Retrospective analysis of stereotactic radiotherapy for primary intrapulmonary lesions

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RETROSPECTIVE ANALYSIS OF STEREOTACTIC RADIOTHERAPY FOR PRIMARY INTRAPULMONARY LESIONS

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List of Abbreviations

COPD – Chronic Obstructive Pulmonary Disease

CT – Computed Tomography

DLCO – Diffusion Capacity of the Lung for Carbon Monoxide

ECOG – Eastern Cooperative Oncology Group

EORTC – European Organisation for Research and Treatment of Cancer

FEV1 – Forced Expiratory Volume During the First Second of the Expiration

GTV – Gross Tumor Volume

HR – Hazard Ratio

LC – Local Control

LPFS – Local Progression-Free Survival

NSCLC – Non-Small Cell Lung Cancer

OS – Overall Survival

PET-CT – Positron Emission Tomography-Computed Tomography

PFS – Progression-Free Survival

PROMs – Patient Reported Outcome Measures

PTV – Planning Target Volume

QoL – Quality of Life

SBRT – Stereotactic Body Radiation Therapy

SCLC – Small Cell Lung Cancer

SCT – Stair Climbing Test

SWT – Shuttle Walk Test

1. INTRODUCTION

1.1. Epidemiology of Lung Cancer

According to GLOBOCAN 2020, lung cancer is the leading cause of cancer-related death worldwide, causing 1,796,144 deaths in 2020 (1). In 2020, a total of 1,435,943 men were diagnosed with lung cancer, making it the most prevalent cancer in men. The corresponding number in women was 770,828, making it the third most common cancer in women after breast and colorectal carcinoma (2–4). In Germany in 2019, 35,675 men and 23,546 women were newly diagnosed with lung cancer, and 27,882 men and 16,999 women passed away because of it (5).

1.2. Risk Factors for Lung Cancer

The development of lung cancer is associated with various factors. Smoking is widely recognized as the primary cause of the major histologic types of lung cancer. Continuous smokers face a significantly increased risk, ranging from 20 to 50 times higher, compared to individuals who have never smoked. The duration of smoking is a crucial factor in determining the risk of developing lung cancer among smokers, with longer smoking durations being associated with a higher risk. However, it is important to note that quitting smoking leads to a reduced relative risk compared to current smokers (6). Additionally, second-hand smoking, which refers to exposure to tobacco smoke from others, increases the risk of developing lung cancer by approximately 25% (7).

Genetic factors may also play a role in the development of lung cancer. Individuals with a positive family history of lung cancer in a first-degree relative are at an approximately 50% increased risk of developing the disease (8). Although identifying specific genes associated with familial lung cancer is challenging, a few lung-cancer-specific genes have been identified to date. Independent genome-wide association studies have demonstrated an association between chromosomal region 15q24-25.1 and an elevated risk for both nicotine dependence and the development of lung cancer (9).

Occupational exposures also contribute significantly to the development of lung cancer. Asbestos, a known carcinogen that specifically targets the human lung, remains a prevalent occupational hazard in many low- and medium-income countries, posing a continued risk for lung cancer. Individuals with silicosis, a lung disease caused by the inhalation of silica dust, have consistently shown an increased risk of lung cancer. Additionally, polycyclic aromatic hydrocarbons (PAHs), a diverse group of chemicals formed during the combustion of organic

materials, have been linked to a higher risk of lung cancer in various industries and occupations (6).

Furthermore, ionizing radiation is known to increase the risk of developing lung cancer. This association has been observed in individuals exposed to ionizing radiation, such as atomic bomb survivors and pediatric patients who underwent radiotherapy. Additionally, miners who have been exposed to radioactive radon and its α-particle decaying products, also face an elevated risk (6). In a systematic review conducted by Darby *et al.*, it was found that residential exposure to radon and its decay products increases the risk of developing lung cancer by 8.4% per every 100Bq/m^3 increase in radon concentration (10).

A history of lung diseases has been associated with an increased risk of developing lung cancer. The pathogenesis is attributed to inflammatory processes. According to a systematic review and meta-analysis conducted by Brenner *et al.*, pneumonia has been associated with a 43% increased risk, tuberculosis with a 76% increased risk, and chronic obstructive pulmonary disease (COPD) with a 122% increased risk of developing lung cancer (11).

1.3. Classification of Lung Cancer

Traditionally, lung cancer is categorized into two main histologic groups, small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). The latter is divided into subtypes such as adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and large cell neuroendocrine carcinoma. The separation of SCLC and NSCLC was necessary due to the fact that almost all SCLCs have metastasized by the time of diagnosis, requiring systemic chemotherapy with or without radiotherapy as the primary treatment approach. On the other hand, NSCLCs are more likely to be resectable but typically exhibit poor responses to conventional chemotherapy. However, targeted therapies that focus on specific oncoproteins found in certain subgroups of NSCLC, particularly adenocarcinomas and also squamous cell carcinomas, have emerged. Molecular analysis is conducted on NSCLC tissue samples, if available, to determine eligibility for targeted therapy. Furthermore, novel immunotherapy treatments have been approved for a subset of NSCLC patients and are currently being investigated for SCLC (12).

The World Health Organization (WHO) revised the classification of lung cancer in 2021, with a great emphasis on genetic testing and the classification of small diagnostic samples. This revision enhances the accuracy of classification, which is crucial in determining the most appropriate treatment options and ultimately improving patient outcomes.

Nevertheless, the classification of lung cancer still relies on morphology, immunohistochemistry, and subsequent molecular methods (13).

1.4. Staging of Lung Cancer

Staging plays a vital role in the diagnostic workup of lung cancer. In patients with NSCLC, staging is essential for determining the optimal treatment approach for those with resectable disease and avoiding unnecessary surgical interventions for those with advanced disease.

Consequently, staging can be divided into two types: anatomic and physiologic staging. Anatomic staging assesses the location and extent of the tumor as well as any metastatic sites. On the other hand, physiologic staging evaluates the patient's ability to tolerate different treatment options. It is particularly important to decide, which patient is a candidate for surgical resection and which is inoperable but could benefit from chemotherapy or radiotherapy (14).

1.4.1. Anatomic Staging

In the initial evaluation of patients with NSCLC, it is recommended to perform a CT scan of the chest and abdomen, or better an FDG-PET-CT. Additionally, an MRI of the brain is mandatory to rule out cerebral metastasis. Despite the availability of these imaging techniques, a thorough medical history and physical examination remain crucial in predicting the presence of metastatic disease. If a malignancy is suspected, appropriate imaging studies should be conducted. However, if the clinical assessment yields negative results, additional imaging beyond PET-CT is unnecessary.

The application of the 8th edition of the TNM staging system (Table 1) for NSCLC is essential, as it provides important prognostic information and guides therapeutic decisions. It provides detailed information about tumor (T), lymph node involvement (N), and the presence of metastasis (M). Therefore, it is utilized in all patients with NSCLC (14). Treatment decisions are based on the UICC stages (Table 2), which are derived from the TNM staging system.

Table 1. TNM-classification for NSCLC, 8th edition (14)

Primary Tumor (T)	
T1	T1 tumor ≤3 cm in diameter surrounds by lung or visceral pleural without evidence of main bronchus
T1a	Tumor <1 cm
T1b	Tumor ≥1 cm but ≤2 cm
T1c	Tumor >2 cm but ≤3 cm
T2	T2 tumor >3 cm but ≤5 cm or tumor with any of the following features that does not involve the entire lung • Involves main bronchus ≥2 cm distal to carina • Invades visceral pleura • Associated with atelectasis or obstructive pneumonitis that extends to the hilar region
T2a	Tumor >3 cm but ≤4 cm
T2b	Tumor >4cm but ≤5cm
T3	>5 cm but ≤7 cm or any of the following: • Directly invades any of the following chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, main bronchus <2 cm from carina (without involvement of carina) • Atelectasis or obstructive pneumonitis of the entire lung
T4	7 cm or any of the following invades the mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, or with separate tumor nodules in a different ipsilateral lobe
Regional Lymph Nodes (N)	
N0	No regional lymph nodes metastases
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
M1a	Separate nodule(s) in a contralateral tumor with pleural nodules or malignant pleural or pericardial effusion
M1b	Single metastasis in a single organ
M1c	Multiple metastases in a single organ or in several organs

TNM, tumor-node-metastasis

Table 2. Staging of NSCLC according to UICC8 (14)

Stage IA1	T1a	N0	M0
Stage IA2	T1b	N0	M0
Stage IA3	T1c	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T2b		M0
Stage IIB	T1a-T2b	N1	M0
	T3	N0	M0
Stage IIIA	T1-T2b	N2	M0
	T3	N1	M0
	T4	N0/N1	M0
Stage IIIB	T1-T2b	N3	M0
	T3/4	N0/N1	M0
Stage IIIC	T3/T4	N3	M0
Stage IVA	Any T	Any N	M1a/M1b
Stage IVB	Any T	Any N	M1c

TNM, tumor-node-metastasis

1.4.2. Physiologic Staging

To evaluate the patient's ability to tolerate surgical resection and determine to what extent, physiologic staging is conducted (14). It serves as a valuable tool for selecting the appropriate treatment option for each patient, thereby minimizing the occurrence of complications and improving survival during the peri- and postoperative periods (15).

Baseline investigations, which are essential for every patient, include spirometry and the measurement of the diffusion capacity of the lung for carbon monoxide (DLCO). A forced expiratory volume during the first second of expiration (FEV1) of more than 2L or more than 80% indicates that the patient can tolerate a pneumonectomy, while an FEV1 of more than 1.5L suggests sufficient reserves for a lobectomy (14, 16).

As part of the second level of preoperative investigations, the stair climbing test (SCT) and the shuttle walk test (SWT) are performed. The SCT is utilized as a screening tool to identify patients that are suitable for pulmonary resection. Eligibility for surgery is determined if a patient can ascend more than 22m without experiencing discomfort. On the other hand, the SWT is a standardized test, in which the patient walks between two markers set 10m apart. The walking speed is progressively increased every minute. If a patient is not able to complete 250m on two different occasions, it suggests a decrease in their maximum oxygen consumption (16).

The third level of preoperative evaluation is necessary in situations where there is a high cardiovascular risk or if the patient has demonstrated poor performance during previous pulmonary function assessments. In such cases, the gold standard used is the cardiopulmonary

exercise test (CPET). The CPET assesses various systems including cardiovascular, respiratory, skeletal muscles, and neurophysiological, during exercise. It provides measurements of maximum aerobic capacity, anaerobic threshold, respiratory exchange ratio, oxygen pulse, ventilatory equivalents of carbon dioxide, oxygen desaturation, and cardiac indices, such as peak heart rate or electrocardiographic changes (16).

1.5. Treatment of NSCLC

Treatment decisions for lung cancer are influenced by several factors, including the histologic and molecular classification, disease stage at the time of diagnosis, and the performance status of the patient. In stages I and II, the treatment of choice is a lobectomy. However, for patients who are not willing to undergo surgery or have contraindications due to comorbidities, impaired lung function, or the location of the tumor, stereotactic body radiation therapy (SBRT) should be considered (14, 17). SBRT is also indicated in cases where a suspicious malignant mass identified on a CT scan, shows a typically malignant appearance on FDG-PET and persists for at least one month without the possibility of histologic diagnosis due to safety concerns. All patients undergoing curative surgery should receive a systematic lymph node dissection (17).

The management of stage III disease varies based on subgroups and should be discussed by an interdisciplinary tumor board. For stages IIIA1 and IIIA2, following complete surgery, adjuvant chemotherapy is recommended if the patient's performance status allows it. In case of an activated EGFR mutation, osimertinib should be administered. Adjuvant mediastinal radiotherapy should be considered if mediastinal lymph nodes are affected. For patients who are fit to undergo surgery in stage IIIA3, combined neoadjuvant radiochemotherapy is recommended. Stages IIIA4, IIIB, and IIIC should be treated based on tumor extent and performance status, with a combination of chemotherapy and radiotherapy. Patients who are not eligible for curative treatment regimens should be offered radiation therapy (17).

Fundamental care for patients with stage IV lung cancer involves standard medical management, appropriate pain management, and the judicious use of radiation therapy and chemotherapy including immunotherapy with checkpoint-inhibitors. Systemic treatment aims to alleviate symptoms, improve quality of life, and extend survival in patients with advanced NSCLC, particularly those with a good functioning status. Early implementation of palliative care along with chemotherapy has been associated with improved survival and quality of life (14). In the case of oligometastatic disease, a curative approach can be considered (17). The

distinction between squamous or non-squamous NSCLC of stage IV disease is important as it determines the molecular tests to be performed and, consequently, the choice of first-line therapy. For squamous NSCLC PD-L1 status should be determined. Pembrolizumab is the treatment of choice if PD-L1 expression is 50% or greater. However, if the PD-L1 expression is smaller than 50%, platinum-based chemotherapy in combination with gemcitabine, docetaxel, or paclitaxel should be administered (14). For non-squamous NSCLC, the treatment options are more diverse and depend on the molecular testing results. In cases where an EGFR mutation is present, recommended first-line treatment includes osimertinib with mostly very good response that usually will last for several years. If the tumor is positive for either ALK or ROS1, crizotinib is the preferred treatment. Pembrolizumab is used when PD-L1 expression is 50% or more and both EGFR and ALK1 are negative. If PD-L1 expression is negative and EGFR, ALK, and ROS1 are negative, platinum-based chemotherapy with pemetrexed or paclitaxel with or without bevacizumab, and as second-line treatment docetaxel, or nab-paclitaxel should be considered as therapeutic options (14).

