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## Perioperative course and quality of life in a prospective randomized multicenter phase III trial, comparing standard lobectomy versus anatomical segmentectomy in patients with non-small cell lung cancer up to 2 cm, stage IA (7th edition of TNM staging system)

Georgios Stamatis<sup>a,\*</sup>, Gunda Leschber<sup>b</sup>, Birte Schwarz<sup>a</sup>, Diana Lütke Brintrup<sup>c</sup>, Claudia Ose<sup>c</sup>, Gerhard Weinreich<sup>d</sup>, Bernward Passlick<sup>e</sup>, Erich Hecker<sup>f</sup>, Christian Kugler<sup>g</sup>, Hendrik Dienemann<sup>h</sup>, Thomas Krbeke<sup>i</sup>, Stephan Eggeling<sup>j</sup>, Rudolf Hatz<sup>k</sup>, Michael Rolf Müller<sup>l</sup>, Walter Weder<sup>m</sup>, Clemens Aigner<sup>a</sup>, Karl-Heinz Jöckel<sup>c</sup>

<sup>a</sup> Thoracic Surgery and Endoscopy, University Medicine Essen- Ruhrlandklinik, University of Duisburg-Essen, Essen, Germany

<sup>b</sup> Departement of Thoracic Surgery, Evangelische Lungenklinik ELK Chest Hospital, Berlin, Germany

<sup>c</sup> Institute for Medical Informatics, Biometry and Epidemiology (IMIBE), University of Duisburg-Essen, Essen, Germany

<sup>d</sup> Pneumology, Ruhrlandklinik, University Medicine Essen- Ruhrlandklinik, University of Duisburg-Essen, Essen, Germany

<sup>e</sup> Departement of Thoracic Surgery, University Freiburg, Germany

<sup>f</sup> Departement of Thoracic Surgery, Evangelisches Krankenhaus Herne, Germany

<sup>g</sup> Departement of Thoracic Surgery, LungenClinic Grosshansdorf, Germany

<sup>h</sup> Departement of Thoracic Surgery, Heidelberg University, Germany

<sup>i</sup> Departement of Thoracic Surgery, Krankenhaus Bethanien Moers, Germany

<sup>j</sup> Departement of Thoracic Surgery, Vivantes Klinikum Neukölln, Berlin, Germany

<sup>k</sup> Departement of Thoracic Surgery, Asklepios Fachkliniken München-Gauting, Germany

<sup>l</sup> Departement of Thoracic Surgery, Otto Wagner Spital Wien, Austria

<sup>m</sup> Departement of Thoracic Surgery, UniversitätsSpital Zürich, Switzerland

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## ABSTRACT

**Objectives:** For early stage non-small cell lung cancer (NSCLC) retrospective data of functionally compromised patients undergoing segmentectomy showed equal outcomes for perioperative complications and quality of life (QoL) compared with lobectomy patients. However no prospectively randomized data comparing patients eligible for both procedures are available.

**Materials and methods:** We conducted a prospective, randomized, multicenter phase III trial and investigated perioperative complications and QoL in patients with NSCLC stage IA (7th edition) undergoing segmentectomy versus lobectomy. The EORTC Questionnaire Core-30 (QLQ C-30) supplemented by thirteen-item lung cancer-specific module (LC13) was assessed before surgery, at discharge, 6 weeks, 3, 6 and 12 months post-surgery.

**Results:** 108 patients with verified or suspected NSCLC up to 2 cm diameter were enrolled, whereby 54 were assigned to lobectomy and 54 to segmentectomy. Due to nodal disease, tumor size and surgical reasons estimated during the operation, eight patients of the segmentectomy group received a lobectomy. In hospital and 90 days mortality was 0% in both groups. Perioperative complications were observed in 6 (11.3%) patients after segmentectomy and in 8 patients (14.8%) after lobectomy ( $p = 0.563$ ), while the 90-day morbidity were 17% and 25.9% (9 and 14 patients), respectively ( $p = 0.452$ ). Twelve months after surgery, there was a significant deterioration to the baselines of physical ( $p < 0.001$ ) and cognitive functioning ( $p = 0.025$ ), dyspnea ( $p < 0.001$ ) and fatigue ( $p = 0.003$ ) in the lobectomy group. Dyspnea showed a faster recovery in the seg-

\* Corresponding author at: Ruhrlandklinik, West German-Lung-Center, University Medicine Essen, University of Duisburg-Essen, Tuschener Weg 40, 45239, Essen, Germany.

E-mail address: [georgios.stamatis@uk-essen.de](mailto:georgios.stamatis@uk-essen.de) (G. Stamatis).

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mentectomy compared to lobectomy group with statistical significance ( $p = 0.016$  after 12 months).

**Conclusion:** In patients with early-stage NSCLC, segmentectomy is associated with a statistically not significant lower perioperative morbidity and appears to provide a superior recovery in QoL compared with lobectomy patients.

## 1. Introduction

According to current guidelines, lobectomy is the recommended primary therapeutic option for patients with NSCLC stage I and adequate lung function [1–3]. For patients with early-stage NSCLC and a tumor diameter up to 2 cm, current medical literature reports five-year survival rates between 77% and 88% after surgical treatment alone [4,5]. A segmentectomy with tumor-free margins of about 2 cm has shown comparable survival rates to lobectomy in some series [6–8]. Additionally, published data of retrospective studies refer to a lower post-operative morbidity and mortality as well as a better lung function in the segmentectomy group without taking the underlying reason for segmentectomy into account [9,10].

