Sublobar Resection Without Staging and Diagnostic for Tumors <2 cm is no Adequate Therapy for Non-Small Cell Lung Cancer Patients

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Abstract

Purpose: Sublobar resection is a frequently performed surgical approach for Non-Small Cell Lung Cancer (NSCLC) patients with <2cm nodules. Retrospective studies are claiming that survival rates after sublobar resection are comparable to that after anatomical resection although studies dealing with sublobar resection do not perform guideline-based staging and little to no lymphadenectomy.

Methods: 747 patients underwent surgery for NSCLC at our institution between 2012 and 2020. We retrospectively reviewed data of NSCLC patients with <2cm tumors (n=236). Nodal upstaging and lymphangiosis- (L1) and hemangiosis carcinomatosa (V1) were analyzed. pN0 patients were compared to patients with nodal upstaging. One-, three and five-year survival rates were measured. Survival was assessed by Kaplan-Meier curves.

Results: Mean tumor size was $1.4\text{cm} \pm 0.39$ in our cohort. Of our patients, 14% showed a cT1a tumor and 86% of patients cT1b. 24.0 ± 12.3 lymph nodes were dissected and analyzed per patient, and 0.7 ± 2.0 of those were affected. Of our patients, 16.1% showed an L1 affection and 7.6% a V1 affection. Lymph node involvement was diagnosed in 11(4.7%) patients preoperatively. 39(16.5%) patients were upstaged due to lymph node involvement postoperatively ($p < 0.001$). Upstaged patients showed significantly worse 3- (upstaged: 60.6% vs. pN0: 83.2%; $p = 0.01$) and 5-year (upstages: 38% vs. pN0 71.5%; $p = 0.02$) survival rates.

Conclusion: Of our patients with <2cm NSCLC 16.5% were nodal upstaged postoperatively. These results underline that lymphadenectomy during surgery is crucial for NSCLC patients irrespective of the tumor size and the surgical approach.

Introduction

Anatomical resection remains the gold standard for early-stage Non-Small Cell Lung Cancer (NSCLC), providing the best opportunity for cure [1]. Lobectomy with radical lymphadenectomy is accepted to be the treatment of choice independently of the NSCLC UICC 8 stage, providing the best overall survival [2, 3]. Patients undergoing lobectomy need a certain pulmonary function and fitness. Due to a variety of reasons the pulmonary function may be impaired in patients with potentially resectable tumors. This is due to frequent pulmonary comorbidities like chronic obstructive pulmonary disease (COPD) or pulmonary emphysema [4]. Furthermore, the incidence of early-stage NSCLC among the elderly above 65 years, with corresponding comorbidities, and impaired lung function is expected to rise dramatically, at least in the western world [3].

Therefore, those patients are unable to tolerate lobectomy due to compromised cardiopulmonary function. Additionally, due to the widespread use of high-resolution computed tomography (CT), there is an increase in detecting small-sized lung nodules [5]. Hence, the margin of pulmonary resection required to achieve complete resection of the malignancy has been an eagerly debated issue in the last years [2, 6]. Thus, there is a special interest in the selective use of sublobar, parenchyma-sparing resection

techniques like anatomic segmentectomy, subsegmentectomy, or even extended wedge resection in the management of small < 2cm nodules [3, 5, 7]. The comparison of long-term survival rates between lobectomy and sublobar resections is discussed controversially [8, 9]. Retrospective studies are claiming that survival rates after sublobar resection are comparable to that after anatomic resection [10]. The majority of those studies dealing with sublobar resection do not perform guideline-based staging, containing Positron emission tomography CT (PET-CT) and cerebral magnetic resonance imaging (cMRI) [1]. Furthermore, little to no lymphadenectomy is performed intraoperatively. In addition, some studies do not present data on long-term survival rates [7, 10–12].

