survival in univariate analysis: male gender (p=0.10), PS (p<0.001), length of stay (p=0.001), comorbidities (p=0.013), previous lung cancer surgery (p=0.037), histology (adenocarcinoma) (p=0.025). The survival was similar (p=0.55) between patients who had adjuvant chemotherapy (68.9%) and those who did not (79.8%). In multivariable analysis, male gender (p=0.053, HR= 1.83), PS (p<0.001, HR= 3.85) and length of stay (p=0.021, HR=1.04), were statistically influencing survival.

After stratified cox regression analysis using propensity score matching, only PS was statistically impacting survival (p< 0.001, HR= 5.96).

DISCUSSION

One main limitation in VPI studies is the assessment of VPI itself. In its proposals of the 8th TNM staging, the IASLC classified the extent of VPI as following : PL0 when invasion is beneath elastic layer, PL1 when invasion is beyond the elastic layer, PL2 when invasion extends to the visceral pleural surface (18). According to the Japan lung cancer society, for small-sized tumor with VPI, only PL2 should be upstaged to pT2a (stage IB) while PL1 tumors remain T1 (stage IA). In our series, as in most others, PL1 and PL2 were upstaged (pT2a) (12,19). Elastic stains are recommended for the diagnosis of VPI, it increases up to 20 % the identification of VPI compared to

hematoxylin eosin (9,12,20), even though many pathologists have been reluctant to use elastic stains (20). In fact, even with elastic stains, the diagnosis of VPI is not always evident, because of anatomical and pathological variations of visceral pleural caused by inflammation and fibrosis (9).

VPI has been known as an adverse prognostic factor for NSCLC as it correlates with, higher recurrence rate and poor survival (12), even in case of small-sized NSCLC (7,8).

The question raises when at final pathological examination, VPI upstages from cT1N0 to pT2aN0 NSCLC in patients who had only segmentectomy; should these patients be reoperated for completion to lobectomy?

They are several series with VPI upstaged pT2a patients who underwent only segmentectomy (1–5,14,19,21), without mentioning any completion to lobectomy; some authors (5,14) have suggested adjuvant treatment for these patients as an alternative.

We therefore investigated the prognosis of early-stage NSCLC (cT1N0) patients who underwent either lobectomy or segmentectomy with VPI at final pathological examination (upstaged pT2aN0) in standard practice outside of study protocol over three experienced French centers. We found that five-year DFS and OS rates were similar between the two groups; segmentectomy did not increase loco-regional recurrence (including ipsilateral pleural recurrence), second primary lung cancer compared to lobectomy. In multivariable analysis segmentectomy was not associated with an increased recurrence rate neither with a worse survival rate. Our results were comparable with those of Kagimoto et al. who investigated oncological outcome of segmentectomy for small-sized NSCLC in patients with invasive characteristics,

including VPI (21); Moon et al. attested the same when they assessed at completion of resection to lobectomy in patients that underwent sublobar resection with VPI or lymphovascular invasion at final pathological examination (22). But, in our survey, only the distant recurrence rate was statistically increased in the segmentectomy group. A possible explanation would be the higher number of patients with previous lung cancer surgery in this group without being able to determine whether the distant recurrence is attributed to the first or second resected NSCLC.

In our cohort, adjuvant chemotherapy did not prevent recurrence. It was not either improving survival. Huang relies on adjuvant treatment in case of VPI even for stage IA lung cancer (8). However, they are some nuances rose by Hattori et al who do not recommend adjuvant chemotherapy based on the VPI, in stage IA patients in case of partial ground glass nodules (14); and by Chang et al who suggested adjuvant chemotherapy in stage IA patients only with PL2 VPI (23). The benefit of adjuvant treatment for stage IB, has been a matter of discussion.

Even though overall survival and disease-free survival rates between segmentectomy and lobectomy were statistically similar, the disease-free survival difference increased from the 5th year in favor of lobectomy. We think that any explanation may be found if we reported some variables that are a part of actual clinical practice context, for instance CTR, adenosarcoma subtype, margin measurements.

There is a real need of further investigations on the impact of adjuvant treatment, CTR, adenocarcinoma subtypes, VPI extent in VPI pT2a upstaged patients with the current clinical settings. Notwithstanding, a conservative attitude upon VPI pT2a upstaged patients after segmentectomy, seems promising.

Several limitations of our study must be underlined, the limited size of the sample and those generally related to its retrospective nature and to its large span time coverage, especially the lack of radiological pattern, surgical margins details, and of adenocarcinoma subtypes. Nevertheless, we have not found any argument of extending resection in VPI pT2a upstaged patients who underwent segmentectomy.

