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Article

Histology of the Primary Tumor, Lymph Node, and Tumor Size Upon Neoadjuvant Treatment Predict Effectiveness of Complete Pathologic Response in Patients Undergoing Primary Lung Cancer Resections

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Simple summary: Lung cancer continues to be the leading cause of cancer-related deaths worldwide. Many patients present advanced disease at the time of the diagnosis. The neoadjuvant therapy aims to reduce the tumor stage, improve operability of patients, and simultaneously leads to tumor regression. The tumor regression grade reflects the degree of pathological response to therapy. Thus, we conducted this study to identify the predictors for pathologic response after neoadjuvant treatment following by surgery. The second goal of our study was to find the relationship between survival and tumor regression. Our study revealed the histology of the primary tumor, lymph node size in the preoperative CT scan (>1.7cm) and absolute tumor size reduction after neoadjuvant treatment (>2.6 cm) independently predict effectiveness of tumor regression. Age >70 years, extended resection >one lobe, and tumor recurrence or metastasis were identified as significant independent predictors of reduced overall survival.

Abstract: Our study aimed to identify predictors for the effectiveness of tumor regression in lung cancer patients undergoing neoadjuvant treatment and cancer resections. Patients admitted between 2016 and 2022 were included in the study. Based on the histology of the tumor, patients were categorized into lung adenocarcinoma group (LUAD), and squamous cell carcinoma group (SQCA). Ninety-five patients with non-small cell lung cancer were included in the study. Fifty-eight (61.1%) and 37 (38.9%) patients were included in the LUAD and SQCA groups, respectively. Nine (9.5%), 56 (58.9%), and 30 (31.6%) patients were categorized with a tumor regression score of I, II, and III respectively. In multivariable analyses, histology of the primary tumor (SQCA), lymph node size in the preoperative CT scan (>1.7cm) and absolute tumor size reduction after neoadjuvant treatment (>2.6 cm) independently predict effectiveness of tumor regression (OR, [95% Confidence interval, p-value] of 6.88 [2.40-19.77, p<0.0001], 3.13 [1.11-8.83, p=0.0310]; 3.76 [1.20-11.81, p=0.0233], respectively). Age >70 years, extended resection >one lobe, and tumor recurrence or metastasis were identified as significant independent predictors of reduced overall survival. Assessment of tumor size before and after neoadjuvant treatment might help to identify high-risk patients with decreased survival and to improve patient management and care.

Keywords: lung cancer; PET/CT-scan; lymph node staging; neoadjuvant therapy; pathological response; tumor regression; overall survival

1. Introduction

Non-small cell lung cancer (NSCLC) continues to be the leading cause of cancer-related deaths worldwide [1]. Patients with early stages of NSCLC can usually be cured with surgery alone with a 5-year overall survival (OS) rate of 92 % in Stage IA [2]. Unfortunately, many patients with NSCLC present advanced disease at the time of the diagnosis [1]. Patients with locally advanced NSCLC who receive surgery alone show poor OS [2]. The neoadjuvant therapy to reduce the tumor stage, followed by surgery, is the routine treatment of choice in clinical practice by advanced NSCLC [3]. This therapeutical approach aims to reduce the tumor stage, improve operability, and possibly eradicate microscopic metastases, in that way offering a complete curative approach [4]. However, there are no established common standards for neoadjuvant therapy yet [5–7]. It is suggested that different neoadjuvant therapy modalities can lead to different tumor regressions.

The assessment of tumor regression grade (TRG) has emerged as a valuable prognostic indicator in evaluating the efficacy of neoadjuvant therapies [8]. TRG reflects the degree of pathological response to therapy and holds the potential to guide clinical decisions, improve patient outcomes, and enhance treatment methods [9]. Thus, understanding the complex relationship between neoadjuvant therapy and TRG is critical for optimizing therapeutic approaches and establishing suitable treatment strategies for individual patients.

By examining the perioperative parameters (laboratory, radiological, histological, and clinical comorbidities), we aim to identify in our recent study the predictors for the effectiveness of tumor regression in lung cancer patients undergoing neoadjuvant treatment and major lung cancer resections to improve the perioperative risk stratification and optimizing patient management. The second goal of our study was to analyze the OS of the patients included in this study and find the relationship between survival and tumor regression.

2. Materials and Methods

2.1. Study Population

This single institution retrospective cohort study was performed after approval by the Ethics Committee of the Ludwig Maximilian University of Munich (LMU), Germany, file number 24-0114 by the Declaration of Helsinki and STROBE recommendations for clinical studies. Patients' recruitment and treatment were performed at the Department of Thoracic Surgery of the Robert Bosch Hospital (Stuttgart, Germany) between 01.01.2016 and 31.12.2022.

All patients with resectable malignant primary lung tumors undergoing neoadjuvant therapy and major surgical resections (lobectomy, bilobectomy, or pneumonectomy) with histologically reported lung adenocarcinoma (LUAD group) and squamous cell carcinoma (SQCA group) in the intraoperative histological specimens were included in the study. Patients undergoing similar treatment experiencing rare histological subtypes in the intraoperative specimens (e.g. adenosquamous carcinoma (n=2), synovial sarcoma (n=2), sarcomatoid lung carcinoma (n=2), low-grade differentiated sarcoma of the lung (n=1), neuroendocrine/ small cell lung cancer (n=2), and not otherwise specified tumors (NOS, n=4) were excluded (**Figure 1**).