But NSCLC patients may develop lymph node metastases, lymphangiosis carcinomatosa (L1), hemangiosis carcinomatosa (V1), or even distant metastases independently of the size of the nodules [13–15].

We decided to evaluate the number of pN1 and pN2 lymph node metastases, the number of postoperative nodal upstaging, and the occurrence of L1 in patients undergoing pulmonary resection due to NSCLC with tumors < 2cm at our institution. Furthermore, we compared the long-term survival rates of patients with and without nodal upstaging and L1.

Methods

Between 2012 and 2020 747 patients underwent surgery. We performed anatomical pulmonary resections combined with radical lymphadenectomy, due to NSCLC at our institution. Perioperative data were collected retrospectively from our institutional patients' database.

Inclusion and exclusion criteria

All consecutive patients with tumors $\leq$ 2cm were considered in our analysis. Patients were only included if they underwent a curative radical anatomical R0 resection (lobectomy, bilobectomy, segmentectomy, sleeve resection). We excluded patients after neoadjuvant treatment, UICC 8 > T1b, and stage IV oligometastatic patients.

Diagnosis and treatment

Patients with reasonable suspicion of lung cancer were staged and diagnosed according to European lung cancer guidelines [1, 16]. To exclude distant metastases, diagnosis and staging included high-resolution CT scan, PET-CT scan and cMRI. Mediastinal lymph node involvement was frequently extended and diagnosed by endobronchial ultrasound (EBUS). Pulmonary function testing was obligatory, included measurements of the diffusing capacity for carbon monoxide (DLCO) and the forced expiratory volume in the first second (FEV1). All patients were discussed in the multi-disciplinary team (MDT). The surgical approach for anatomic resection was uniportal video-assisted thoracic surgery (VATS). Surgery was performed by experienced senior surgeons only. We applied the same algorithm for the radical lymphadenectomy in all patients. Including the dissection of the hilar- (station 10), the

interlobar- (station 11) and the (lobar- 12) as pN1 nodes. The segmental (station 13) and the subsegmental lymph nodes (station 14) were mostly left in the specimen. The lymph node dissection of the pN2 lymph nodes was dependent on the side. Lymph node dissection on the left side included the aortic nodes (stations 5 and 6) and the inferior mediastinal lymph nodes (stations: 7, 8, 9). On the right side, we dissected the superior mediastinal lymph nodes (stations 2 and 4) and the inferior mediastinal lymph nodes. The specimens and the resected lymph nodes were examined for lung cancer in the department of pathology.

Statistical analysis

Follow-up data were gathered from the cancer registry, as our department is a registered lung cancer center. The mean follow-up duration was 39.2 ± 24.1 months. One-year, three-year, and five-year survival were measured from the date of surgery to the date of death. Median overall survival was assessed by Kaplan-Meier curves and compared by log-rank test. Furthermore, multinomial logistic regression analysis was performed for the occurrence of lymph node metastases and L1. Differences were described by odds ratio (OR) and 95% CI. Categorical variables were analyzed using Pearson's chi-squared or Fisher exact test. Continuous parameters were expressed as mean $\pm$ standard deviation (SD) of the mean and were analyzed via unpaired Student t-test. A p-value <0.05 was considered statistically significant.

Results

Ethic statement

The investigation was approved by the institutional review board of our university hospital of Cologne and conformed to the principles outlined in the Declaration of Helsinki. Due to its retrospective study, the need for written informed consent was waived.

268 (35.9%) patients had small tumors $< 2\text{cm}$ and were included in our analysis. 27 patients were excluded due to neoadjuvant treatment and five oligometastatic UICC 8 stage IV patients were excluded. In summary 236 (31.6%) patients met all criteria and were included in our analysis.