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CONFLICT OF INTEREST STATEMENT

Joseph Lula Lukadi: No conflict of interest

Alessio Vincenzo Mariolo: No conflict of interest

Emrah Gokay Ozgur: No conflict of interest

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Joseph Lula Lukadi: data collection, statistical analysis, paper writing.

Alessio Vincenzo Mariolo: data collection, manuscript edition

Emrah Gokay Ozgur : statistical analysis

Dominique Gossot: work conception, data collection, manuscript edition.

Jean-Marc Baste: data collection, manuscript edition.

Bertrand De Latour: data collection, manuscript edition.

Agathe Seguin-Givelet: Work conception, data collection, manuscript edition

All authors have read and approved the manuscript

FIGURE LEGENDS

1. Figure 1: Disease free survival
2. Figure 2: Overall survival

TABLES

1. Table1: Patients and tumors characteristics stratified by type of operation before propensity score matching
2. Table 2: Patients and tumors characteristics stratified by type of operation before propensity score matching
3. Table 3: Oncological events stratified by type of operation.

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1. Table 1: Patients and tumors characteristics stratified by type of operation before propensity score matching

	Lobectomy (n=191)	**Segmentectomy (n=62)**	**p Value**
Age, median (IQR)	64 (58 - 71)	67 (59 - 72)	0.42
Sex male/female**, n (%)**	119 (62.3) / 72 (37.7)	36 (58.1) / 26 (41.9)	0.65
ppo FEV1, median (IQR)	69.7 (60 - 77.2)	80.1 (62.4 – 93.6)	0.009
PS			0.85
0, n (%)	134 (70.2)	44 (71.0)	
1, n (%)	53 (27.7)	16 (25.8)	
2, n (%)	4 (2.1)	2 (3.2)	
Comorbidity			0.24
No comorditity, n (%)	23 (12)	7 (11.3)	
Cardiovascular & pulmonary, n (%)	43 (22.5)	18 (29.0)	
Oncological, n (%)	19 (9.9)	11 (17.7)	
Others (1), n (%)	105 (54.9)	26 (41.9)	
Previous NSCLC surgery, n (%)	2 (1.0)	10 (16.1)	<0.001
Clinical stage			0.001
cT1aN0, n (%)	7 (3.7)	9 (14.5)	0.002
cT1bN0, n (%)	91 (47.6)	37 (59.7)	0.10
cT1cN0, n (%)	93 (48.7)	16 (25.8)	0.001
Histology			0.21
Adenocarcinoma, n (%)	155 (81.2)	56 (90.3)	
Squamous, n (%)	25 (13.1)	6 (9.7)	
Larger cells carcinoma, n (%)	8 (4.2)	0 (0%)	
Others (2), n (%)	3 (1.6)	0 (0%)	
Adjuvant chemotherapy, n (%)	37 (19.4)	8 (12.9)	0.33

(1): diabetes mellitus, exposure to asbestos, alcoholism, scleroderma, or other comorbidities association

(2): sarcomatous carcinoma, lymphoepithelioma-like carcinoma, carcinoid tumor.