1.6. Background on SBRT

Stereotactic radiotherapy is an advanced form of external radiation therapy that involves high doses of radiation delivered precisely to the tumor. Initially developed for treating cranial tumors, it has since evolved into an established therapy for a wide range of cancer types throughout the body, where it is called SBRT. Unlike conventional radiation therapy, which typically involves multiple treatment sessions over several weeks, stereotactic radiotherapy delivers radiation in a small number of fractions, while maintaining the desired high radiation doses to the tumor (18, 19).

In contrast to conventional radiotherapy, where the therapeutic advantage lies in exploiting differential radiation repair between tumor and normal tissue, SBRT takes a different approach. It aims to precisely target the tumor while minimizing exposure to the surrounding healthy tissues. This approach is achieved through meticulous treatment planning and advanced imaging techniques, allowing for the accurate localization of the tumor and precise delivery of radiation (18).

However, the presence of internal target motion, particularly due to respiratory movements, can pose a significant challenge to the effectiveness of highly conformal radiation therapy, especially for thoracic and abdominal tumors. Various methods have been developed to address this challenge. One approach is to use large treatment margins that encompass the

full range of motion. However, this results in unnecessary irradiation of normal surrounding tissue. Another method involves restricting tumor motion by applying abdominal compression, which forces patients to take shallow and fast breaths. Active breathing control is another technique that reduces tumor motion by temporarily suspending breathing in a specific phase of the respiratory cycle. This is achieved using a computer-controlled valve to close the airflow to the patient at a predetermined point. Limiting tumor motion can also be achieved through the breath hold technique, where patients are instructed to hold their breath in a reproducible manner. Different respiration monitoring devices, such as a spirometer, cameras tracking the expansion of the torso, or a strap monitoring torso circumference, assist in maintaining the reproducibility of breath holds. Gating is a method that synchronizes radiation treatment with respiratory motion using a breathing monitor. Set thresholds within the breathing monitor turn the radiation beam on and off at specific phases of the respiratory cycle. Usually, a 4 dimensional-CT is performed to determine which phases to include within the gating window (20). Real-time tumor tracking based on a dynamic multileaf collimator is another technique. This method continuously aligns and adjusts the treatment machine aperture in real time to track the motion of the target. As a result, it allows for narrower treatment margins and enables the dose delivery to be adapted to the target throughout the treatment session (20, 21).

2. OBJECTIVES

2.1. Aim of the Study

The primary objective of this study was to assess the overall survival (OS), local control (LC), and local progression-free survival (LPFS) outcomes after SBRT for primary lung cancer. The study aimed to examine also factors that may influence these outcomes. Additionally, the study assessed the quality of life (QoL) in patients who were still alive.

2.2. Hypothesis

1. Gender is a significant determinant of OS outcomes in patients undergoing SBRT.
2. Patients diagnosed with early-stage lung cancer exhibit a superior OS compared to those with advanced stages.
3. A positive history of smoking is associated with reduced OS.

3. MATERIALS AND METHODS

3.1. Study Design

This study combines a retrospective analysis with a prospective component, utilizing patient data obtained from the Coburg Cancer Center / Department of Radiation Oncology, in conjunction with the implementation of the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and QLQ-LC29 questionnaires (22). The data included in the retrospective analysis was collected from patient records at the aforementioned institutions, which were documented by medical professionals during the treatment and follow-up period. Additionally, the evaluation of tumor control involved assessing tumor volume based on follow-up CT scans conducted after the completion of radiotherapy. The data collection and evaluation were carried out by myself under the supervision of my mentor.

In the prospective part of this study, patients who were still alive were informed about the study and asked for their consent to participate in this study. They were requested to complete the EORTC QLQ-C30 and QLQ-LC29 questionnaires to evaluate their quality of life (QoL) in order to assess patient reported outcome measures (PROMs). Participants who expressed willingness to take part received the questionnaires through mail and were asked to return them by June 24, 2023. The evaluation of the questionnaires was conducted by myself, following the specifications of the EORTC scoring manuals.

Ethical approval for this study was granted by the Ethics Committee of the Friedrich-Alexander Universität Erlangen-Nürnberg (Registration Number: 23-23-B) on March 8, 2023.

3.2. Inclusion and Exclusion Criteria

The sample consists of all patients who underwent stereotactic radiotherapy for a primary pulmonary lesion with one of the three following treatment schedules in the period from January 1, 2014, to December 31, 2021: 3 x 12.5-15 Gy, 8 x 7.5 Gy, and 12 x 4-6 Gy.

For the assessment of the QoL using the EORTC questionnaires, only patients who were still alive at the time of the study were invited to participate. Patients who chose not to participate were excluded from the analysis.

Patients under the age of 18 years were excluded from the study. Furthermore, patients with missing data were excluded from the analysis for the specific data points that were missing.

3.3. Identification of the Sample

Figure 1 illustrates the process of identifying the study sample.

A comprehensive databank search was conducted, initially identifying a total of 1,158 patients. Among them, 1,093 were excluded as they did not meet the inclusion criteria of having a primary pulmonary lesion. An additional 14 patients were excluded from the study because they did not receive one of the three specified dose fractionation schemes mentioned earlier. This results in a final sample size of 51 patients eligible for inclusion in the study.

Survival analysis will be conducted using data from all 51 patients, with the exception of a few individuals who may be excluded from subgroup analyses due to missing data.

Out of the 51 patients, 33 individuals with a total of 37 lesions had at least one follow-up CT available for analysis of LC and LPFS.

Among the total 51 patients, 14 were still alive at the time of analysis. Informed consent was obtained from these 14 patients to complete the EORTC QLQ-C30 and QLQ-LC-29 questionnaires. However, 9 declined to participate in the QoL assessment, resulting in a final analysis of QoL data from 5 patients.

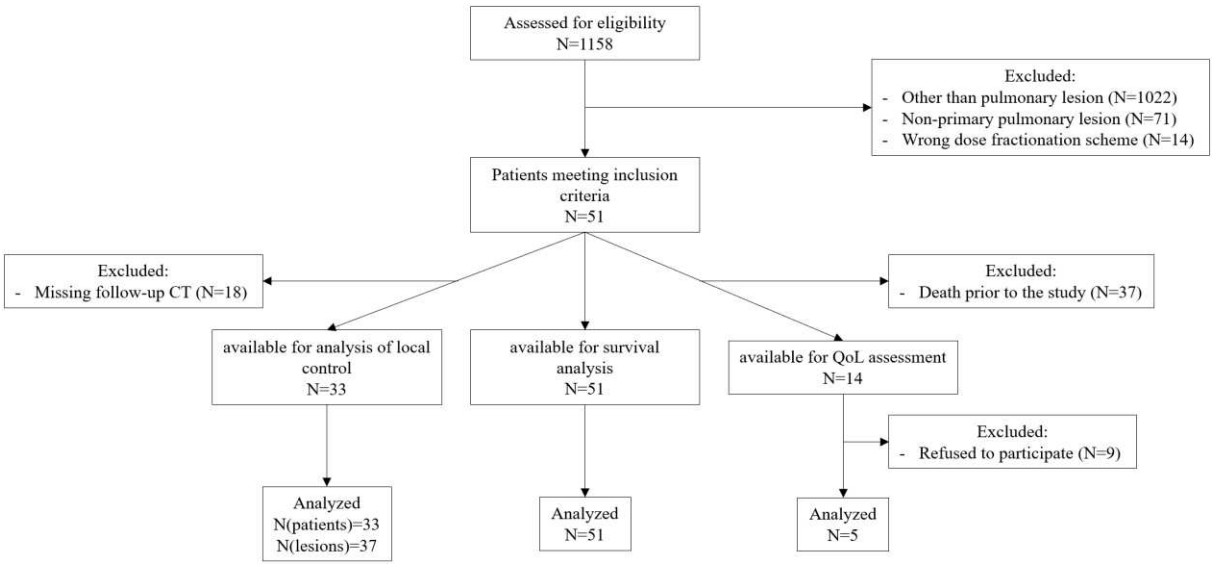

Figure 1. Flowchart diagram to illustrate patient selection

3.4. Treatment Technique

For radiation planning, each patient underwent a 4d-CT scan. The gross tumor volume (GTV), including all spiculae, was delineated based on lung and soft tissue windows. To ensure adequate coverage, a clinical target volume (CTV) was created by adding a 3mm margin to the GTV. Furthermore, an additional 4mm safety margin was applied to the CTV creating the planning target volume (PTV). The treatment plan was specified to the 65% isodose. In this study, three different dose fractionation schemes were applied, including 12Gy to 15Gy in 3 fractions, 7.5Gy in 8 fractions, and 4Gy to 6Gy in 12 fractions. All treatment planning was carried out using the Eclipse^{TM} treatment planning system v18.0 (Varian Medical System).

To ensure accurate and reproducible patient positioning, an immobilization device was used. Patients were positioned in supine positions with their arms raised above their head. Additionally, cone-beam-CT scans were performed before every treatment fraction to verify the alignment of the treatment field with the target area. To deliver the radiation dose, gating technique was used. All radiation treatments were performed using the advanced radiation equipment of a Truebeam^{TM} 2.0 linear accelerator with a 6-degree of freedom couch (Varian Medical System).

3.5. Statistical Analysis

IBM SPSS statistics (version 29.0.1.0) and Microsoft Excel 2019 for Windows were used to analyze the data. The OS-, LC-, and LPFS rates were calculated using the Kaplan-Meier method with the log-rank test used to identify differences in survival among patient groups. A *P*-value of 0.05 or less was considered statistically significant. Tumor progression was defined as any increase in volume observed on follow-up CT compared to prior CT scans. The multivariate Cox proportional hazard regression was used to identify prognostic factors. The covariates included gender, age dichotomized, stage of disease, intent of treatment, and previous surgery.

3.6. Evaluation of the EORTC QLQ-C30 and QLQ-LC29 Questionnaires

The EORTC QLQ-C30 and QLQ-LC29 were evaluated in accordance to the EORTC manuals, which describe the analysis and interpretation of the data in full detail (23, 24).

The QLQ-C30 questionnaire is composed of multi-item scales as well as single-item measures. Each item corresponds to one question. Multi-item scales include a minimum of two items. Five functional scales, three symptom scales, a global health status / QoL scale, and six

single-items constitute the QLQ-C30. Items 1 through 28 are scored from 1 to 4, giving a range of 3. Items 29 and 30, which contribute to the global health status / QoL scale, are rated from 1 to 7, giving a range of 6.

The QLQ-LC29 consists of five multi-item scales, which assess symptoms, and QoL, as well as five single-item measures, that assess symptoms. All scales and items are scored from 1 to 4, giving a range of 3.

The same scoring system applies to all scales. Initially, the raw score will be calculated by averaging the items in the scale using the following formula, where RS is the raw score, I is the item, and n is the number of items in the corresponding scale:

$$RS = (I_1 + I_2 + \cdots + I_n)/n$$

The second step includes a linear transformation to standardize the raw score. The standardized score (S) is then assigned a value between 0 and 100. Depending on the scale, the following formulae will be used:

- Functional scale:

$$S = \left\{1 - \frac{RS - 1}{range}\right\} \times 100$$

- Symptom scale, global health status / QoL scale, and single-items:

$$S = \left\{\frac{RS - 1}{range}\right\} \times 100$$

3.7. Interpretation of the EORTC QLQ-C30 and QLQ-LC29 Scores

The scores for all scales and single-item measures range from 0 to 100. A high score on a functional scale indicates a high degree of functioning. A high score in global health status / QoL represents a high QoL. In contrast, a high score on a symptom scale or item indicates a high level of symptomatology (23).

4. RESULTS

4.1. Patient Characteristics

The data collected from the clinical reports of patients has been collected and displayed in Table 3.

A total of 51 patients were included in this study. The median age of the patients was 71 years (range, 37-85 years).

In terms of gender distribution, there were 35 (68.6%) male and 16 (31.4%) female patients.

Regarding the Eastern Cooperative Oncology Group (ECOG) performance status, the majority of patients, 41 (80.4%), had a status of 1 or better. However, the ECOG status was not documented in 4 (7.8%) patients, while the remaining 6 (11.8%) patients had an ECOG status between 1 and 3.

A positive family history of cancer was reported by 13 (25.5%) patients. Moreover, 30 (58.8%) had a positive medical history of lung disease, and an equal number of patients had a history of cardiac disease. Among the enrolled patients, 14 (27.5%) had a history of smoking.

Before undergoing SBRT, 18 (35.3%) patients had previously undergone lung surgery, 5 (9.8%) had received radiation therapy to the lung at some point, and 17 (33.3%) patients had undergone chemotherapy.

