Original Article

Tumor stage, squamous histology and male sex predict positive resection margins in non-small cell lung cancer patients undergoing anatomical resection—a retrospective study from a high-volume thoracic surgery unit

Mircea Gabriel Stoleriu[1,2], Konrad Steinestel[3,4], Matteo Grimmer[3,4], Lena-Maria Löwer-Kiem[3,4], Moritz Witzenhausen[4,5], Jan Sölter[4,5], Sebastian Brill[4,5#], Annette Arndt[3,4#]

[1]Division for Thoracic Surgery Munich, Ludwig-Maximilians-University of Munich (LMU) and Asklepios Lung Clinic Munich-Gauting, Gauting, Germany; [2]Institute for Lung Health and Immunity and Comprehensive Pneumology Center with the CPC-M bioArchive, Helmholtz Center Munich, German Lung Research Center (DZL), Munich, Germany; [3]Institute of Pathology and Molecular Pathology, Bundeswehrkrankenhaus Ulm, Ulm, Germany; [4]Interdisciplinary Lung Cancer Center, Bundeswehrkrankenhaus Ulm, Ulm, Germany; [5]Department of Visceral and Thoracic Surgery, Bundeswehrkrankenhaus Ulm, Ulm, Germany

Contributions: (I) Conception and design: K Steinestel, A Arndt, S Brill, M Grimmer, MG Stoleriu; (II) Administrative support: K Steinestel, A Arndt, S Brill, M Grimmer, MG Stoleriu; (III) Provision of study materials or patients: K Steinestel, A Arndt, S Brill, M Grimmer; (IV) Collection and assembly of data: M Grimmer, LM Löwer-Kiem; (V) Data analysis and interpretation: MG Stoleriu, M Grimmer, K Steinestel, LM Löwer-Kiem; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Mircea Gabriel Stoleriu, MD, PhD. Division for Thoracic Surgery Munich, Ludwig-Maximilians-University of Munich (LMU) and Asklepios Lung Clinic Munich-Gauting, Robert-Koch-Allee 2, 82131 Gauting, Germany; Marchioninistr. 15, 81377 Munich, Germany; Institute for Lung Health and Immunity and Comprehensive Pneumology Center with the CPC-M bioArchive, Helmholtz Center Munich, Member of the German Lung Research Center (DZL), 81377 Munich, Germany. Email: gabriel.stoleriu@helmholtz-munich.de.

Background: The aim of the study is to identify perioperative predictors of positive resection margins in patients with non-small cell lung cancer (NSCLC) undergoing anatomical resections to improve perioperative risk stratification and ultimately, patient care.

Methods: All patients with primary NSCLC admitted at the Bundeswehrkrankenhaus (Armed Forces Hospital) Ulm for anatomical resections between 01.01.2019 and 31.12.2024 were retrospectively included into the study. Based on resection margins, patients were categorized in two groups: Group 1 (with negative resection margins, R_0) and Group 2 (with tumor involvement at the level of resection margins/positive resection margins at bronchial level, or adjacent structures, R_+). A comparative analysis of patients' demographics, topographical, pathological tumor characteristics and surgical approach was performed by Mann-Whitney U test, Chi-squared test, and Fisher test. A logistic regression model was performed to assess the independent predictive value of the selected variables.

Results: Of 232 NSCLC patients [median age 69.00 (63.00, 75.00) years, 22% aged >75 years, and 2.2% with an Eastern Cooperative Oncology Group (ECOG) >2] who underwent anatomical resections, 107 (46.1%) female patients were included. While R_0 resections were observed in 214 (92.2%) patients, 18 (7.8%) patients had positive resection margins on histopathological evaluation. R_+ was more frequently reported in male patients (83.3% *vs.* 16.7%, P=0.009), large tumors (>50 mm/> pT_2, P<0.001), as well as in resection specimens with lymph node metastasis ($pN_{1–2}$, P<0.001), lymphangiosis (L_1, P=0.006), vascular invasion (V_1, P=0.008) and squamous histology (P<0.001). No significant differences were observed between groups in terms of lobar distribution, tumor mutational status, regression grade upon neoadjuvant therapy, as well as surgical approach (open/minimally invasive). Multivariable analysis revealed male sex (P=0.042), squamous histology (P=0.02), and pT >2 (P<0.001) as independent predictors for R_+. These predictors increased the risk of resection margin positivity by 4.1-, 3.7-, and 8.5-fold, respectively.

Conclusions: T stage (pT >2), squamous histology and male sex predict positive resection margins in lung cancer patients undergoing anatomical resections. Consideration of these parameters could help in patients' stratification and care and thus, should be further evaluated in larger patients' cohorts.

Keywords: Non-small cell lung cancer (NSCLC); risk stratification; lung cancer; positive resection margins

Submitted Feb 28, 2026. Accepted for publication Apr 13, 2026. Published online May 27, 2026.
doi: 10.21037/jtd-2026-0511
View this article at: https://dx.doi.org/10.21037/jtd-2026-0511

Introduction

Background

Complete surgical resection is essential in oncological surgery, in particular in the treatment of lung cancer (1,2), the leading cause of cancer-related mortality worldwide (3). A microscopically margin-negative resection (R_0) in patients with non-small cell lung cancer (NSCLC) is a prerequisite for an accurate treatment reflecting surgical quality and expertise (2,4-6).

Clinical evidence supporting the multimodal treatment of lung cancer indicates that achieving R_0 resection significantly reduces local relapse rates, and consecutively leads to an improved outcome and survival (7-9).

On the other side, microscopically (R_1) and macroscopically (R_2) incomplete resections are associated with a higher risk of recurrence [5-year disease-free survival (DFS) rates 43.2% for R_0 *vs.* 21.1% for $R_{1/2}$] (10) and significantly decreased survival [5-year overall survival (OS) ranging between 10% and 42% for R_0 patients *vs.* 14% in R_1 patients] (11-13). Given the established association between margin positivity and lymph node involvement, recent studies have increasingly examined the risk of uncertain resection attributable to incomplete tumor removal and insufficient lymphadenectomy (10,14-16).

Therefore, the International Association for the Study of Lung Cancer (IASLC) proposed a new definition for uncertain surgical resection (R_{un}) and extensively discussed on its potential clinical impact, particularly affecting treatment planning and decision-making based on tumor-node-metastasis (TNM) classification (1,17,18).

Rationale and knowledge gap

To improve treatment quality and prognosis, many studies already addressed a variety of perioperative factors that could be associated with the presence of residual tumor or questionable lymphadenectomy. Specifically, older age (>75 years), black race, higher Charlson comorbidity index (CCI >3), clinical TNM (cTNM) descriptors (e.g., tumor size, localization, lymph node involvement), as well as surgical extent (e.g., pneumonectomy) were found to be associated with a higher rate of R_1 or R_2 resections (19-21).

These studies provide substantial clinical evidence on TNM descriptors and surgical approach; however, few reports sufficiently address the complete morpho-molecular patterns of lung cancer, leaving further relevant aspects such as growth pattern and mutational status insufficiently

Highlight box

Key findings
- Tumor stage (pT >2), squamous histology and male sex predict positive resection margins in lung cancer patients undergoing anatomical resections.

What is known and what is new?
- Achieving R_0 upon lung cancer surgery significantly reduces local relapse rates, and consecutively leads to an improved outcome and survival. Despite substantial clinical evidence, the relationship between tumor histology including growth pattern and mutational status and resection margin completeness in lung cancer patients is still insufficiently characterized.
- We specifically addressed the relationship between perioperative clinical demographics, tumor topography, pathological tumor-node-metastasis descriptors, as well as histological subtypes, morpho-molecular pattern of the resected tumor, and likelihood of positive resection margins as predictors of tumor recurrence and survival.

What is the implication, and what should change now?
- Assessment of tumor stage (pT >2), squamous histology and male sex may guide risk stratification, refine perioperative care, and enhance patient outcomes.
- A frequent use of frozen section examination by suspected adjacent tumor involvement could possibly lead to an extended resection and decrease the R_+ rate.

characterized.

Objectives

The aim of the present study is to perform a comprehensive analysis of perioperative clinical and histopathological parameters that could influence the certainty of the resection margins and ultimately influence the curative intent of the treatment. We specifically addressed the potential relationship between perioperative clinical demographics, tumor topography, pathological TNM (pTNM) descriptors, as well as histological subtypes, growth pattern, mutational status and likelihood of positive resection margins as negative predictors of tumor recurrence and survival. These findings may guide risk stratification, refine perioperative care, and enhance patient outcomes. The present work was designed as a retrospective study rigorously conducted in a high-volume Thoracic Surgery Unit. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-2026-0511/rc).

Methods

Study population

This monocentric retrospective cohort study was performed after approval by the Ethics Committee of University of Ulm, Germany (No. 112/23 and No. 293/24) and individual consent for this retrospective analysis was waived. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments.

All patients with primary NSCLC admitted for anatomical resections of primary tumors (segmentectomy, lobectomy, bilobectomy, or pneumonectomy) at the Bundeswehrkrankenhaus (Armed Forces Hospital) Ulm, Germany between 01.01.2019 and 31.12.2024 were included into the study. Patients who underwent anatomical resection for lung metastases (n=20) and with indeterminate resection margins (R_x, n=7) of the histological specimen or who were lost to follow-up (n=1) were excluded (*Figure 1*).