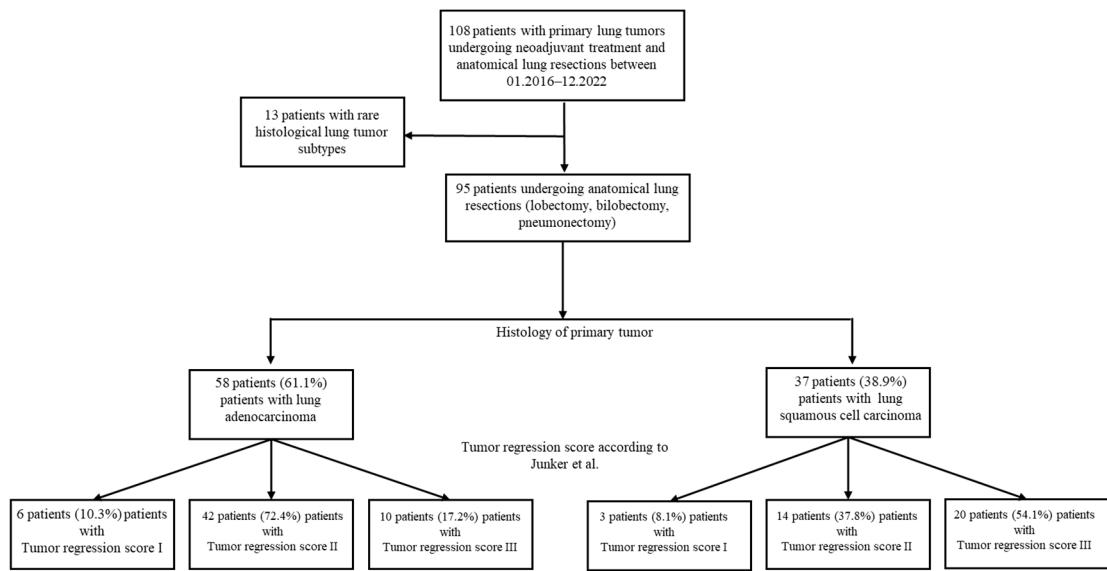


Figure 1. Study flow chart illustrating patient enrollment at study entry. Of 892 patients undergoing oncological thoracic surgery between 01.2016 and 12.2022, 108 (12.1%) patients with resectable primary lung tumors underwent neoadjuvant treatment and primary lung cancer resections. Thirteen (12.04%) patients experiencing rare histological tumor subtypes (e.g. adenosquamous carcinoma, synovial sarcoma, sarcomatoid carcinoma, low-grade differentiated sarcoma of the lung, neuroendocrine/ small cell lung cancer, and not otherwise specified tumors) were excluded from the study, thus 95 of 108 patients (87.96%) with primary resectable lung tumors of the lung were included. Based on the histology of the primary tumor, patients were categorized into two groups: lung adenocarcinoma group (LUAD, 58 patients, 61.1%), and squamous cell carcinoma group (SQCA, 37 patients, 38.9%). Based on the tumor regression grade (TRG) of the intraoperative specimens, patients were further stratified in TRG_I (LUAD:10.3%, SQCA:8.1%), TRG_II (LUAD:72.4%, SQCA:37.8%) and TRG_III (LUAD:17.2%, SQCA: 54.1%), respectively.

2.2. Data Assessments/Sources

Clinical data were collected from medical reports and patients' files stored in the hospital and the Onkostar database of the Baden-Wuerttemberg Cancer Registry. Primary lung tumors were categorized according to the 7th edition of the TNM staging system [10], and histopathological analysis according to the World Health Organization Classification of lung tumors [11].

Clinical data included patients' demographics (age, sex, BMI, smoking status, nicotine, and alcohol consumption, comorbidities), laboratory (blood counts, C-reactive protein (CRP), creatinine, lactate dehydrogenase (LDH), and albumin), respiratory (FVC: functional vital capacity; FEV₁: forced expiratory volume in one second; DLCO: diffusing capacity of the lung for carbon monoxide), radiological (cTNM) parameters with tumor and lymph node size as tumor and lymph node size was chosen the largest distance in transverse, coronal and sagittal plane in CT imaging. Histological parameters and pTNM. Data on patient treatment including neoadjuvant regimen ((combined) chemotherapy, immunotherapy, radiation therapy)), intraoperative approach (minimally invasive or open surgery, surgical time), adjuvant regimen ((combined) chemotherapy, immunotherapy, radiation therapy), as well as postoperative morbidity (complications, in hospital and ICU stay, tumor recurrence/ metastasis) and mortality were collected.

2.3. Outcome

The correlation between the abovementioned clinical parameters and the intraoperative tumor regression score was analyzed concerning the histological subtype of the primary tumor (LUAD or SQCA). Tumor regression grade (TRG) was defined according to the initial study of Junker et al. (TRG_I: >95% vital tumor cells, TRG_IIa: >10% vital tumor cells, TRG_IIb: <10% vital tumor cells,

TRG_III: absent vital tumor cells in the intraoperative histological specimens), respectively [8]. TRG_III was also defined as complete pathologic response (CPR) according to Travis et al [12].

2.4. Data Analysis

Parametric variables are presented as median and interquartile range. Comparisons between groups were performed using the Mann-Whitney U-test (for continuous variables, e.g. laboratory parameters, age, BMI, Pack years, lung function parameters, lymph node size, tumor size) or by Chi-square test statistics and Fisher's exact test (for binary variables). Tumor size reduction values after neoadjuvant treatment were given as absolute values (absolute delta= tumor size before neoadjuvant treatment – tumor size after neoadjuvant treatment, values given in CM). To assess the percentual decrease of the tumor size, relative values were calculated as follows: (relative delta = ((tumor size before neoadjuvant treatment – tumor size after neoadjuvant treatment) / tumor size before neoadjuvant treatment) x 100), values given in %. Multivariable analysis was performed by binary logistic regression analysis validated by three methods (enter, forward LR, and backward LR). Odds ratios (OR) with 95% confidence intervals (CI) were assessed for independent predictors. Optimal cut-off values were evaluated using receiver-operator characteristics (ROC) and the Youden criterion. Survival data were generated by Kaplan Meier analysis (log-rank test) and the independent predictive value of the significant variables by stratified Cox proportional hazard regression analysis. Overall survival is defined as the time interval between lung cancer surgery and event (death) or census (last recorded follow-up). Analyses were performed after excluding the missing values (under 10% for selected variables), by using SPSS (Version 26, IBM, Armonk, New York, USA). P Values <0.05 were considered statistically significant.

3. Results

3.1. Study Population

Of 892 patients admitted for thoracic surgery between 01.01.2016 and 31.12.2022, 95 patients fulfilled the inclusion criteria. The analyzed cohort (n= 32/95 female patients, 33.7 %) included patients with a median age of 64.20 [57.90; 69.06] years (n=42, 44.2% older than 65 years) and a median BMI of 24.54 [22.16; 27.04] kg/m² (n=49, 51.6%. with a BMI between 18.5 and 25 kg/m²).

Based on the histology of the primary tumor, 58 patients (61.1%) and 37 patients (38.9%) patients were included in the LUAD and SQCA groups, respectively.

The inclusion process and groups of patients categorized by the histology of the primary tumor are illustrated in **Figure 1**.

Overall, 13 patients (13.7%) were never smokers, 50 patients (52.6%) were current smokers, and 32 patients (33.7%) were ex-smokers at the time of diagnosis.

LUAD group comprised significantly more female patients (27/58 (46.6 %) vs 5/37 (13.5 %, p=0.0009), overweighted patients (29/58 (50.0 %) vs 10/37 (27.0 %), p=0.0264), as well as smokers reporting a lower nicotine consumption (30.0 [4.25; 45.0] vs 40.0 [22.5; 52.5], p=0.0288).