Pre-SBRT FEV1 was recorded in 29 (56.9%) patients, with a median of 47% of the predicted pulmonary function, ranging from 22% to 103.7% of the predicted.

Among the treated patients, 47 (92.2%) had one pulmonary lesion treated with SBRT, while in 4 (7.8%), more than one lesion was treated.

6 patients had a history of primary lung cancer and were classified as recurrent.

Table 3. Patient characteristics

Variable		Total (N=51)
Age at diagnosis (in years)	Median	71
	Range	37-85
	Mean	68
Gender	Male	35 (68.6%)
	Female	16 (31.4%)
ECOG status	0	7 (13.7%)
	0-1	3 (5.9%)
	1	31 (60.8%)
	1-2	2 (3.2%)
	2	3 (5.9%)
	2-3	1 (2.0%)
	Unknown	4 (7.8%)
UICC-Staging	IA1-IIB	32 (62.7%)
	IIIA-IVB	16 (31.4%)
	Unknown	3 (5.9%)
Family predisposition	Yes	13 (25.5%)
	No	38 (74.5%)
Pulmonary comorbidity	Yes	30 (58.8%)
	No	21 (41.2%)
Cardiac comorbidity	Yes	30 (58.8%)
	No	21 (41.2%)
History of smoking	Yes	14 (27.5%)
	No	37 (72.5%)
Previous lung surgery	Yes	18 (35.3%)
	No	33 (64.7%)
Previous lung irradiation	Yes	5 (9.8%)
	No	46 (90.2%)
Chemotherapy	Yes	17 (33.3%)
	No	34 (66.7%)
Pre-SBRT FEV1 (in % of predicted)	Available	29 (56.9%)
	Not available	22 (43.1%)
	Median	47
	Range	22-103.7
	Mean	50.4
Number of treated lesions	Single lesion	47 (92.2%)
	More than one lesion	4 (7.8%)
Recurrent primary lung cancer	Yes	6 (11.8)
	No	45 (88.2%)

ECOG, Eastern Cooperative Oncology Group; FEV1, Forced Expiratory Volume During the First Second of the Expiration; SBRT, Stereotactic Body Radiation Therapy; UICC, Union for International Cancer Control

4.2. Lesion Characteristics

The characteristics of the treated pulmonary lesions are summarized in Table 4.

Out of a total of 55 lesions, 38 (69.1%) were diagnosed by biopsy, 6 (10.9%) based on CT criteria, and 11 (20.0%) based on PET-CT criteria.

Histologically, 21 (38.2%) lesions were classified as adenocarcinomas, 11 (20.0%) as squamous cell carcinomas, 6 (10.9%) were otherwise classified, and 17 (30.9%) remained unknown.

When considering the distribution of lesions across lung lobes, the majority, 22 (40.0%) lesions, were located in the left upper lobe. This was followed by 13 (23.6%) lesions in the right upper lobe, 8 (14.5%) in the left lower lobe, 7 (12.7%) in the right lower lobe, and 5 (9.1%) in the right middle lobe.

The median GTV was 6.11 cm3, ranging from 0.29cm3 to 352.98cm3. The median PTV was 29.2 cm3 with a range of 5.06cm3 to 603.50cm3.

Table 4. Treatment characteristics

Variable		Total (N=55)
Method of diagnosis	Biopsy proven	38 (69.1%)
	CT criteria	6 (10.9%)
	PET-CT criteria	11 (20.0%)
Histologic type	Adenocarcinoma	21 (38.2%)
	Squamous cell carcinoma	11 (20.0%)
	Unknown	17 (30.9%)
	Others	6 (10.9%)
Anatomic location	Right upper lobe	13 (23.6%)
	Right middle lobe	5 (9.1%)
	Right lower lobe	7 (12.7%)
	Left upper lobe	22 (40.0%)
	Left lower lobe	8 (14.5%)
GTV (in cm^3)	Median	6.11
	Range	0.29-352.98
	Mean	26.9
PTV (in cm^3)	Median	29.2
	Range	5.06-603.50
	Mean	65.65

CT, Computed Tomography; GTV, Gross Tumor Volume; PET-CT, Positron Emission Tomography-Computed Tomography; PTV, Planning Target Volume

4.3. Survival Analysis

The median OS, of the entire cohort of 51 patients, was 32 months (95% CI: 18-46 months; SD±7), ranging from a minimum of 2 months to a maximum of 149 months. The actuarial 1-year, 2-year, 3-year, and 5-year OS rates were 77%, 61%, 46%, and 26% respectively (Figure 2).

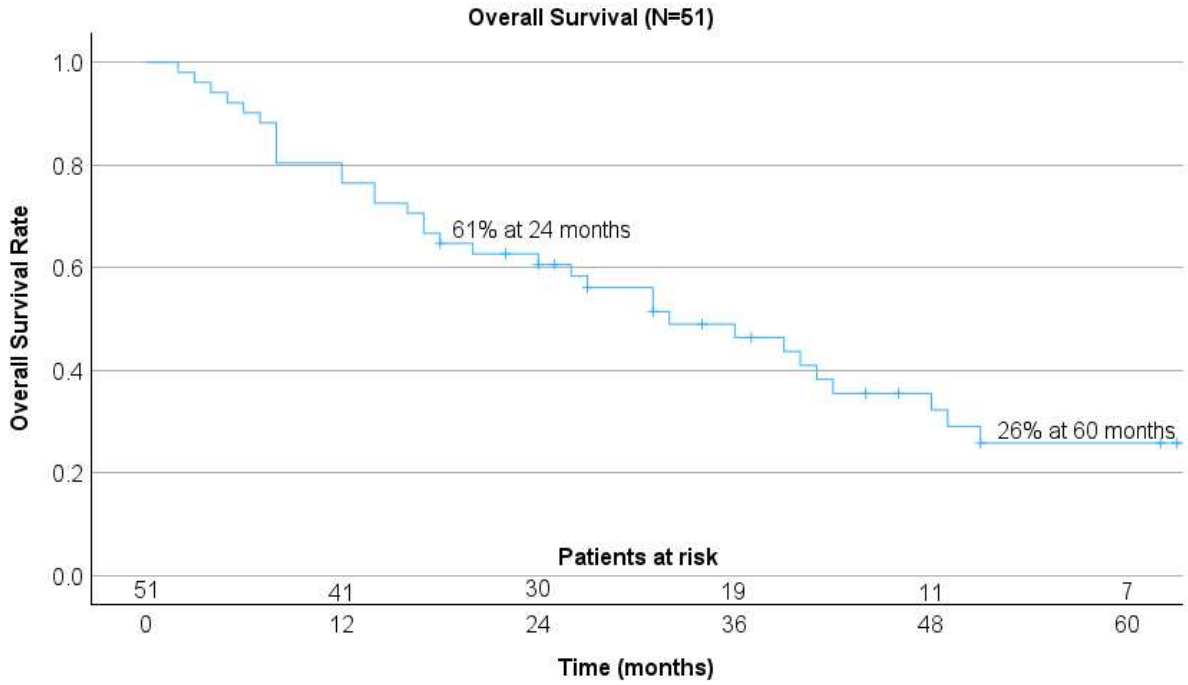

Figure 2. Overall survival rate according to Kaplan-Meier for all 51 patients following stereotactic radiation of early lung cancer

There was a statistically significant better survival in female patients (*P*=0.016). The median survival time of the 35 (69%) male patients was 26 months (95% CI: 15-37 months; SD±6), with a minimum of 2 months and a maximum of 92 months. One (13%) male patient survived for 60 months. The median survival time of the 16 (31%) female patients was better at 51 months (95% CI: 26-76 months; SD±13). Their minimum survival was 12 months and the maximum was 149 months. 5-year OS rates differed with 46% for female vs 13% for male patients, respectively (Figure 3).

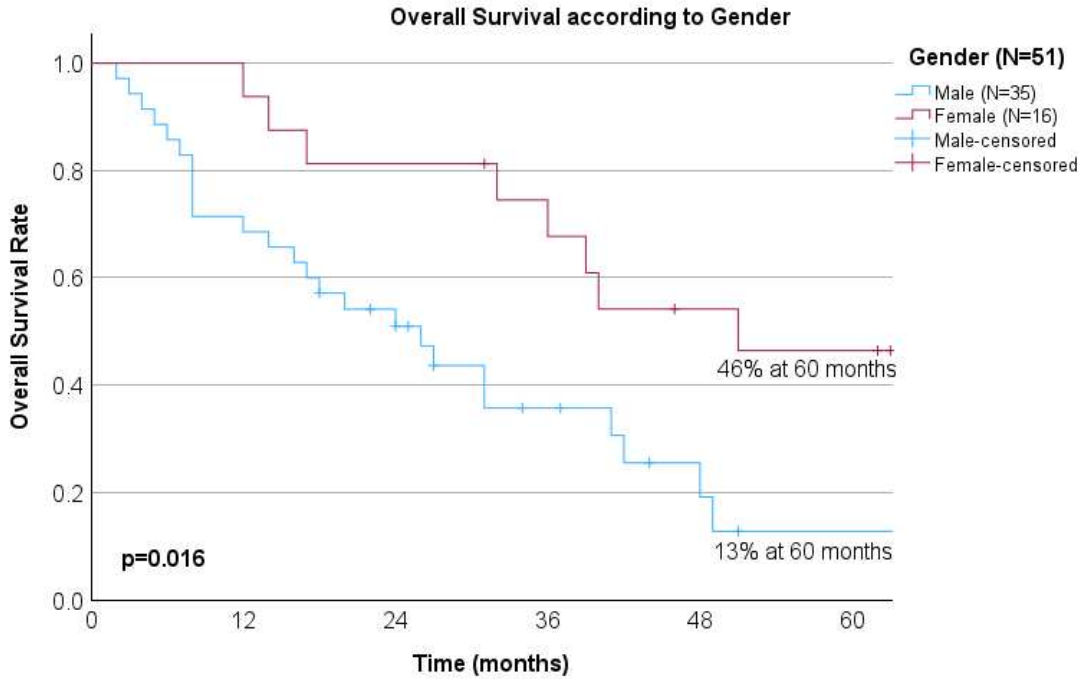

Figure 3. Overall survival rate (Kaplan-Meier) according to gender following stereotactic radiation of early lung cancer

The median age of the study population was 71 years. Kaplan-Meier analyses of patients under the age of 71 (N=25; 49%) compared to those of 71 years and above (N=26; 51%) revealed no statistically significant difference in the OS rates (*P*=0.440). At 60 months, OS rate was 29% for patients under the age of 71 years. Their median survival time was 32 months (95% CI: 14-50 months; SD±9) with a minimum of 2 months and a maximum of 149 months. 5-year OS rate was 22% for patients of age 71 years and above, with a median of survival time of 31 months (95% CI: 6-56 months; SD±13). Their minimum and maximum survival times were 3 and 95 months respectively (Figure 4).

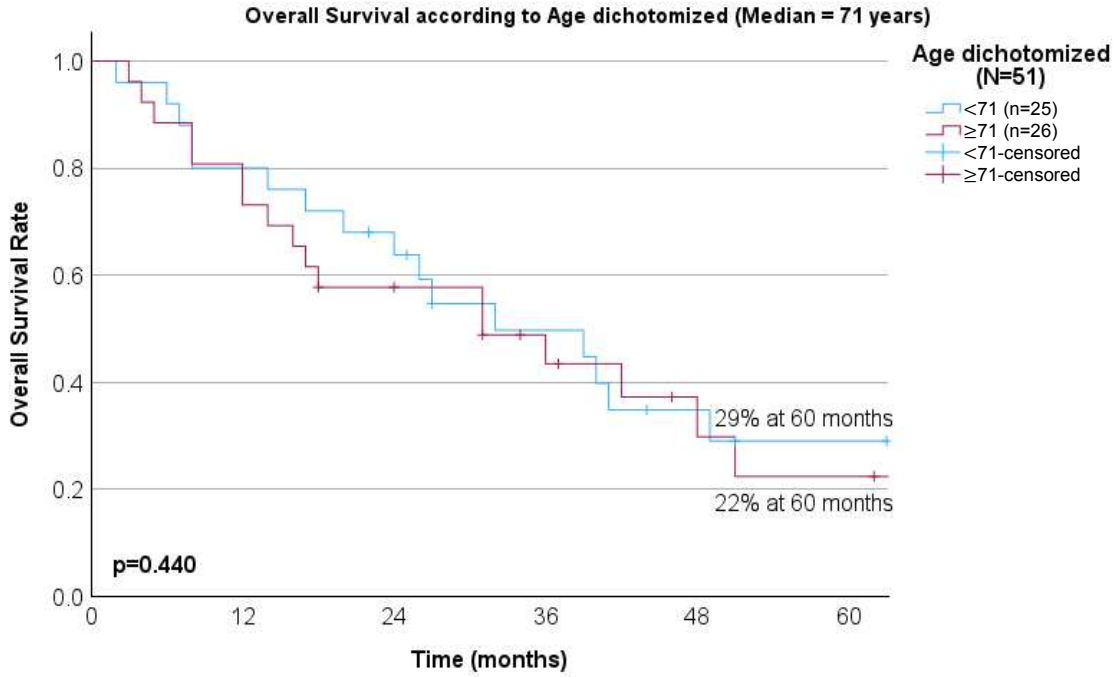

Figure 4. Overall survival rate (Kaplan-Meier) according to age at diagnosis following stereotactic radiation of early lung cancer

Three patients were excluded from survival analysis according to stage of disease due to missing data. There was no statistically significant difference in the OS rates for patients with stages IA1 to IIB compared to IIIA to IVB (*P*=0.085). The median survival time for 32 (67%) patients with stage IA1 to IIB was 36 months (95% CI: 21-51 months; SD±8) with the 5-year OS rate being 38%. Their respective minimum and maximum survival times were 2 and 149 months. The group of patients belonging to stages IIIA to IVB consisted of 16 (33%) with a median survival time of 20 months (95% CI: 0-40 months; SD±10). In this group the minimum survival time was 3 months and the maximum 63 months. 5-year OS rate was here at 7% (Figure 5).