Data assessments/sources

Clinical follow-up (data during in hospital stay following thoracic surgery) was obtained from hospital medical reports included patients' demographics [age, sex, Eastern Cooperative Oncology Group (ECOG) performance status], lung function tests [forced expiratory volume in 1 second (FEV_1) and diffusing capacity of the lung for carbon monoxide (DLCO)], and histological parameters [TNM and World Health Organization (WHO) classification of histological subtypes]. Primary lung tumors were analyzed using the 8th edition of the TNM staging system [2017] (22,23). Histopathological specimens were based on the WHO classification of lung tumors [2015] (24,25). For lung adenocarcinoma or the adenocarcinoma component of adenosquamous carcinoma, the following growth patterns were discerned: low grade/well-differentiated (G1): lepidic with less than 30% high-grade pattern; intermediate grade/moderately-differentiated (G2): acinar or papillary with less than 30% high-grade pattern; and high-grade/poorly-differentiated (G3): solid or micropapillary pattern (26,27). For mixed adeno(squamous) carcinoma including more than two growth patterns, the frequency of each individual and dominant component was separately assessed. In addition, a comprehensive next-generation sequencing approach including assessment of mutations in epidermal growth factor receptor (*EGFR*), Kirsten rat sarcoma viral oncogene homolog (*KRAS*), v-Raf murine sarcoma viral oncogene homolog B1 (*BRAF*), serine/threonine kinase 11 (*STK11*), and Kelch-like ECH-associated protein 1 (*KEAP1*) was performed (Illumina TSO500 NGS panel on an Illumina 550 NextSeq, San Diego, CA, USA). Alterations/translocations in anaplastic lymphoma kinase (*ALK*), ROS proto-oncogene 1 receptor tyrosine kinase (*ROS1*), and RET/rearranged during transfection were assessed by immunohistochemistry (IHC) and/or fluorescence in situ hybridization (FISH) following routine protocols (26,27). In patients undergoing neoadjuvant or perioperative chemoimmunotherapy, a tumor regression grade was applied on the resection specimen according to the IASLC including major pathological response (MPR; ≤10% vital tumor cells) or complete pathological response (cPR; no vital tumor cells) (28,29). Data on patients' treatment included surgical approach [open or minimally invasive by video-assisted thoracic surgery (VATS) or robotic-assisted thoracic surgery (RATS)] and extent of anatomical resection (segmentectomy, lobectomy, bilobectomy, and pneumonectomy).

Outcomes and endpoints

The primary outcome of the study was the assessment of the resection margins status upon surgery. Margins completeness refers to microscopically proven negative

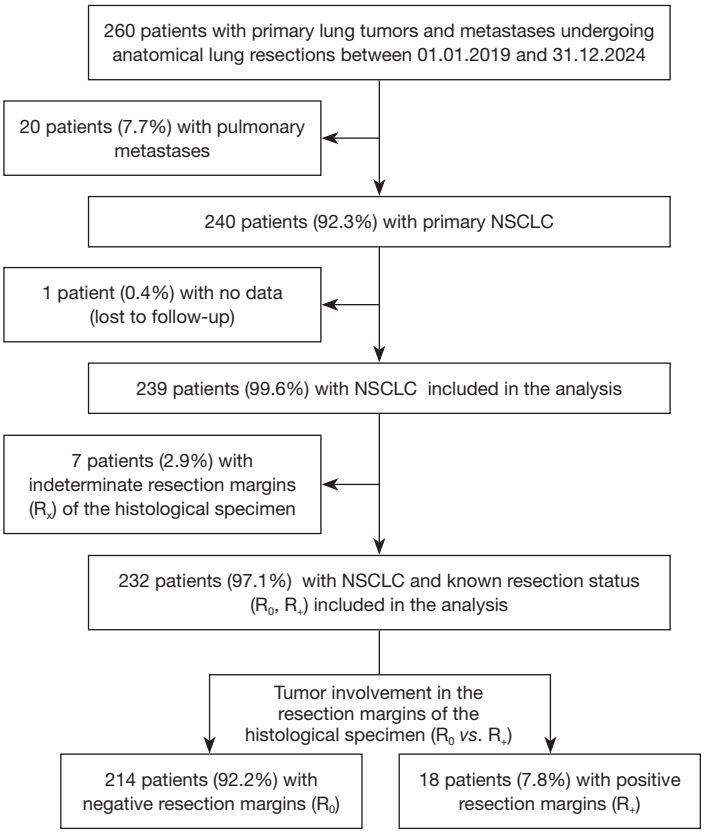

Figure 1 Study flow chart illustrating patient enrollment at study entry. Of 260 patients with primary and secondary malignancies of the lung undergoing anatomical resections between 01.01.2019 and 31.12.2024, 20 (7.7%) patients experiencing lung metastases of non-pulmonary tumors, 1 (0.4%) patient lost to follow-up and 7 (2.9%) patients with indeterminate resection status (R_x) were excluded from the study. Accordingly, 240 patients (92.3%) with primary NSCLC were included into the study. Based on tumor involvement of the resection margins, patients were categorized into two groups: Group 1 with negative resection margins (R_0, 214 patients, 92.2%) and Group 2 including patients with positive resection margins (R_+, 18 patients, 7.8%). NSCLC, non-small cell lung cancer.

margins (R_0), while incomplete resections (R_+) discriminate a microscopic (R_1) and a macroscopic (R_2) involvement. Following the aim of the study, R_+ was defined in accordance to the IASLC proposal as tumor involvement at the margin of the resected bronchus, vessels (artery, vein), central or peripheral parenchyma, parietal pleura/chest wall, as well as lymph node involvement at the highest mediastinal station (15). Accordingly, patients were categorized in two groups: Group 1 (with negative resection margins, R_0) and Group 2 (with tumor involvement at the level of resection margins/positive resection margins, R_+). The primary endpoint was defined as R_+. The correlation between abovementioned clinical parameters and the resection margin status (R_0 *vs.* R_+) was performed in order to identify potential risk factors for positive resection margins.

Statistical analysis

Continuous variables are assessed as median and quartiles (1st quartile, 3rd quartile). Comparisons between groups were performed using the Mann-Whitney U test for continuous variables [age, pack years (PY), lung function parameters, tumor size] and by Chi-squared test or Fisher's exact test (if appropriate) for categorical variables (sex, smoking history, ECOG, tumor localization, TNM, Union for International Cancer Control (UICC), histological growth pattern, mutational status, surgical approach). Multivariable analysis was performed by binary logistic regression analysis with three selection methods [enter, forward likelihood ratio (LR) and backward LR]. To minimize potential confounding bias, the discrimination ability of the logistic regression model was investigated by receiver operating characteristic (ROC)

Table 1 Demographic characteristics of study population

Patient demographics at study entry	Group 1 (R_0, n=214)	Group 2 (R_+, n=18)	P value
Age (years)	69.00 (62.00, 75.00)	68.00 (63.75, 75.25)	0.95
>75	47/214 (22.0)	4/18 (22.2)	0.98
Sex			0.009*
Female	104/214 (48.6)	3/18 (16.7)	
Male	110/214 (51.4)	15/18 (83.3)	
Smoking history			
Never smokers	41/213 (19.2)	2/18 (11.1)	0.39
Active smokers	65/213 (30.5)	6/18 (33.3)	0.80
Ex-smokers >1 year	107/213 (50.2)	10/18 (55.6)	0.67
PY	35.00 (20.00, 50.00)	50.00 (31.25, 67.50)	0.02*
≥30	109/167 (65.3)	15/16 (93.8)	0.02*
ECOG			
ECOG 0	111/192 (57.8)	5/16 (31.3)	0.040*
ECOG 1	65/192 (33.9)	10/16 (62.5)	0.02*
ECOG 2	11/192 (5.7)	1/16 (6.3)	0.93
ECOG 3	5/192 (2.6)	0/16 (0.0)	>0.99†
ECOG >1	16/192 (8.3)	1/16 (6.3)	0.77
Lung function parameters			
FEV_1 (% predicted)	82.00 (69.00, 97.00)	63.50 (51.00, 76.50)	0.001*
DLCO (% predicted)	77.00 (66.00, 92.00)	65.00 (53.50, 81.50)	0.10

Demographic characteristics of lung cancer patients undergoing anatomical resections, stratified by resection margins. Median and quartiles (1st, 3rd) or absolute values with relative frequency (n/total, %) were presented. Group comparisons (R_0 *vs.* R_+) were performed using the Mann-Whitney U test for continuous variables (e.g., age, PY, FEV_1, DLCO) and Chi-squared or Fisher's exact test (if appropriate) for categorical variables. Missing data were found when assessing smoking history (one patient in R_0 group) and ECOG status (n=22 patients in R_0 group and n=2 patients in R_1 group). †, Fisher's exact test. *, P<0.05. DLCO, diffusing capacity of the lung for carbon monoxide; ECOG, Eastern Cooperative Oncology Group; FEV_1, forced expiratory volume in 1 second; PY, pack years.

curves and decision tree analysis.

An algorithm for clinical setting was developed using the independent predictors identified in the multivariable analysis, using decision tree analysis [classification and regression trees (CRT) algorithm]. The internal validation of the cohort was performed using a 5- and 10-fold cross-validation. Odds ratios (ORs) with 95% confidence intervals (CIs) were assessed to show the independent value of the selected parameters in predicting resection margins positivity. Missing data were accordingly reported, while any records with essential missing variables were excluded from the analysis (*Tables 1-6*). All analyses were performed using the software SPSS (version 26, IBM, Armonk, NY, USA). P values <0.05 were considered as statistically significant.