SQCA group encompasses significantly more patients aged 65 years or older (21/37 (56.8 %) vs 21/58 (36.2 %), p=0.0492) and with a normal BMI range (24/37 (64.9 %) vs 25/58 (43.1 %), p=0.0385).

Patients with SQCA were admitted with significantly lower lung function parameters in comparison to the LUAD patients (FEV₁: 69.00 [55.50-85.00] vs 80.50 [67.00-90.25] % predicted, p=0.0103; DLCO: 48.00 [42.00-62.00] vs 62.50 [50.50-70.50] % predicted, p=0.0023 and Tiffeneau Index 88.00 [78.00-95.00] vs 95.00 [87.00-102.00] %, p=0.0014, respectively). The patients' demographics and comorbidities are summarized in **Table 1**.

Table 1. Demographics of patients undergoing neoadjuvant chemotherapy and surgical resection of primary lung tumors classified by histology of primary tumor.

Patient demographics at study entry	LUAD n=58	SQCA n=37	P-value
Age (median, quartiles [1st; 3rd]) years	60.73 [54.5; 69.0]	65.6 [60.5; 70.3]	0.0687
Age > 65 (n, %)	21/58 (36.2 %)	21/37 (56.8 %)	0.0492
Age > 70 (n, %)	11/58 (19.0 %)	10/37 (27.0 %)	0.3558
Age > 80 (n, %)	0/58 (0 %)	0/37 (0 %)	
Sex (n, %)			
Female	27/58 (46.6 %)	5/37 (13.5 %)	0.0009
Male	31/58 (53.4 %)	32/37 (86.5 %)	
BMI (median, quartiles [1st; 3rd])	25.3 [23.0; 27.2]	23.8 [21.8; 26.6]	0.1842
BMI < 18.5 kg/m ² (n, %)	0/58 (0 %)	0/37 (0 %)	
BMI > 18.5, < 25 kg/m ² (n, %)	25/58 (43.1 %)	24/37 (64.9 %)	0.0385
BMI > 25, < 30 kg/m ² (n, %)	29/58 (50.0 %)	10/37 (27.0 %)	0.0264
BMI > 30 kg/m ² (n, %)	4/58 (6.9 %)	3/37 (8.1 %)	1.0000
Pack years (median, quartiles [1st; 3rd])	30.0 [4.25; 45.0] PY	40.0 [22.5; 52.5] PY	0.0288
Never smokers (n, %)	10/58 (17.2 %)	3/37 (8.1 %)	0.2066
Current smokers (n, %)	32/58 (55.2 %)	18/37 (48.6 %)	0.5346
Ex-smokers (n, %)	16/58 (27.6 %)	16/37 (43.2 %)	0.1143
Alcohol (n, %)	10/58 (17.2 %)	6/37 (16.2 %)	0.8964
Comorbidities (n, %)			
Respiratory	21/58 (36.2 %)	18/37 (48.6 %)	0.4546
Cardiovascular	9/58 (15.5 %)	2/37 (5.4 %)	0.1331
Renal	2/58 (3.4 %)	3/37 (8.1 %)	0.3744
Liver	3/57 (5.3 %)	3/37 (8.1 %)	0.6769
Neurological/ psychiatric	8/58 (13.8 %)	3/37 (8.1 %)	0.3984
Diabetes mellitus	5/58 (8.6 %)	7/37 (18.9 %)	0.1407
Non-pulmonary malignancies	12/58 (20.7 %)	4/37 (10.8 %)	0.2096
Lung function parameters (median, quartiles [1st; 3rd])			
FVC (absolute values, L)	3.18 [2.76-3.79]	3.37 [2.84-4.19]	0.2476
FEV ₁ (absolute values, L)	2.25 [1.97-2.92]	2.24 [1.64-3.07]	0.4897
DLCO (absolute values, L)	5.29 [4.23-6.25]	4.40 [3.31-6.05]	0.0393
Lung function parameters (median, quartiles [1st; 3rd])			
FVC (predicted, %)	82.50 [72.75-98.00]	79.00 [71.50-91.00]	0.2903
FEV ₁ (predicted, %)	80.50 [67.00-90.25]	69.00 [55.50-85.00]	0.0103
DLCO (predicted, %)	62.50 [50.50-70.50]	48.00 [42.00-62.00]	0.0023
FEV ₁ / FVC(%)	95.00 [87.00-102.00]	88.00 [78.00-95.00]	0.0014

Abbreviations: BMI: body mass index; PY: pack years; FVC: functional vital capacity; FEV₁: forced expiratory volume in one second; DLCO: diffusing capacity of the lung for carbon monoxide.

Specific comorbidities (**Table 1**) were not significantly associated with the histology of the primary tumor.

Laboratory parameters on admission day (routinely 1 - 5 days before surgery) showed a low hemoglobin level in all patients upon neoadjuvant therapy. There was no significant difference in the sex-specific hemoglobin level (< 12g/dl in females and < 13g/dl in males) between LUAD and SQCA groups ($p=0.7246$). Patients from LUAD group were admitted with lower serum C-reactive protein levels (CRP 0.20 [0.10; 0.60] vs 0.50 [0.10; 1.30], $p=0.0206$) and higher serum albumin levels (4.27 [3.90; 4.46] vs 4.00 [3.60; 4.35], $p=0.0281$). The standard laboratory parameters on admission day stratified by the histological subtypes of the primary tumor are illustrated in **Table 2**.

Table 2. Preoperative laboratory tests in patients undergoing neoadjuvant chemotherapy and surgical resection of primary lung tumors classified by histology of primary tumor.

Parameters preoperatively (median, quartiles [1 st ; 3 rd])	LUAD n=58	SQCA n=37	P-value
Blood counts			
Leukocytes (/nL)	6.15 [4.58; 7.30]	5.60 [4.35; 7.90]	0.7923
Erythrocytes (/pL)	3.74 [3.48; 3.91]	3.56 [3.33; 4.01]	0.7688
Hemoglobin (g/dL)	11.9 [11.10; 12.43]	11.6 [10.85; 12.60]	0.8396
Thrombocytes (/nL)	240.5 [204.0; 288.25]	221.0 [198.5; 268.5]	0.3046
Clinical chemistry			
CRP (mg/dL)	0.20 [0.10; 0.60]	0.50 [0.10; 1.30]	0.0206
Creatinine (mg/dL)	0.90 [0.78; 1.00]	1.0 [0.80; 1.10]	0.1304
Albumin (g/dL)	4.27 [3.90; 4.46]	4.00 [3.60; 4.35]	0.0281
LDH (IU/L)	200.0 [169.8; 244.0]	188.0 [174.0; 211.0]	0.2323

Abbreviations: CRP: C-reactive protein; eGFR: estimated glomerular filtration rate; LDH: lactate dehydrogenase.