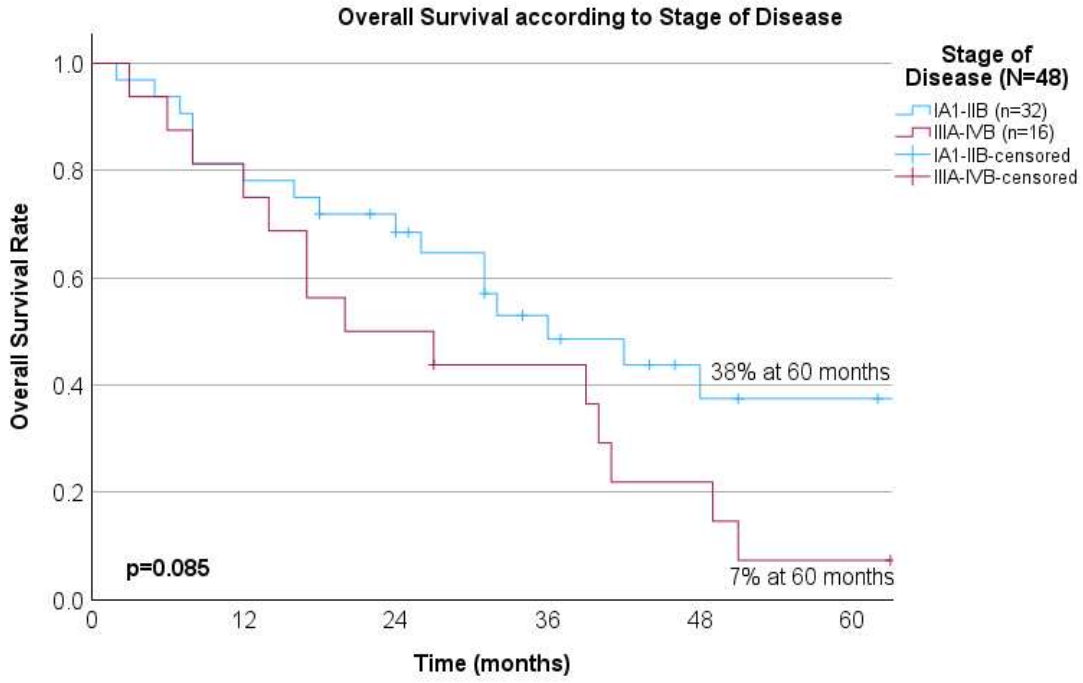

Figure 5. Overall survival rate (Kaplan-Meier) according to UICC-staging at diagnosis following stereotactic radiation of early lung cancer

For the survival analysis according to treatment intent, five patients were excluded from this survival analysis due to missing data. The 34 (74%) patients who were treated with curative intent had a statistically significant (*P*=0.014) better survival at a median survival time of 39 months (95% CI: 25-53 months; SD±7) than the 12 patients (26%) who were treated with palliative intent at a median survival time of 14 months (95% CI: 0-28 months; SD±7). 5-year OS rates differed with 33% for curative intent vs 0% for patients with palliative intent, respectively (Figure 6).

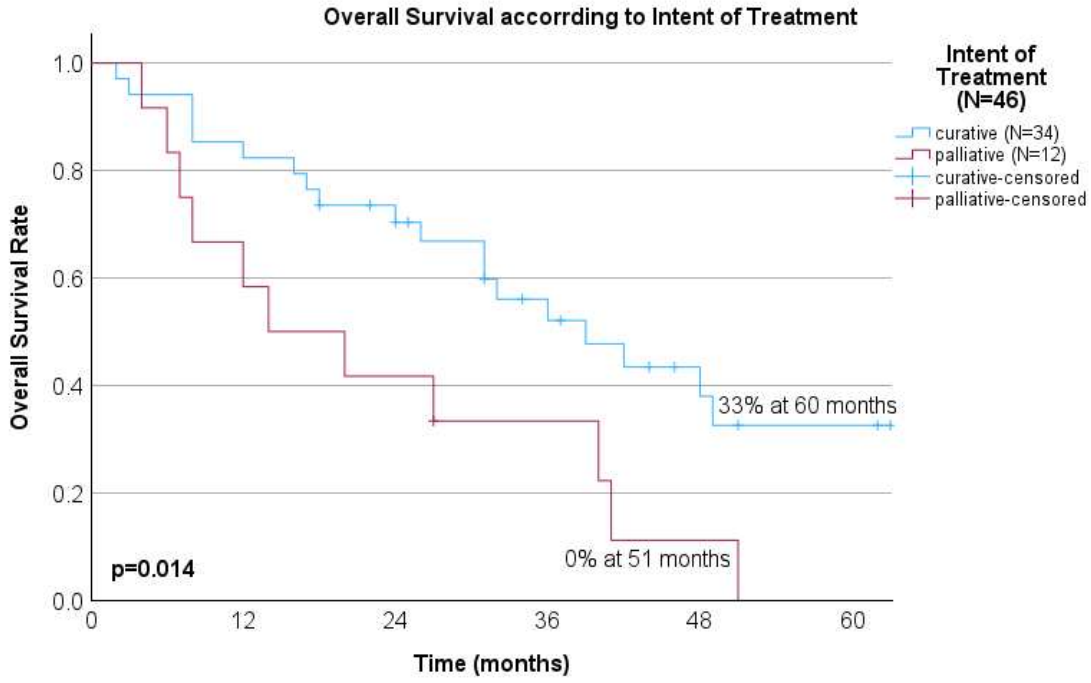

Figure 6. Overall survival rate (Kaplan-Meier) according to intent of treatment following stereotactic radiation of early lung cancer

There was no statistically significant difference in survival according to the fractionation scheme (*P*=0.293), family predisposition (*P*=0.784), pulmonary comorbidities (*P*=0.468), cardiac comorbidities (*P*=0.591), and history of smoking (*P*=0.656; Figures 7-11).

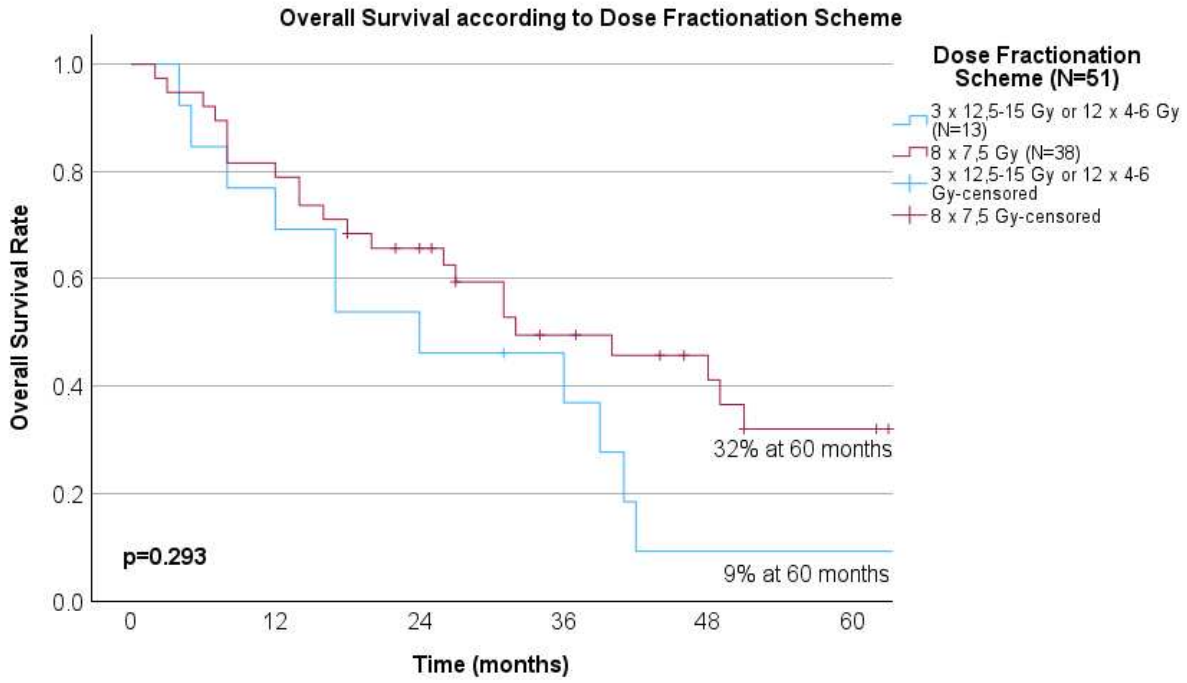

Figure 7. Overall survival rate (Kaplan-Meier) according to fractionation scheme

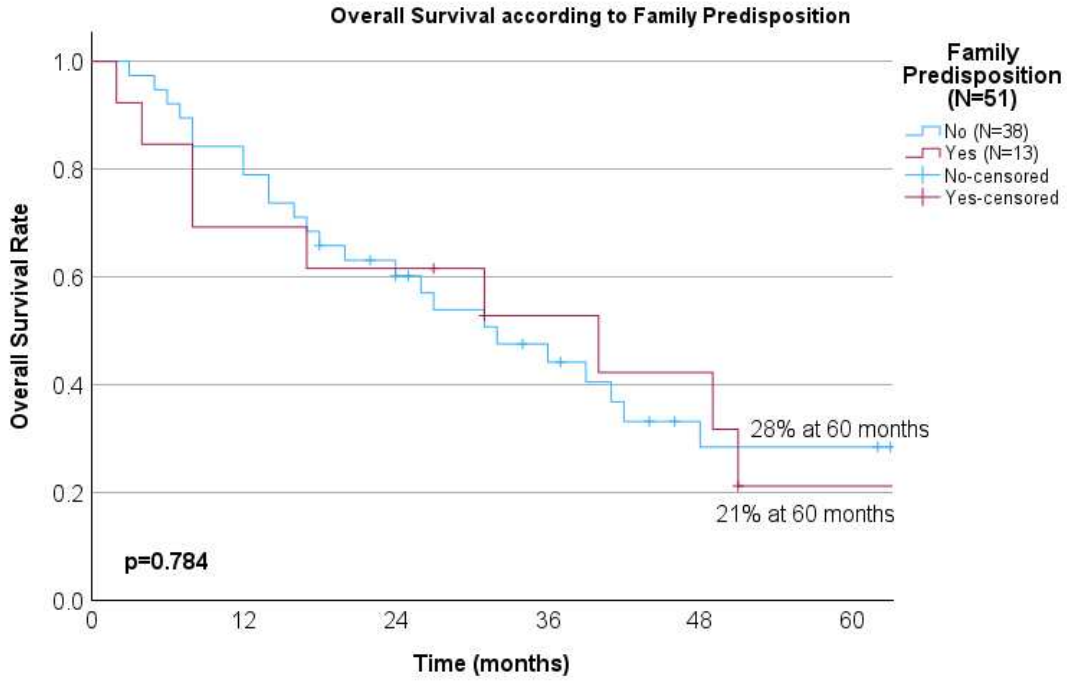

Figure 8. Overall survival rate (Kaplan-Meier) according to family predisposition