Baseline characteristics

Baseline characteristics are presented in Table 1. The mean age of our cohort was 64.2 ± 10.2 years. The proportion of male to female patients was 53.8%. All patients in our cohort underwent preoperative pulmonary function with an average of DLCO of $78.9\% \pm 22.5$ and an FEV1 of $2.3\text{l} \pm 0.8$. Of our patients 33.5% were diagnosed with COPD preoperatively, whereas 29.7% of our patients were already diagnosed and treated for second cancer. Patients with tumors $< 2\text{cm}$ smoked 34.3 ± 32.3 packyears. Overall, 37.7% of patients had a tumor in the left lung, and 62.3% of patients in the right lung. The tumor size was measured preoperatively during MDT by radiologists. The tumor size was $1.4 \pm 0.39\text{cm}$ in our cohort. Of our patients, 14% showed a cT1a tumor, and 86% of patients were preoperatively diagnosed with cT1b.

Table 1
Baseline characteristics

Total cohort n=236	
Age (years)	64.2 ± 10.2
Male gender (%)	53.8
DLCO (%)	78.9 ± 22.5
FEV1 (ml)	2.3 ± 0.8
COPD (%)	33.5
Multiple cancers (%)	29.7
Packyears (number)	34.3 ± 32.3
Tumor localization	
left (%)	37.7
right (%)	62.3
Tumorsize (cm)	
cT1a (%)	14.0
cT1b (%)	86.0
Abbreviations: COPD: chronic obstructive pulmonary disease; DLCO: diffusing capacity for carbon monoxide; FEV1: forced expiratory volume in the first second	

Postoperative outcome

Postoperative outcomes are presented in Table 2. The majority of our patients underwent a lobectomy (97.5%). Only six patients (2.5%) of our patients underwent a segmentectomy.

Table 2
Postoperative outcome

Total cohort n=236	
Operation:	
Lobectomy (%)	97.5
Segmentectomy (%)	2.5
Frozen section (%)	39.8
Resected LN per patient (n.)	24.0 ± 12.3
Positive LN per patient (n.)	0.7 ± 2.0
L1 (%)	16.1
L1 without N1 (%)	7.5
V1 (%)	7.6
Hospital stay (days)	6.95 ± 3.5
Histology:	
AC (%)	68.6
SCC (%)	22.0
Atypical carcinoid (%)	3.4
Carcinoid (%)	5.9
Abbreviations: AC: adenocarcinoma; L1: lymphangiosis carcinomatosa; LN: lymph nodes; SCC: squamous cell carcinoma; V1: hemangiosis carcinomatosa	

All patients underwent surgery with radical lymphadenectomy. A total of 24.0 ± 12.3 lymph nodes were dissected and analyzed per patient, and an average of 0.7 ± 2.0 of those was affected. Of these patients, 16.1% showed L1 affection and 7.5% of patients showed L1 without simultaneous lymph node affection. V1 was diagnosed in 7.6% of patients. The majority of resected NSCLC specimens were adenocarcinomas (AC) (68.6%). Squamous cell carcinomas (SCC) were pathologically diagnosed in 22%, whereas 5.9% appeared to be typical carcinoids and a small group of 3.4% of the patients had atypical carcinoids.

Postoperative upstaging

Postoperative upstaging is presented in Table 3. Lymph node involvement was examined by PET-CT scan. Lymph node involvement preoperatively was diagnosed in 11 (4.7%) patients.

Table 3
Postoperative upstaging

Total cohort n=236	Preoperative stage	Postoperative upstage	p-value
Lymphnode involvement n. (%)	11 (4.7)	39 (16.5)	<0.001
N1 n. (%)	8 (3.4)	15 (6.4)	<0.001
N2 n. (%)	3 (1.3)	24 (10.2)	<0.001
UICC 8 Upstaging n. (%)			
IA1 n. (%)	32 (13.6)	28 (11.9)	0.31
IA2 n. (%)	193 (81.8)	158 (66.9)	0.05
IIB n. (%)	8 (3.4)	22 (9.3)	0.003
IIIA n. (%)	3 (1.3)	28 (11.9)	<0.001