No significant differences regarding tumor side, localization, and lymph node involvement were reported between groups. LUAD group comprised significantly more patients with cT₁ tumors (11/58 (19.0 %) vs 0/37 (0 %), $p=0.0048$) and fewer patients with cT₄ tumors (23/58 (39.7 %) vs 24/37 (64.9 %), $p=0.0166$).

Upon neoadjuvant therapy, significantly more patients with yT₀ tumors were reported in the SQCA group (22/37 (59.5 %) vs 10/58 (17.2 %), $p <0.0001$). The tumor characteristics are presented in **Table 3**.

Table 3. Tumor characteristics in patients undergoing neoadjuvant chemotherapy and surgical resection of primary lung tumors classified by histology of primary tumor.

Tumor characteristics	LUAD n=58	SQCA n=37	P-value
Tumor side (n, %)			
Left	27/58 (46.6 %)	16/37 (43.2 %)	0.7521
Right	31/58 (53.4 %)	21/37 (56.8 %)	
Tumor localization (n, %)			
Left upper lobe	17/58 (29.3 %)	13/37 (35.1 %)	0.5515
Left lower lobe	10/58 (17.2 %)	3/37 (8.11 %)	0.2066
Right upper lobe	22/58 (37.9 %)	11/37 (29.7 %)	0.3521
middle lobe	2/58 (3.4 %)	2/37 (5.4 %)	0.6432
Right lower lobe	7/58 (12.1 %)	8/37 (21.6 %)	0.2131
TNM7 classification (n, %)			
cT ₁	11/58 (19.0 %)	4/37 (10.8 %)	0.0048

cT ₂	10/58 (17.2 %)	9/37 (24.3 %)	0.3886
cT ₃	14/58 (24.1 %)	24/37 (64.9 %)	0.9830
cT ₄	23/58 (39.7 %)		0.0166
Lymph node involvement (n, %)		4/37 (10.8 %)	
cN ₀	9/58 (15.5 %)	7/37 (18.9 %)	0.5151
cN ₁	11/58 (19.0 %)	22/37 (59.5 %)	0.9955
cN ₂	35/58 (60.3 %)	4/37 (10.8 %)	0.9315
cN ₃	3/58 (5.2 %)		0.3050
Pleura visceralis infiltration (n, %)	21/58 (36.2 %)	4/37 (10.8 %)	0.0061
TNM7 classification (n, %)		22/37 (59.5 %)	<0.0001
yT ₀	10/58 (17.2 %)	10/37 (27.0 %)	0.4459
yT ₁	20/58 (34.5 %)	2/37 (5.4 %)	0.0608
yT ₂	11/58 (19.0 %)	2/37 (5.4 %)	0.1331
yT ₃	9/58 (15.5 %)	1/37 (2.7 %)	0.0719
yT ₄	8/58 (13.8 %)		
Lymph node involvement (n, %)		33/37 (89.2 %)	0.0014
yN ₀	34/58 (58.6 %)	4/37 (10.8 %)	0.9425
yN ₁	6/58 (10.3 %)	0/37 (0 %)	0.0003
yN ₂	17/58 (29.3 %)	0/37 (0 %)	0.4220
yN ₃	1/58 (1.7 %)		

cT₁₋₄: tumor stage 1-4 according to the TNM7 (tumor node metastasis staging system 7, [10]) assessed on computed tomography, cN₀₋₃: lymph node involvement N₀₋₃ according to the TNM7 on computed tomography. yT₀₋₄: tumor stage 0-4 according to the TNM7 upon neoadjuvant therapy assessed from the intraoperative histology; yN₀₋₃: lymph node involvement N₀₋₃ according to the TNM7 upon neoadjuvant therapy assessed from the intraoperative histology.

The characteristics of the surgical procedures are illustrated in **Table 4**.

Table 4. Technical aspects of the tumor resection in patients undergoing neoadjuvant chemotherapy and surgical resection classified by histology of primary tumor.

Features of the surgical procedures	LUAD n=58	SQCA n=37	P-value
Resection side (n, %)			
Left	27/58 (46.6 %)	16/37 (43.2 %)	
Right	31/58 (53.4 %)	21/37 (56.8 %)	0.7521
Surgical approach (n, %)			
Open (thoracotomy)	50/58 (86.2 %)	35/37 (94.6%)	0.1939
Minimally invasive (VATS)	5/58 (8.6 %)	2/37 (5.4%)	0.7017
Conversion to open	3/58 (5.2 %)	0/37 (0.0%)	0.2791
Resection extent (n, %)			
Lobectomy	50/58 (86.2 %)	25/37 (67.6%)	0.0298
Multilobar -Bilobectomy	4/58 (6.9 %)	4/37 (10.8%)	0.7071
-Pneumonectomy	4/58 (6.9 %)	8/37 (21.6%)	0.0351
Topographical resection (n, %)			
Sleeve resection	11/58 (19.0 %)	9/37 (24.3%)	0.5321