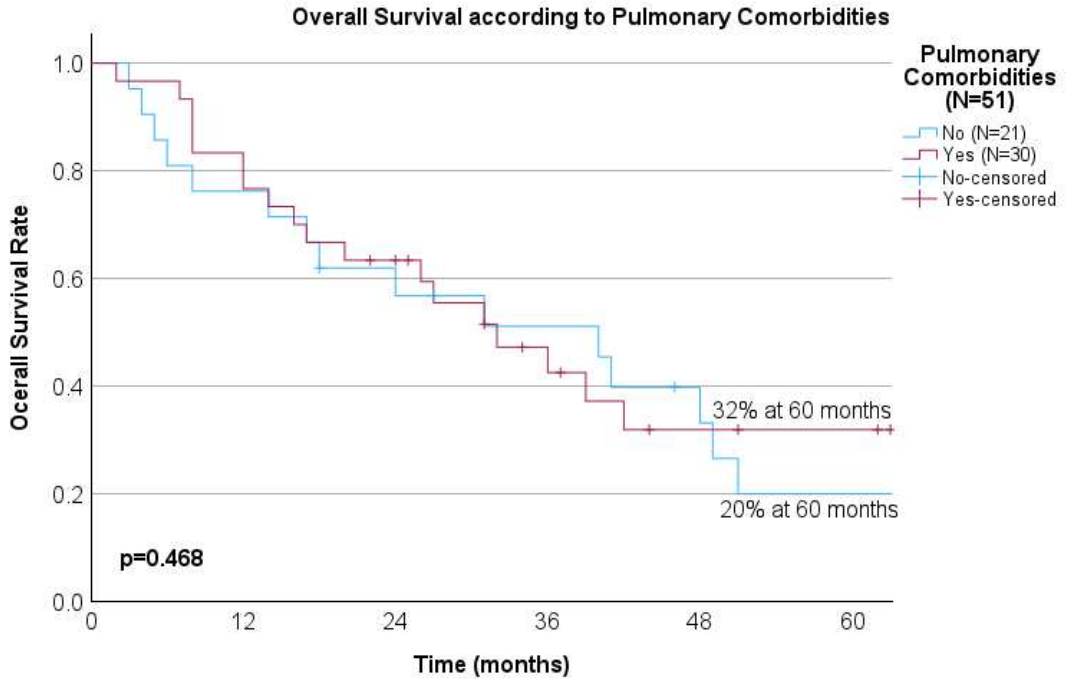

Figure 9. Overall survival rate (Kaplan-Meier) according to pulmonary comorbidities

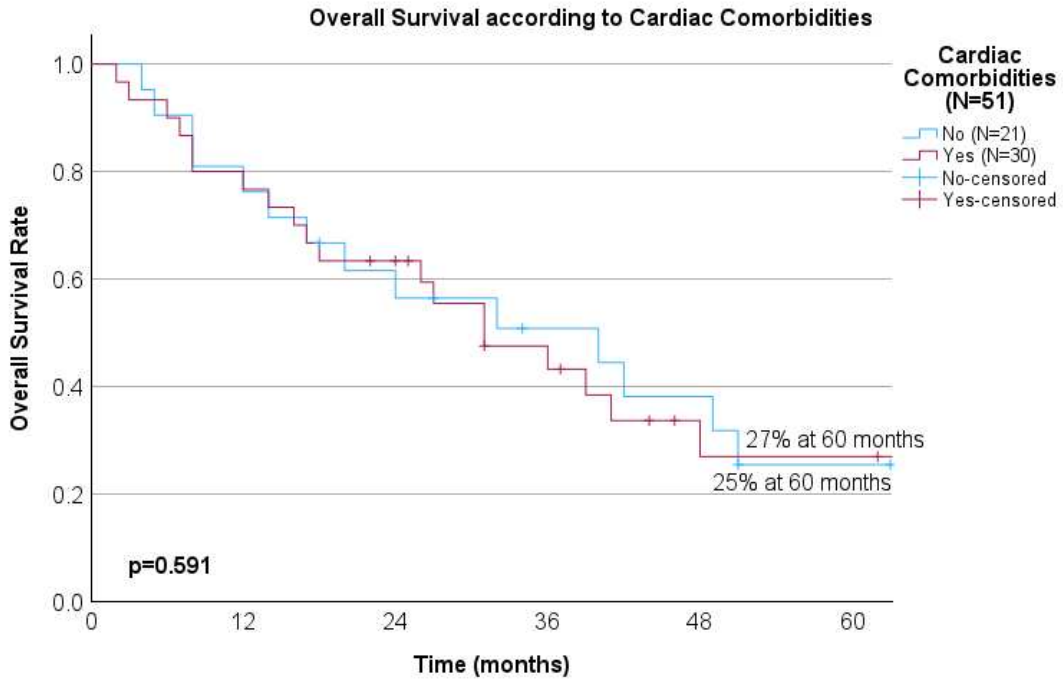

Figure 10. Overall survival rate (Kaplan-Meier) according to cardiac comorbidities

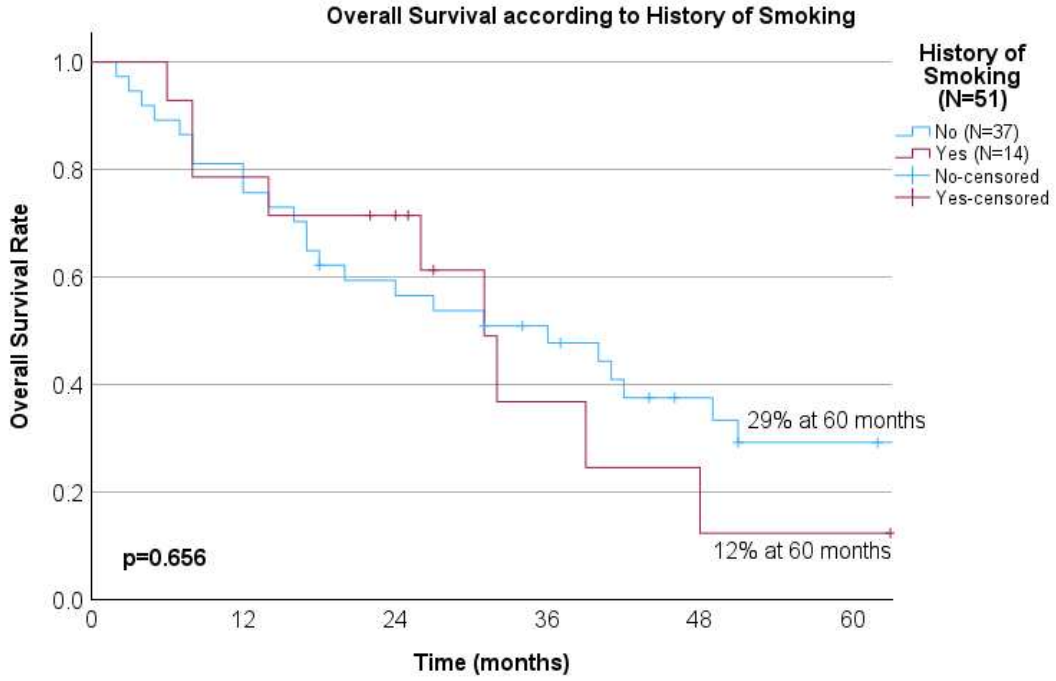

Figure 11. Overall survival rate (Kaplan-Meier) according to history of smoking

The 18 (35%) patients who underwent surgery prior to receiving SBRT demonstrated a statistically significant (*P*=0.008) improvement in survival compared to the 33 (65%) patients who received SBRT alone. The median survival time for the prior-surgery group was 49 months (95% CI: 32-66 months; SD±9), while the median survival time for the SBRT-only group was 26 months (95% CI: 14-38 months; SD±6). The respective survival rates at 60 months were 49% for the prior-surgery group and 12% for the SBRT-only group (Figure 12).

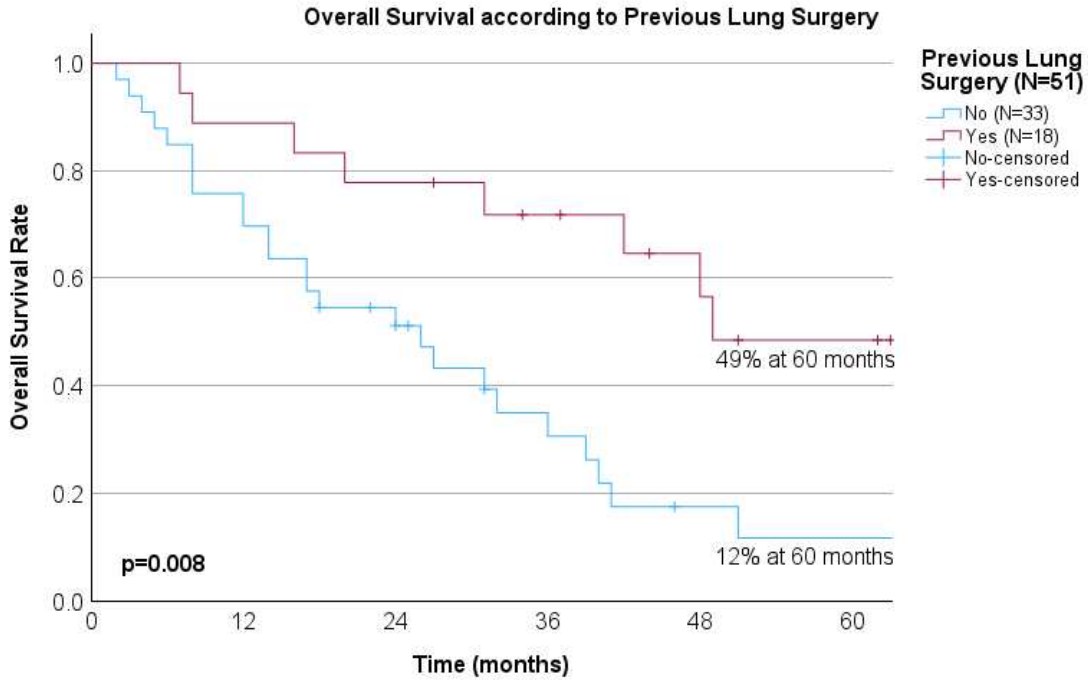

Figure 12. Overall survival rate (Kaplan-Meier) according to previous lung surgery

No statistically significant difference in survival was observed among patients who had at some point received radiotherapy to the lung before SBRT compared to those who had not (*P*=0.090; Figure 13). Similarly, there was no statistically significant difference in survival between patients who received chemotherapy and those who did not (*P*=0.509; Figure 14).

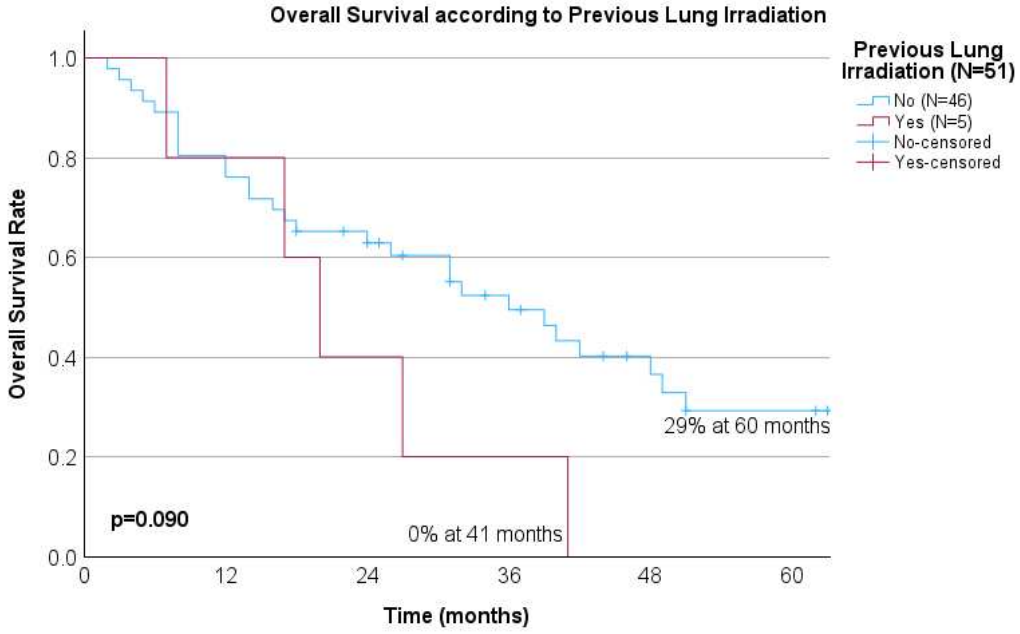

Figure 13. Overall survival rate (Kaplan-Meier) according to previous lung irradiation