8 (3.4) patients were preoperatively diagnosed with N1 and 3 (1.3) patients an N2 involvement. 39 (16.5%) patients were upstaged due to lymph node involvement postoperatively ($p<0.001$). Of those 15 (6.4%) showed an pN1 ($p<0.001$) involvement and 24 (10.2%) of patients showed even an pN2 involvement ($p<0.001$). This resulted in UICC 8 upstaging in 16.5% of patients. 13.6% were diagnosed with stage IA1 preoperatively and 11.9% patients were diagnosed postoperatively. Upstaging was not significant in patients with UICC 8 stage IA1 tumors with a diameter of $<1\text{cm}$ ($p=0.31$). The majority of patients (81.9%) were diagnosed as stage IA2 during MDT, preoperatively. Of patients, 66.9% were confirmed to be in stage IA2 postoperatively ($p=0.05$). 8 patients (3.4%) were diagnosed as stage IIB preoperatively, 22 (9.3%) patients were upstaged after the operation into stage IIB ($p=0.003$). Finally, only 3 patients (1.3%) were confirmed as stage IIIA before surgery in our cohort. After surgery 28 patients (11.9%) were upstaged IIIA ($p<0.001$).

To clarify the occurrence of lymph node involvement in patients with tumors $<2\text{cm}$, we applied multinomial logistic regression analysis for the occurrence of lymph node affection (Table 4). We observed no significant correlation of lymph node involvement with age (OR 0.98, CI 0.93-1.03; $p=0.38$), male gender (OR 1.0, CI 0.4-2.64; $p=0.96$), tumor histology (OR 0.78, CI 0.47-1.29; $p=0.34$), heavy smoking $>30\text{ py}$ (OR 1.38, CI 0.53-3.62; $p=0.51$), or V1 (OR 0.50, CI 0.16-1.57; $p=0.23$). L1 was an independent parameter for the occurrence of lymph node involvement in our cohort (OR 9.71, CI 3.39-27.78; $p<0.001$). Patients with cancer in addition to NSCLC were significantly more likely to have lymph node involvement (OR 4.23, CI 1.06-9.30; $p=0.04$).

Table 4
Multinomial Regression analysis for the occurrence of pN1 and pN2

Variables	OR	95% CI	P-value
Age	0.98	0.93 – 1.03	0.38
Male gender	1.0	0.4 – 2.64	0.96
L1	9.71	3.39 – 27.78	<0.001
V1	0.5	0.16 – 1.57	0.23
Multiple cancers	4.23	1.06 – 9.30	0.04
Heavy smoking > 30 py	1.38	0.53 – 3.62	0.51
Histology	0.78	0.47 – 1.29	0.34
Abbreviations: CI: confidence interval OR: Odds ratio; L1: lymphangiosis carcinomatosa; V1: hemangiosis carcinomatosa			

Overall survival

One-year, three-year, and five-year overall survival rates are presented in Table 5.

Table 5
Overall survival: pN0 compared to pN1+ pN2

	Total cohort n=236	pN0 n=186	pN1+pN2 n=50	p-Value
1 year survival rates (%)	97.4	98.1	94.9	0.26
3 year survival rates (%)	77.9	83.2	60.6	0.01
5 year survival rates (%)	57.8	71.5	38.0	0.02
Overall survival: L0 vs L1				
	Total cohort n=236	L0 n=198	L1 n=38	p-Value
1 year survival rates (%)	97.4	97.5	96.7	0.58
3 year survival rates (%)	77.9	80.0	68.0	0.04
5 year survival rates (%)	57.8	60.8	43.8	0.08
Abbreviations: L0: No lymphangiosis carcinom; L1: lymphangiosis carcinomatosa;				

The one-year survival rate of patients with lymph node involvement was 94.9%, whereas the one-year survival rate of patients without lymph node involvement was 98.1 (p=0.26).