Thoracic wall	4/58 (6.9 %)	2/37 (5.4%)	1.000
Surgery time (median, quartiles [1st; 3rd])			
(minutes)	213.0 [171.5; 262.5]	216.0 [165.5;275.0]	0.6333
Neoadjuvant therapy			
Chemotherapy	14/58 (24.1 %)	4/37 (10.8 %)	0.1060
Chemo- and Immunotherapy	5/58 (8.6 %)	2/37 (5.4 %)	0.7017
Radiation therapy	0/58 (0.0 %)	1/37 (2.7 %)	0.3895
Chemo- and Radiation therapy	34/58 (58.6 %)	30/37 (81.1 %)	0.0228
Chemo-, Immuno, and Radiation therapy	5/58 (8.6 %)	0/37 (0.0 %)	0.1527
Adjuvant therapy			
Chemotherapy	1/57 (1.8 %)	0/36 (0.0 %)	1.0000
Immunotherapy	9/57 (15.8 %)	0/36 (0.0 %)	0.0121
Chemo- and Immunotherapy	0/57 (0.0 %)	1/36 (2.8 %)	0.3871
Radiation therapy	8/57 (14.0 %)	1/36 (2.8 %)	0.0737
Chemo-, Immuno, and Radiation therapy	1/57 (1.8 %)	1/36 (2.8 %)	1.0000
Length of stay (median, quartiles [1st; 3rd])			
(days)			
In-hospital stay	11.0 [8.0; 14.0]	13.0 [9.5; 24.5]	0.0458
ICU stay	1.0 [1.0; 2.0]	3.0 [1.0; 5.0]	0.0039
ICU > 3 days (n, %)	10/58 (17.2 %)	12/37 (32.4%)	0.0870
ICU > 7 days (n, %)	3/58 (5.2 %)	4/37 (10.8%)	0.4255
Readmission within 30 days (n, %)	4/58 (6.9 %)	4/37 (10.8%)	0.7071
Primary Tumor relapse or metastasis (n, %)	31/57 (54.4 %)	8/36 (22.2%)	0.0022
Mortality (n, %)			
During maximal follow-up	25/58 (43.1 %)	21/37 (56.8%)	0.5041
Within 30 days postoperatively	2/58 (3.5 %)	2/37 (5.4%)	1.0000
Overall survival (estimate [lower bound; upper bound], months)	55.00 [17.06; 92.94]	71.00 [44.89; 97.11]	0.5041

Abbreviations: ABT: allogenic blood transfusion; VATS: video-assisted thoracoscopic surgery.

No significant differences on the tumor resection side ($p=0.7521$), surgical approach (open vs minimally invasive surgery, $p=0.1939$), and operative time ($p=0.6333$) were reported. Whereas the LUAD group included more patients undergoing lobectomies upon neoadjuvant treatment (50/58 (86.2 %) vs 25/37 (67.6%), $p=0.0298$), the SQCA group comprised more patients undergoing multilobar resections (pneumonectomy, 8/37 (21.6%) vs 4/58 (6.9 %), $p= 0.0351$).

Regarding the neoadjuvant regimen, 18 patients (18.9%) underwent chemotherapy alone, 7 patients (7.4%) chemoimmunotherapy, one patient (1.1%) radiation therapy, 64 patients (67.4%) chemoradiation and 5 patients (5.3%) a combination of all three approaches. Patients with combined neoadjuvant chemo- and radiation therapy were significantly more frequent in the SQCA group (30/37 (81.1 %) vs 34/58 (58.6 %), $p=0.0228$, Table 4).

The median in-hospital stay upon surgery was significantly longer in patients with SQCA (13.0 [9.5; 24.5] vs 11.0 [8.0; 14.0] days, $p= 0.0458$). Proportionally, the stay in the intensive care unit was longer in the SQCA group (3.0 [1.0; 5.0] vs 1.0 [1.0; 2.0] days, $p=0.0039$).

The analysis of the intraoperative histological specimens revealed significantly more patients experiencing >10% vital tumor cells (TRG_Ila) in the LUAD group (27/58 (46.6 %) vs 5/37 (13.5%), p= 0.0009) and more patients with no vital tumor cells (TRG_III) in the SQCA group (20/37 (54.1%) vs 10/58 (17.2 %), p=0.0002). This was under the significantly higher incidence of yT₀ tumors in the SQCA group (22/37 (59.5%) vs 10/58 (17.2 %), p<0.0001) and lower incidence of yT₄ tumors in the SQCA group (1/37 (2.7%) vs 8/58 (13.8 %), p= 0.0719, **Table 5**).

Table 5. Characterization of tumor regression proportion score according to Junker et al. in patients undergoing neoadjuvant therapy and major surgical resections classified by histology of the primary tumor.

Characterization of Tumor regression score	LUAD n=58	SQCA n=37	P-value
TNM7 classification (n, %)			
yT ₀	10/58 (17.2 %)	22/37 (59.5%)	<0.0001
yT ₁	20/58 (34.5 %)	10/37 (27.0%)	0.4459
yT ₂	11/58 (19.0 %)	2/37 (5.4%)	0.0608
yT ₃	9/58 (15.5 %)	2/37 (5.4%)	0.1331
yT ₄	8/58 (13.8 %)	1/37 (2.7%)	0.0719
Lymph node involvement (n, %)			
yN ₀	34/58 (58.6 %)	33/37 (89.2%)	0.0014
yN ₁	6/58 (10.3 %)	4/37 (10.8%)	0.9425
yN ₂	17/58 (29.3 %)	0/37 (0.0%)	0.0003
yN ₃	1/58 (1.7 %)	0/37 (0.0%)	1.0000
Tumor Regression Score (Junker et al) (n, %)			
TRG_I (> 95% vital tumor cells)	27/58 (46.6 %)	3/37 (8.1%)	0.7166
TRG_Ila (> 10% vital tumor cells)	15/58 (25.9 %)	5/37 (13.5%)	0.0009
TRG_Ilb (< 10% vital tumor cells)	10/58 (17.2 %)	9/37 (24.3%)	0.8664
TRG_III (no vital tumor cells)		20/37 (54.1%)	0.0002
Tumor size in CT (median, quartiles [1st; 3rd] (cm)			
Before neoadjuvant treatment	3.95 [2.40; 6.68]	5.50 [3.60; 6.35]	0.2105
After neoadjuvant treatment before surgery	2.55 [1.50; 4.60]	3.30 [1.85; 4.35]	0.3758
Delta (before-after) neoadjuvant treatment before surgery (absolute)	1.15 [0.55; 2.50]	1.70 [0.60; 3.10]	0.4248
Delta (before-after) neoadjuvant treatment before surgery (relative)	30.73 [14.95; 53.55]	32.14 [14.17; 51.05]	0.8397
Lymph node size in CT (median, quartiles [1st; 3rd] (cm)			
Before neoadjuvant treatment	1.60 [1.20; 2.03]	1.60 [1.00; 2.20]	0.9299

yT₀₋₄: tumor stage 0-4 according to the TNM7 staging system upon neoadjuvant therapy assessed from the intraoperative histology; yN₀₋₃: lymph node involvement N₀₋₃ according to the TNM7 upon neoadjuvant therapy assessed from the intraoperative histology; TRG: tumor regression grade according to the classification of Junker et al [8]. Absolute delta values = tumor size before neoadjuvant treatment - tumor size after neoadjuvant treatment. Relative delta values = ((tumor size before neoadjuvant treatment - tumor size after neoadjuvant treatment) / tumor size before neoadjuvant treatment) x 100.

The tumor size before and after neoadjuvant treatment was larger in the SQCA group in comparison to the LUAD group (**Table 5**).