Considering the current treatment options for early-stage NSCLC, analysis of QoL has gained growing interest in the last decade as an important measure of the outcome of tumor treatment, including physical and mental handicaps, because the risk of death for these patients is proportionally low. However, post-operative symptoms such as pain, dyspnea and functional limitations can have a lasting effect on daily activities. A number of studies of QoL have been performed, comparing thoracoscopic procedures versus open surgery [11–13] or analyzing the impact of the extent of surgical resection, comparing lobectomy/bilobectomy vs pneumonectomy [14,15] or lobectomy vs bilobectomy [16]. Only two studies have compared lobectomy vs limited resection, although in these studies most of the patients received a wedge resection and only a small number underwent a segmentectomy [17].

In view of these data in the literature, we conducted a phase-III trial to compare only patients undergoing anatomical segmentectomy or lobectomy and complete ipsilateral lymphadenectomy for NSCLC stage IA (TNM 7<sup>th</sup> edition). Patients with wedge resection were not included in the study. Furthermore, resection margins of at least 2 cm healthy parenchyma was required in the frozen section. If this was not achieved, the resection was extended to the proximate segment. The primary efficacy outcomes for these procedures were QoL scores and overall survival (OS), while the secondary outcomes were perioperative morbidity and mortality and disease-free survival (DFS). We used the Quality of Life Questionnaire-C30 of the European Organisation for Research and Treatment Cancer (EORTC QLQ-C30), together with the

lung cancer module (LC13), because it reflected the most convenient and accurate instrument for determining health-related QoL in lung cancer patients in Europe at the time of study [18,19]. In this manuscript, attention was paid to perioperative outcomes and QoL in both groups. A relevant statistical outcome of OS and DFS will be estimated once a sufficient long follow-up period is achieved.

## 2. Material and methods

### 2.1. Study design

This is a prospective, randomized, non-blinded parallel group phase-III multicenter trial at eleven high-volume centers for thoracic surgery in Germany, Switzerland and Austria. The primary outcomes combine a non-inferiority (OS) and a superiority (QoL) hypothesis by the “intersection-union” principle, which means that both null hypotheses have to be rejected for a claim in favor of segmentectomy. This trial was approved by the Ethics Committee of the University of Essen (13-5520-BO), as well as the appropriate Ethics Committee of all participating centers. All German study sites are Lung Cancer Centers, certified by the German Cancer Society. The minimum qualification of a surgeon performing surgery within the study was national board certification as a general thoracic surgeon. All centers have named specialized pathologists for lung disease. The data monitoring and safety board comprised five external accredited experts in biometry, thoracic oncology, radiation oncology, pathology and thoracic surgery. The study was registered on 02/09/2013 at the German Clinical Trials Register (DRKS00004897).

After the initiation of each site, all patients were consecutively screened and all eligible patients, -who were willing to provide written informed consent-, were included in the trial. Pre-operative evaluation included positron emission tomography-computed tomography (PET-CT) and magnetic imaging (MRI) of the brain. Invasive mediastinal staging by endoscopic bronchial ultrasound guided fine needle aspiration (EBUS-TBNA) or mediastinoscopy was only conducted if positive mediastinal nodes were suspected in the PET-CT scan. Referring to the German S3 guidelines (AWMF register number 020/007OL), lung function testing including forced vital capacity (FVC), forced expiratory

**Table 1**  
Inclusion and exclusion criteria.

<b>Main inclusion criteria</b>	<ul style="list-style-type: none"> <li>● 41–80 years of age</li> <li>● Written informed consent before randomization and surgery</li> <li>● Full legal capacity</li> <li>● Negative pregnancy in pre-menopausal women</li> <li>● Karnofsky performance status 70–100%</li> <li>● Histological proven or suspected NSCLC <math>\leq 2</math> cm size without any known c/pN or any cM before surgery</li> <li>● Sufficient cardio-pulmonary function to perform a standard lobectomy plus radical lymphadenectomy (according to S3 guideline of German Cancer Society)</li> <li>● If tumor histology is definitively known before surgery, intraoperative definition of tumor size <math>\leq 2</math> cm might be sufficient</li> <li>● If tumor histology is not known before surgery, intraoperative definition of NSCLC in frozen section and tumor size <math>\leq 2</math> cm is mandatory before randomization</li> </ul>
<b>Main exclusion criteria</b>	<ul style="list-style-type: none"> <li>● In patients randomized for segmentectomy, resection margins must be at least 2 cm tumor-free considered by native lung tissue by pathology</li> <li>● Histologically-proven malignant tumor other than NSCLC or absence of any malignant tumor</li> <li>● Histologically-proven malignant lymph nodes</li> <li>● Patients with psychiatric or addictive disorders or dementia that may compromise the ability to give informed consent or have a complete follow-up</li> <li>● Known radiation or chemotherapy within the last 5 years</li> <li>● Second malignancy within the last 5 years (except basalioma)</li> <li>● NSCLC of the middle lobe (technical reasons)</li> <li>● Major cardiac surgery planned within 8 weeks from randomization</li> <li>● Participation in another therapeutic trial</li> </ul>

volume in 1 s (FEV1), diffusing lung capacity for carbon monoxide (DLCO) and blood gas analysis was conducted. Lung perfusion scan was performed in case of a history of lung embolism and echocardiography in case of previous cardiac history. Laboratory tests were standard care of major thoracic surgery. All patients were presented to an interdisciplinary board for the treatment decision. Inclusion and exclusion criteria are described in Table 1.