We found that 60.6% of patients with lymph node involvement were still alive after three years compared to 83.2% of patients with pN0 ($p=0.01$). Finally, after five years, 38% of patients with pN1 or pN2 were alive compared to 71.5% of pN0 patients ($p=0.02$). Furthermore, the one-year survival rate of patients with L1 was 96.7% compared to 97.5% with L0. Of the L1 patients, 68.0% were still alive after three years compared to 80.0% with L0 ($p=0.04$). After five years, 43.8% of patients with L1 were alive compared to 60.8% of L0 patients ($p=0.08$).

Survival curves according to the lymph node involvement are shown in Figure 1. We assessed overall survival in the two groups statistically using the Kaplan-Meier method. Patients with pN0 had significantly reduced survival compared to patients without pN1+pN2 (log-rank pN0, pN1+N2 $p=0.002$).

Discussion

The margin of pulmonary resection required to achieve complete resection for NSCLC patients has been a hot debated issue in the last years. Sublobar resections like segmentectomy, subsegmentectomy, and even wedge resection are becoming increasingly popular, which is also reflected in the literature in recent years [7, 12]. In particular, small tumors with a diameter $<2\text{cm}$, are potentially most suitable for sublobar resection [17, 18]. In this study, we demonstrated, that 16.5% of patients were upstaged postoperatively due to lymph node involvement. Furthermore, L1 was diagnosed in 15.1% and V1 in 7.6% of cases.

Both the lymph node involvement and L1 and V1 would probably not have been noticed if our patients had undergone sublobar resection instead of lobectomy with radical lymphadenectomy. Especially the influence of L1 and V1 in NSCLC has not been sufficiently investigated so far.

Preoperative tumor staging according to guidelines with nodule $< 2\text{cm}$: is it mandatory?

According to European, American, and Pan Asian lung cancer guidelines patients with reasonable suspicion of lung cancer should be staged and diagnosed [1, 19, 20]. This staging should include PET-CT and cMRI to exclude distant metastases and lymph node involvement [1, 2]. Some of the studies dealing with surgical resection of $<2\text{cm}$ tumors partially or completely omit tumor staging. Kato et al. and Yoshimoto et al. only performed segmentectomy without conducting PET-CT or cMRI [21–23]. PET-CT is not only performed to diagnose lymph node involvement but to exclude distant metastases as well. Yang et al. performed a query from the surveillance, epidemiology, and end results (SEER) database including $>42,000$ NSCLC patients. They demonstrated, that 1.5% of pT1a patients showed distant metastases in the preoperative PET-CT scans and 8.2% of pT1b patients, respectively [24]. In some studies, PET-CT was performed but cMRI was not conducted as part of tumor staging [12, 25]. However, patients with tumors $<2\text{cm}$ may already have brain metastasis at presentation. Waqar et al. queried data from the National Cancer Data Base (NCDB) and they included 511,050 patients in this analysis. Approximately 100,000 patients showed nodules $< 2\text{cm}$, roughly 6% of those patients were diagnosed with brain metastases by

cMRI at presentation. If these results are considered, it should be clear that guideline-based staging should not be abandoned, even in the case of small tumors <2cm.

Mediastinal lymph node resection with nodule < 2cm: is it mandatory?