3.2. Logistic Regression Analysis of Risk Factors

Since TRG_III, which is defined by the absence of the vital tumor cells (CPR) in the histological specimens, occurred significantly more frequently in the SQCA group (20/37 (54.1%) vs 10/58 (17.2%), $p=0.0002$), it is of particular interest to characterize this patient subgroup to identify meaningful parameters that independently predict tumor regression.

For this reason, a univariate analysis considering two groups (TRG_I-II and TRG_III) was performed, considering the histological classification of the primary tumor (LUAD, SQCA). Intraoperative histology, lymph node size, as well as tumor size after neoadjuvant treatment were significantly associated with tumor regression grade ($p<0.05$ each). To assess easily available continuous parameters for clinical routine, optimal cut-off values derived by ROC analysis were computed as binary variables and incorporated in a multivariable binary regression analysis. The following parameters were further confirmed as statistically significant: intraoperative histology (SQCA), lymph node size $> 1.7\text{cm}$, and absolute delta tumor size before-after neoadjuvant therapy $> 2.6\text{ cm}$. The corresponding odds ratios (OR) in predicting TPG_III and their 95% confidence intervals were 6.88 (2.40-19.77, $p=0.0003$), 3.13 (1.11-8.83, $p=0.0310$) and 3.76 (1.20-11.81, $p=0.0233$). The robustness of the regression analysis was confirmed by three independent methods (Enter, Forward LR, and Backward LR). The results were also reproduced by using absolute values instead of binary variables (derived from cut-off values) with qualitatively unchanged results.

The logistic regression model is summarized in **Table 6**.

Table 6. Binary logistic regression model predicting complete pathologic response in primary lung cancer patients undergoing neoadjuvant chemotherapy and major surgical resections.

Covariates for tumor regression	Exp(B) [95% CI]	P-value
Intraoperative histology (LUAD vs SQCA)	6.88 [2.40-19.77]	0.0003
Lymph node size in preoperative PET $> 1.7\text{cm}$	3.13 [1.11-8.83]	0.0310
Absolute Delta tumor size post neoadjuvant Therapy $> 2.6\text{cm}$	3.76 [1.20-11.81]	0.0233

Abbreviations: SQCA: squamous cell lung cancer; LUAD: Lung adenocarcinoma; Exp(B) = Odds ratio, 95% Confidence interval [lower bound-upper bound]. Absolute delta values = tumor size before neoadjuvant treatment - tumor size after neoadjuvant treatment.

To assess easily available parameters for clinical routine, relative delta values ((tumor size before neoadjuvant treatment - tumor size after neoadjuvant treatment/tumor size before neoadjuvant treatment) $\times 100$) were also calculated. By using ROC Analysis and the Youden criterion we identified a relative delta value $> 30\%$, which coincides with a 30% tumor reduction after neoadjuvant treatment, as an independent predictor of complete pathologic response. The multivariable analysis was reproduced as sensitivity analysis when using relative delta values for tumor reduction ($> 30\%$), with qualitatively unchanged results (Table 7). This result was consistently verified with three selection methods (Enter, Forward, and Backward).

Table 7. Binary logistic regression model predicting complete pathologic response in primary lung cancer patients undergoing neoadjuvant chemotherapy and major surgical resections.

Covariates for tumor regression	Exp(B) [95% CI]	P-value
Intraoperative histology (LUAD vs SQCA)	6.81 [2.34-19.77]	0.0004
Lymph node size in preoperative PET $> 1.7\text{cm}$	3.86 [1.35-11.10]	0.0119
Relative delta (tumor size post neoadjuvant Therapy) $> 30\%$	4.54 [1.49-13.84]	0.0079

Abbreviations: SQCA: squamous cell lung cancer; LUAD: Lung adenocarcinoma; Exp(B) = Odds ratio, 95% Confidence interval [lower bound-upper bound]. Relative delta values = ((tumor size before neoadjuvant treatment - tumor size after neoadjuvant treatment) / tumor size before neoadjuvant treatment) $\times 100$.

3.3. Survival Analysis

To assess the overall survival (OS) of the patients included in the study, we further analyzed each clinical parameter presented in Tables 1-5 with the Kaplan-Meier method. Median overall survival for the whole cohort was 71 [47.0-95.0] months. Forty-six death events were recorded in the whole cohort during 330 cumulative follow-up years (Figure 2A).

Patients aged 70 years or older experienced a reduced OS (n= 21, 5-year OS 38.1%) in comparison to younger patients (n=74, 5-year OS=55.9%, p=0.0325, Figure 2B)

No significant difference was noted in the OS of patients when considering BMI, smoking status, alcohol consumption, and comorbidities. Patients with FEV₁, FVC, and DLCO >70% have a slightly improved OS (without statistical significance) in comparison to those patients with reduced lung function parameters. Patients suffering from LUAD (n=58) had an almost similar OS (5-year OS=49.4%) when compared to SQCA patients (n= 37, 5-year OS=53.5%, p=0.5041, Figure 2C).

Tumor side, lobe localization, and surgical approach (open vs. minimally invasive surgery) were not significantly associated with OS. An extended resection (>1 lobe, n=20) was significantly associated with a worse prognosis (5-year OS =30.0%) in comparison with patients undergoing standard lobectomies (n=75, 5-year OS 58.3%, p=0.0070, Figure 2D).

A tumor stage >yT₃ (n=20) had a significantly decreased OS (5-year OS=26.8%) in comparison to smaller tumor stages (<yT₃, n=75, 5-year OS 60.1%, p=0.0251, Figure 2E). The lymph node involvement after neoadjuvant therapy was not significantly associated with OS. No significant differences in OS could be reported when considering comparisons between tumor regression scores (TRG I vs II vs III, Figure 3A).

An absolute tumor size reduction > 2.6 cm after neoadjuvant therapy (absolute delta > 2.6cm) was significantly associated with an improved OS (n=24, 5-year OS=81.8% vs. n=71, 5-year OS=43.1%, p=0.0122, Figure 3B). Qualitatively unchanged results were obtained when using relative delta values (tumor size reduction > 30%). Accordingly, an improved OS was observed in the patient's group experiencing a relative tumor size reduction> 30% (n=52, 5-year OS=65.1% vs. n=43, 5-year OS=38.8%, p=0.0415).

Patients experiencing a tumor recurrence or metastasis during follow-up had a significantly worse prognosis in comparison to those patients without (n=39, 5-year OS=26.0% vs. n=54, 5-year OS=77.3%, p=0.0017, Figure 3C).