## 2.2. Randomization and surgical procedure

Patients underwent surgery if they fulfilled all inclusion criteria. If pre-operative histology or intraoperative frozen section provided proof of NSCLC with a maximum of up to 2 cm diameter and no lymph node involvement (NO), the patients were randomized to one of the two groups during surgery. Randomization was performed web-based by the center and surgery was performed accordingly. The operative approach – open versus video-assisted thoracic procedure (VATS) – was decided by the surgeon depending on his individual experience with either technique. Thoracotomy was performed through a muscle-sparing anterolateral incision, VATS using three trocars. Standard ipsilateral systematic lymphadenectomy was performed to facilitate histopathological examination and exclude patients with N1 or N2 disease from the study. Lymph node stations No. 2, 4, 7, 8, 9, 10 and 11 were removed on the right, and stations No. 4, 5, 6, 7, 8, 9, 10 and 11 on the left side. The procedure of standard lobectomy is well described in all manuals of thoracic surgery and most surgeons use a lobectomy as the procedure of choice in the treatment of lung cancer. Anatomical segmentectomy included the meticulous preparation of hilar structures with the identification of the artery, vein and bronchus of all interested segments in their hilar or intrafissural position. Vessels were closed by ligation, suture or stapler, and the bronchus by sutures or staplers. The intersegmental plane was identified by keeping the resected segments inflated and the preserved segments collapsed. Lung parenchyma division was conducted by cautery, stapler or the use of ultrasonic dissection devices. All enrolling surgeons were required to comply with a standardized protocol of anatomical segmentectomy and mediastinal lymphadenectomy, to ensure that the surgical technique was as similar as possible in all participating centers. Native pulmonary tissue after segmentectomy were sent for intraoperative histopathological

examination. If resection margins were found to be less than 2 cm, partial or complete resection of the proximate segment/s was indicated. In case of lymph node involvement, a lobectomy was performed.

## 2.3. QoL questionnaires

QoL was assessed with the Questionnaire Core-30 (QLQ C-30), supplemented by a thirteen-item lung cancer-specific questionnaire module, the EORTC QLQ-LC13. The QLQ-C30 is a 30-item cancer-specific questionnaire that incorporates five function scales (physical, role, emotional, cognitive and social), nine symptoms (fatigue, pain, nausea/vomiting, dyspnea, insomnia, loss of appetite, constipation, diarrhea and financial problems), and a global health status/QoL scale. The LC13 is a thirteen-item questionnaire that assesses lung cancer-specific symptoms such as cough, hemoptysis, severity of shortness of breath, chest/body pain, as well as chemotherapy/radiotherapy side effects such as a sore mouth, dysphagia, peripheral neuropathy and hair loss. Scores range from 0 to 100, with high scores reflecting a better level of functioning scales and more severe symptoms for symptoms scales. According to Osaba and associates, a difference between pre-treatment standardized scores and standardized scores after treatment of 5 to 10 points was rated as a small change, 10 to 20 points as a moderate change, and more than 20 points as a large, clinically-significant change from the patient's perspective [20].

## 2.4. Statistical analysis

Data are presented as numbers (%) or median and range unless otherwise stated. Statistical analysis of perioperative morbidity and mortality were conducted on an intention-to-treat (ITT) basis. For each patient and questionnaire, the QLQ-C30 as well as the QLQ-LC13 scores were summarized according the scoring manual. Analyses regarding the changes to the pre-operative baselines were conducted in the ITT basis. All fifteen of the scores from the QLQ-C30 as well as the ten scores from the QLQ-LC13 questionnaire were analyzed separately. Thus, a high score for a functional scale represents a high/healthy level of functioning, and a high score for the global health status/QoL represents a high QoL, whereas a high score for a symptom scale represents a high level of symptomatology and problems. Results are reported as means.

**Table 2**  
Demographics.

	Segmentectomy (n = 53)	Lobectomy (n = 54)	p
<b>Age, median (range) (years)</b>	69 (42-80)	66 (52-79)	0.760
<b>Sex (N patients %)</b>	32 males (60.4%) 21 females (39.6%)	30 males (55.6%) 24 females (44.4%)	0.613
<b>Smoker (N patients %)</b>	2 never smoked (3.8%) 14 ex-smokers (26.4%) 37 current smokers (69.8%)	2 never smoked (3.7%) 24 ex-smokers (44.4%) 28 current smokers (51.9%)	0.145
<b>BMI, median (range) (kg/m<sup>2</sup>)</b>	25.9 (17.6-49.1)	25.8 (17.6-37.4)	0.591
<b>Karnofsky index (N patients %)</b>			
70%	2 (3.8%)	–	
80%	2 (3.8%)	5 (9.3%)	0.268
90%	23 (43.4%)	19 (35.2%)	
100%	26 (49.1%)	30 (55.5%)	
<b>Comorbidities (N)</b>	(39/53 patients)	(40/54 patients)	
Pulmonary	21	23	
Cardiac	11	11	
Gastrointestinal	5	4	
Peripheral vessels	17	18	
Neurological	5	8	0.502
Endocrinological incl. diabetes	6	9	
Major extrathoracic surgery	9	5	
Other extrathoracic malignancies	5	3	
Orthopedics	6	5	
Others	12	3	
<b>total</b>	<b>97</b>	<b>89</b>	

