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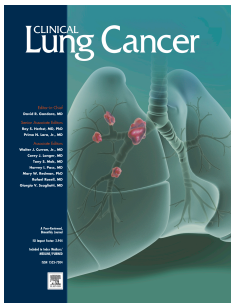

Surgically treated unsuspected N2-positive NSCLC: role of extent and location of lymph node metastasis

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PII: S1525-7304(18)30093-7

DOI: 10.1016/j.cllc.2018.04.011

Reference: CLLC 781

To appear in: *Clinical Lung Cancer*

Received Date: 24 September 2017

Revised Date: 25 March 2018

Accepted Date: 24 April 2018

Please cite this article as: Andersson S, Ilonen I, Järvinen T, Rauma V, Räsänen J, Salo J, Surgically treated unsuspected N2-positive NSCLC: role of extent and location of lymph node metastasis, *Clinical Lung Cancer* (2018), doi: 10.1016/j.cllc.2018.04.011.

Surgically treated unsuspected N2-positive NSCLC: role of extent and location of lymph node metastasis

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Micro abstract:

The role of positive lymph node location in NSCLC patients and effects on survival was assessed. A total of 88 operated patients with unsuspected N2 disease or station 10 lymph nodes were included in this study. No difference was found in survival between inferior positive mediastinal N2 node patients compared with multilevel N2 disease patients. The survival of patients with positive hilar disease was similar to the inferior mediastinal positive N2 group.

Surgically treated unsuspected N2-positive NSCLC: role of extent and location of lymph node metastasis

Background: The role of surgery in the treatment of non-small cell lung cancer (NSCLC) that has spread to ipsilateral mediastinal or hilar lymph nodes is controversial. We examined whether the location of lymph nodes positive for NSCLC in mediastinum or hilum influences survival of these patients.

Patients and methods: We reviewed 881 patients and analysed those with unsuspected N2 disease or hilar (station 10) lymph nodes. The patients were stratified into the following groups: **group A** with positive hilar Naruke 10; **group B** with superior mediastinal and aortic nodes (Naruke 1, 2, 3, 4, 5 and 6); **group C** with inferior mediastinal nodes (Naruke 7, 8 and 9); multilevel **group D** (two or more positive N2 levels).

Results: A total of 69 pN2 and 19 pN1 patients were included. Progression-free survival (PFS) was statistically significant better in group B versus group C (*P*=.044) and group B versus group D (*P*=.0086). The overall-survival (OS) of group A did not differ from that of group C. A statistically significant better OS was between B and D (*P*=.051).

Conclusions: Inferior positive mediastinal N2 node patients seem to have an OS and PFS as poor as multilevel N2 disease patients. The OS and PFS of patients with positive hilar disease are similar to those in the inferior mediastinal positive N2 group. Superior positive mediastinal N2 node patients has better OS and PFS than inferior mediastinal positive N2 group.

INTRODUCTION

According to the Finnish Cancer Registry, lung cancer is the leading cause of cancer-related deaths in men (21.6%) and the second most common cause in women (13.5%).[1]The optimal treatment and prognosis of lung cancer depends on the stage. The role of surgery in Stage IIIA patients is controversial, especially in mediastinal N2 disease[2]. Despite systemic induction chemotherapy[3,4], patients with mediastinal lymph node involvement have a poor prognosis. The correlation of prognosis to location and extent of mediastinal lymph node involvement is unclear [5-8]. Recently, it has been shown that single-level N2 disease survival differs from that of multilevel N2 disease[9]. There are also reports on patients with lower mediastinal metastasis that indicate a significantly better prognosis than those with upper mediastinal metastasis[10].

To further clarify this matter, we retrospectively analysed our patient series to understand the correlation between the extent of mediastinal disease involvement and given location of the involvement to progression-free and overall survival.

Patients and methods

Patients

Between January 2004 and December 2014, 881 patients underwent anatomic R0 lung resection with mediastinal lymphadenectomy for primary lung cancer in Helsinki University Hospital. All patients were preoperatively evaluated by a multidisciplinary lung tumour board for primary operative management. The study group consisted of patients who were clinically staged as N0 disease. We excluded patients with clinically suspected N1 or N2 disease on imaging or confirmed before resection. Of these, we excluded 34 patients who had intraparenchymal positive lymph nodes limited to stations 11 or 12 or both. The type of surgery performed was lobectomy, sleeve or bilobectomy (Table 1).