To assess the independent predictive value of the abovementioned parameters on OS, a multivariate Cox regression analysis was performed. Here, we identified age (>70 years), extended resections (>1 lobe), and tumor recurrence or metastasis during follow-up as independent negative predictors of long-term OS. These predictors increased the risk of death by 2.70-, 2.11-, and 2.41-fold, respectively (Exp(B) OR 2.70 [1.37-5.36], p=0.0043, 2.11 [1.10-4.08], p=0.0257; 2.41 [1.27-4.54], p=0.0068. On the contrary, the tumor size reduction after neoadjuvant therapy (> 2.6 cm) was an independent parameter of improved OS (Exp(B) 3.82 [1.33-10.92], p=0.0126. Figure 3D, Table 8.

Table 8. Binary logistic regression model predicting overall survival in primary lung cancer patients undergoing neoadjuvant chemotherapy and major surgical resections.

Independent predictors of overall survival	Exp(B) [95% CI]	P-value
Age (>70 years)	2.70 [1.37-5.36]	p=0.0043
Extended resections (>one lobe)	2.11 [1.10-4.08]	p=0.0257
Absolute tumor size reduction >2.6 cm after neoadjuvant therapy (absolute delta)	3.82 [1.33-10.92]	p=0.0126
Tumor recurrence or metastasis during follow-up	2.41 [1.27-4.54]	p=0.0068

Abbreviations: Exp(B) = Hazard ratio, 95% Confidence interval [lower bound-upper bound]. Absolute delta values = tumor size before neoadjuvant treatment - tumor size after neoadjuvant treatment.

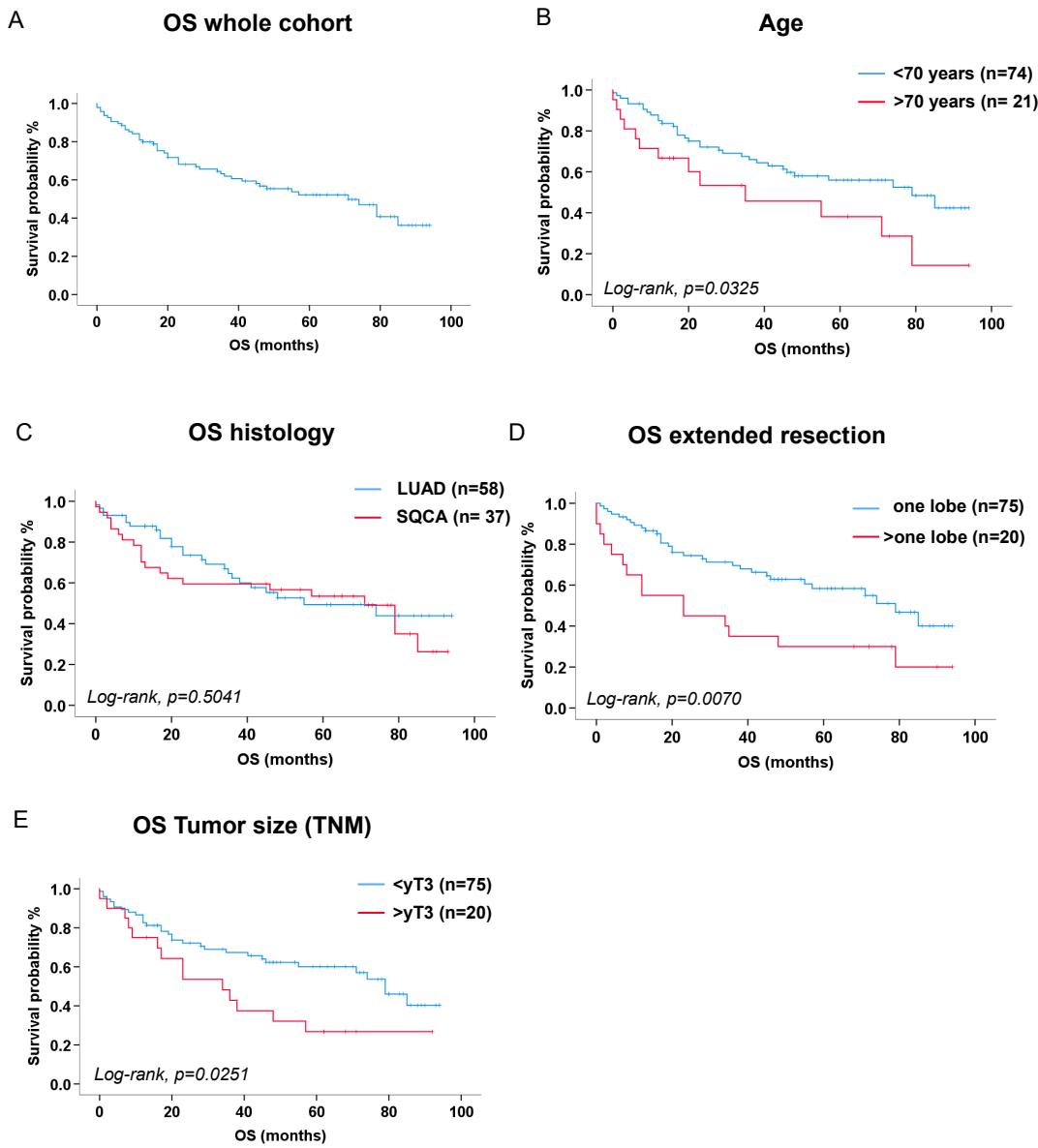


Figure 2. Survival analysis. Kaplan-Meier curves depicting overall survival (A), OS according to age (B), OS according to histology (C), OS according to the extent of resection (D), and OS according to tumor size (TNM).