The Wilcoxon signed rank test is used to compare the mean value before and after surgery. A student's test was used to compare parametric QoL data between different groups. The Mann Whitney *U* test was performed to compare frequencies and non-parametric QoL data between different groups. Chi2 test was used to test categorical variables. For a small-sample size with frequencies and non-parametric QoL data, Fisher's exact test was applied. P-values were calculated as an explorative measurement. Statistical analysis was performed using statistical software (SPSS, version 21.0, Chicago, IL and SAS version 9.4, SAS Institute Inc., Cary, NC, USA).

### 3. Results

#### 3.1. Demographics and tumor characteristics

Between October 2013 and June 2016, 108 patients with a radiologically suspected or confirmed NSCLC with a maximum size of up to 2 cm diameter were enrolled. 54 patients were assigned to lobectomy and 54 to anatomical segmentectomy. In eight patients randomized for a segmentectomy, histological study of intraoperative specimens or surgical reasons resulted in conversion to a lobectomy. The reasons were an upstaging to pN1/N2 disease (n = 2), pN1 disease (n = 1), pT1b (25 mm) (n = 1), pT3 (second NSCLC in the same lobe) (n = 1), technical difficulties due to severe emphysema (n = 1). In two patients after bisegmentectomy, resection margins of at least 2 cm healthy parenchyma was not required in the frozen section, whereby a right-side upper lobectomy followed. Furthermore, the definitive histology resulted in a benign disease in one patient after segmentectomy, so that this patient was excluded from the study. There were 32 males and 21 females in the segmentectomy and 30 males and 24 females in the lobectomy group, whereby the median age in the segmentectomy group was 69 years and 66 years in the lobectomy group. Comorbidities are registered in Table 2.

The distribution of the tumors in both groups and the number of resected segments per patient are shown in Table 3. Twelve (22.6%) resections in the segmentectomy group and 23 (42.6%) resections in the lobectomy group were conducted using VATS, while the rest were performed using a muscle-sparing anterolateral thoracotomy. The median number of removed lymph nodes was 16 (5–55) in the anatomical segmentectomy group and 17 (5–35) in the lobectomy group.

#### 3.2. Perioperative outcomes

Operative mortality was 0% in both groups, overall morbidity during hospital stay were 11.3% in the segmentectomy group and 14.8% (p = 0.563) in the lobectomy group. The 90-day mortality rate was also 0% in both groups, while the 90-day overall morbidity were 17% and 25.9%, respectively (p = 0.452). There were no significant differences between the two groups regarding operative time (183 min versus 196 min), blood loss intraoperative (200 ml in both groups) and drainage secretion during the first 24 h (400 ml versus 300 ml). The median length of intercostal drainage and hospital stay was 4 and 8 days after segmentectomy and 4 and 9 days after lobectomy, respectively (Table 4). Histology revealed squamous cell carcinoma in 28 cases (11 versus 17), adenocarcinoma in 74 cases (41 versus 33), four large cell carcinomas (1 versus 3) and one neuroendocrine carcinoma in the lobectomy group. Tumor diameter amounted to a median of 15 (5–25) mm in the segmentectomy group and 15 (6–20) mm in the lobectomy group.

#### 3.3. QoL-C30 follow-up

After a one-year follow-up period, all segmentectomy and lobectomy patients were alive. Four patients after lobectomy and three patients after segmentectomy developed a local or distant recurrent disease or another extrathoracic tumor. We posted the QLQ-C30 as well

as the QLQ-LC13 questionnaires to all patients, whereby 94.3% (50/53) of segmentectomy patients and 98.1% (53/54) of lobectomy patients at discharge, 92.5% (49/53) and 90.7% (49/54) after 6 weeks, 88.7% (47/53) and 87% (47/54) after 3 months, 84.9% (45/53) and 85.2% (46/54) after 6 months, and finally 90.6% (48/53) and 81.5% (44/54) after 12 months, respectively, returned data.

There was a significant difference in all scales and scores in both groups between pre-operative values and the post-operative period during hospital stay, caused by the surgical procedure. For the entire follow-up period, patients after segmentectomy showed a fast recovery, documented from baseline to follow-up at 3 months for physical functioning and from baseline to follow-up at 6 weeks for global QoL and social functioning. Emotional functioning showed 3 and 6 months after surgery superior scores than the baseline scores. Cognitive functioning scores are not different from the baseline scores at the complete follow-up of 12 months. By contrast, in the lobectomy group there was a statistically significant decrease in physical (p < 0.001) and cognitive (p = 0.025) functioning from baseline up to 12 months, in social functioning (p < 0.001) and in the global QoL (p < 0.001) up to 6 weeks post-surgery. Twelve months after surgery, we found significantly lower scores for role functioning in both groups (Table 5).