Methods

For staging, we utilised the 7th edition of the TNM Classification (American Joint Committee on Cancer, 2009). We defined unsuspected N2 disease as final pathological N2 without suspected mediastinal lymph node involvement in preoperative examinations. Every patient was staged with computed tomography (CT). Fifty-four (61.4%) patients were staged with positron emission tomography PET-CT and selective mediastinoscopy was performed on three patients (3.4%) patients. Both mediastinoscopy and PET-CT were performed on two (2.3%) patients. Preoperative evaluations included a spirometry test (according to the guidelines of the European Respiratory Society and measurements of pulmonary diffusing capacity for carbon monoxide (DLCO) using the single-breath method (American Thoracic Society Guidelines, 1996). Naruke lymph node map was used for classification[11], on which station 10 lymph nodes were regarded as N1 nodes (hilar, main bronchus nodes). The sites of N2 lymph nodes were grouped as follows: superior mediastinal (station 1, highest mediastinal nodes; station 2, upper paratracheal nodes; station 3, pre-vascular and retrotracheal; station 4, lower paratracheal nodes; station 5,

sub-aortic nodes; and station 6, para-aortic nodes) and inferior mediastinal (station 7, subcarinal nodes; station 8, paraesophageal nodes; and station 9, pulmonary ligament nodes) lymph nodes. We excluded nine pneumonectomy patients from our analysis, due inherent increased morbidity and mortality in the follow-up of this subpopulation. The patient flowchart is shown in Figure 1 and preoperative data is shown in Table 2.

LN subclassification

We classified our patients into the following four groups: **group A** consisted of pN1 with positive hilar Naruke 10 (n=19), **group B** consisted of pN2 patients with superior mediastinal and aortic positive nodes (Naruke 1, 2, 3, 4, 5 and 6 levels, n=20), **group C** consisted of pN2 patients with inferior mediastinal positive nodes (Naruke 7, 8 and 9 levels, n=24) and **group D** consisted of multilevel pN2 (two or more positive N2 levels, n=25).

Statistical analysis

Statistical analysis was performed using SPSS statistical software (version 22.0, Chicago, IL, USA). Results are reported as the median (range). Normality was tested using Shapiro-Wilk's test. The Student's *t*-test was used to compare scalar values for groups with normal distributions. The Mann-Whitney *U*-test was used for non-normal scalar analysis. Comparisons of progression free survival (PFS) and overall survival (OS) were performed using Kaplan-Meier analysis and the log-rank test. A *P*-value less than .05 was considered statistically significant. Consent was granted for the study by the hospital scientific review board.

Results

A total of 88 patients met the inclusion criteria for this study. We included 19 hilar pN1 and 69 pN2 patients in our final analysis (Figure 1). Tumour characteristics are presented in Table 2. The incidence of unsuspected pN2 disease was 7.8% in our study. Fourthy-eight patients (52.3%) received adjuvant chemotherapy; none received postoperative radiotherapy (RT). Thirty-day mortality was 2.3% (2 patients). Causes of death were stroke (1 patient) and ARDS (1 patient). The operative morbidity was 27.3%; the most common morbidity was pneumonia. Tumours were localised in upper lobes (n=42, 47.7%), middle lobe (n=6, 6.8%) and lower lobes (n=40, 45.5%). Group B and D had the most upper-lobe tumour affision (n=12 vs n=14, 60% vs 56%, respectively). Lower-lobe affision was most common in group C (n=16, 66.7%).

The median PFS was 24 months (range, 0-133 months). The 5-year PFS rates were 21.1% (group A), 30% (group B), 12.5% (group C) and 12% (group D). No statistically significant difference in PFS was observed between groups A and B (*P*=.170), A and C (*P*=.625), A and D (*P*=.420) or C and D (*P*=.735). PFS was statistically significant better in group B versus group C (*P*=.044) (Figure 2) and group B versus group D (*P*=.0086) (Figure 3); the Kaplan-Meier survival plot overlapped for groups C and group D .

The median OS and the 5-year overall survival (5-year OS) for the whole group were 34.5 months (range, 0-134 months) and 23.9%, respectively. The median OS values were 39 months (group A), 51 months (group B), 33 months (group C) and 22 months (group D). The 5-year OS rates were 21% (group A), 35% (group B), 16.7% (group C) and 24% (group D). A statistically significant better OS was between B and D (*P*=.051) (Figure 4). There was no statistically significant difference in OS between groups A and B (*P*=.143), A and C (*P*=.846) and C and D (*P*=.82); the Kaplan-Meier survival plot overlapped for groups

C and group D (Figure 5 and Figure 6).

A multivariate Cox regression analysis was performed between groups A, B, C and D (Table 3). Age and CCI were covariant affecting to OS, i.e. older patients had better OS than young patients. No other covariates reached significance (sex, FEV_1%, thoracotomy vs. VATS, pre.op. stage) (Table 3).