Results

Study population

Of 260 patients with primary NSCLC or pulmonary metastases admitted for anatomical resections, 20 patients with pulmonary metastases, 1 patient who was lost to follow-up and 7 patients with indeterminate resection status (R_x) were excluded from the study. Accordingly, 232 patients were further characterized based on clinical demographics, tumor localization, TNM, and WHO histological classification of primary tumor, resection margins, mutational status and surgical approach. The patient selection process is depicted in *Figure 1*.

Following the primary outcome of the study, 214 (92.2%)

Table 2 Tumor characteristics of study population

Tumor characteristics	Group 1 (R_0, n=214)	Group 2 (R_+, n=18)	P value
Tumor side			0.65
Left	95/214 (44.4)	7/18 (38.9)	
Right	119/214 (55.6)	11/18 (61.1)	
Tumor localization			
Left upper lobe	42/214 (19.6)	2/18 (11.1)	0.38
Left lower lobe	45/214 (21.0)	3/18 (16.7)	0.66
Left combined/centrally located	8/214 (3.7)	2/18 (11.1)	0.14
Right upper lobe	57/214 (26.6)	6/18 (33.3)	0.54
Right middle lobe	11/214 (5.1)	–	–
Right lower lobe	41/214 (19.2)	3/18 (16.7)	0.80
Right combined/centrally located	10/214 (4.7)	2/18 (11.1)	0.24
Tumor diameter (mm)	22.00 (14.00, 38.00)	66.00 (40.50, 92.25)	<0.001*
>30	72/214 (33.6)	16/18 (88.9)	<0.001*
>50	30/214 (14.0)	12/18 (66.7)	<0.001*
TNM7 classification			
pT_{is}	2/214 (0.9)	0/18 (0.0)	>0.99†
pT_0	10/214 (4.7)	0/18 (0.0)	0.35
pT_1	105/214 (49.1)	1/18 (5.6)	<0.001*
pT_2	52/214 (24.3)	4/18 (22.2)	0.84
pT_3	28/214 (13.1)	4/18 (22.2)	0.28
pT_4	17/214 (7.9)	9/18 (50.0)	<0.001*
> pT_1	97/214 (45.3)	17/18 (94.4)	<0.001*
> pT_2	45/214 (21.0)	13/18 (72.2)	<0.001*
Lymph node involvement			
pN_0	167/213 (78.4)	6/18 (33.3)	<0.001*
pN_1	18/213 (8.5)	6/18 (33.3)	<0.001*
pN_2	28/213 (13.1)	5/18 (27.8)	0.09
pN_3	0/213 (0.0)	1/18 (5.6)	0.08†
Lymphangiosis			0.006*
L_0	120/176 (68.2)	5/15 (33.3)	
L_1	56/176 (31.8)	10/15 (66.7)	
Vascular invasion			0.008*
V_0	147/167 (88.0)	8/13 (61.5)	
V_1	20/167 (12.0)	5/13 (38.5)	

Table 2 (*continued*)

Table 2 (*continued*)

Tumor characteristics	Group 1 (R_0, n=214)	Group 2 (R_+, n=18)	P value
UICC stage			
0	2/214 (0.9)	0/18 (0.0)	>0.99†
I	111/214 (51.9)	1/18 (5.6)	<0.001*
II	41/214 (19.2)	2/18 (11.1)	0.40
III	47/214 (22.0)	9/18 (50.0)	0.008*
IV	13/214 (6.1)	6/18 (33.3)	<0.001*
UICC >1	101/214 (47.2)	17/18 (94.4)	<0.001*
UICC >2	60/214 (28.0)	15/18 (83.3)	<0.001*

Pathological characteristics of resected lung cancer specimens, stratified by resection margins positivity (R_0 *vs*. R_+). Median and quartiles (1^{st}, 3^{rd}) or absolute values with relative frequency (n/total, %) were presented. Group comparisons (R_0 *vs*. R_+) were performed using the Mann-Whitney U-test for continuous variables (e.g. tumor diameter) and Chi-squared or Fisher's exact test (if appropriate) for categorical variables. Missing data were found when assessing pN status (one patient in R_0 group), lymphangiosis (n=38 patients in R_0 group and n=3 patients in R_1 group), and vascular invasion (n=47 patients in R_0 group and n=5 patients in R_1 group). †, Fisher's exact test. *, P<0.05. pTNM: TNM8 staging system applied for intraoperative histopathological specimens (19,22); UICC: tumor staging according to the UICC (22,23). pTNM, pathological tumor-node-metastasis; TNM, tumor-node-metastasis; UICC, Union for International Cancer Control.

patients had negative resection margins (Group 1), while 18 (7.8%) patients had positive resection margins on histopathological evaluation (Group 2).

Univariate analysis

Patient demographics are presented in *Table 1*. Missing data were found when assessing smoking history (one patient in R_0 group) and ECOG status (22 patients in R_0 group and 2 patients in R_1 group). The median age of the whole patient's cohort was 69.00 (63.00, 75.00) years with 22.0% of patients being aged 75 years or older. No significant age differences were observed between groups. Of 232 patients, 107 (46.1%) patients were female. Positive resection margins were more frequent in male patients (R_0 51.4% *vs.* R_+ 83.3%, P=0.009).

While smoking history (active, never, ex) was not significantly correlated with R_+, smoking intensity (quantified in PY) was significantly associated with the resection margins completeness. In particular, a smoking intensity >30 PY was significantly associated with R_+. When considering sex distribution, more never smokers among female patients [27/106 (25.5%) *vs.* 16/125 (12.8%), P=0.01], and more active smokers among male patients [25/106 (23.6%) *vs.* 46/125 (36.8%), P=0.03] were observed. In addition, male patients smoked significantly more than female patients [20.00 (0.00, 40.00) *vs.* 40.00 (20.00, 50.00) PY, P<0.001].

Patients with reduced preoperative lung function parameters were more likely to present with positive resection margins [FEV_1; R_0 82.00 (69.00, 97.00) *vs.* R_+ 63.50 (51.00, 76.50) % predicted, P=0.001; *Table 1*]. One hundred and ninety-one (82.3%) patients were admitted with low ECOG grades (0 and 1), while only 17 (7.3%) patients presented with an ECOG >1 with no significant differences with respect to resection status (R_0 8.3% *vs.* R_+ 6.3%, P=0.77; *Table 1*). Tumors were homogenously distributed in both lungs and no specific localization was particularly associated with R_+ status. Tumors with pT >1 (pT_{2-4}, 45.3% *vs.* 94.4%, P<0.001), lymph node metastasis (pN_+, 21.6% *vs.* 66.7%, P<0.001), lymphangiosis (L_1, 31.8% *vs.* 66.7%, P=0.006) and vascular invasion (V_1, 12.0% *vs.* 38.5%, P=0.008) were significantly more frequent in the R_+ group. Accordingly, an UICC stage >1 was significantly associated with R_+ status (47.2% *vs.* 94.4%, P<0.001). The tumor characteristics including localization, size, TNM and UICC status are summarized in *Table 2*.

Adenocarcinoma histology was more frequent among R_0 resections (67.8% *vs.* 33.3%, P=0.003), while squamous histology was more frequently reported in the R_+ group (19.2% *vs.* 61.1%, P<0.001). Among patients with adenocarcinoma histology more never smokers were found in comparison to the patients presenting squamous carcinoma histology [34/151 (22.5%) *vs.* 1/51 (2.0%),

Table 3 Histological characteristics of resected tumors

Histological characteristics of resected tumors	Group 1 (R_0, n=214)	Group 2 (R_+, n=18)	P value
Histology of the primary tumor (WHO)			
Adenocarcinoma	145/214 (67.8)	6/18 (33.3)	0.003*
Squamous cell carcinoma	41/214 (19.2)	11/18 (61.1)	<0.001*
Carcinoid	18/214 (8.4)	0/18 (0.0)	0.20
Adenosquamous carcinoma	6/214 (2.8)	1/18 (5.6)	0.51
Large cell carcinoma	5/214 (2.3)	0/18 (0.0)	>0.99†
Dominant growth pattern in adenocarcinoma			
Lepidic	36/151 (23.8)	0/7 (0.0)	0.14
Acinar	62/151 (41.1)	4/7 (57.1)	0.45†
Papillary	13/151 (8.6)	2/7 (28.6)	0.08
Micropapillary	2/151 (1.3)	1/7 (14.3)	0.13†
Solid	34/151 (22.5)	0/7 (0.0)	0.16
Mucinous	4/151 (2.6)	0/7 (0.0)	>0.99†
Mutational status			
None	117/214 (54.7)	14/18 (77.8)	0.058
EGFR	26/214 (12.1)	2/18 (11.1)	0.90
KRAS G12C	28/214 (13.1)	0/18 (0.0)	0.10
KRAS (other)	26/214 (12.1)	1/18 (5.6)	0.40
BRAF	4/214 (1.9)	0/18 (0.0)	>0.99†
ALK	3/214 (1.4)	0/18 (0.0)	>0.99†
ROS	2/214 (0.9)	1/18 (5.6)	0.22†
STK11	9/214 (4.2)	0/18 (0.0)	0.38
KEAP1	3/214 (1.4)	0/18 (0.0)	>0.99†
RET	2/214 (0.9)	0/21 (0.0)	>0.99†

Histological characteristics of resected tumors in lung cancer patients undergoing anatomical resections, stratified by resection margins positivity (R_0 *vs*. R_+). For all adenocarcinoma specimens, the frequency of the dominant component in tumors with mixed growth pattern was assessed. Absolute values with relative frequency (n/total, %) were presented. Group comparisons (R_0 *vs*. R_+) were performed using the Chi-squared or Fisher's exact test (if appropriate). †, Fisher's exact test. *, P<0.05. *ALK*, anaplastic lymphoma kinase; *BRAF*, v-Raf murine sarcoma viral oncogene homolog B1; *EGFR*, epidermal growth factor receptor; *KEAP1*, Kelch-like ECH-associated protein 1; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; *RET*, rearranged during transfection; *ROS*, ROS proto-oncogene 1 receptor tyrosine kinase; *STK11*, serine/threonine kinase 11; WHO, World Health Organization.