There was no difference between the baseline and the post-operative scores up to 12 months for symptoms scales regarding nausea and vomiting, insomnia, appetite loss, constipation and diarrhea, as well as in each group separately, including in comparison between the segmentectomy and lobectomy cohort. The scores for symptoms scales of fatigue and pain in general were significantly higher than the baseline scores up to 6 months post-operatively in the segmentectomy group (p < 0.001 and p < 0.001) and up to 12 months in the lobectomy group (p = 0.003 and p = 0.003). There was no difference when comparing the scores of the two groups at the appropriate point in time (Table 6). In order to assess homogeneous data, we analysed the scores for the symptom dyspnoea only in the lung-specific questionnaire LC13.

#### 3.4. QoL-LC13 follow-up

Due to the absence of any systemic treatment or radiotherapy, no differences to baselines were found at the follow-up for the symptoms

**Table 3**  
Distribution of tumor and operative procedure.

	Segmentectomy		Lobectomy	
	Procedure	N	Procedure	N
Left upper lobe	Segment 3	1	Upper lobectomy	14
	Segment 1/2	2		
	Segment 1/2/3	11		
	Segment 2/4/5	1		
	Segment 4/5	4		
Left lower lobe	Segment 6	2	Lower lobectomy	12
	Segment 8	1		
	Segment 8/9/10	1		
Right upper lobe	Segment 1	2	Upper lobectomy	26
	Segment 2	7		
	Segment 1/2	2		
	Segment 1/3	1		
Right lower lobe	Segment 6	4	Lower lobectomy	10
	Segment 10	1		
	Segment 8/9/10	1		
	Segment 7/8/9/10	4		
	<b>total</b>	<b>45</b>		<b>62</b>
<b>Number of removed segments</b>				
	One segment	18		
	Two segments	9		
	Three segments	14		
	Four segments	4		
	<b>total</b>	<b>45</b>		

**Table 4**  
Perioperative Mortality and Morbidity.

Variable	Segmentectomy (n = 53)	Lobectomy (n = 54)	p-value
VATS	12 (22.6%)	23 (42.6%)	0.028
Thoracotomy	41 (77.4%)	31 (57.4%)	
Operative time, median (range) min	183 (110-292)	196 (112-295)	0.220
Blood loss intraoperative, median (range) mL	200 (20-400)	200 (20-500)	0.502
Drainage secretion first 24 h, median (range) mL	400 (50-850)	300 (100-1100)	0.963
Drainage time, median(range) d	4 (2-14)	4 (2-21)	0.311
Hospitalization time, median (range) d	8 (4-27)	9 (4-22)	0.059
In hospital mortality N patients (%)	0.0%	0.0%	–
90-day mortality, N patients (%)	0.0%	0.0%	–
In hospital overall morbidity, N patients (%)	6 (11.3%)	8(14.8%)	0.563
90-day overall morbidity, N patients (%)	9 (17.0%)	14 (25.9%)	0.452
N of complications during hospital stay			
Hemothorax	–	1	
Cardiac arrhythmia	–	1	
Persistent air leak (> 5days)	3	4	
Pneumonia	1	1	
Pneumothorax	–	1	
Intubation injury	1	–	
Prolonged wound healing	1	–	
<b>total</b>	<b>6</b>	<b>8</b>	
Additionally, N of 90 days complications			
Transitory ischemic attach (TIA)	–	1	
Pneumothorax	1	1	
Chronic pain	–	1	
Pulmonary embolism	–	1	
Pleural effusion (paracentesis or drainage necessary)	1	2	
Prolonged wound healing	1	–	
<b>total</b>	<b>3</b>	<b>6</b>	

alopecia, appetite loss, diarrhea, constipation, sore mouth, dysphagia and peripheral neuropathy. Significant changes to baselines were found for hemoptysis in both groups at discharge. The scores for dyspnea were significantly higher than the baseline scores up to 3 months post-operatively in the segmentectomy group ( $p = 0.003$ ) and up to 12 months in the lobectomy group ( $p < 0.001$ ), with statistical difference between the two groups at 3 and 12 months ( $p = 0.033$  and  $p = 0.016$ ). The scores for pain in the chest significantly increased in both groups up to 12 months. There were no significant differences found between groups. Only the item for pain in arm and shoulder showed up to 6 weeks a difference in favor of the lobectomy cohort with statistical significance at discharge and up to 6 weeks ( $p = 0.025$  and  $p = 0.003$ ) (Table 6).

#### 4. Discussion

Pulmonary resection has been established as the primary treatment of choice for patients with early-stage NSCLC. Over the past two decades, studies addressing morbidity and mortality after anatomical segmentectomy in the treatment of lung cancer have generated heterogeneous results because the reason for limited resection differed between studies, with poor cardiopulmonary function (seven studies) being the most frequent reason [21]. Kilic et al. found that segmentectomy is associated with favorable perioperative outcomes among the elderly. Operative mortality was low (1.3%) and major morbidity was significantly lower than in the lobectomy group (11.5% vs 25.5%,  $p = 0.02$ ) [22]. Data from other series shows that age does not significantly increase mortality or major morbidity in patients undergoing segmentectomy [23–25]. Moreover, in a retrospective analysis of 182 anatomic segmentectomies, Schuchert et al. found no significant

differences in post-operative mortality (1.1% vs 3.3%) and morbidity (32.4% vs 33.7%) when comparing segmentectomy and lobectomy [26]. The Lung Cancer Study Group conducted the only randomized trial comparing sublobar resection versus lobectomy for NSCLC up to 3 cm. There was no difference in hospital mortality and perioperative morbidity between the two groups of patients, although patients who underwent a lobectomy had significantly more post-operative pulmonary complications requiring mechanical ventilator support [27]. In a recently-published randomized study (CALGB/Alliance 140503), a hospital mortality of 1.1% after lobectomy and 0.6% after sublobar resection was reported in functionally-fit patients. The 90-days mortality was 1.7% and 1.2%, respectively [28].