DISCUSSION

Accurate assessment of lymph node involvement is crucial for treatment and prognosis of NSCLC. Variability in identifying lymph node stations can lead to ambiguous staging of lymph node stations. Previous studies have shown that involvement of station number 10 significantly worsens prognosis compared with other N1 diseases and is similar to that of N2 disease. [12,13,10]. We sought to determine the correlation between the extent of mediastinal disease involvement and given location of involvement to progression-free and overall survival. We use the Naruke map at our institution and consider those lymph nodes located around the main bronchus as number 10 (N1).[11]

The International Association for the Study of Lung Cancer map defines the whole subcarinal LN as level 7, which in the Naruke map corresponds to both levels 7 and 10 LN. In the American Joint Committee on Cancer (American Joint Committee on Cancer, 2009) and Mountain's map, station number 10 (N1 nodes) is located distally to the mediastinal pleural reflection.

Our study group consisted of patients with clinical IA to IIB disease. The unsuspected N2 involvement of 7.8% is in agreement with those of previous studies showing that about 10% of patients with clinical N0 NSCLC were confirmed as having pathologic N2 disease after lobectomy. [14 15-17].

Our results did not show a statistically significant difference in long-term OS between single-station pN2 and station number 10 metastasis. This result was also observed between pN1 and pN2 patients with superior mediastinal and positive aortic nodes. Our findings are consistent with Rea *et al*., [18] who reported similar 5-year survival rates in patients with pN1 and those with single-station N2 (31% and 18% respectively).

Asamura *et al.* also reported similar results with 5-year survival rates (54% for pN1 and 48% for pN2).[22] We believe that this reflects the similarity of pN1 and single-level pN2 disease in superior mediastinal and aortic lymph node metastasis.

Riquet *et al.* analysed 1779 lobectomies and observed that pN2 frequency was similar regardless of the lobes[19]. In their material, the overall 5-year survival rate was 30.9% in N2 patients. Asamura *et al.* demonstrated that the most common site of metastasis in right, upper-lobe tumours was the lower paratracheal station (74%), whereas metastases to the subcarinal station were only seen in 13% [20]. Superior mediastinal and subcarinal stations were involved in patients with right, lower-lobe tumours. Left upper-lobe tumours most commonly metastasised to the aortic pulmonary window (59%), followed by the para-aortic station (32%) and the subcarinal (21%). The subcarinal station was the most common for metastasis in left, lower-lobe tumours (58%), with infrequent metastases to the aortic pulmonary window[20]. Consistent with the results from Asamura *et al.*, the affected lobe was also most commonly the upper lobe in our study on patients with superior mediastinal lymph node metastasis[17]. With inferior mediastinal lymph node metastasis, tumours were more likely in the lower lobe (60%) than in the upper lobe, which is consistent with the findings from Asamura *et al*. In our study, while group D (multilevel) tumours were more commonly found in the upper than in the lower lobe, the difference was not statistically significant.

In our study, we found out better OS among older patients. This might be because of that patients were older in group B (single level N2 superior) who had better OS than group C (single level N2 inferior) or multilevel N2 patients.

In the present study, we observed statistically significantly better progression free survival in superior N2 patients than in inferior N2 patients. We find out trend for better

overall survival between inferior N2 versus superior N2 even though it wasn't statistically proven. We did not observe any statistically significant difference in PFS or OS between inferior N2 versus multilevel N2 or comparing pN1 (10) to superior or inferior pN2 single-station lymph node metastasis. Although there are reports that suggest that subcarinal lymphadenectomy is not always necessary for tumours of the upper lobes [20], we suggest that for lymph node sampling, station number 7 is relevant for patient outcome irrespective of the location of the primary tumour. Our main finding was that inferior positive mediastinal N2 node patients seem to have as unfavourable OS and PFS as multilevel N2 disease patients and significantly worse prognosis than superior mediastinal node patients. We also noted that patients with positive hilar disease did not have different PFS than patients with inferior mediastinal positive N2 disease. Both the location of mediastinal lymph node metastasis and extent of disease are significant factors in the overall prognosis of NSCLC after surgery.

Limitations of the study

The most significant limitation is the retrospective study design, even with a prospective patient registry. A prospective study would be challenging due to the time required to collect study material, even in a multicentre setting. We also do not have accurate knowledge regarding the quantity of total lymph nodes in all patients, as with VATS surgery removal of lymph nodes can be performed in a piecemeal nature. Our sample size was relatively small but comparable to previous studies in unsuspected N2 disease [14-17]; therefore a risk for type II error exists. We are a specialised high-volume centre and perform careful lymph node sampling on all NSCLC patients. There was no collective re-

evaluation for micrometastasis in lymph nodes, as this evaluation would be easily biased due to the retrospective nature of the study and the quality of re-evaluation for N0 and N1 (stations 11 and 12) would not yield a significant new patient cohort for our study.