Mediastinal lymph node resection might be challenging during VATS sublobar pulmonary resection for small tumors <2cm [22]. Hence, there are studies in which mediastinal lymphadenectomy is almost not performed [7, 21, 26]. Kawaguchi et al. analyzed 149 NSCLC patients after wedge resection. Most patients in their cohort did not undergo lymph node resection during surgery [26]. Liu et al. analyzed 149 patients undergoing segmentectomy. In their analysis, the average number of lymph nodes resected was 3.2 [27]. Kato et al. performed segmentectomy in 144 patients. The authors at least performed a frozen section of the hilar lymph nodes of the corresponding resected segment. Although in 20-30% of cases mediastinal lymph nodes may also occur in the absence of N1 lymph nodes as skip-N2 metastases [28]. On the other side, Okada et al. analyzed 262 patients undergoing sublobar resection with cT1a NSCLC including radical lymphadenectomy. Of these patients, 20 (7%) were found to have lymph node affection (pN1=11 and pN2=9) [29]. Defrachi et al. demonstrated that 6.1% of 968 pT1a and pT1b patients were postoperatively identified with pN2 disease [25]. In our cohort 24.0 ± 12.3 , hilar and mediastinal lymph nodes were resected per patient. We demonstrated that 16.5% of patients were nodal upstaged postoperatively, although > 75% of our patients underwent EBUS before surgery. These results indicate that if adequate lymphadenectomy is not performed, these patients cannot be adequately treated. [1, 16]. Therefore, mediastinal lymphadenectomy is mandatory for tumors < 2cm [18, 30].

Frozen section for the evaluation of L1 involvement during segmentectomy?

Lymphangiosis carcinomatosa (L1) is a well-known but yet an underestimated histopathological factor. In our current study, we showed, that 16.1% of patients were diagnosed with L1 postoperatively. Of the patients 7.5% showed L1 without any lymph node involvement. The influence of L1 in NSCLC patients has not been sufficiently investigated so far. Our study group demonstrated, that L1 independently affects long-term survival [31]. In most tumor entities, L1 leads to a worse prognosis. L1 was an independent predictor in head and neck cancer and vulva carcinoma [32, 33]. In colorectal cancer, however, an L1 in the frozen section leads to a much more radical surgical approach [34]. These results about L1 in colorectal i.e., gastric cancer found their way into the European guidelines [35]. For NSCLC, on the other hand, based on the data available, a more radical approach can only be speculated in the case of an L1 detected intraoperatively in the frozen section.

Conclusion

The present study demonstrates that 16.5% of patients with <2cm tumors were nodal upstaged postoperatively. Furthermore, 15.8% of patients showed lymphangiosis carcinomatosa postoperatively. Therefore, preoperative staging and surgical management of NSCLC <2 cm should always follow current

guidelines. Staging should include CT thorax, PET CT, cMRI in all cases. Reduced staging is not sufficient, as shown in our study. Wedge resection should not be performed in case of NSCLC. Segmental resection should always include radical lymphadenectomy. Following the Gastric cancer guidelines, if a sublobar pulmonary resection is planned for NSCLC, a frozen section should be performed. If L1 is seen, anatomic resection should be considered.

Declarations

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Conflict of interest

None declared.

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References

1. Postmus PE, Kerr KM, Oudkerk M, Senan S, Waller DA, Vansteenkiste J et al (2017) Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of oncology: official journal of the European Society for Medical Oncology* 28:iv1–iv21
2. Howington JA, Blum MG, Chang AC, Balekian AA, Murthy SC (2013) Treatment of stage I and II non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 143:e278S–e313S