P=0.001]. In contrast, patients with squamous histology were more frequently active smokers [43/151 (28.5%) *vs.* 21/51 (41.2%), P=0.09] and presented a significantly increased nicotine consumption, when compared to adenocarcinoma patients [30.00 (1.25, 45.00) *vs.* 42.50 (29.25, 60.00) PY, P<0.001]. When analyzing each individual (not the dominant) component of the growth pattern in mixed adeno(squamous) carcinoma, papillary tumors were more frequent in the R_+ group (25.2% *vs.* 71.4%, P=0.007). When analyzing the dominant component of the growth pattern in mixed adeno(squamous) carcinoma, no significant differences were reported between groups (*Table 3*). While no specific driver mutation was associated with R status, the absence of such genetic alterations showed borderline

Table 4 Technical aspects of the surgical approach

Features of the surgical approach	Group 1 (R_0, n=214)	Group 2 (R_+, n=18)	P value
Surgical approach			
Open (thoracotomy)	126/214 (58.9)	14/18 (77.8)	0.12
VATS	29/214 (13.6)	1/18 (5.6)	0.33
RATS	31/214 (14.5)	3/18 (16.7)	0.80
VATS conversion to open	22/214 (10.3)	0/18 (0.0)	0.15
RATS conversion to open	6/214 (2.8)	0/18 (0.0)	0.47
Resection extent			
Segmentectomy	24/214 (11.2)	2/18 (11.1)	0.99
Lobectomy or bilobectomy	176/214 (82.2)	12/18 (66.7)	0.11
Pneumonectomy	14/214 (6.5)	4/18 (22.2)	0.02*
Lymphadenectomy	211/214 (98.6)	16/18 (88.9)	0.050†
Neoadjuvant treatment			0.52
No	192/214 (89.7)	17/18 (94.4)	
Yes	22/214 (10.3)	1/18 (5.6)	
Tumor regression grade			
No vital tumor cells (CPR, IASLC)	10/22 (45.5)	0/1 (0.0)	>0.99†
Vital tumor cells ≤10% (MPR, IASLC)	3/22 (13.6)	0/1 (0.0)	>0.99†
Vital tumor cells >10%	9/22 (40.9)	1/1 (100.0)	0.44†

Technical aspects of the surgical approach in lung cancer patients undergoing anatomical resections, stratified by resection margins positivity (R_0 *vs*. R_+). Absolute values with relative frequency (n/total, %) were presented. Group comparisons (R_0 *vs*. R_+) were performed using the Chi-squared or Fisher's exact test (if appropriate). †, Fisher's exact test. *, P<0.05. CPR, complete pathological response; IASLC, International Association for the Study of Lung Cancer; MPR, moderate pathological response; RATS, robotic-assisted thoracic surgery; VATS, video-assisted thoracic surgery.

significant association with positive resection margins (54.7% *vs.* 77.8%, P=0.058). The histopathological and molecular characteristics of resected tumors are summarized in *Table 3*.

Open surgery was more frequent in patients group experiencing incomplete resections (58.9% *vs.* 77.8%, P=0.12; *Table 4*). No significant differences were reported between patients undergoing thoracoscopic (VATS, 13.6% *vs.* 5.6%, P=0.33) or robotic (RATS, 14.5% *vs.* 16.7%, P=0.80) minimally invasive procedures. In patients with large tumors, who underwent pneumonectomies, a significantly higher rate of incomplete resections was reported (6.5% *vs.* 22.2%, P=0.02; *Table 4*). Specifically, patients undergoing pneumonectomies experienced more frequently tumors >5 cm (> pT_2, 61.1% *vs.* 23.0%, P<0.001 or UICC >2, 88.9% *vs.* 28.5%, P<0.001) and presented more frequently a lymph node involvement (pN_+ 66.7% *vs.* 22.7%, P<0.001). In addition, squamous cell carcinoma histology appeared significantly more frequent in specimens upon pneumonectomy than other anatomical resections (55.6% *vs.* 20.3%, P=0.01). Of 23 patients undergoing neoadjuvant treatment, one patient experienced an incomplete R_+ resection and present >10% viable tumor cells in the histological specimen. Technical aspects of the surgical approach are summarized in *Table 4*.

Combining all parameters presented above, a detailed description including clinical demographics, lung function parameters, morpho-molecular pattern of the tumor, as well as surgical approach was assessed in the R_+ group (n=18 patients, *Table 5*). Of note, a descriptive analysis did not reveal a significant difference in the distribution of bronchovascular and mediastinal positive margins between

Table 5 Clinical description of patients with R_+ following lung cancer resection

Patient No.	R status	Preop. demographics			Preop. lung function		Histology (WHO), pTNM8, morpho-molecular pattern							Mutations	Surgical approach							Surgery time (min)
	Localization R_+	Age (years)	Sex	ECOG	FEV_1 (%)	FEV_1 (L)	Histology	LUAD diff.	pT	pN	cM	L	V		Anatomical extent	Open approach	Side	Upper lobe	Middle lobe	Lower lobe	Central/combined	
Patient 1	Par	78	Male	2	46	1.32	LUAD	Pap, sol, ac, lep	pT_4	pN_0	cM_0	L_0	V_0	*EGFR*	Segm	Yes	Left	Yes	No	No	No	238
Patient 2	Par	60	Male		31	0.96	LUAD	Ac	pT_1	pN_0	cM_0	L_0	V_0	0	Segm	No	Right	Yes	No	No	No	76
Patient 3	Par	64	Male	1	58	2.33	SQCA	–	pT_4	pN_2	cM_0	L_1	V_0	0	Pneumo	Yes	Right	No	No	No	Yes	179
Patient 4	Par, Bro	76	Male	0	73	2.31	SQCA	–	pT_4	pN_3	cM_0	L_1	V_1	0	Lobect	Yes	Right	No	No	Yes	No	180
Patient 5	Par, Ves	65	Male	1	42	1.24	SQCA	–	pT_4	pN_2	cM_0	L_1	V_1	0	Pneumo	Yes	Left	No	No	No	Yes	260
Patient 6	Chest	87	Female	1	88	1.5	SQCA	–	pT_3	pN_1	cM_0	L_1	V_0	0	Lobect	Yes	Left	No	No	Yes	No	126
Patient 7	Ves	65	Male	0	76	2.47	SQCA	–	pT_2	pN_2	cM_0	L_1	V_1	0	Lobect	Yes	Right	Yes	No	No	No	198
Patient 8	Bro	69	Male	1	67	1.98	SQCA	–	pT_2	pN_1	cM_0	L_0	V_0	0	Lobect	Yes	Right	Yes	No	No	No	141
Patient 9	Chest	71	Female	1	78	1.72	SQCA	–	pT_4	pN_0	cM_0			0	Lobect	Yes	Right	No	No	Yes	No	133
Patient 10	Par	65	Male	1	48	1.43	SQCA	–	pT_4	pN_2	cM_0	L_1	V_0	0	Lobect	No	Right	Yes	No	No	No	249
Patient 11	Par, Ves	67	Male	1	74	2.37	LUAD	Pap	pT_4	pN_0	cM_0	L_0	V_0	*KRAS* (other)	Lobect	No	Left	No	No	Yes	No	346
Patient 12	Ves, Bro	59	Male	0	91	4	LUAD	Ac, pap, sol	pT_2	pN_2	cM_0	L_1	V_1	*EGFR*	Pneumo	Yes	Right	No	No	No	Yes	197
Patient 13	Bro	63	Male	1	59	1.92	SQCA	–	pT_4	pN_1	cM_0	L_1	V_1	0	Pneumo	Yes	Left	No	No	No	Yes	154
Patient 14	LK Hilus	69	Male	1	52	1.77	SQCA	–	pT_2	pN_1	cM_0			0	Lobect	Yes	Right	Yes	No	No	No	186
Patient 15	Par, Bro	70	Male	0	62	1.85	LUAD	Mpap, ac	pT_4	pN_0	cM_0	L_0	V_0	*ROS*	Lobect	Yes	Right	No	No	Yes	No	214
Patient 16	Chest	81	Male	1	65	1.8	SQCA	–	pT_3	pN_1	cM_1	L_1		0	Lobect	No	Right	Yes	No	No	No	279
Patient 17	Chest	75	Female	0	113	2.35	LUAD	Ac, pap, lep	pT_3	pN_0	cM_0			0	Lobect	Yes	Left	No	No	Yes	No	99
Patient 18	Par, Bro	55	Male	–	55	1.87	LUAD	Ac, pap	pT_3	pN_1	cM_0	L_1		0	Lobect	Yes	Left	Yes	No	No	No	216

Detailed description of patients with positive resection margins (R_+) following lung cancer resection with focus on the tumor and R_+ localization, as well as clinical, topographical and morpho-molecular profile of the resection margins. Ves: artery/vein; Chest: pleura/chest; LK Hilus: highest mediastinal positive lymph node station; pTNM: TNM8 staging system applied for intraoperative histopathological specimens (19,22). Ac, acinar; Bro, bronchus; ECOG, Eastern Cooperative Oncology Group; *EGFR*, epidermal growth factor receptor; FEV_1, forced expiratory volume in 1 second; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; L, lymphangiosis; lep, lepidic; lobect, lobectomy or bilobectomy; LUAD, lung adenocarcinoma; mpap, micropapillary; pap, papillary; Par, parenchyma; pneumo, pneumonectomy; pTNM, pathological tumor-node-metastasis; *ROS*, ROS proto-oncogene 1 receptor tyrosine kinase; segm, segmentectomy; sol, solid; SQCA, squamous cell carcinoma; TNM, tumor-node-metastasis; V, vascular involvement; Ves, vessels; WHO, World Health Organization.