Conclusion

The current TNM staging in lung cancer only assesses the localisation of the lymph node stations for the lymph node examination. It seems, however, that the localisation of the positive lymph node stations alone is not sufficient for a reliable estimation of survival. In particular, the number of lymph node stations involved not only affects survival, but also the anatomic location of the single-level lymph node metastasis. We observed statistically significant poorer survival in the multilevel N2 patients than the single-station N2-patients. Inferior positive mediastinal N2 node patients seem to have OS and PFS as poor as multilevel N2 disease patients.

Clinical practise points

Involvement of station number 10 significantly worsens prognosis compared with other N1 diseases and is similar to that of N2 disease. [10,13,18]. Unsuspected mediastinal lymph node metastasis is found in approximately 10% of patient who have surgery for NSCLC. [14-17]. We found out that inferior positive mediastinal N2 node patients seem to have as unfavourable OS and PFS as multilevel N2 disease patients and significantly worse prognosis than upper mediastinal node patients. We also noted that patients with positive hilar disease did not have different PFS than patients with inferior mediastinal positive N2 disease. We suggest that during lobectomy station number 10 and 7 should be dissected.

Acknowledgments

This study was supported by grants from Helsinki University Central Hospital Research Funds and Jalmari and Rauha Ahokas Foundation.

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

Figure 1. Patient flowchart

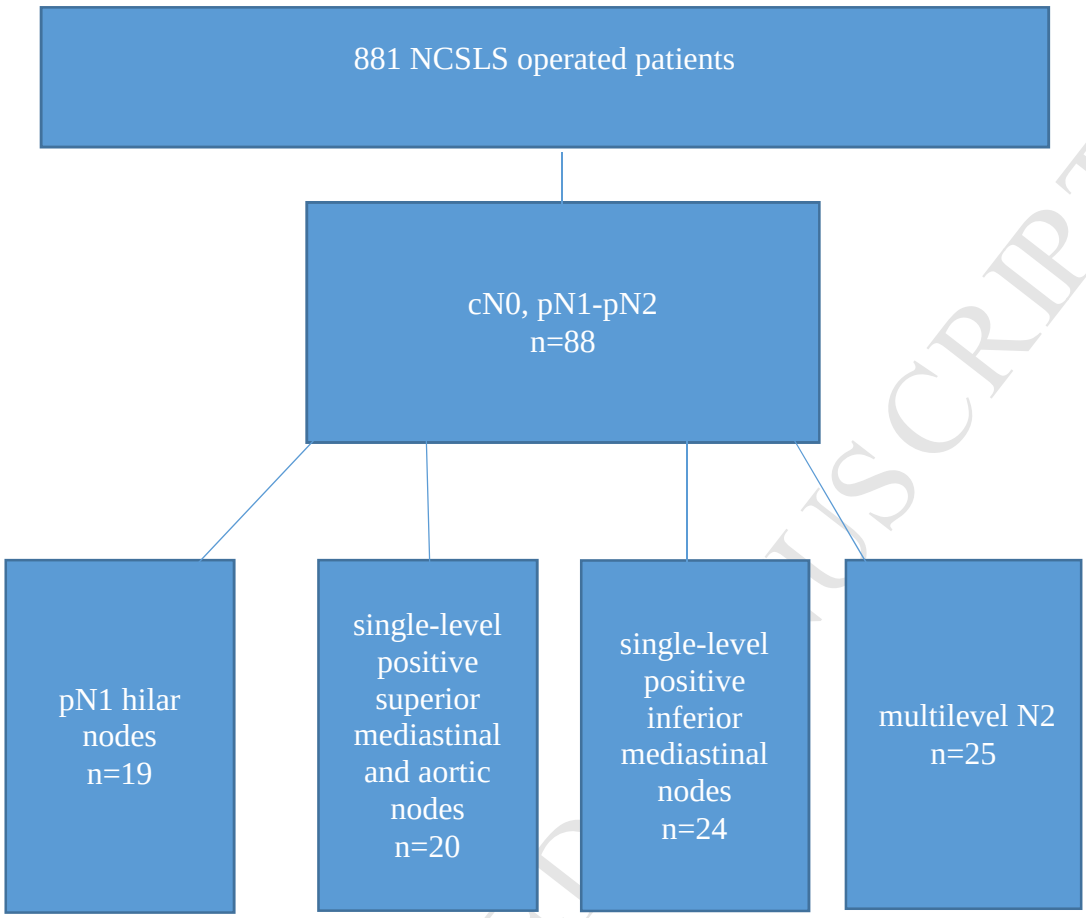


Figure 2.