3. Shirvani SM, Jiang J, Chang JY, Welsh J, Likhacheva A, Buchholz TA et al (2014) Lobectomy, sublobar resection, and stereotactic ablative radiotherapy for early-stage non-small cell lung cancers in the elderly. *JAMA surgery* 149:1244–1253
4. Licker MJ, Widikker I, Robert J, Frey JG, Spiliopoulos A, Ellenberger C et al (2006) Operative mortality and respiratory complications after lung resection for cancer: impact of chronic obstructive pulmonary disease and time trends. *Ann Thorac Surg* 81:1830–1837
5. Kato H, Oizumi H, Suzuki J, Hamada A, Watarai H, Nakahashi K et al (2017) Thoracoscopic wedge resection and segmentectomy for small-sized pulmonary nodules. *Journal of visualized surgery* 3:66
6. El-Sherif A, Gooding WE, Santos R, Pettiford B, Ferson PF, Fernando HC *Outcomes of sublobar resection versus lobectomy for stage I non-small cell lung cancer: a 13-year analysis*. *The Annals of thoracic surgery* et al (2006) ;82:408-15; discussion 15-6
7. Matsui T, Takahashi Y, Shirai S, Nakanishi K, Nakada T, Sakakura N et al (2021) Comparison of surgical outcomes between thoracoscopic anatomical sublobar resection including and excluding subsegmentectomy. *General thoracic and cardiovascular surgery* 69:850–858
8. Schuchert MJ, Abbas G, Awais O, Pennathur A, Nason KS, Wilson DO et al (2012) Anatomic segmentectomy for the solitary pulmonary nodule and early-stage lung cancer. *Ann Thorac Surg* 93:1780–1785. discussion 86-7.
9. Lutz JA, Seguin-Givelet A, Grigoriu M, Brian E, Girard P, Gossot D (2019) Oncological results of full thoracoscopic major pulmonary resections for clinical Stage I non-small-cell lung cancer. *European journal of cardio-thoracic surgery: official journal of the European Association for Cardio-thoracic Surgery* 55:263–270
10. Chang CC, Yen YT, Lin CY, Chen YY, Huang WL, Tseng YL (2020) Single-port video-assisted thoracoscopic surgery subsegmentectomy: The learning curve and initial outcome. *Asian J Surg* 43:625–632
11. Subramanian M, McMurry T, Meyers BF, Puri V, Kozower BD (2018) Long-Term Results for Clinical Stage IA Lung Cancer: Comparing Lobectomy and Sublobar Resection. *Ann Thorac Surg* 106:375–381
12. Matsuura N, Igai H, Ohsawa F, Yazawa T, Kamiyoshihara M (2021) Safety and feasibility of uniportal video-assisted thoracoscopic uncommon segmentectomy. *Journal of thoracic disease* 13:3001–3009
13. Waqar SN, Samson PP, Robinson CG, Bradley J, Devarakonda S, Du L et al (2018) Non-small-cell Lung Cancer With Brain Metastasis at Presentation. *Clin Lung Cancer* 19:e373–ee79
14. Li J, Liu F, Yu H, Zhao C, Li Z, Wang H (2019) Different distant metastasis patterns based on tumor size could be found in extensive-stage small cell lung cancer patients: a large, population-based SEER study. *PeerJ* 7:e8163
15. Moon Y, Choi SY, Park JK, Lee KY (2020) Risk Factors for Occult Lymph Node Metastasis in Peripheral Non-Small Cell Lung Cancer with Invasive Component Size 3 cm or Less. *World J Surg* 44:1658–1665