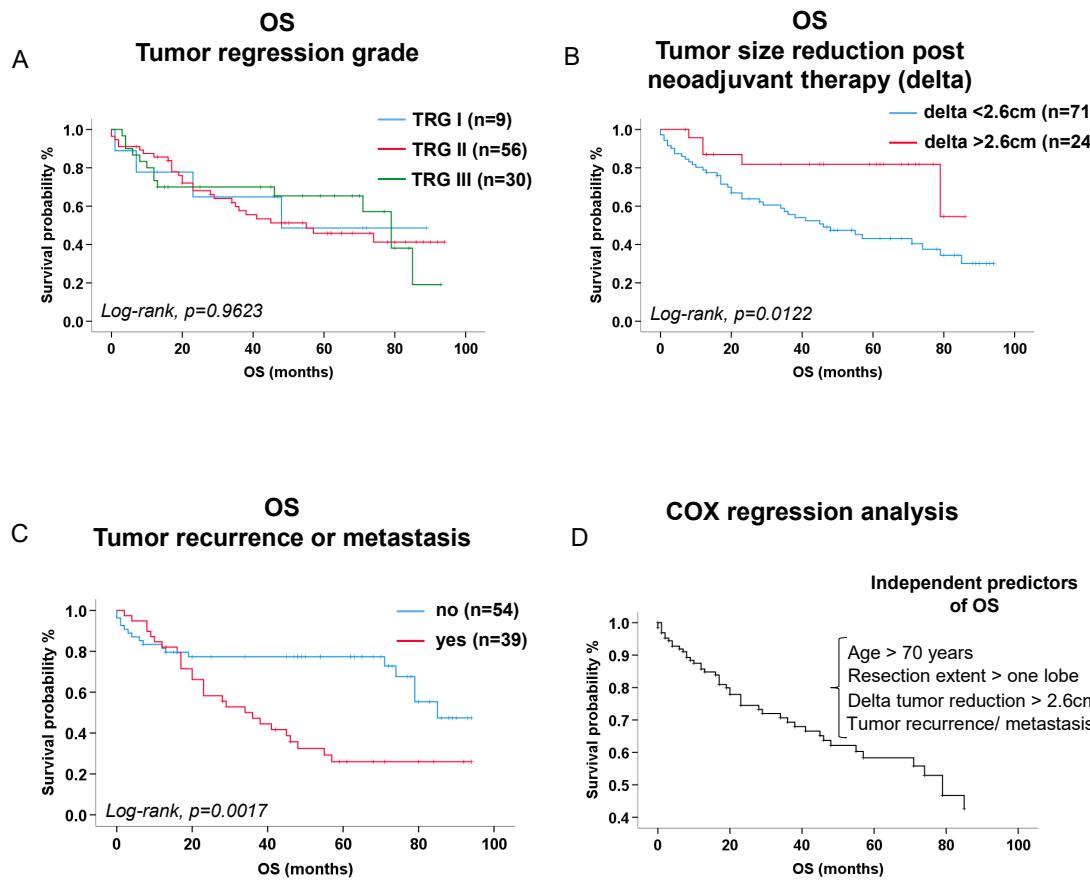


Figure 3. Survival analysis. Kaplan-Meier curves depicting OS according to tumor regression grade (A), OS according to tumor size reduction after neoadjuvant therapy (B), OS according to tumor recurrence and metastasis (C), Cox proportional hazard regression analysis depicting independent predictors of OS (D).

4. Discussion

The findings of our study shed light on the predictive value of histological and radiological parameters, including primary tumor histology, lymph node size, and tumor size upon neoadjuvant treatment initiation, in determining the effectiveness of tumor regression in patients undergoing major lung cancer resections. These insights have significant implications for treatment planning, prognostic assessment, and therapeutic decision-making in the management of advanced lung cancer.

In our cohort 30 patients (31.57%) experience CPR upon neoadjuvant therapy. Interestingly CPR was significantly higher in the SQCA group, by previous published data (4%-33%) [13–15].

Histological assessment of the primary tumor emerges as a critical determinant of treatment response in patients undergoing neoadjuvant therapy. In contrast to our results, Zens et al. showed that the major pathological response after neoadjuvant treatment was more observed in lung adenocarcinoma patients, where only 11% of SQCA had a complete pathological response [9]. In the retrospective analyses from Schreiner et al. CPR was more observed in patients with adenocarcinoma also [16].

Furthermore, various anatomical measurements of changes in tumor size and lymph node size on CT or PET/CT scans were analyzed to improve the preoperative CPR prediction. CT scan delivers anatomical information based on morphological tumor alterations. However, even after dramatic tumor downstaging, vital cells may still be present. Therefore, the morphological evaluation may be misleading in some patients. Despite this, we identified the rate of reduction in the primary tumor size on CT or PET/CT scans as an independent predictor of CPR. This result is in line with existing

literature [17,18]. In contrast, a lack of correlation between CT-based volume reduction and pathologic response was identified by Cerfolio *et al.* and Pöttgen *et al.* [19,20]. The inconsistency might have resulted from the small sample size of these studies. Moreover, we identified the lymph node size > 1.7 cm at the time of diagnosis also as an independent predictor of CPR. Coroller *et al.* could also identify radiological features of lymph nodes as predictors of CPR after neoadjuvant treatment in NSCLC patients [21].

In our study, OS estimates were reduced in patients aged over 70 years, in resections of more than one lobe group, and in patients experiencing recurrence or metastasis during the follow-up period. Pilotto *et al.* developed a scoring system for squamous cell carcinoma patients of the lung, where the age of patients was also one of the risk factors in predicting OS in adjuvant and neoadjuvant therapy groups [22].

Patients with a tumor size reduction of more than 2.6 cm after neoadjuvant therapy could show better OS in our cohort. In contrast to our findings, Tanahashi *et al.* couldn't find any survival benefits in patients with tumor size reduction after neoadjuvant therapy [17]. This could be explained by the difference in study population heterogeneity, cohort size, and chosen therapy regimens.

Surprisingly in our cohort, we couldn't identify any significant benefit of OS in patients with pathological complete response in comparison to CheckMate 816 and Keynote 671 studies [23,24]. It can also be explained by the heterogeneity of patient populations and treatment regimens. Another reason for this may be the shorter follow-up periods in above mentioned studies.

While our study provides valuable insights into the predictive factors of tumor regression effectiveness in neoadjuvant-treated lung cancer patients, several limitations warrant consideration. The retrospective nature of our analysis may introduce inherent biases and confounding variables that could impact the interpretation of results. Additionally, the heterogeneity of patient populations and treatment regimens may limit the generalizability of our findings.

Our sample size is comparable to other retrospective cohorts investigating potential survival predictors in NSCLC after neoadjuvant treatment and the role of tumor regression: Zens *et al.* (n=117), Remark *et al.* (n=122), Betticher *et al.* (n=75) [9,25,26].

5. Conclusions

Prospective studies incorporating larger patient cohorts and standardized treatment protocols are needed to validate the prognostic utility of these histological parameters and refine predictive models for treatment response in neoadjuvant-treated lung cancer patients.

In summary, our study elucidates the predictive value of histological parameters, including primary tumor histology, lymph node involvement, and tumor size upon neoadjuvant treatment initiation, in determining the effectiveness of tumor regression in patients undergoing major lung cancer resections. These findings have significant implications for personalized treatment planning and prognostic assessment in the management of advanced lung cancer, ultimately guiding therapeutic decisions and improving patient outcomes.

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