Kaplan-Meier plot comparing progression free survival for pN2 single level superior (group B) patients (n=20) to pN2 single level inferior (group C) patients (n=24) *(P=.044).*

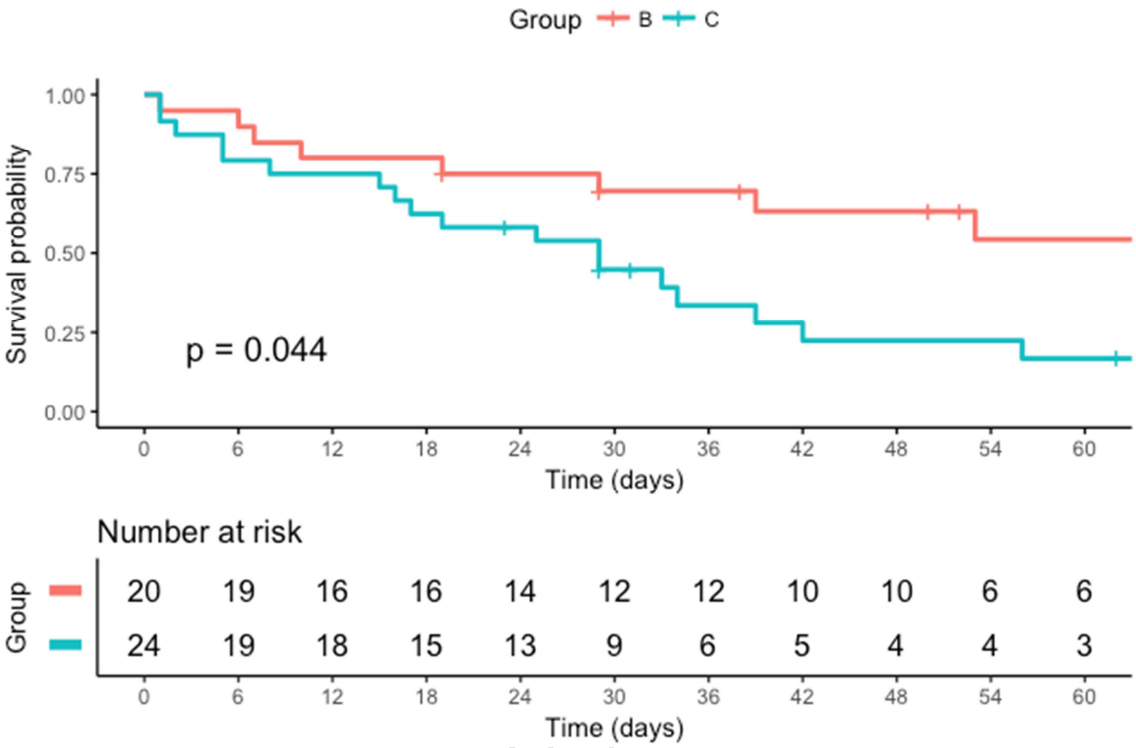
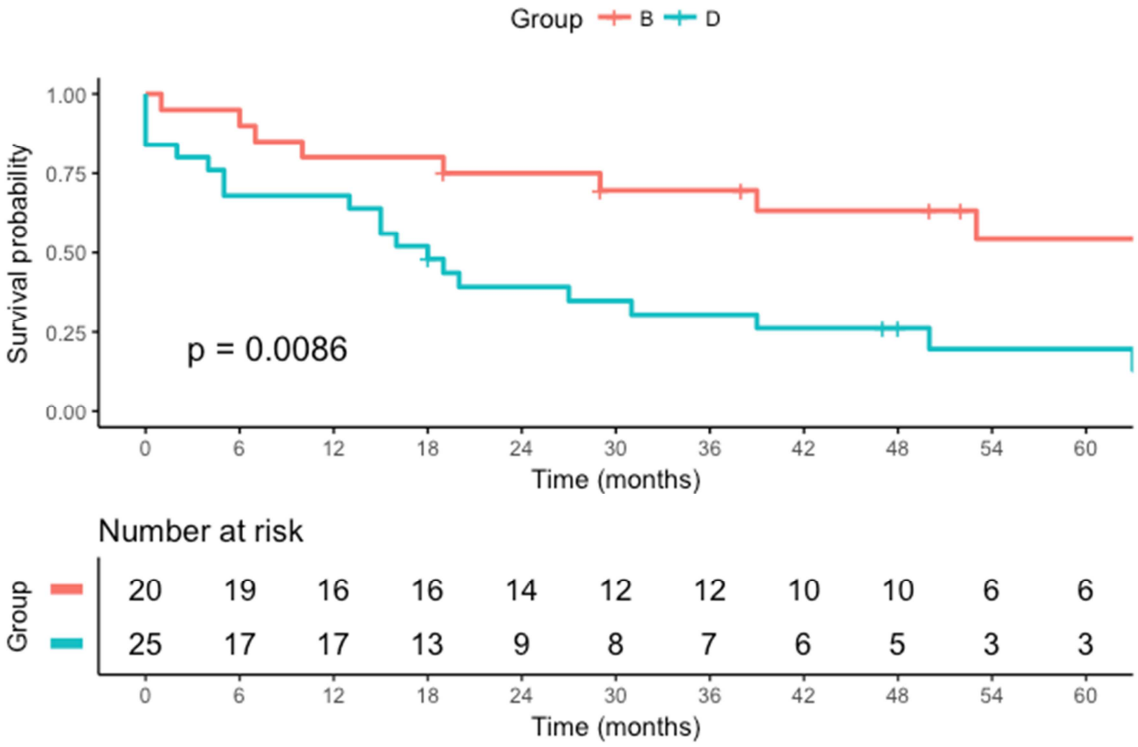