In the present study, neither perioperative nor 90-day mortality were observed. Similar results were reported by Kodama among 312 patients after lobectomy or segmentectomy [29]. We found lower post-operative and 90-days morbidity in the segmentectomy compared with the lobectomy group ( $p = 0.563$  and  $p = 0.452$ ) without statistical significance. Due to our protocol, one might expect an even better post-operative outcome in patients without relevant respiratory or cardiac comorbidities being randomized in the segmentectomy group. There were no significant differences in operative time, intraoperative blood loss, first 24-h drainage secretion, drainage time and hospitalization time between the two groups.

QoL following surgery for lung cancer has gained increasing interest and addresses various aspects, including physical and mental handicaps. These investigations are not limited to patients in palliative treatments concepts and best-supportive care settings, but have increasingly enrolled patients with early-stage NSCLC and expected prolonged survival or the good chance of a cure. QoL has been studied comparing the surgical approach [11–13,30] or analyzed the impact of resected lung volume [15–17,31]. Furthermore, some studies have assessed the duration of recovery of QoL post-surgery in disease-free patients [14,32,33]. The most consistent decline in the QoL was documented in the first 6 weeks after surgery. Schulte et al. used the EORTC QLQ-C30 together with the LC-13 questionnaire in 159 patients after surgical resection for NSCLC, finding that patients after lobectomy failed to have a complete recovery after a 24-months follow-up [14]. Handy et al. used the Short-Form 36 Health Survey questionnaire and Ferrans and Powers' Quality of Life Index to assess the QoL of 192 patients after open lobectomy and 49 patients after VATS lobectomy. Despite finding better outcomes in the VATS lobectomy group, at 6 months after surgery physical, role, emotional and social function scores did not completely recover [30]. Using the SF-12 QoL questionnaire, Schwartz et al. compared the average change in Physical Component Summary Score (PCS) post-surgery and found that patients who underwent limited resection had a significantly higher PCS than those who underwent lobectomy [17]. Other authors have reported a restriction in role and physical functioning after lobectomy, which increased in the first 3 months after surgery but improved again within 6–9 months [15,34]. However, there is no universal method describing the clinical significance or even the minimally-important difference of QoL data. Möller et al. noted that only 25% of the study population of 166 patients after lung surgery reported a clinically-relevant deterioration in the physical and mental aspects of health-related QoL up to 2 years after surgery [35]. In the current study, patients after segmentectomy showed a superior recovery in QoL compared with lobectomy patients. The scores for physical and social functioning approximated the pre-operative QoL baseline at a time between 3 and 6 months, global health scores returned to pre-operative levels 6 weeks after surgery. Emotional functioning showed in the 6 and 12 months follow-up superior scores compared to the baselines scores. By contrast, the lobectomy group did not experience a return to pre-operative QoL for physical, role and cognitive functioning, even 12 months post-surgery.

Both lobectomy and segmentectomy were characterized by increases in dyspnea and pain scores. Balduyck et al. reported an increase

**Table 5**  
Mean score changes from mean preoperative scores in regard to resection (all patients) in QoL functional scales (EORTC QLQ-C30).