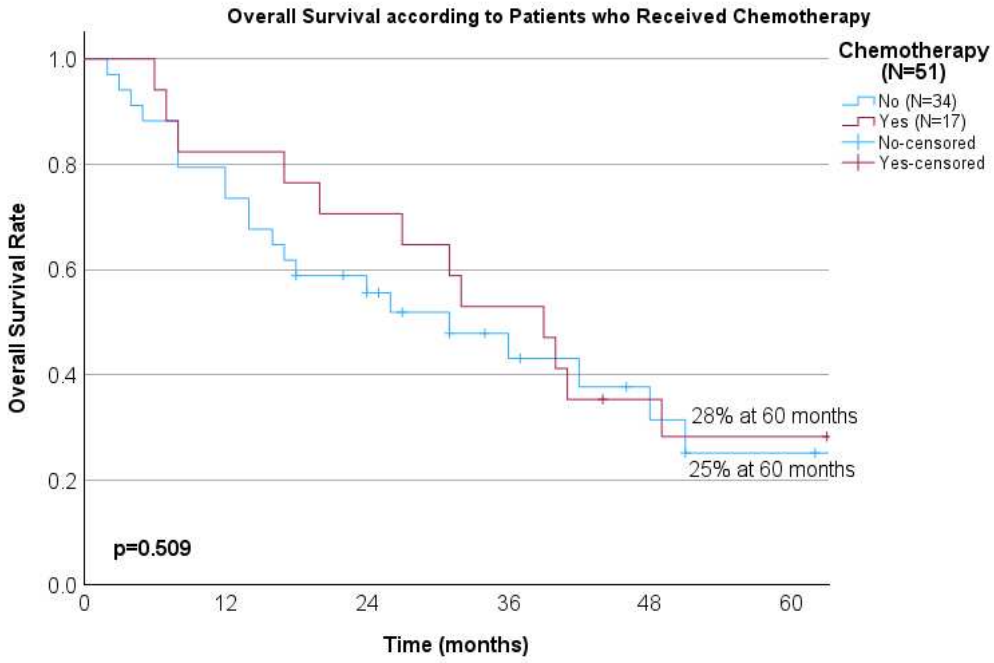

Figure 14. Overall survival rate (Kaplan-Meier) according to chemotherapy

Table 5. Prognostic factors with possible impact on overall survival

Variable		5-year survival rate	*P*-value
Overall		26%	
Gender			0.016
	Male	13%	
	Female	46%	
Age			0.440
	<71	29%	
	≥71	22%	
UICC-Staging			0.085
	IA1-IIB	38%	
	IIIA-IVB	7%	
Intent of treatment			0.014
	Curative	33%	
	Palliative	0%	
Dose fractionation Scheme			0.293
	3 x 12.5-15 Gy or 12 x 4-6 Gy	9%	
	8 x 7.5 Gy	32%	
Family predisposition			0.784
	No	28%	
	Yes	21%	
Pulmonary comorbidities			0.468
	No	20%	
	Yes	32%	
Cardiac comorbidities			0.591
	No	25%	
	Yes	27%	
History of smoking			0.656
	No	29%	
	Yes	12%	
Previous lung surgery			0.008
	No	12%	
	Yes	49%	
Previous lung irradiation			0.090
	No	29%	
	Yes	0%	
Chemotherapy			0.509
	No	25%	
	Yes	28%	

UICC, Union for International Cancer Control

4.4. Analysis of Prognostic Factors

Due to missing data, the multivariate Cox proportional hazard regression analysis included a total of 44 patients. The results, as summarized in Table 6, revealed an independent impact of gender and previous lung surgery on mortality from a pulmonary lesion following SBRT.

Gender was found to be a statistically significant predictor of survival (HR=0.273; 95% CI: 0.104-.0717; *P*=0.008). Patients who underwent lung surgery prior to SBRT also demonstrated a statistically significant lower risk of mortality (HR=0.378; 95% CI: 0.159-0.901; *P*=0.028). However, there were no statistically significant associations between age dichotomized (*P*=0.111), stage of disease (*P*=0.331), and intent of treatment (*P*=0.729) with the risk of mortality from pulmonary lesions after SBRT.

Table 6. Cox regression analysis for overall survival

Variable	HR	95% CI	*P*-value
Gender (male vs. female)	0.273	0.104-.0717	0.008
Age dichotomized (<71 vs. ≥71)	1.954	0.858-4.451	0.111
Stage of disease (IA1-IIB vs. IIIA-IVB)	1.757	0.564-5.470	0.331
Intent of treatment (curative vs. palliative)	1.236	0.373-4.102	0.729
Previous lung surgery (No vs. Yes)	0.378	0.159-0.901	0.028

4.5. Local Control and Local Progression-Free Survival

Out of the total 51 patients, only 33 had available follow-up CT scans for evaluating the tumor response to SBRT. Therefore, a total of 37 lesions were analyzed in 33 patients.

Among the analyzed lesions 3 (8.1%) showed tumor progression in 3 (9.1%) different patients, as observed on a subsequent CT scan compared to, either the planning CT or a follow-up CT. The 1-year, 2-year, and 3-year LC rates were 91%, 91%, and 76% respectively (Figure 15).

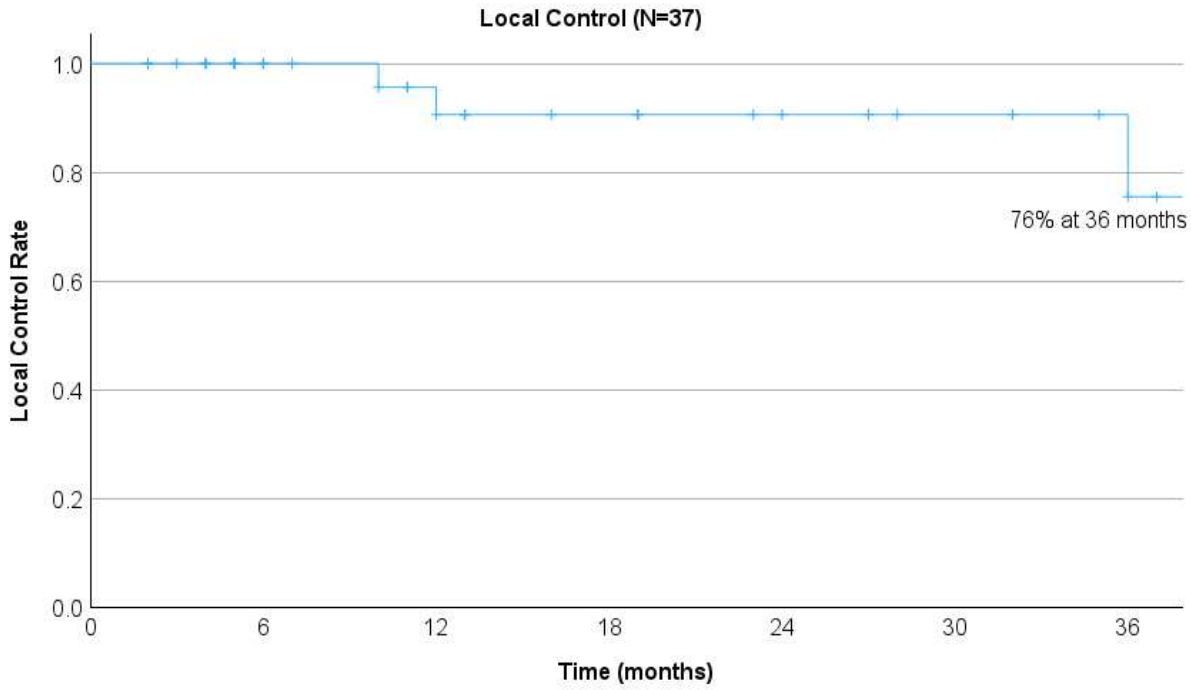

Figure 15. Local control (Kaplan-Meier) for 37 lesions in 33 patients following stereotactic radiotherapy

Figures 16 and 17 display the changes in pulmonary lesions over time. The median GTV on planning CT was 5.57 cm^3, ranging from 0.29cm^3 to 111.61cm^3.

3 lesions among the 37 lesions analyzed, showed progression on a follow-up CT. One lesion, initially measuring 111.61cm^3, increased in volume to 213.66cm^3 on the first follow-up CT. Another lesion initially decreased from 28.39cm^3 to 13.23cm^3 but then showed a slight increase to 14.28cm^3 on the second follow-up CT. The third lesion initially decreased in volume from 28.75cm^3 to 10.06cm^3 and further to 6.08cm^3, but it subsequently exhibited an increase to 15.7cm^3 on the third follow-up CT.

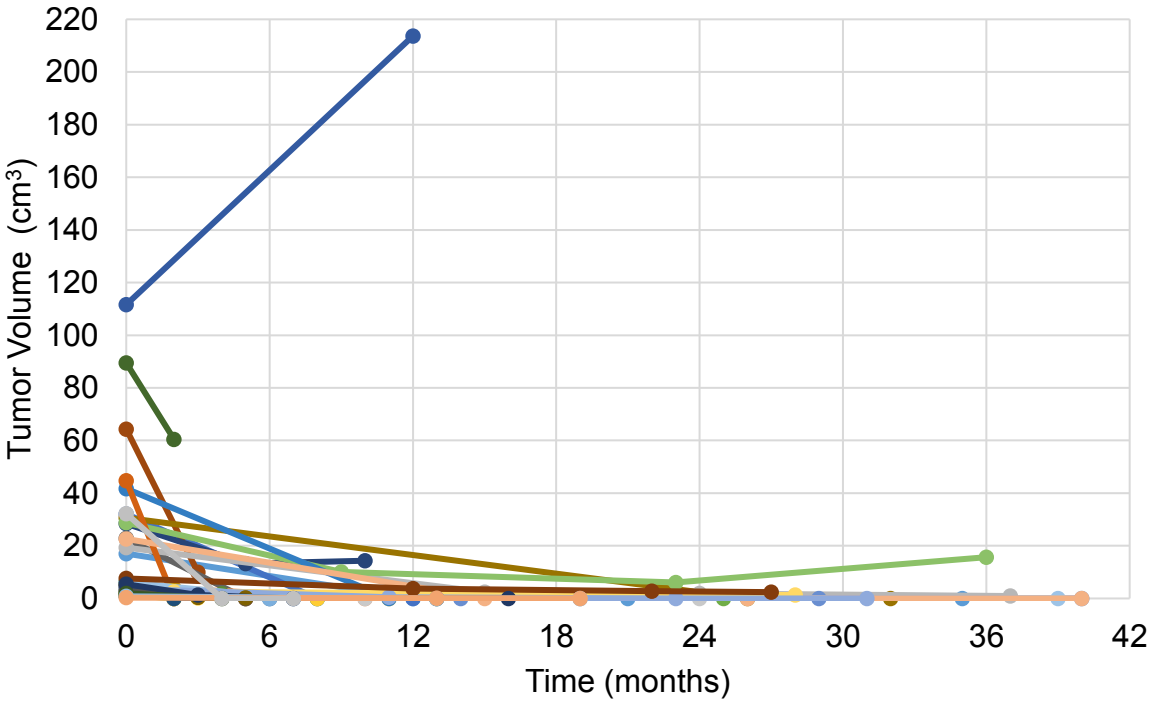

Figure 16. Absolute volume of pulmonary lesions over time (Spider-Plot)

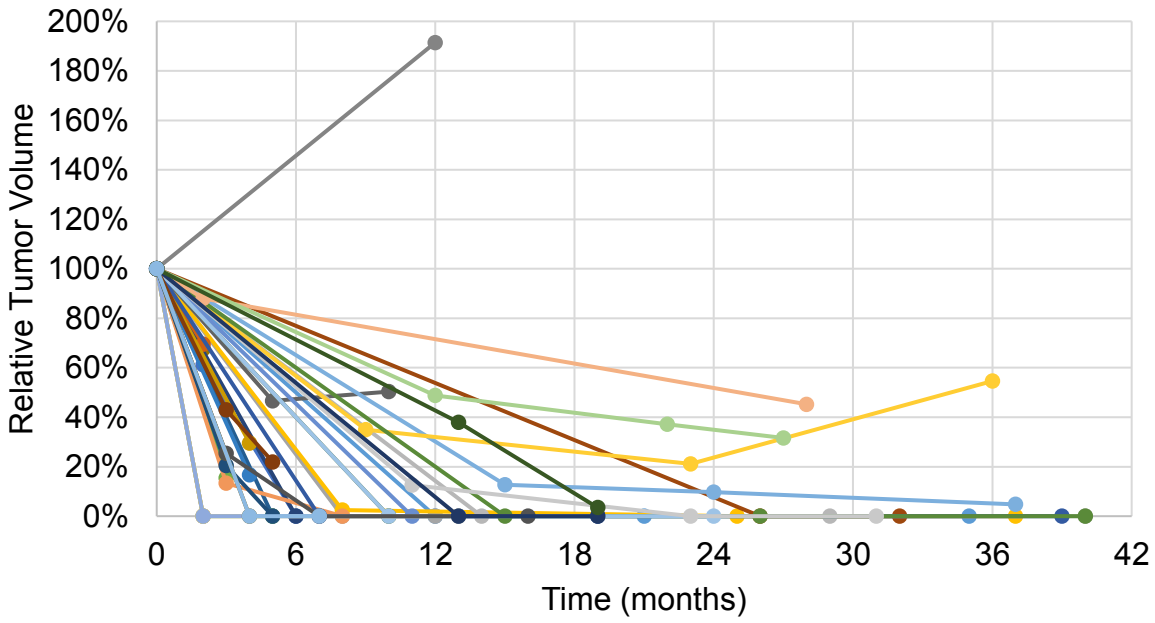

Figure 17. Relative volume of pulmonary lesions over time (Spider-Plot)

Median LPFS was 36 months (95% CI: 21-51 months; SD±8). The 1-year, 2-year, 3-year, and 5-year LPFS rates were 82%, 70%, 49%, and 28% (Figure 18).