2. Table 2: Patients and tumors characteristics stratified by type of operation after propensity score matching.

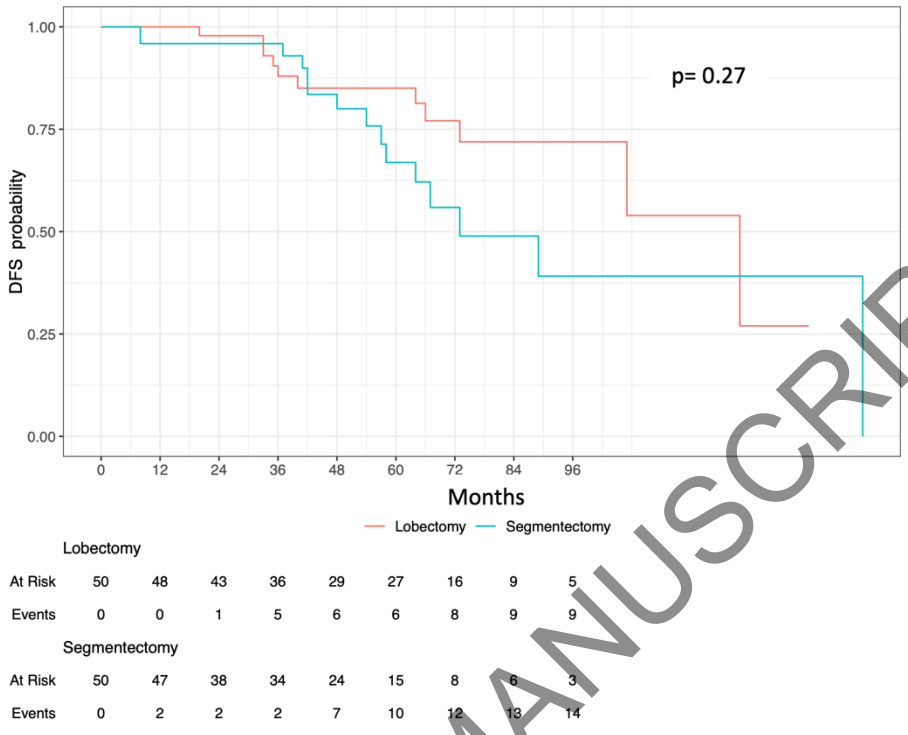
	Lobectomy (n= (50)	**Segmentectomy (n=50)**	**SMD**
Age, mean (± SD)	64.3 (±10.8)	65 (±10.3)	0.113
Sex male/female, n (%)	24 (48.0) / 26 (52.0)	24 (48.0) / 26 (52.0)	0.055
ppo FEV1, mean (± SD)	65.7 (±16.7)	78.9 (±22.6)	
PS			0.039
0, n (%)	35 (70.0)	36 (72.0)	
1, n (%)	14 (28.0)	13 (26.0)	
2, n (%)	1 (2.0)	2 (2.0)	
Comorbidity			0.201
No comorditity, n (%)	5 (10.0)	7 (14.0)	
Cardiovascular & pulmonary, n (%)	12 (24.0)	13 (26.0)	
Oncological, n (%)	6 (12.0)	9 (18.0)	
Others (1), n (%)	27 (54.0)	21 (42.0)	
Previous NSCLC surgery, n (%)	1 (2.0)	1 (2.0)	0.000
Clinical stage			0.033
cT1aN0, n (%)	7 (14.0)	6 (12.0)	
cT1bN0, n (%)	31 (62.0)	32 (64.0)	
cT1cN0, n (%)	12 (24.0)	12 (24.0)	
Histology			0.356
Adenocarcinoma, n (%)	40 (80.0)	45 (90.0)	
Squamous, n (%)	7 (14.0)	5 (10.0)	
Larger cells carcinoma, n (%)	3 (6.0)	0 (0%)	
Adjuvant chemotherapy, n (%)	6 (12.0)	7 (14.0)	0.059

(1): diabetes mellitus, exposure to asbestos, alcoholism, scleroderma, or other comorbidities association

3. Table 3: Oncological Events stratified by type of operation

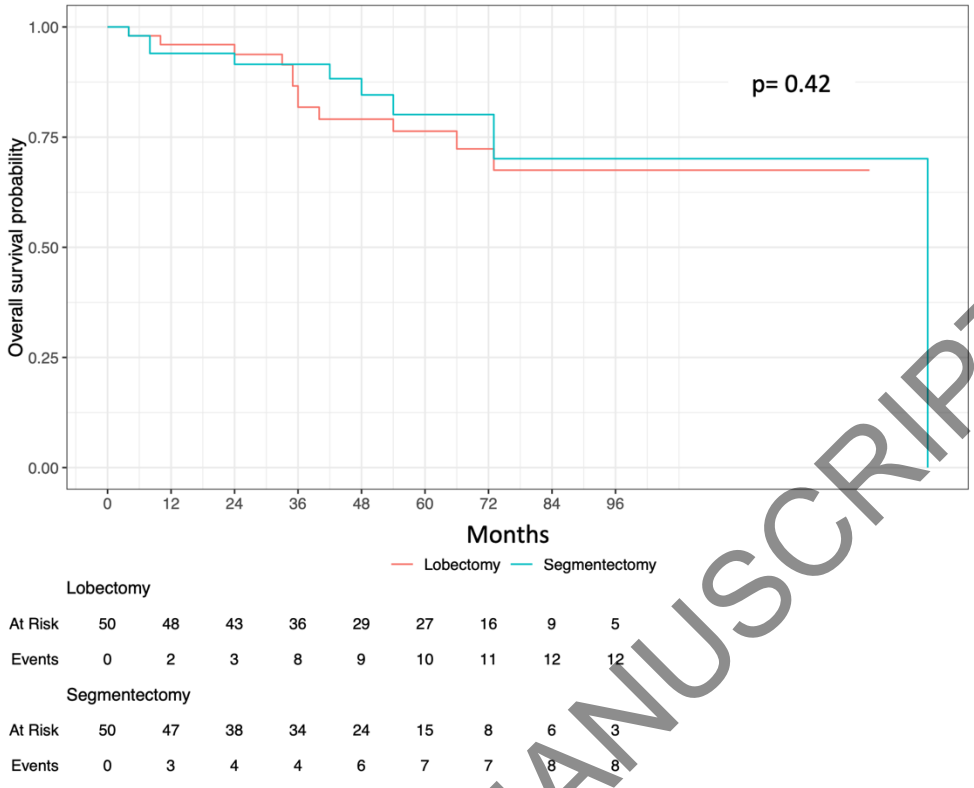
	Lobectomy (n=191)	Segmentectomy (n=62)	p Value
Recurrences			
Locoregional, n (%)	34 (17.8)	10 (16.1)	0.84
Ipsilateral Pleural, n (%)	13 (6.8)	4 (6.5)	0.92
Distant, n (%)	24 (12.5)	15 (24.2)	0.027
Brain, n (%)	9 (4.7)	4 (6.4)	0.86
2nd NSCLC, n (%)	19.9 (9.9)	4 (6.4)	0.40