Table 6 Binary logistic regression model including three independent predictors

Independent predictors of positive resection margins	Exp(B) (95% CI)	P value
Male sex	4.08 (1.05–15.87)	0.042
Squamous cell carcinoma histology	3.65 (1.21–11.04)	0.02
pT >2	8.47 (2.71–26.48)	<0.001

Binary logistic regression model assessing the independent predictors of positive resection margins in patients with NSCLC undergoing anatomical resections, stratified by resection margins positivity (R_0 *vs.* R_+). The multivariable regression analysis was performed by using the enter method and validated by forward LR and backward LR selection methods. pT: tumor stage according to the TNM8 staging system [2017] (19,22); Exp(B): odds ratio; CI, lower bound–upper bound. CI, confidence interval; LR, likelihood ratio; NSCLC, non-small cell lung cancer; TNM, tumor-node-metastasis.

segmentectomy, lobectomy and pneumonectomy cases (Tables S1,S2).

Accordingly, 9 of 18 patients (50%), 4 of 18 patients (22.2%), and 4 of 18 (22.2%), patients experienced positive resections margins at the level of parenchyma, vessels (artery/vein) and pleura/chest wall, respectively. One patient (5.6%) presented a lymph node involvement at the highest mediastinal station, while 6 of 18 patients (33.3%) presented tumor cells at the level of the resected bronchus. In 8 of 18 (44.4%), a tumor involvement at the level of the resected parenchyma (R_1, Par) at the final histological analysis was reported. In these patients, no intraoperative frozen section examination was performed. Patients with R_1, were in majority male sex (15 of 18, 83.3%) and had a median age of 68.00 (63.75, 75.25) years, a reduced FEV_1 [63.50 (51.00, 76.50) % predicted] and large tumors (pT_3: 4 of 18, 22% and pT_4: 9 of 18, 50%). The dominant and the most frequent pattern in adeno(squamous)carcinoma was acinar pattern (4 of 7, 57.1% and 6 of 7, 85.7%, respectively). Patients with incomplete resections underwent frequently an open approach (14 of 18, 77.8%) and extended resections (at least lobectomy, 16 of 18, 88.9%). Of note, none of the R_+ patients experienced a bronchial stump insufficiency following surgical resection. This complication was reported in only one female patient (72-year-old, ex-smoker, 30 PY) with a R_0 resected squamous cell carcinoma localized in the left lower lobe.

Multivariable analysis

The clinically relevant and statistically significant variables at univariate analysis were incorporated into a binary logistic regression model. Accordingly, male sex (P=0.042), squamous histology (P=0.02), and pT >2 (P<0.001) were identified as independent predictors for R_+. These predictors increased the risk of resection margins positivity by 4.1-, 3.7-, and 8.5-fold, respectively (*Table 6*).

The independent predictiveness of these parameters was separately confirmed by using three selection methods for the logistic regression analysis (enter, forward LR, and backward LR). The discrimination ability of the logistic regression model was investigated by ROC curves (Figure S1).

An algorithm for the clinical setting using the abovementioned independent predictors was performed by decision tree analysis (CRT algorithm) using a 5- and 10-fold cross–validation as internal validation method (Figure S2).

Given the various R_+ localizations and patterns upon surgery (*Table 5*, Tables S1,S2), the surgical extent (categorized as segmentectomies, lobectomies, bilobectomies, and pneumonectomies) was further analyzed in relation to the abovementioned predictors. When incorporating the surgical extent as covariate in the final logistic regression model, the analysis turned out unchanged results, while surgical extent was not found to independently predict resection margin positivity (Table S3).

Discussion

Complete surgical resection is a key aspect in the multimodal treatment of lung cancer that directly influences the curative intent of the treatment and ultimately, the short- and long-term prognosis of patients (30). Despite existing evidence on the role of TNM descriptors and surgical approach on the patients' prognosis, the description of the morpho-molecular patterns of lung cancer in relation to the resection margins patterns remains still insufficient. This is in part due to the fact that tumor genetic analyses are mostly performed in non-resectable/advanced cases. To address this knowledge gap, our study focuses on the relationship between perioperative clinical,

histopathological, and molecular parameters and the resection margin status.

The present study addressed all NSCLC patients admitted for anatomical surgical resections at the Bundeswehrkrankenhaus (Armed Forces Hospital) Ulm, Germany between January 1st, 2019 and December 31st, 2024. Our cohort had a median age of 69 years, and included 46.1% female patients. These clinical demographics align with previous patients cohorts (31-34).

Following the aim of the study, the R_+ rate in the histopathological specimen and potential associations with perioperative clinical and morpho-molecular parameters were further evaluated. The definition of R_+ includes the tumor involvement at the margin of the resected bronchus, vessels (artery, vein), parenchyma, pleura/chest wall, as well as lymph node involvement at the highest mediastinal station. This definition is in line with the publication by Edwards *et al.* (IASLC Staging Project database, n=14, 293 patients) (15). The rate of R_+ found in our study was 7.8%. It was comparable with the rate reported by Rasing *et al.* (R_1: 7.1%) in a Dutch national database including 7156 patients (21), but higher than the rate published by Edwards *et al.* (R_+: 2–4%) in the IASLC database (15). Importantly, Edwards *et al.* reported a stage dependent R_1 rate ($pT_1/pT_2/pT_3/pT_4$: 0.5%/1.7%/4.3%/7.3%) and R_2 rate ($pT_1/pT_2/pT_3/pT_4$: 0.4%/0.9%/1.8%/5.7%). Thus, our results align with the R_1 rate reported in pT_4 by Edwards *et al.* (15). One potential explanation for the lower R_1 rate in the IASLC database might be the higher percentage of patients with $pT_{1/2}$ in the IASLC database, in the context of a systematic screening. In contrast, our study included more patients with pT_4 (12.1%) than the IASLC database (pT_4: 5.7%), potentially reflecting more challenging cases and explaining the higher R_+ rate.

Beside the registry evidence described by Rasing *et al.* (21) and Edwards *et al.* (15) a wider R_+ range between 4% and 20% was reported in previous studies (19,30,35,36). Multifactorial explanations include differences in R_+ definition, individual clinical parameters, demographics, tumor topography, time of diagnosis, and pTNM descriptors in different countries and databases.

In detail, the highest R_+ rates were reported in large (>5 cm, pT_{3-4}) NSCLC with radiologically confirmed invasion of neighboring structures including mediastinal vessels, trachea, esophagus, nerves or chest wall (19). Importantly, R_+ was also influenced by patient-independent factors such as individual surgical experience, and intraoperative management of resection margins in hospitals with varying surgical volume. These aspects underscore the importance of complete surgical resections in order to achieve a curative intent and ultimately, best outcomes in NSCLC patients.

Our patient cohort revealed significantly reduced preoperative lung function parameters in patients experiencing R_+ resections, which aligns with a higher rate of larger tumors reported in the R_+ group. This result underscores the relationship between lung function and tumor stage, as previously validated in other patients cohorts by us or others (33,37).

Notably, R_+ was frequent in patients with large tumors (> pT_2, UICC >2), lymph node metastases (pN_+), lymphangiosis (L_1), and vascular invasion (V_1) in line with previous studies (19,21,38). Correspondingly, complete resections were more frequent in adenocarcinoma, while we observed more incomplete resections in squamous cell carcinoma (19). This aspect could be potentially explained by the topography of the resected tumors, with adenocarcinoma occurring more frequently in the lung periphery, while squamous cell carcinoma arises in close neighborhood of the bronchial tree and mediastinal structures (39-41).

Based on these considerations, it could be assumed that peripheral adenocarcinomas could be resected more easily in comparison to centrally located squamous cell carcinomas. Even though some studies showed more frequent open approaches in squamous cell carcinomas, and minimally invasive approaches in adenocarcinomas (31,42,43), these findings cannot be generalized due to the advances and steadily increasing expertise on minimally invasive approaches in high volume centers (44-47). Reflecting this, our study showed an almost similar rate of open procedures in both adenocarcinoma (59.6%) and squamous cell carcinoma (63.5%). On the other hand, recent studies showed that larger and centrally located lung tumors (locally advanced lung tumors) can also be resected by minimally invasive approaches (32,34).