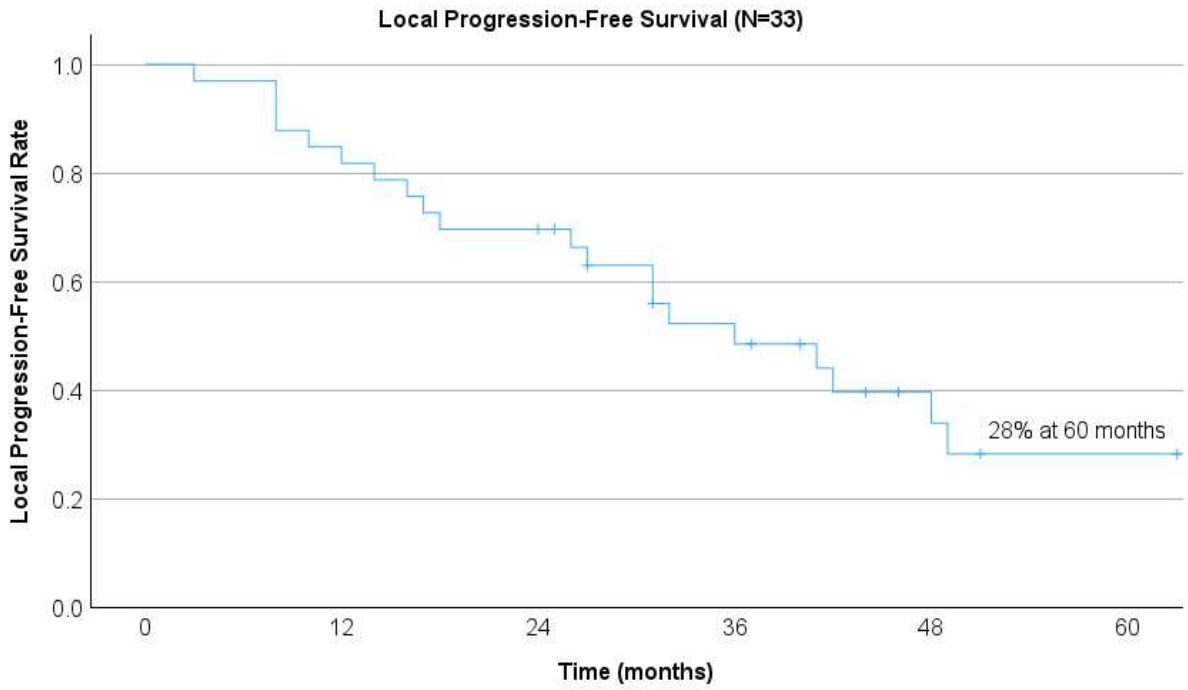

Figure 18. Local progression-free survival (Kaplan-Meier)

Figure 19 shows an example of regression of a recurrent intrapulmonary lesion in a patient with an adenocarcinoma and radiation-induced changes. After the initial regression of the tumor, progressive fibrosis with later complete regression was observed.

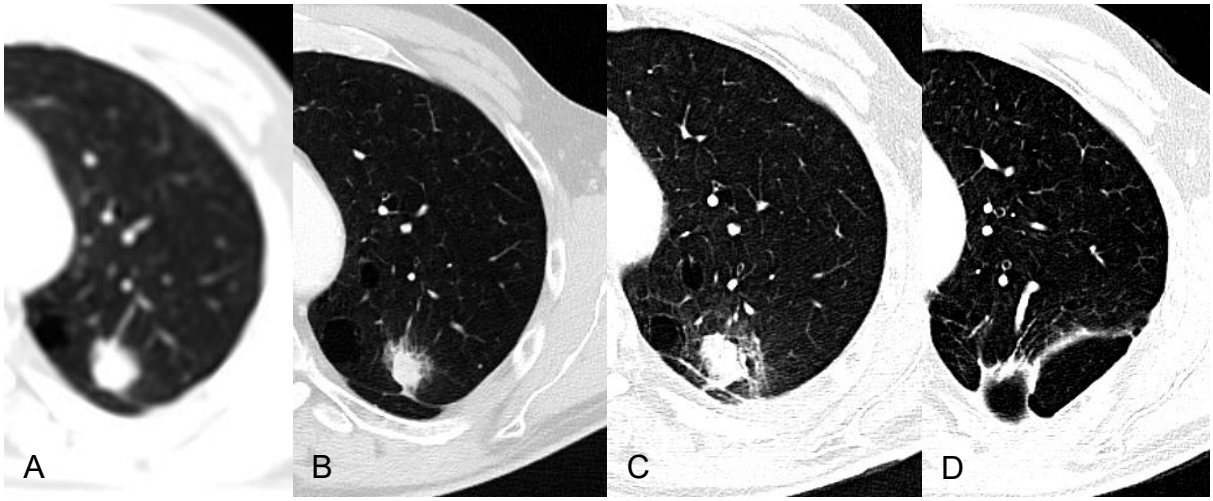

Figure 19. CT series with 4d-CT (A) and control scans at 3 (B), 7 (C), and 16 months (D) with finally complete tumor regression;
Source: archive of the Coburg Cancer Center / Department of Radiation Oncology

4.6. Quality of Life

QoL assessments were conducted among the surviving participants of the study, which included 14 patients. However, 9 patients opted not to participate in the QoL assessment and were consequently excluded from this aspect of the study. As a result, a total of 5 patients were recruited to complete the EORTC QLQ-C30 and QLQ-LC29 questionnaires, and their responses are summarized in Tables 7 and 8.

According to the EORTC QLQ-C30 questionnaire, patients in this study had a mean global health status of 33.3. In terms of function scales, their mean scores were 50.7 for physical function, 36.7 for role function, 60.0 for emotional function, 73.3 for cognitive function, and 36.7 for social function. Regarding the symptom scales or items, patients reported a mean score of 60.0 for fatigue, 13.3 for nausea and vomiting, 46.7 for pain, 60.0 for dyspnea, 46.7 for insomnia, 26.7 for appetite loss, 20.0 for constipation, 6.7 for diarrhea, and 13.3 for financial situation (Table 7).

Table 7. Scores for the EORTC QLQ-C30

EORTC QLQ-C30		Study sample (N=5)	Reference Values[a]
		Mean	**Mean**
Global health status / QoL	Global health status/QoL	33.3	56.6
Functional scales	Physical function	50.7	71.9
	Role function	36.7	61.5
	Emotional function	60.0	68.9
	Cognitive function	73.3	82.3
	Social function	36.7	71.3
Symptoms scales / items	Fatigue	60.0	41.1
	Nausea and vomiting	13.3	10.8
	Pain	46.7	29.7
	Dyspnea	60.0	37.9
	Insomnia	46.7	31.6
	Appetite loss	26.7	28.1
	Constipation	20.0	19.2
	Diarrhea	6.7	7.4
	Financial situation	13.3	17.4

[a] EORTC reference values for lung cancer: all stages (25)
EORTC, European Organisation for Research and Treatment of Cancer; QoL, Quality of Life

Regarding the EORTC QLQ-LC29 questionnaire, which focuses on symptom scales or items specifically for lung cancer, patients reported a score of 50.0 for coughing, 57.8 for shortness of breath, 34.8 for side effects of treatment, and 40.0 for fear of progression. Surgery-related problems was only completed in 3 patients with a mean score of 22.2, due to the fact, that the other 2 patients did not undergo lung surgery. Coughing blood or hemoptysis was reported with a mean score of 13.3, while pain in the chest, pain in the arm or shoulder, pain in other parts of the body, and weight loss were reported with mean scores of 26.7, 33.3, 40.0, and 26.7 respectively (Table 8).

Table 8. Scores for the EORTC QLQ-LC29

EORTC QLQ-LC29		Mean (N=5)
Symptom scales / items	Coughing	50.0
	Shortness of breath	57.8
	Side effects of treatment	34.8
	Fear of progression	40.0
	Surgery-related problems (N=3)	22.2
	Coughing blood / Hemoptysis	13.3
	Pain in chest	26.7
	Pain in arm or shoulder	33.3
	Pain in other parts of body	40.0
	Weight loss	26.7

EORTC, European Organisation for Research and Treatment of Cancer

5. DISCUSSION

SBRT has been established as first-line therapy for inoperable patients with NSCLC of stage I and II. This study analyzed the outcomes of patients with primary pulmonary lesions treated with SBRT. The measured outcomes included overall survival rates, LC rates, LPFS rates, and QoL. Furthermore, data was evaluated to identify prognostic factors with possible impact on mortality.

The study found statistically significant improved survival among female patients and those who underwent lung surgery prior to receiving SBRT. However, age, stage of disease, dose fractionation scheme, family predisposition, pulmonary comorbidities, cardiac comorbidities, history of smoking, previous lung irradiation, and chemotherapy were not statistically significantly associated with survival in this cohort. Interestingly, patients with pulmonary or cardiac comorbidities exhibited better survival rates compared to those without, although this difference was not statistically significant. It is important to note that these results should be interpreted with caution due to the small sample size, which may introduce potential skewing of the findings.

In this analysis, the 1-year OS rate of 77% is slightly lower compared to the reported rates of 82% to 86.23% in the literature (26–29). However, it is important to consider the differences in patient samples between them. Many of the previously conducted studies included only patients with early-stage NSCLC (26–28). In contrast, this study sample consisted of 16 (31.4%) patients diagnosed with stage III and IV NSCLC. Patients with advanced-stage NSCLC typically have a worse prognosis, as their disease is more advanced and may be associated with a higher tumor burden and potential metastases. Analyzing OS according to the stage of disease, a slightly higher 1-year OS rate of 78% for stage I and II NSCLC was seen, while the 1-year OS rate for stage III and IV NSCLC was 75%. The difference in OS between early- and advanced-stage NSCLC becomes more pronounced over time. At 5 years, the OS rate for stage I and II NSCLC reached 38%, while it was 7% for stage III and IV NSCLC. When comparing the 3-year OS rates, the literature reports a wider range from 32% to 60%, with three out of the five studies reporting OS rates above 50% (26, 28, 30–32). In comparison, this study achieved a 3-year OS rate of 46%. Similarly, fewer studies report 5-year OS rates, ranging from 18% to 34% compared to the 26% identified in this study (26, 27, 30).

Gender was found to be a statistically significant predictor of survival, with females having a lower risk of mortality compared to males. The hazard ratio (HR) for gender was 0.273 (P=0.008), indicating that females had a 0.273 times lower risk of dying from a pulmonary lesion after SBRT. Conversely males had a 3.66 times higher risk. Patients who underwent lung

surgery prior to SBRT also demonstrated a statistically significant lower risk of mortality. The HR for previous lung surgery was 0.378 (P=0.028), indicating a 0.378 times lower risk of dying from a pulmonary lesion. In contrast, patients who did not undergo lung surgery had a 2.646 times increased risk.

LC rates in this study were found to be 91% at 1 and 2 years, and 76 % at 3 years. These results are slightly lower compared to the findings of a meta-analysis by Li *et al.*, which reported LC rates of 97% at 1 year, 90% at 2 years, 86% at 3 years, and 83% at 4 years (26). Other published studies have also reported favorable 3-year LC rates ranging from 90.6% to 92.6% (28, 30–32). However, Oskan *et al.* had lower 1-year and 2-year LC rates of 79.3% and 52.6% respectively (29). These variations in LC rates may be attributed to several factors, including differences in the patient sample, the definition of tumor progression, and the method of measurement. In this study, tumor volume rather than diameter was used to identify tumor progression. Progression was defined as any increase in volume compared to the smallest volume in prior CT scans. On the other hand, other studies often use the RECIST (Response Evaluation Criteria in Solid Tumors) criteria to assess tumor progression. The RECIST criteria define progressive disease as an increase of at least 20% in the sum of diameters of the target lesion, compared to the smallest sum in previous imaging studies (33).

Comparing LPFS with other studies is difficult due to variations in reporting. Many studies focus on progression-free survival (PFS), which encompasses both distant and local tumor progression, whereas LPFS only includes local progression. In this study, the 1-year, 2-year, 3-year, and 5-year LPFS rates were at 82%, 70%, 49%, and 28% respectively. PFS rates reported in other studies have shown a wide range. At 1 year, PFS rates ranged from 53.6% to 92.52%, and at 3 years, they ranged from 52% to 76.23% (26, 28, 29). For comparison, Timmerman *et al.* calculated a disease-free survival rate of 48.3% at 3 years (32).

The QoL data obtained in this study reflect the poor clinical condition of patients with multiple comorbidities and an intrapulmonary lesion that was treated by stereotactic radiation rather than being a good candidate for lung surgery. Indeed, a very poor global health status together with low functional scales including role function, and social function as well as leading symptom scales of dyspnea and fatigue are being reported by the few surviving patients. This is compatible with clinical data and PROMs from the literature (24).

Limitations of this study include both its retrospective nature, together with a relatively small sample size that may give rise to concerns in terms of a not too high-quality evidence-based data set. On the other hand, this data reflects “real world” conditions with a consecutive series of non-selected patients and their typical clinical outcome parameters.

6. CONCLUSION

1. Actuarial 1-year, 2-year, 3-year, and 5-year OS rates were 77%, 61%, 46%, and 26% respectively.
2. The 1-year, 2-year, and 3-year LC rates were 91%, 91%, and 76% respectively.
3. Independent prognostic factors with a positive impact on OS were female gender-and previous lung surgery.
4. UICC-staging or a history of smoking did not demonstrate a statistically significant influence on OS.
5. Stereotactic radiotherapy for early-stage lung cancer proved to be a very effective and safe treatment.