Figure 3.

Kaplan-Meier plot comparing progression free survival for pN2 single level superior (group B) patients (n=20) to pN2 multilevel (group D) patients (n=25) *(P=.0086)*



278 **Figure 4.**

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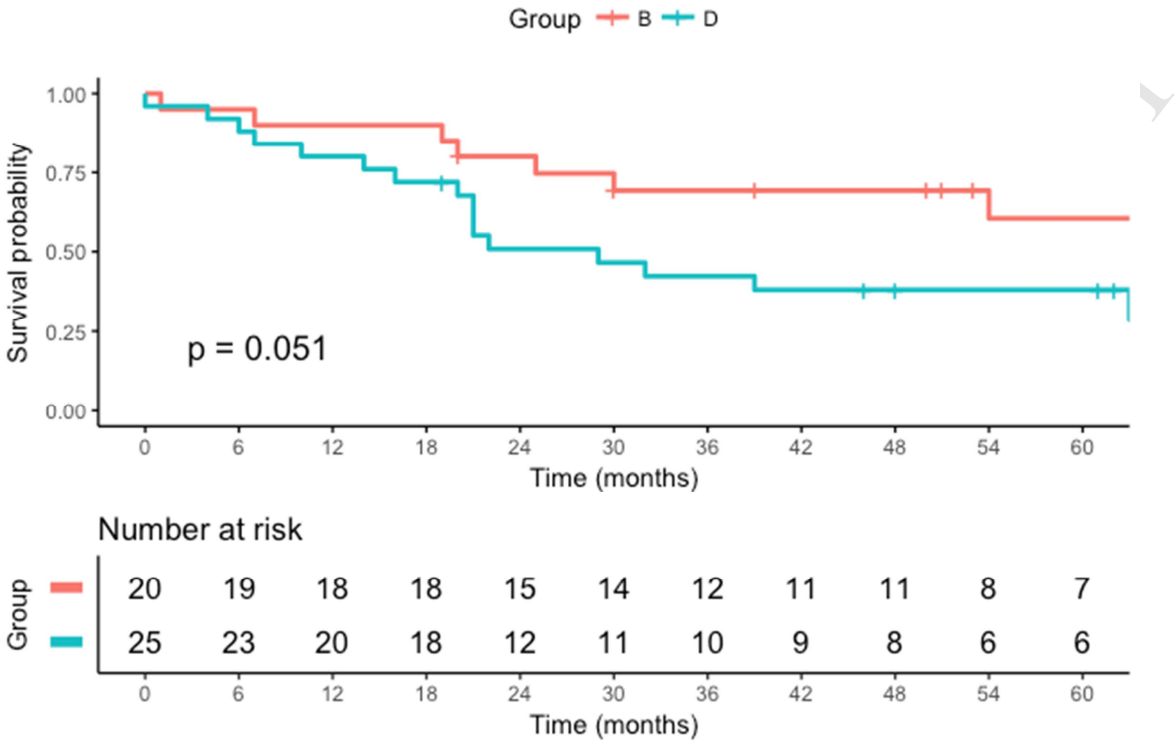
280 Kaplan-Meier plot comparing overall survival for pN2 single level superior (group B)

281 patients (n=20) to pN2 multilevel (group D) patients (n=25) (*P*=.051).



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283 **Figure 5.**

284 Kaplan-Meier plot comparing overall survival between pN2 single level inferior (group C)

285 patients (n=24) to pN2 multi-level (group D) patients (n=25) (*P*=.84).