16. Planchard D, Popat S, Kerr K, Novello S, Smit EF, Faivre-Finn C et al (2018) Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of oncology: official journal of the European Society for Medical Oncology* 29:iv192–iv237
17. Okada M, Sakamoto T, Nishio W, Uchino K, Tsubota N (2003) Characteristics and prognosis of patients after resection of nonsmall cell lung carcinoma measuring 2 cm or less in greatest dimension. *Cancer* 98:535–541
18. Bai W, Li S (2021) Prognosis of segmentectomy in the treatment of stage IA non-small cell lung cancer. *Oncology letters* 21:74
19. Wu YL, Planchard D, Lu S, Sun H, Yamamoto N, Kim DW et al (2019) Pan-Asian adapted Clinical Practice Guidelines for the management of patients with metastatic non-small-cell lung cancer: a CSCO-ESMO initiative endorsed by JSMO, KSMO, MOS, SSO and TOS. *Annals of oncology: official journal of the European Society for Medical Oncology* 30:171–210
20. Gould MK, Donington J, Lynch WR, Mazzone PJ, Midthun DE, Naidich DP *Evaluation of individuals with pulmonary nodules: when is it lung cancer? Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines*. Chest et al (2013) ;**143**:e93S-e120S
21. Kato H, Oizumi H, Suzuki J, Hamada A, Watarai H, Sadahiro M (2017) Thoracoscopic anatomical lung segmentectomy using 3D computed tomography simulation without tumour markings for non-palpable and non-visualized small lung nodules. *Interact Cardiovasc Thorac Surg* 25:434–441
22. Yoshimoto K, Nomori H, Mori T, Ohba Y, Shiraishi K, Ikeda K (2011) Combined subsegmentectomy: postoperative pulmonary function compared to multiple segmental resection. *J Cardiothorac Surg* 6:17
23. Asamura H, Aokage K, Yotsukura M (2017) *Wedge Resection Versus Anatomic Resection: Extent of Surgical Resection for Stage I and II Lung Cancer*. American Society of Clinical Oncology educational book American Society of Clinical Oncology Annual Meeting ;**37**:426-33
24. Yang J, Peng A, Wang B, Gusdon AM, Sun X, Jiang G et al (2019) The prognostic impact of lymph node metastasis in patients with non-small cell lung cancer and distant organ metastasis. *Clin Exp Metastasis* 36:457–466
25. Defranchi SA, Cassivi SD, Nichols FC, Allen MS, Shen KR, Deschamps C et al (2009) N2 disease in T1 non-small cell lung cancer. *Ann Thorac Surg* 88:924–928
26. Kawaguchi T, Sawabata N, Miura S, Kawai N, Yasukawa M, Tojo T et al (2019) Prognostic impact of underlying lung disease in pulmonary wedge resection for lung cancer. *Int J Clin Oncol* 24:366–374
27. Liu Z, Yang R, Cao H (2020) Near-infrared intraoperative imaging with indocyanine green is beneficial in video-assisted thoracoscopic segmentectomy for patients with chronic lung diseases: a retrospective single-center propensity-score matched analysis. *J Cardiothorac Surg* 15:303
28. Schlachtenberger G, Doerr F, Menghesha H, Heldwein MB, Hagmeyer L, Michel M et al (2020) Postoperative long-term survival of non-small cell lung cancer patients with skip-N2 metastases. *Surg Oncol* 38:101505

29. Okada M, Koike T, Higashiyama M, Yamato Y, Kodama K, Tsubota N (2006) Radical sublobar resection for small-sized non-small cell lung cancer: a multicenter study. *J Thorac Cardiovasc Surg* 132:769–775
30. Kim DK (2017) Mediastinal lymph node resection in stage IA non-small cell lung cancer with small nodule: is it mandatory? *Journal of thoracic disease* 9:2276–2278
31. Heldwein MB, Doerr F, Schlachtenberger G, Menghesha H, Kuhn EW, Scheel AH et al (2021) Lymphangiosis carcinomatosa independently affects long-term survival of Non-Small Cell Lung Cancer patients. *Surg Oncol* 37:101611
32. Ettl T, El-Gindi A, Hautmann M, Gosau M, Weber F, Rohrmeier C et al (2016) Positive frozen section margins predict local recurrence in R0-resected squamous cell carcinoma of the head and neck. *Oral Oncol* 55:17–23
33. Ayhan A, Velipasaoglu M, Salman MC, Guven S, Gultekin M, Bayraktar O (2008) Prognostic factors for recurrence and survival in primary vulvar squamous cell cancer. *Acta Obstet Gynecol Scand* 87:1143–1149
34. Argilés G, Tabernero J, Labianca R, Hochhauser D, Salazar R, Iveson T et al (2020) Localised colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of oncology: official journal of the European Society for Medical Oncology* 31:1291–1305
35. Smyth EC, Verheij M, Allum W, Cunningham D, Cervantes A, Arnold D (2016) Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of oncology: official journal of the European Society for Medical Oncology* 27:v38–v49

Figures

Figure 1

Kaplan-Meier plot to overall survival months after surgery, censors indicating the death of a particular patient.