7. REFERENCES

1. Cancer Today [Internet]. Lyon: Global Cancer Observatory; 2020. Estimated number of deaths in 2020, World, both sexes, all ages; 2023 [cited 2023 Apr 9]. Available from: https://gco.iarc.fr/today/online-analysis-pie?v=2020&mode=cancer&mode_population=continents&population=900&populations=900&key=total&sex=0&cancer=39&type=1&statistic=5&prevalence=0&population_group=0&ages_group%5B%5D=0&ages_group%5B%5D=17&nb_items=7&group_cancer=1&include_nmsc=1&include_nmsc_other=1&half_pie=0&donut=0
2. Cancer Today [Internet]. Lyon: Global Cancer Observatory; 2020. Estimated number of new cases in 2020, World, males, all ages; 2023 [cited 2023 Apr 9]. Available from: https://gco.iarc.fr/today/online-analysis-pie?v=2020&mode=cancer&mode_population=continents&population=900&populations=900&key=total&sex=1&cancer=39&type=0&statistic=5&prevalence=0&population_group=0&ages_group%5B%5D=0&ages_group%5B%5D=17&nb_items=7&group_cancer=1&include_nmsc=1&include_nmsc_other=1&half_pie=0&donut=0
3. Cancer Today [Internet]. Lyon: Global Cancer Observatory; 2020. Estimated number of new cases in 2020, World, females, all ages; 2023 [cited 2023 Apr 9]. Available from: https://gco.iarc.fr/today/online-analysis-pie?v=2020&mode=cancer&mode_population=continents&population=900&populations=900&key=total&sex=2&cancer=39&type=0&statistic=5&prevalence=0&population_group=0&ages_group%5B%5D=0&ages_group%5B%5D=17&nb_items=7&group_cancer=1&include_nmsc=1&include_nmsc_other=1&half_pie=0&donut=0
4. Cancer Today [Internet]. Lyon: Global Cancer Observatory; 2020. Lung. 2020 Dec [cited 2023 Apr 9]. Available from: https://gco.iarc.fr/today/data/factsheets/cancers/15-Lung-fact-sheet.pdf
5. Zentrum für Krebsregisterdaten. Lungenkrebs (Bronchialkarzinom) [Internet]. Berlin: Robert Koch-Institut; 2022 Sep 30 [cited 2023 Apr 9]. Available from: https://www.krebsdaten.de/Krebs/DE/Content/Krebsarten/Lungenkrebs/lungenkrebs_node.html
6. Malhotra J, Malvezzi M, Negri E, La Vecchia C, Boffetta P. Risk factors for lung cancer worldwide. Eur Respir J. 2016;48:889-902.
7. Kim AS, Ko HJ, Kwon JH, Lee JM. Exposure to secondhand smoke and risk of cancer in never smokers: A meta-analysis of epidemiologic studies. Int J Environ Res Public Health. 2018;15:1981.

8. Coté ML, Liu M, Bonassi S, Neri M, Schwartz AG, Christiani DC, et al. Increased risk of lung cancer in individuals with a family history of the disease: A pooled analysis from the International Lung Cancer Consortium. Eur J Cancer. 2012;48:1957-68.
9. Kanwal M, Ding XJ, Cao Y. Familial risk for lung cancer. Oncol Lett. 2017;13:535-42.
10. Darby S, Hill D, Auvinen A, Barros-Dios JM, Baysson H, Bochicchio F, et al. Radon in homes and risk of lung cancer: Collaborative analysis of individual data from 13 European case-control studies. Br Med J. 2005;330:223-6.
11. Brenner DR, McLaughlin JR, Hung RJ. Previous lung diseases and lung cancer risk: A systematic review and meta-analysis. PLoS One. 2011;6:e17479.
12. Husain AN. Lung. In: Kumar V, Abbas AK, Aster JC, editors. Robbins basic pathology. 10th ed. Philadelphia, Pennsylvania: Elsevier; 2018. p. 495-548.
13. Nicholson AG, Tsao MS, Beasley MB, Borczuk AC, Brambilla E, Cooper WA, et al. The 2021 WHO Classification of Lung Tumors: Impact of Advances Since 2015. J Thorac Oncol. 2022;17:362-87.
14. Horn L, Lovly CM. Neoplasms of the Lung. In: Jameson JL, Kasper DL, Longo DL, Fauci AS, Hauser SL, Loscalzo J, editors. Harrison's principles of Internal Medicine. 20th ed. Vol. 1. New York: McGraw-Hill Education; 2018. p. 537-55.
15. Spyratos D, Zarogoulidis P, Porpodis K, Angelis N, Papaiwannou A, Kioumis I, et al. Preoperative evaluation for lung cancer resection. J Thorac Dis. 2014;6:S162-6.
16. Roy PM. Preoperative pulmonary evaluation for lung resection. J Anaesthesiol Clin Pharmacol. 2018;34:296-300.
17. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF). Prävention, Diagnostik und Nachsorge des Lungenkarzinoms (Langversion 2.1) [Internet]. Berlin: Office Leitlinienprogramm Onkologie: 2022 [cited 2023 Jan 8]. Available from: https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Lungenkarzinom/Version_2/LL_Lungenkarzinom_Langversion_2.1.pdf
18. Timmerman RD, Herman J, Cho LC. Emergence of stereotactic body radiation therapy and its impact on current and future clinical practice. J Clin Oncol. 2014;32:2847-54.
19. Haridass A. Developments in stereotactic body radiotherapy. Cancers. 2018;10:497.
20. Brandner ED, Chetty IJ, Giaddui TG, Xiao Y, Huq MS. Motion management strategies and technical issues associated with stereotactic body radiotherapy of thoracic and upper abdominal tumors: A review from NRG oncology. Med Phys. 2017;44:2595-612.

21. Ceberg S, Falk M, Af Rosenschöld PM, Cattell H, Gustafsson H, Keall P, et al. Tumor-tracking radiotherapy of moving targets; verification using 3D polymer gel, 2D ion-chamber array and biplanar diode array. J Phys: Conf Ser. 2010;250.
22. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organisation for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993; 85:365-76.
23. Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A, on behalf of the EORTC Quality of life Group. The EORTC QLQ-C30 Scoring Manual (3rd Edition). Published by: European Organisation for Research and Treatment of Cancer, Brussels 2001.
24. Koller M, Hjermstad MJ, Tomaszewski KA, Tomaszewska IM, Hornslien K, Harle A, et al. An international study to revise the EORTC questionnaire for assessing quality of life in lung cancer patients. Ann Oncol. 2017;28:2874-81.
25. Scott NW, Fayers PM, Aaronson NK, Bottomley A, De Graeff A, Groenvold M, et al. EORTC QLQ-C30 Reference Values [Internet]. Brussels: EORTC Quality of Life Group; 2008 [cited 2023 June 29]. Available from: https://www.eortc.org/app/uploads/sites/2/2018/02/reference_values_manual2008.pdf
26. Li C, Wang L, Wu Q, Zhao J, Yi F, Xu J, et al. A meta-analysis comparing stereotactic body radiotherapy vs conventional radiotherapy in inoperable stage I non-small cell lung cancer. Medicine. 2020;99:e21715.
27. Jeppesen SS, Schytte T, Jensen HR, Brink C, Hansen O. Stereotactic body radiation therapy versus conventional radiation therapy in patients with early stage non-small cell lung cancer: An updated retrospective study on local failure and survival rates. Acta Oncol. 2013;52:1552-8.
28. Baumann P, Nyman J, Hoyer M, Wennberg B, Gagliardi G, Lax I, et al. Outcome in a prospective phase II trial of medically inoperable stage I non-small-cell lung cancer patients treated with stereotactic body radiotherapy. J Clin Oncol. 2009;27:3290-6.
29. Oskan F, Dzierma Y, Wagenpfeil S, Rübe C, Fleckenstein J. Retrospective analysis of stereotactic ablative radiotherapy (SABR) for metastatic lung lesions (MLLs) in comparison with a contemporaneous cohort of primary lung lesions (PLLs). J Thorac Dis. 2017;9:742-56.

30. Wulf J, Haedinger U, Oppitz U, Thiele W, Mueller G, Flentje M. Stereotactic radiotherapy for primary lung cancer and pulmonary metastases: A noninvasive treatment approach in medically inoperable patients. Int J Radiat Oncol Biol Phys. 2004;60:186-96.
31. Guckenberger M, Allgäuer M, Appold S, Dieckmann K, Ernst I, Ganswindt U, et al. Safety and efficacy of stereotactic body radiotherapy for stage I non-small-cell lung cancer in routine clinical practice: A patterns-of-care and outcome analysis. J Thorac Oncol. 2013;8:1050-8.
32. Timmerman R, Paulus R, Galvin J, Michalski J, Straube W, Bradley J, et al. Stereotactic Body Radiation Therapy for Inoperable Early Stage Lung Cancer. JAMA. 2010;303:1070-6.
33. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228-47.

8. SUMMARY

Objectives: The objective of this retrospective study was to evaluate the outcomes of patients with early-stage lung cancer that were treated by stereotactic radiotherapy. Endpoints included overall survival, local control, local progression-free survival and their possible prognostic factors as well as quality of life data.

Materials and methods: Between 2014 and 2021, a total of 51 patients meeting the inclusion criteria were evaluated. All patients have been treated by stereotactic radiotherapy using either 3 x 12.5-15 Gy, 8 x 7.5 Gy, or 12 x 4-6 Gy. Treatment planning was carried out using the Eclipse™ treatment planning system v18.0 (Varian Medical Systems). All radiation treatments were performed using the advanced radiation equipment of a Truebeam™ 2.0-linear accelerator with a 6-degree of freedom couch (Varian Medical Systems). Surviving patients were requested to complete the EORTC QLQ-C30 and QLQ-LC29 questionnaires to evaluate their quality of life (QoL) in order to assess patient reported outcome measures (PROMs).

Results: The actuarial 1-year, 2-year, 3-year, and 5-year OS rates were 77%, 61%, 46%, and 26%, respectively. The 1-year, 2-year, and 3-year LC rates were 91%, 91%, and 76%, respectively. Independent prognostic factors with positive impact on OS were female gender (HR: 0.273; *P*=0.008), and previous lung surgery (HR: 0.378; *P*=0.028). In terms of QoL, a very poor global health status together with low functional scales including role function, and social function as well as leading symptom scales of dyspnea and fatigue are being reported by the surviving patient cohort.

Conclusion: Stereotactic radiotherapy for early lung cancer proved to be a very effective and safe treatment.

9. CROATIAN SUMMARY

Naslov: Retrospektivna analiza stereotaktičke radioterapije za primarne intrapulmonalne lezije

Ciljevi: Cilj ove retrospektivne studije bio je procijeniti ishode liječenja u bolesnika s ranim stadijem karcinoma pluća koji su liječeni stereotaktičkom radioterapijom. Kao krajnji ciljevi su uzeti opće preživljenje, lokalna kontrola, lokalno preživljenje bez progresije te njihovi mogući prognostički faktori, kao i podaci o kvaliteti života.

Materijali i metoda: Od 2014. do 2021. godine procijenjen je ukupno 51 bolesnik koji ispunjavaju uključne kriterije. Svi bolesnici liječeni su stereotaktičkom radioterapijom koristeći doze od 3 x 12,5-15 Gy, 8 x 7,5 Gy ili 12 x 4-6 Gy. Planiranje liječenja provedeno je pomoću sustava za planiranje liječenja Eclipse^{TM} verzije 18.0 (Varian Medical Systems). Radioterapija je izvedena korištenjem napredne radijacijske opreme Truebeam^{TM} 2.0 - linearni akcelerator s kaučom s 6 stupnjeva slobode (Varian Medical Systems). Bolesnicima koji su preživjeli zatraženo je da ispune upitnike EORTC QLQ-C30 i QLQ-LC29 kako bi se procijenila njihova kvaliteta života i rezultati prijavljeni od strane pacijenta.

Rezultati: Aktuarske stope preživljenja u razdoblju od 1 godine, 2 godine, 3 godine i 5 godina iznosile su redom 77%, 61%, 46% i 26%. Stope lokalne kontrole u razdoblju od 1 godine, 2 godine i 3 godine iznosile su redom 91%, 91% i 76%. Neovisni prognostički faktori s pozitivnim utjecajem na preživljenje bili su ženski spol (HR: 0.273; *P*=0.008) i prethodna plućna operacija (HR: 0.378; *P*=0.028). Što se tiče kvalitete života, vrlo loš opći status zdravlja zajedno s niskim funkcionalnim skalama, uključujući ulogu u funkcioniranju i društvenu funkciju, kao i vodeće simptomatske skale dispneje i umora, prijavljuje se u preživjeloj skupini pacijenata.

Zaključci: Stereotaktička radioterapija za rani karcinom pluća pokazala se vrlo učinkovitom i sigurnom terapijom.