QLQ-C30 functional scales	Mean preop QoL scores	Δ QoL scores at discharge	Δ QoL scores 6 weeks	Δ QoL scores 3 months	Δ QoL scores 6 months	Δ QoL scores 12 months
<b>Physical functioning</b>						
Segmentectomy*	83.8	−19.6 (p < 0.001)	−15.8 (p=0.001)	−8.8 (p=0.030)	−5.5 (NS)	−8.6 (p=0.030)
Lobectomy*	81.7	−20.0 (p < 0.001)	−19.2 (p < 0.001)	−15.2 (p < 0.001)	−11.2 (p < 0.001)	−13.8 (p < 0.001)
seg vs lob**		p (NS)	p (NS)	p (NS)	p (NS)	p (NS)
(N patients seg/lob)	(53/54)	(49/53)	(49/49)	(47/47)	(45/46)	(48/44)
<b>Role functioning</b>						
Segmentectomy*	80.8	−38.8 (p < 0.001)	−25.9 (p < 0.001)	−15.2 (p < 0.001)	−8.9 (p=0.036)	−18.4 (p < 0.001)
Lobectomy*	77.2	−30.2 (p < 0.001)	−30.3 (p < 0.001)	−22.7 (p < 0.001)	−17.0 (p=0.002)	−21.3 (p < 0.001)
seg vs lob**		p (NS)	p (NS)	p (NS)	p (NS)	p (NS)
(N patients seg/lob)	(53/54)	(49/53)	(49/49)	(47/47)	(45/45)	(48/43)
<b>Emotional functioning</b>						
Segmentectomy*	67.0	−6.0 (NS)	−1.2 (NS)	8.5 (p=0.047)	9.4 (p=0.035)	6.3 (NS)
Lobectomy*	66.0	−0.9 (NS)	0.0 (NS)	6.8 p(NS)	5.0 (NS)	5.5 (NS)
seg vs lob**		p (NS)	p (NS)	p (NS)	p (NS)	p (NS)
(N patients seg/lob)	(53/53)	(49/52)	(48/48)	(47/46)	(45/44)	(48/43)
<b>Cognitive functioning</b>						
Segmentectomy*	85.5	−7.1 (p=0.003)	−4.8 (NS)	−5.3 (NS)	−1.9 (NS)	−3.5 (NS)
Lobectomy*	84.9	−7.1 (NS)	−5.2 (NS)	−2.5 (NS)	−6.4 (NS)	−9.3 (p=0.025)
seg vs lob**		p (NS)	p (NS)	p (NS)	p (NS)	p (NS)
(N patients seg/lob)	(53/53)	(49/52)	(49/48)	(47/46)	(45/44)	(48/43)
<b>Social functioning</b>						
Segmentectomy*	79.9	−22.9 (p < 0.001)	−9.5 (p=0.014)	−3.5 (NS)	4.4 (NS)	−6.3 (NS)
Lobectomy*	85.2	−20.2 (p < 0.001)	−20.8 (p < 0.001)	−10.5 (p=0.010)	−8.7 (p=0.042)	−7.4 (NS)
seg vs lob**		p (NS)	p (NS)	p (NS)	p=0.031	p (NS)
(N patients seg/lob)	(53/53)	(48/52)	(49/48)	(47/46)	(45/44)	(48/43)
<b>Global QoL</b>						
Segmentectomy*	59.8	−17.4 (p < 0.001)	−5.4 (NS)	−0.2 (NS)	1.3 (NS)	0.5 (NS)
Lobectomy*	63.9	−15.0 (p < 0.001)	−15.3 (p < 0.001)	−1.1 (NS)	−2.3 (NS)	−5.2 (NS)
seg vs lob**		p (NS)	p=0.022	p (NS)	p (NS)	p (NS)
(N patients seg/lob)	(52/52)	(48/50)	(48/48)	(46/45)	(44/43)	(47/43)

Negative scores indicate a deterioration, positive scores a higher functioning at follow-up.

P-values were calculated as an explorative measurement.

NS indicates a p-value > 0.05.

\* p-value are for comparisons of differences of the means of the baseline preoperative value and the value at discharge, 6 weeks, 3, 6 and 12 months after surgery.

\*\* p-value are for comparisons of the means score changes between segmentectomy and lobectomy.

in dyspnea in the first month post-operatively, which was not seen after wedge resection. With the exception of thoracic pain, QoL scores in all domains returned to baseline values at 12 months despite the strong prevalence of distressing symptoms such as dyspnea, coughing, fatigue and pain [15]. Similar results were reported by Dales et al., finding that the degree of dyspnea returned to pre-operative levels at 6–9 months after surgery [36]. Using the generic SF36 questionnaire, Handy et al. found that pain and impaired functioning persisted for 6 months after lung cancer resection through various access modalities [30]. In our study, patients after lobectomy showed a significantly aggravated score for fatigue, dyspnea and pain in general, including 12 months after surgery. These symptoms returned to the baseline scores in the segmentectomy cohort after 6 months follow-up time.

The present study has some limitations based on the small cohort size. Strict inclusion and exclusion criteria, the pre-determined operative procedure in the anatomical segmentectomy cohort and the reservation of a number of thoracic surgeons to participate in randomized studies or abstain from operations suitable for the training of junior surgeons could be possible explanations for non-offered enrollment. QoL instruments often comprise several scales designed to measure one of many specific aspects of QoL. Wyrwich et al. rightfully noted that that p-values indicating statistically significant changes in QoL measures do not necessarily imply that a particular finding has clinical significance or relevance. An appropriate anchor such as exercise tests or a 6-minute walking test should be both interpretable and appreciably correlated with a QoL change [37]. Further trials should be conducted

including daily activity tests and more specific surgery-related questionnaire [38]. The EORTC QoL group has already developed a revised lung cancer module (LC-29), so that all QoL aspects in the newly-available diagnostic and therapeutic options should be covered [39]. Although the findings of this study suggest that in some scales of QoL anatomical segmentectomy is superior to lobectomy in the treatment of early-stage NSCLC, we believe that the results of other randomized studies including a significantly higher number of patients (CALGB-140503, JPRN-UMIN00002317, ChiCTR-IPR-15006654) should be awaited before final conclusion are drawn. OS and DFS are ultimately the most important parameters in choosing the appropriate operative approach. The outcome of this trial regarding survival data will be published once follow-up is mature.

## 5. Conclusion

In this study, anatomical segmentectomy was associated with early and late post-operative benefits over lobectomy for early lung cancer. Less morbidity, better physical, emotional and cognitive functioning, less symptoms of dyspnea and fatigue are well documented. We showed that QoL does change post-operatively and these changes depend on the extent of the resection. These findings in conjunction with the forthcoming results of OS and DFS can provide useful informations for clinicians and should be taken into consideration when counseling and preparing patients with early lung cancer prior to surgery.

**Table 6**

Mean score changes from mean preoperative scores in regard to resection (all patients) in QoL symptoms scales (EORTC QLQ-C30 and lung specific questionnaire LC13).