Importantly, when considering only patients undergoing minimally invasive approaches, 1 patient (3.3%) undergoing VATS and 3 patients (8.8%) undergoing RATS experienced incomplete resections. As expected, open approaches were commonly preferred in larger and centrally located tumors, where infiltration of the bronchial tree and mediastinal structures might impact the completeness of resection. Accordingly, the R_+ rate was higher in patients undergoing pneumonectomies. Potential explanations are the presence of large tumors >5 cm (> pT_2, 61.1% *vs.* 23.0%, P<0.001 or UICC >2, 88.9% *vs.* 28.5%, P<0.001), lymph node involvement (pN_+ 66.7% *vs.* 22.7%, P<0.001), and squamous

cell carcinoma histology (55.6% *vs.* 20.3%, P=0.01). Thus, it seems plausible to consider that centrally located, large tumors with positive lymph node involvement resected by pneumonectomy are more frequently associated with positive resection margins than those tumors approached by segmentectomy or lobectomy. All these correlations are in accordance with previous studies (21,48-51).

In the subgroup of patients with neoadjuvant treatment (n=23), only one patient had a R_+ resection, with >10% vital tumor cells in the histological specimen. Even though this subgroup includes only a small number of patients, the presence of residual vital tumor cells in the resected specimen could point toward the aggressiveness of the tumor growth and potentially explain incomplete resection. Further potential explanations could be a slower growth pattern of adenocarcinomas (especially in low-grade/lepidic predominant subtypes) and more aggressive biological behavior of squamous cell carcinoma that tends to spread centrally very close to the bronchial tree (39,40,52-55).

Taking etiological factors into account, squamous histology is more frequently associated with smoking and chronic obstructive pulmonary disease (COPD) (56-58), while a subgroup of patients experiencing adenocarcinomas are nonsmokers (59,60). Consequently, history of smoking/COPD associated with parenchymal hyperinflation might additionally impact the extent of the surgical resections, in particular in patients with squamous histology (61,62). Furthermore, postoperative complications such as pneumonia, air leak, and prolonged in-hospital stay are more frequent in these high-risk patients (62). While some studies demonstrate a decreased survival in COPD patients who underwent lung cancer resection (63-65), other authors show no causal relationship with the long-term survival (62).

In alignment with previous considerations, histological analysis of the resected specimens showed significantly more squamous cell carcinomas in patients experiencing incomplete resections. On the other side, adenocarcinoma histology was significantly more frequent in patients with complete resections. When considering the frequency of the dominant growth pattern in adenocarcinoma specimens, no significant differences were reported between groups and no pattern was associated with R_+. The lack of statistical significance between high grade (G3, micropapillary or solid) tumors and R_+ could be justified by the low R_+ rate (n=7 of 158 patients, 4.4%) in adeno(squamous) carcinoma. Existing evidence shows however, that micropapillary and solid subtypes are independent predictors for curative resection for stage I lung cancer when complete lymphadenectomy is additionally performed (66). It has also to be noted that histological grading is based on a fraction estimate of high-grade patterns, and these patterns are not necessarily observed in the areas of positive resection margins, but may also be observed in the tumor center. Taking these considerations into account, we still consider reporting the growth pattern in histological specimens as a key aspect with prognostic consequences, that has to be systematically assessed and thoroughly characterized in further high-volume studies. One might discuss that in cases with positive resection margins, the respective growth pattern along the positive margin might be reported, comparable to the recommendations in prostatic adenocarcinoma. This approach might allow for a more granular correlation between actual growth patterns and biological aggressiveness in NSCLC (67).

One novel aspect addressed in our study was a comprehensive description of the mutational status of the examined histological specimens in relation to the resection status. More than 50% of the patients included in our study [54.7% (R_0) and 77.8% (R_+)] did not harbor any oncogenic driver mutations. These rates consistently vary in different studies taking the ethnic, and demographic variability of the patients into account (68-70). The low rate of mutations found in our patient cohort and, in particular, in patients with incomplete resections could be correlated with the fraction of squamous histology. Of note, from nine distinct genes analyzed in the whole patient cohort, only two patients with *EGFR* mutations, one patient with *KRAS* (other) mutation and *ROS* alteration had an incomplete surgical resection. There was no clustering of *STK11* and/or *KEAP1* mutations which have been previously associated with tumor aggressiveness in the R_+ resection group (71). Our results confirm previous data that assume that the histologic subtype and localization of the primary tumor seem to remain the most important factors associated with complete resections, however a relationship with the mutational status of the tumor cannot be excluded, as reported in previous studies (72-74). Mechanistically, early somatic events driving progenitor clonality and secondary tumor growth are considered responsible for the abovementioned association (75,76).

Beside tumor stage, and histology of the primary tumor, male sex was identified in our multivariable model, ROC and decision tree analysis as independent predictor of incomplete tumor resections. There is robust confirmatory evidence that male sex is associated with adverse postoperative outcomes and poor survival upon lung cancer

surgery, when compared to the female patients. However, to the best of our knowledge, male sex was not identified until now at multivariable analysis as independent predictor of incomplete resections in large scale patients' cohorts. While the predictive role of squamous cell carcinoma and tumor size (pT >2) was previously confirmed (19,21), we consider the significant correlation between male sex and R_+ a novel aspect, to date insufficiently discussed. Specifically, among all patients with incomplete resections, 83.3% of the patients were of male sex. The association between male sex and R_+ could be linked with the pTNM descriptors, histology of the primary tumor, surgical approach and nicotine history and intensity. Accordingly, 52.8% of the male patients had a tumor stage > pT_1, while 25% showed lymph node metastasis, along with higher fractions of lymphangiosis (33%), vascular invasion (16.8%), and squamous histology (29.6%) in the resected specimen. Notably, 62.4% of the male patients underwent open surgery and 12% underwent multilobar approaches. In addition, the higher nicotine consumption among male patients who are active smokers, along with the higher prevalence of squamous histology in the R_+ group, may represent further explanations for this association.

When considering only the R_+ subgroup in males, 60% of the patients had squamous histology, 93.3% presented with tumor stage > pT_1, 73.3% had lymph node metastasis, 64.3% had lymphangiosis, 41.7% had vascular involvement, while 73.3% of tumors were approached as open procedures and 26.7% requiring multilobar resections.

Interestingly, no specific mutational profile could be found in the majority of the male patients with incomplete resections [73.3% no oncogenic driver mutation, 13.3% *EGFR* mutation, 6.7% *KRAS* (other) mutation, and 6.7% *ROS* alteration]. Based on these results, we assume that TNM descriptors, squamous histology, and surgical approach could explain an R_+ status to some extent. Accordingly, these findings align with existing evidence that advanced TNM descriptors are unfavorable predictors and thus significantly linked with a worse survival in male patients (9,77). On the contrary, a survival advantage upon lung cancer treatment was reported in female patients in several cohorts with varying ethnic and demographic characteristics (77–80). Furthermore, one Swedish high-volume patient cohort found this survival advantage in female patients independent of age, comorbidities, socioeconomic status, physical performance, type and extent of surgery, tumor stage and characteristics (80).

In summary, patients with R_1, were in majority male sex, and presented a reduced FEV_1 [63.50 (51.00, 76.50) % predicted] and large tumors (pT_4 9 of 18 patients, 50%) approached in the majority of cases by open procedures (14 of 18 patients, 77.8%) with extended resections (at least lobectomy, 16 of 18 patients, 88.9%).

When addressing the individual patients' characteristics that potentially led to R_+ resection, further aspects could be emphasized. The impossibility of surgical extension (and thus no further intraoperative frozen sections examination) might be justified in certain situations by very low FEV_1 values <50% (in 4 of 18 patients, 22.2%), vascular or pleura /chest wall involvement (in 8 of 18 patients, 44.4%), and large (pT_4) and centrally located tumors (in 9 of 18 patients, 50%). Of note, some patients have a combination of abovementioned factors (e.g., parenchymal/chest/vessel involvement, low FEV_1, pT_4 tumor) thus justifying the R_+ outcome.

These parameters reflect the heterogeneity of NSCLC patients admitted for surgical resection. In clinical practice, managing such diverse patient groups requires individualized decisions regarding the extent of resection. Consequently, no predefined surgical approach (e.g., segmentectomy or lobectomy or pneumonectomy) can be applied in advance for all patients. Thus, we deliberately pooled all patients and analyzed the entire cohort irrespective of the extent of surgery, in order to present real-word data from our surgical unit.

One important aspect that could be improved in the surgical routine is the surgical management of the resected margins. Basically, frozen section examination of the resection margins is not mandatory in macroscopically non-suspicious cases. However, in 8 of 18 (44.4%) histological specimens where parenchyma resection margins were found positive (R_1) at the final histological analysis, no intraoperative frozen section examination was performed. As a point of criticism for our study, we consider that a more frequent use of frozen section examination by suspected adjacent tumor involvement could possibly lead to an extended peripheral or central resection, which in turn, could decrease the R_+ rate.

The present study has several limitations. Due to the retrospective nature of the study, the assessment of clinical parameters (demographics, comorbidities, postoperative course and follow-up) was not always possible. Thus, the analysis, focused on descriptive distributions could not be adjusted for potential confounders. Due to the various R_+ localizations and patterns upon surgery, pooling all surgical procedures into a single analytical framework, could

introduce potential heterogeneity and confounding effects. In addition, TNM descriptors and histology may partly reflect procedure-selection bias in preoperative decision-making regarding the extent of resection. To minimize methodological bias, our study design aligned with large registry databases (e.g., Dutch national database with n=7,156 patients, assessed by Rasing *et al.*) that clearly identified TNM descriptors and squamous histology as independent predictors for surgical margin completeness (21). In addition, we focused on the morpho-molecular profile of the primary tumors and R_+ status, characteristics that have been consistently investigated in our analysis, with robust results aligning with previous studies.