Figure 1. Disease-Free Survival



Lobectomy									
At Risk	50	48	43	36	29	27	16	9	5
Events	0	0	1	5	6	6	8	9	9
Segmentectomy									
At Risk	50	47	38	34	24	15	8	6	3
Events	0	2	2	2	7	10	12	13	14

Figure 2. Overall Survival



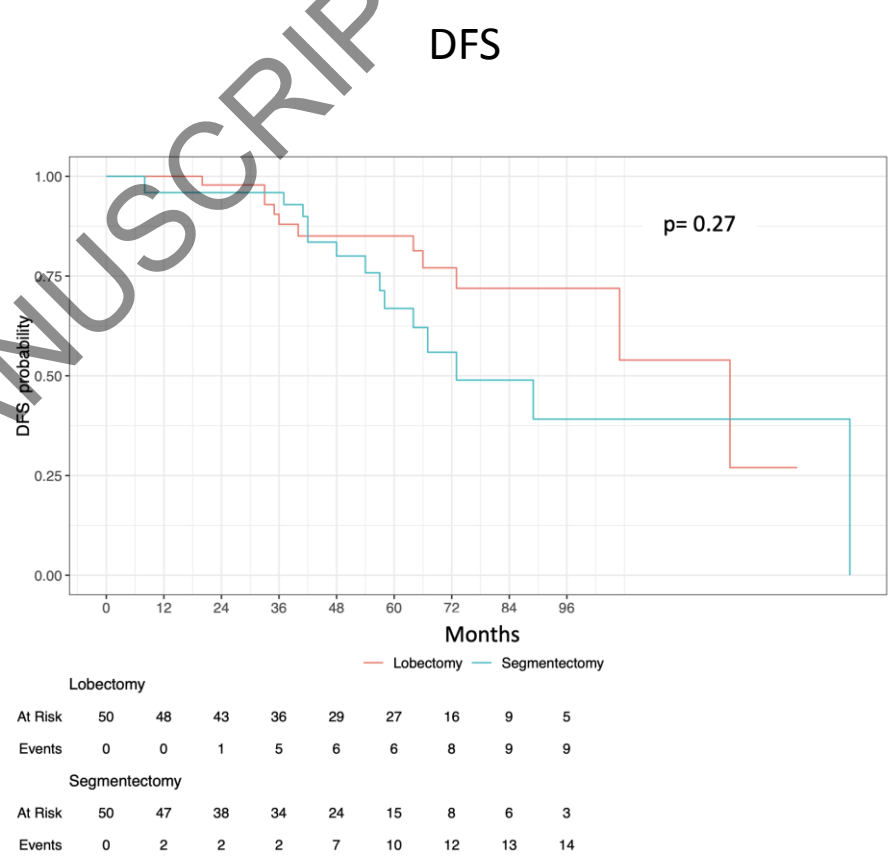
Upstaged from cT1a-c to pT2a lung cancer, related to visceral pleural invasion patients, after segmentectomy: Is it an indication to complete resection to lobectomy?

Summary

In a retrospective study of 253 patients, we investigated if VPI upstaged (pT2a) patients, who underwent segmentectomy compared to those treated by lobectomy, had a worse prognosis.

5-year DFS and OS rates of VPI upstaged patients were similar in both segmentectomy and lobectomy groups. Segmentectomy did not impact recurrence nor survival.

VPI detection does not seem to be an indication of extending resection after segmentectomy.



Legend: VPI (visceral pleural invasion), DFS (disease-free survival), OS (overall survival)