QLQ-C30	Mean preop QoL scores	Δ QoL scores at discharge	Δ QoL scores 6 weeks	Δ QoL scores 3 months	Δ QoL scores 6 months	Δ QoL scores 12 months
<b>Fatigue</b>						
Segmentectomy*	24.9	27.7 (p < 0.001)	22.9 (p < 0.001)	11.8 (p = 0.001)	6.4 (NS)	(p = 0.026)
Lobectomy*	25.8	23.3 (p < 0.001)	26.4 (p < 0.001)	17.6 (p < 0.001)	14.1 (p < 0.001)	(p = 0.003)
seg vs lob**		p (NS)	p (NS)	p (NS)	p (NS)	p (NS)
(N patients seg/lob)	(53/54)	(50/53)	(49/49)	(47/47)	(45/46)	(48/43)
<b>Pain in general</b>						
Segmentectomy*	14.5	36.7 (p < 0.001)	27.2 (p < 0.001)	17.0 (p < 0.001)	7.4 (NS)	(p = 0.001)
Lobectomy*	13.0	28.0 (p < 0.001)	31.6 (p < 0.001)	21.6 (p < 0.001)	14.9 (p < 0.001)	(p = 0.003)
seg vs lob**		p (NS)	p (NS)	p (NS)	p (NS)	p (NS)
(N patients seg/lob)	(53/54)	(50/53)	(49/49)	(47/47)	(45/46)	(48/44)
<b>QLQ-LC13</b>						
QLQ-LC13	Mean preop QoL scores	Δ QoL scores at discharge	Δ QoL scores 6 weeks	Δ QoL scores 3 months	Δ QoL scores 6 months	Δ QoL scores 12 months
<b>Haemoptysis</b>						
Segmentectomy*	2.5	13.5 (p < 0.001)	−1.4 (NS)	−2.8 (NS)	−0.7 (NS)	−0.7 (NS)
Lobectomy*	1.2	10.7 (p < 0.001)	−0.7 (NS)	−1.4 (NS)	0.7 (NS)	−0.8 (NS)
seg vs lob**		p (NS)	p (NS)	p (NS)	p (NS)	p (NS)
(N patients seg/lob)	(53/54)	(50/53)	(49/49)	(47/47)	(45/45)	(48/43)
<b>Coughing</b>						
Segmentectomy*	34.0	11.6 (NS)	5.4 (NS)	10.6 (p = 0.036)	4.4 (NS)	(NS)
Lobectomy*	35.8	6.4 (NS)	4.8 (NS)	8.0 (NS)	8.9 (p = 0.010)	−0.8 (NS)
seg vs lob**		p (NS)	p (NS)	p (NS)	p (NS)	p (NS)
(N patients seg/lob)	(52/53)	(49/52)	(49/49)	(47/46)	(45/45)	(47/43)
<b>Dyspnea</b>						
Segmentectomy*	21.4	14.6 (p = 0.003)	17.5 (p < 0.001)	9.7 (p = 0.003)	6.9 (NS)	(p = 0.011)
Lobectomy*	21.0	18.9 (p < 0.001)	24.9 (p < 0.001)	18.6 (p < 0.001)	17.4 (p < 0.001)	(p < 0.001)
seg vs lob**		p (NS)	p (NS)	p = 0.033	p (NS)	p = 0.016
(N patients seg/lob)	(53/54)	(45/50)	(49/49)	(46/46)	(45/44)	(48/43)
<b>Pain in chest</b>						
Segmentectomy*	10.1	28.0 (p < 0.001)	26.5 (p < 0.001)	20.6 (p < 0.001)	11.9 (p = 0.003)	10.6 (p = 0.030)
Lobectomy*	10.5	18.2 (p < 0.001)	21.1 (p < 0.001)	26.2 (p < 0.001)	21.2 (p < 0.001)	(p = 0.015)
seg vs lob**		p (NS)	p (NS)	p (NS)	p (NS)	p (NS)
(N patients seg/lob)	(53/54)	(50/53)	(48/49)	(47/47)	(45/44)	(47/43)
<b>Pain in arm or shoulder</b>						
Segmentectomy*	10.1	18.7 (p = 0.005)	21.1 (p < 0.001)	15.6 (p = 0.002)	11.1 (NS)	(NS)
Lobectomy*	20.4	2.5 (NS)	2.0 (NS)	5.0 (NS)	7.6 (NS)	(NS)
seg vs lob**		p = 0.025	p = 0.003	p (NS)	p (NS)	p (NS)
(N patients seg/lob)	(53/54)	(50/53)	(49/49)	(47/47)	(45/44)	(48/43)

Positive scores indicate a deterioration, negative scores a symptom's recovery at follow-up.

P-values were calculated as an explorative measurement.

NS indicates a p-value > 0.05.

\* p-value are for comparisons of differences of the means of the baseline preoperative value and the value at discharge, 6 weeks, 3, 6 and 12 months after surgery.

\*\* p-value are for comparisons of the mean score changes between segmentectomy and lobectomy.

## Declaration of Competing Interest

Prof. Dr. Stamatis reports personal fees and other from Deutsche Forschungsgesellschaft, during the conduct of the study. Dr. Ose reports personal fees from MEDICE Arzneimittel Pütter GmbH & Co. KG, outside the submitted work. All other authors confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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