One additional limitation represents the relatively low sample size in comparison to large scale database registries. Consecutively, the relatively low number of events limits the robustness of the multivariable model, potentially leading to misleading interpretations. A final limitation is the monocentric design of the study, without an external validation. In order to demonstrate their generalizability, the presented findings should be further evaluated in large prospective multicenter studies.

Conclusions

Taken together, our study addressing the relationship between topographical, morpho-functional and mutational profile of the primary tumor with the resection margin completeness, identified three clinical parameters that influence resection status: tumor stage, squamous histology, and male sex. A careful assessment of baseline clinical demographics, TNM descriptors, and morpho-molecular status of the tumor can guide risk stratification, refine perioperative care, and enhance patient outcomes.

Acknowledgments

We thank all colleagues from the Department of Visceral and Thoracic Surgery and the Institute of Pathology and Molecular Pathology of the Bundeswehrkrankenhaus (Armed Forces Hospital) Ulm for patient care and clinical/diagnostic expertise.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-2026-0511/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-2026-0511/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-2026-0511/prf

Funding: None.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-2026-0511/coif). K. S. has received consulting fees from Merck Sharp & Dohme, AstraZeneca and Bristol-Myers Squibb for consulting, participation in advisory boards and for lectures and presentations. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Ethics Committee of University of Ulm, Germany (No. 112/23 and No. 293/24). The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. Individual consent for this retrospective analysis was waived.

References

1. Detterbeck FC, Ostrowski M, Hoffmann H, et al. The International Association for the Study of Lung Cancer Lung Cancer Staging Project: Proposals for Revision of the Classification of Residual Tumor After Resection for the Forthcoming (Ninth) Edition of the TNM Classification of Lung Cancer. J Thorac Oncol 2024;19:1052-72.
2. Rami-Porta R. The Evolving Concept of Complete Resection in Lung Cancer Surgery. Cancers (Basel) 2021;13:2583.

3. Zhou J, Xu Y, Liu J, et al. Global burden of lung cancer in 2022 and projections to 2050: Incidence and mortality estimates from GLOBOCAN. Cancer Epidemiol 2024;93:102693.
4. Riely GJ, Wood DE, Aisner DL, et al. NCCN Guidelines® Insights: Non-Small Cell Lung Cancer, Version 7.2025. J Natl Compr Canc Netw 2025;23:354-62.
5. Chen T, Zhong Y, Wen J, et al. Prognostic Significance of the Proposed Residual Tumor Classification in Patients With NSCLC After Sleeve Lobectomy. JTO Clin Res Rep 2023;4:100574.
6. Zens P, Bello C, Scherz A, et al. A prognostic score for non-small cell lung cancer resected after neoadjuvant therapy in comparison with the tumor-node-metastases classification and major pathological response. Mod Pathol 2021;34:1333-44.
7. Xie H, Dai C, Gu C, et al. Validation of the Proposed International Association for the Study of Lung Cancer Residual Tumor Classification to Upgrade Extracapsular Extension of Tumor in Nodes From R0 to Incomplete Resection. J Thorac Oncol 2024;19:130-40.
8. Smeltzer M, Faris N, Lee Y, et al. MA09. 08 Improving Overall Survival in Non-Small Cell Lung Cancer by Reducing R-Uncertain Resections With a Lymph Node Specimen Collection Kit. J Thorac Oncol 2021;16:S167.
9. Tardif A, LeBlanc C, Roy P, et al. Lung Cancer in Patients With COPD: Predictors of Surgery and Long-Term Survival Following Lung Resection. Chronic Obstr Pulm Dis 2026;13:29-38.
10. Kim IH, Lee GD, Choi S, et al. Recurrence Dynamics of Pathological N2 Non-Small Cell Lung Cancer Based on IASLC Residual Tumor Descriptor. Cancer Res Treat 2025;57:105-15.
11. Hofmann HS, Taege C, Lautenschläger C, et al. Microscopic (R1) and macroscopic (R2) residual disease in patients with resected non-small cell lung cancer. Eur J Cardiothorac Surg 2002;21:606-10.
12. Petrella F, Rizzo S, Attili I, et al. Stage III Non-Small-Cell Lung Cancer: An Overview of Treatment Options. Curr Oncol 2023;30:3160-75.
13. Verma S, Breadner D, Mittal A, et al. An Updated Review of Management of Resectable Stage III NSCLC in the Era of Neoadjuvant Immunotherapy. Cancers (Basel) 2024;16:1302.
14. Cansouline X, Elmraki A, Lipan B, et al. Uncertain Resection in Lung Cancer: A Comprehensive Review of the International Association for the Study of Lung Cancer Classification. Cancers (Basel) 2025;17:1386.
15. Edwards JG, Chansky K, Van Schil P, et al. The IASLC Lung Cancer Staging Project: Analysis of Resection Margin Status and Proposals for Residual Tumor Descriptors for Non-Small Cell Lung Cancer. J Thorac Oncol 2020;15:344-59.
16. Vergé R, Rouch A, Rabinel P, et al. Evaluation of Uncertain Resection for Localized Non-small Cell Lung Cancer: The Crucial Prognosis of Suboptimal Lymph Node Assessment. Ann Thorac Surg 2025;120:637-45.
17. Hu M, Li X, Zheng M, et al. The IASLC uncertain resection, general overview, current evidence, and future prospects: a systematic review and meta-analysis. Ther Adv Med Oncol 2025;17:17588359251344789.
18. Van Schil PE, Rami-Porta R, Asamura H. The 8(th) TNM edition for lung cancer: a critical analysis. Ann Transl Med 2018;6:87.
19. Brandt WS, Yang Z, Heiden BT, et al. Factors associated with incomplete resection for large, locally invasive non-small cell lung cancer. J Thorac Dis 2024;16:2894-905.
20. Lee JG, Cho BC, Bae MK, et al. Preoperative C-reactive protein levels are associated with tumor size and lymphovascular invasion in resected non-small cell lung cancer. Lung Cancer 2009;63:106-10.
21. Rasing MJA, Peters M, Moreno AC, et al. Predicting Incomplete Resection in Non-Small Cell Lung Cancer Preoperatively: A Validated Nomogram. Ann Thorac Surg 2021;111:1052-8.
22. Lababede O, Meziane MA. The Eighth Edition of TNM Staging of Lung Cancer: Reference Chart and Diagrams. Oncologist 2018;23:844-8.
23. Goldstraw P, Chansky K, Crowley J, et al. The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer. J Thorac Oncol 2016;11:39-51.
24. Inamura K. Lung Cancer: Understanding Its Molecular Pathology and the 2015 WHO Classification. Front Oncol 2017;7:193.
25. Travis WD, Brambilla E, Burke AP, et al. Introduction to The 2015 World Health Organization Classification of Tumors of the Lung, Pleura, Thymus, and Heart. J Thorac Oncol 2015;10:1240-2.
26. Travis WD, Brambilla E, Nicholson AG, et al. The 2015 World Health Organization Classification of Lung Tumors: Impact of Genetic, Clinical and Radiologic Advances Since the 2004 Classification. J Thorac Oncol 2015;10:1243-60.
27. Steinestel K, Arndt A. Current Biomarkers in Non-