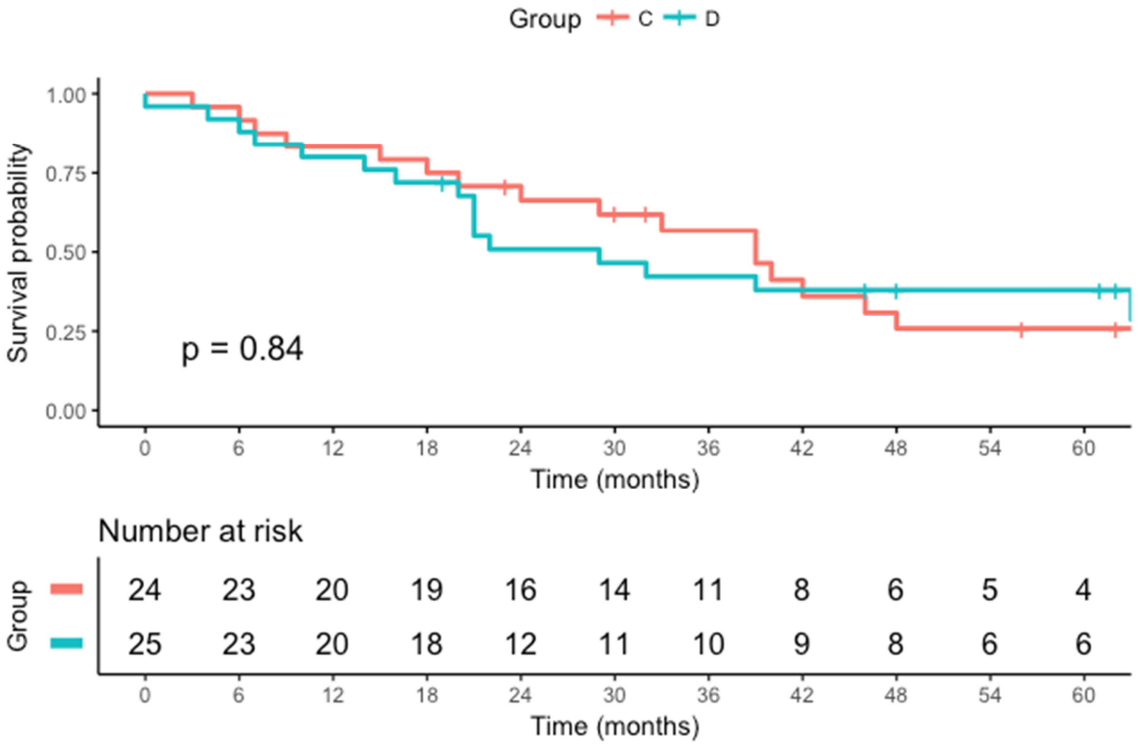

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Figure 6.

Kaplan-Meier plot comparing overall survival between pN1 hilar (group A) patients (n=19) vs pN2 single level superior (group B) patients (n=20) vs pN2 single level inferior (group C) patients (n=24) vs pN2 multi-level (group D) patients (n=25) (*P*=.26).

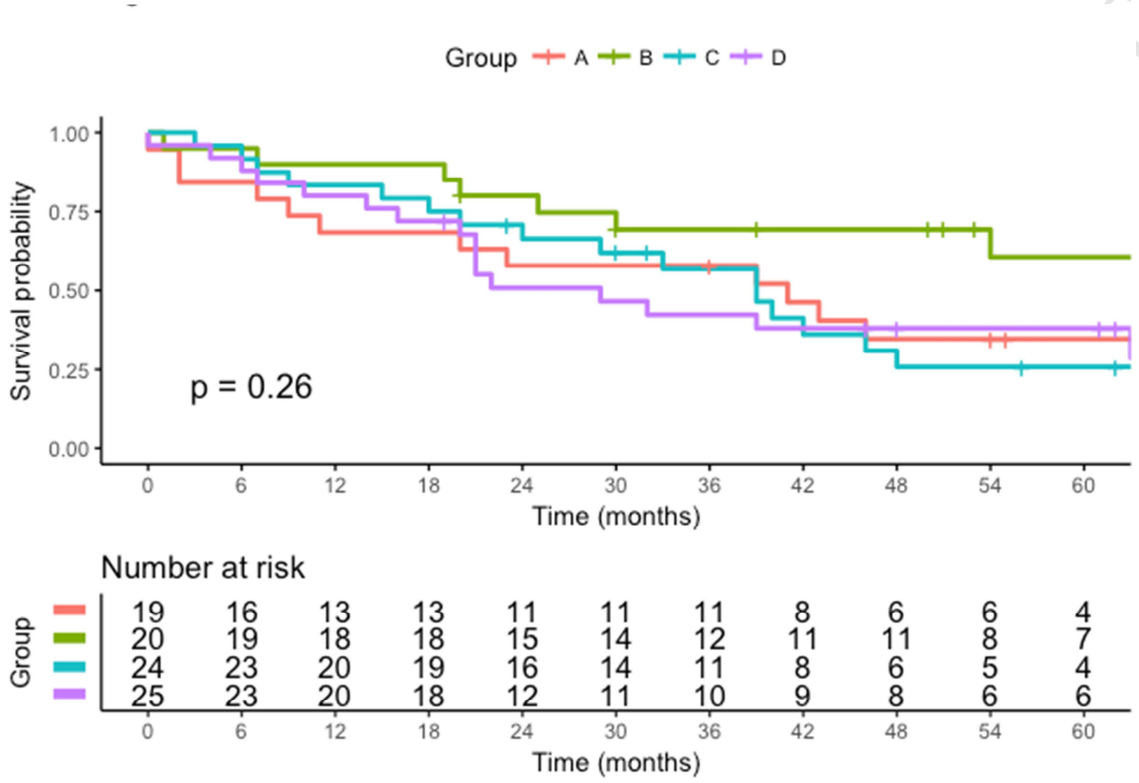

Table 1. Patient Characteristics

	N (%)
Mean age (range)	66 (41-83)
Female	39 (44.3%)
Type of surgery	
VATS	23 (26%)
Lobectomy	71 (80.7%)
Sleeve	11 (12.5%)
Bilobectomy	6 (6.8%)
Site of primary tumour	
Right lung	58 (65,9%)
Right upper lobe	28 (31.8%)
Right middle lobe	6 (6.8%)
Right lower lobe	24 (27.3%)
Left lung	30 (34.1%)
Left upper lobe	14 (15.9%)
Left lower lobe	16 (18.2%)
Adjuvant therapy	
Chemotherapy	46 (52.3%)
Radiotherapy	0 (0 %)
FEV_1% (mean)	91% (52-129)
Charlson Comorbidity Index (CCI)	5.32 (3-10)
Preop. Stage	
IA	34 (38.6%)
IB	23 (26.1%)
IIA	7 (8%)
IIB	20 (22.7%)
IIIA	4 (4.5%)
Other co-morbidities	
Hypertonia	23 (26%)
COPD	12 (13.6%)
MCC	11 (12.5%)
DM	3 (3.4%)

FEV1=Forced expiratory volume in one second
CCI= Charlson Comorbidity Index
VATS= Video-assisted thoracoscopy surgery
COPD=Chronic obstructive pulmonary disease
MCC= Morbus cordis
DM= Diabetes Mellitus

300 **Table 2.** Tumour and Operative Characteristics of the 88 Included Patients

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	pN1 (group A) n=19	pN2 (group B) n=20	pN2 (group C) n=24	pN2 (group D) n=25
Age (mean)	67 ± 9.2y	66± 9.9y	65 ± 7.1y	68 ± 6y
Females (%)	6 (31.6%)	10 (50%)	11 (44%)	12 (50%)
PreOP-FEV$_1$%	85.8% ± 14.3	93.8% ± 15.3	92.6% ± 15.2	91.7% ± 18.9
Histology				
Squamous Ca	7 (36.8%)	7 (35%)	6 (25%)	6 (24%)
Adenoca	11 (57.9%)	13 (65%)	16 (66.7%)	17 (68%)
Large Cell Ca	1 (5.3%)	0 (0 %)	2 (8.3%)	2 (8%)
Localisation, lobe				
Upper	10	12	6	14
Medial	2	-	2	2
Lower	7	8	16	9
Type of surgery				
VATS	4 (21%)	6 (30%)	6 (25%)	7 (30%)
Lobectomy	14 (73%)	17 (85%)	20 (83.3%)	20 (80%)
Bilobectomy	1 (5.3%)	1 (5%)	2 (8.3%)	2 (8%)
Sleeve	4 (21.1%)	2 (10%)	2 (8.3%)	3 (12%)

303 FEV**1=**Forced expiratory volume in one second
304 CCI=Charlson Comorbidity Index
305 VATS=Video-assisted thoracoscopy surgery
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308 **Table 3.** Multivariate Cox regression analysis of the covariates affecting OS (n=88)

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Table 3. Multivariate Cox regression analysis of the covariates affecting OS			
	HR	**95%CI**	***P***
Age	1.056	1.013-1.102	*.011*
Sex	1.427	0.716-2.844	.313
Preop. FEV1	0.994	0.973-1.015	.551
Thoracotomy vs. VATS	0.993	0.706-1.398	.970
CCI	1.245	1.046-1.481	*.014*
Preop. Stage (vs. Stage IA)	0.887	0.4315-1.823	.7440
IB	1.281	0.4740-3.463	.6254
IIA	1.083	0.5105-2.301	.8341
IIB	0.648	0.1805-2.332	.5073
IIIA	1.12267	0.5805-2.171	.7310

310 FEV_1=Forced expiratory volume in one second
311 CCI=Charlson Comorbidity Index
312 VATS=Video-assisted thoracoscopy surgery
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