Small Cell Lung Cancer-The Molecular Pathologist's Perspective. Diagnostics (Basel) 2025;15:631.
28. Travis WD, Dacic S, Wistuba I, et al. IASLC Multidisciplinary Recommendations for Pathologic Assessment of Lung Cancer Resection Specimens After Neoadjuvant Therapy. J Thorac Oncol 2020;15:709-40.
29. Berezowska S, Keyter M, Bouchaab H, et al. Pathology of Surgically Resected Lung Cancers Following Neoadjuvant Therapy. Adv Anat Pathol 2024;31:324-32.
30. Rshaidat H, Whitehorn GL, Collins M, et al. Factors Associated With Margin Positivity After Lung Resection Surgery. Clin Lung Cancer 2024;25:560-6.
31. Zhao Y, Li G, Zhang Y, et al. Comparison of outcomes between muscle-sparing thoracotomy and video-assisted thoracic surgery in patients with cT1 N0 M0 lung cancer. J Thorac Cardiovasc Surg 2017;154:1420-1429.e1.
32. Zimmermann J, Walter J, Pfeiffer V, et al. Propensity score matched comparison of lymph node upstaging in early-stage lung cancer: open versus minimally invasive surgery with standardized lymphadenectomy. J Cardiothorac Surg 2025;20:96.
33. Stoleriu MG, Gerckens M, Zimmermann J, et al. Preoperative risk factors predict perioperative allogenic blood transfusion in patients undergoing primary lung cancer resections: a retrospective cohort study from a high-volume thoracic surgery center. BMC Surg 2023;23:44.
34. Hireche K, Lounes Y, Bacri C, et al. VATS versus Open Lobectomy following Induction Therapy for Stage III NSCLC: A Propensity Score-Matched Analysis. Cancers (Basel) 2023;15:414.
35. Osarogiagbon RU, Faris NR, Stevens W, et al. Beyond Margin Status: Population-Based Validation of the Proposed International Association for the Study of Lung Cancer Residual Tumor Classification Recategorization. J Thorac Oncol 2020;15:371-82.
36. Rami-Porta R, Bolejack V, Crowley J, et al. The IASLC Lung Cancer Staging Project: Proposals for the Revisions of the T Descriptors in the Forthcoming Eighth Edition of the TNM Classification for Lung Cancer. J Thorac Oncol 2015;10:990-1003.
37. Orlandi R, Degiovanni S, Uslenghi C, et al. Pulmonary function prediction in lung cancer resection candidates: the latest insights. Breathe (Sheff) 2025;21:250041.
38. Chansky K, Sculier JP, Crowley JJ, et al. The International Association for the Study of Lung Cancer Staging Project: prognostic factors and pathologic TNM stage in surgically managed non-small cell lung cancer. J Thorac Oncol 2009;4:792-801.
39. Matache RS, Stanciu-Gavan C, Pantile D, et al. Clinical and Paraclinical Characteristics of Endobronchial Pulmonary Squamous Cell Carcinoma-A Brief Review. Diagnostics (Basel) 2023;13:3318.
40. Ulusan A, Tunca İE, Şanlı M, et al. Endobronchial lesions cases treated with interventional bronchoscopic techniques: Our single-center experiences. Turk Gogus Kalp Damar Cerrahisi Derg 2019;28:352-8.
41. Wang S, Ye Q, Tu J, et al. The location, histologic type, and stage of lung cancer are associated with bleeding during endobronchial biopsy. Cancer Manag Res 2018;10:1251-7.
42. Erdogu V, Akin H, Sonmezoglu Y, et al. Comparison of the Video-assisted Thoracoscopic Lobectomy versus Open Thoracotomy for Primary Non-Small Cell Lung Cancer: Single Cohort Study with 269 Cases. Sisli Etfal Hastan Tip Bul 2020;54:291-6.
43. Kahraman S, Evman S, Buz M, et al. Comparison of VATS and open thoracotomy in anatomical lung resections according to multifaceted parameters. Laparosc Endosc Surg Sci 2024;31:110-7.
44. McElnay P, Casali G, Batchelor T, et al. Adopting a standardized anterior approach significantly increases video-assisted thoracoscopic surgery lobectomy rates. Eur J Cardiothorac Surg 2014;46:100-5.
45. Mercier O. VATS versus open thoracotomy for lung cancer resection: is the game still running? Eur J Cardiothorac Surg 2022;62:ezac303.
46. Re Cecconi E, Mangiameli G, De Simone M, et al. Vats lobectomy for lung cancer. What has been the evolution over the time? Front Oncol 2023;13:1268362.
47. Sahai D, Nayak R. The evolution of vats and minimally invasive techniques in the treatment of lung cancer: a narrative review. Video-assist Thorac Surg 2023;8:40.
48. Rami-Porta R. The TNM classification of lung cancer-a historic perspective. J Thorac Dis 2024;16:8053-67.
49. Weisel RD, Cooper JD, Delarue NC, et al. Sleeve lobectomy for carcinoma of the lung. J Thorac Cardiovasc Surg 1979;78:839-49.
50. Gagliasso M, Migliaretti G, Ardissone F. Assessing the prognostic impact of the International Association for the Study of Lung Cancer proposed definitions of complete, uncertain, and incomplete resection in non-small cell lung cancer surgery. Lung Cancer 2017;111:124-30.
51. Ugalde Figueroa PA, Marques E, Cilento VJ, et al. Completeness of Resection and Long-Term Survival of Patients Undergoing Resection for Pathologic T3 NSCLC: An International Association for the Study of

Lung Cancer Analysis. J Thorac Oncol 2024;19:141-52.
52. Jennings SG, Winer-Muram HT, Tann M, et al. Distribution of stage I lung cancer growth rates determined with serial volumetric CT measurements. Radiology 2006;241:554-63.
53. Mikita K, Saito H, Sakuma Y, et al. Growth rate of lung cancer recognized as small solid nodule on initial CT findings. Eur J Radiol 2012;81:e548-53.
54. Henschke CI, Yankelevitz DF, Yip R, et al. Lung cancers diagnosed at annual CT screening: volume doubling times. Radiology 2012;263:578-83.
55. Infante M, Berghmans T, Heuvelmans MA, et al. Slow-growing lung cancer as an emerging entity: from screening to clinical management. Eur Respir J 2013;42:1706-22.
56. Boelens MC, Gustafson AM, Postma DS, et al. A chronic obstructive pulmonary disease related signature in squamous cell lung cancer. Lung Cancer 2011;72:177-83.
57. Zhang X, Lv F, Fu B, et al. Clinical and Computed Tomography Characteristics for Early Diagnosis of Peripheral Small-cell Lung Cancer. Cancer Manag Res 2022;14:589-601.
58. Khuder SA, Dayal HH, Mutgi AB, et al. Effect of cigarette smoking on major histological types of lung cancer in men. Lung Cancer 1998;22:15-21.
59. Sun S, Schiller JH, Gazdar AF. Lung cancer in never smokers--a different disease. Nat Rev Cancer 2007;7:778-90.
60. Huang C, Qu X, Du J. Proportion of lung adenocarcinoma in female never-smokers has increased dramatically over the past 28 years. J Thorac Dis 2019;11:2685-8.
61. Bozinovski S, Vlahos R, Anthony D, et al. COPD and squamous cell lung cancer: aberrant inflammation and immunity is the common link. Br J Pharmacol 2016;173:635-48.
62. Roy E, Rheault J, Pigeon MA, et al. Lung cancer resection and postoperative outcomes in COPD: A single-center experience. Chron Respir Dis 2020;17:1479973120925430.
63. Sekine Y, Suzuki H, Yamada Y, et al. Severity of chronic obstructive pulmonary disease and its relationship to lung cancer prognosis after surgical resection. Thorac Cardiovasc Surg 2013;61:124-30.
64. Zhai R, Yu X, Shafer A, et al. The impact of coexisting COPD on survival of patients with early-stage non-small cell lung cancer undergoing surgical resection. Chest 2014;145:346-53.
65. Bugge A, Lund MB, Brunborg C, et al. Survival After Surgical Resection for Lung Cancer in Patients With Chronic Obstructive Pulmonary Disease. Ann Thorac Surg 2016;101:2125-31.
66. Li R, Li Z, Yang Z, et al. The presence of micropapillary and/or solid subtypes is an independent prognostic factor for patients undergoing curative resection for stage I lung adenocarcinoma with ground-glass opacity. Transl Lung Cancer Res 2024;13:256-68.
67. Kates M, Sopko NA, Han M, et al. Importance of Reporting the Gleason Score at the Positive Surgical Margin Site: Analysis of 4,082 Consecutive Radical Prostatectomy Cases. J Urol 2016;195:337-42.
68. Ding Y, Zhang L, Guo L, et al. Comparative study on the mutational profile of adenocarcinoma and squamous cell carcinoma predominant histologic subtypes in Chinese non-small cell lung cancer patients. Thorac Cancer 2020;11:103-12.
69. Dhanasekaran SM, Balbin OA, Chen G, et al. Transcriptome meta-analysis of lung cancer reveals recurrent aberrations in NRG1 and Hippo pathway genes. Nat Commun 2014;5:5893.
70. Çetin NK, Özkıran E, Taşan SC, et al. Relationship Between Mutation Profile Detected by Next-generation Sequencing and Histopathological Parameters in Lung Squamous Cell Carcinoma. Journal of Clinical and Translational Pathology 2025;5:61-71.
71. Di Federico A, De Giglio A, Parisi C, et al. STK11/LKB1 and KEAP1 mutations in non-small cell lung cancer: Prognostic rather than predictive? Eur J Cancer 2021;157:108-13.
72. Teng F, Xu J, Wang J, et al. Correlation between gene mutation status and clinicopathologic features in early multiple primary lung cancer. Front Oncol 2023;13:1110259.
73. Tukumo M, Toyooka S, Kiura K, et al. PD-160 The relationship between epidermal growth factor receptor (EGFR) mutations and clinicopathologic features in non-small cell lung cancers. Lung Cancer 2005;49:S113.
74. Jiang M, Zhang X, Chen Y, et al. A Review of the Correlation Between Epidermal Growth Factor Receptor Mutation Status and (18)F-FDG Metabolic Activity in Non-Small Cell Lung Cancer. Front Oncol 2022;12:780186.
75. Swanton C. Intratumor heterogeneity: evolution through space and time. Cancer Res 2012;72:4875-82.
76. Yap TA, Gerlinger M, Futreal PA, et al. Intratumor heterogeneity: seeing the wood for the trees. Sci Transl Med 2012;4:127ps10.
77. Wainer Z, Wright GM, Gough K, et al. Sex-Dependent Staging in Non-Small-Cell Lung Cancer; Analysis of the

Effect of Sex Differences in the Eighth Edition of the Tumor, Node, Metastases Staging System. Clin Lung Cancer 2018;19:e933-44.
78. Lærum D, Strand TE, Brustugun OT, et al. Evaluation of sex inequity in lung-cancer-specific survival. Acta Oncol 2024;63:343-50.
79. Wisnivesky JP, Halm EA. Sex differences in lung cancer survival: do tumors behave differently in elderly women? J Clin Oncol 2007;25:1705-12.
80. Sachs E, Sartipy U, Jackson V. Sex and Survival After Surgery for Lung Cancer: A Swedish Nationwide Cohort. Chest 2021;159:2029-39.

Cite this article as: Stoleriu MG, Steinestel K, Grimmer M, Löwer-Kiem LM, Witzenhausen M, Sölter J, Brill S, Arndt A. Tumor stage, squamous histology and male sex predict positive resection margins in non-small cell lung cancer patients undergoing anatomical resection—a retrospective study from a high-volume thoracic surgery unit. J Thorac Dis 2026;18(5):487. doi: 10.21037/jtd-2026-0511