Retrospective analysis of survival data in patients with non-small cell lung cancer (NSCLC) following radiation and chemotherapy : The impact of mutations of the epidermal growth factor receptor (EGFR)

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UNIVERSITY OF SPLIT
SCHOOL OF MEDICINE

KATHARINA ENDRES

RETROSPECTIVE ANALYSIS OF SURVIVAL DATA IN PATIENTS WITH NON-SMALL CELL LUNG CANCER (NSCLC) FOLLOWING RADIATION AND CHEMOTHERAPY: THE IMPACT OF MUTATIONS OF THE EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR)

DIPLOMA THESIS

Academic year: 2021/2022
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Split, September 2022

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LIST OF ABBREVIATIONS:

ADC	Adenocarcinoma
AkT	Protein kinase B
CI	Confidence Interval
cMyc	C Proto-Oncogene
CT	Computed Tomography
CTCAEv4	Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0
ctDNA	Circulating DNA
ErbB	Receptor Tyrosine Kinases
EGFR	Epithelial Growth Factor Receptor
EGFRvIII	Epidermal Growth Factor Receptor Variant III
ERK	Extracellular Signal-Regulated Kinase
IQR	Interquartile Range
K	Karnofsky Index
KRAS	Kirsten Rat Sarcoma Virus Gene
MAPK	Mitogen-Activated Protein Kinase
MEK	Mitogen-Activated Protein Kinase Kinase
mTOR	Mammalian Target of Rapamycin
NF1	Neurofibromatosis Type 1
NFKB	Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells
NSCLC	Non-Small Cell Lung Cancer
PET	Positron Emission Tomogramphy
PFS	Progression Free Survival
Pi3K	Phosphoinositide 3-Kinase
PTEN	Phosphatase and Tensin Homolog
RAF	Serine/Threonine-Specific Protein Kinases
RAS	Rat Sarcoma Virus Gene
Src	Proto-Oncogene Tyrosine-Protein Kinase
SSC	Squamous Cell Carcinoma
TKI	Tyrosine Kinase Inhibitors
TNM stages	Tumor, Node and Metastases Classification
WHO	World Health Organization

1. INTRODUCTION

1.1. Lung cancer

With a total of 1.8 million deaths, lung cancer still is the most common cause of cancer-related deaths worldwide (1). The incidence of disease is much higher in women from industrialized countries than in their counterparts from developing parts of the world (2).

Histologically, lung cancer can be distinguished into two broad groups, small cell lung cancer (SCLC), which only makes up around 10% to 15% of lung cancer, and non-small cell lung cancer (NSCLC). Non-small cell lung cancer can be further divided into adenocarcinomas (ADC), the most common histologic type making up around 40% of cases, and squamous cell carcinomas (SSC), accounting for 25% to 30% (3).

Knowing further molecular characteristics of lung cancers can help to improve treatment. Alterations of the epidermal growth factor receptor (EGFR) and KRAS are the most common mutations of adenocarcinoma of the lung (2). In some studies, the overall prevalence of EGFR mutations in the subpopulation of lung cancer patients can vary from around 30% to over 60%, with adenocarcinoma being more common than squamous cell carcinoma. In Europe, the frequency of EFGR mutation lies between 7% to 40% (4) .

1.1.1 Environmental risk factors

There is a strong correlation between the incidence and mortality of lung cancer and cigarette smoking, which also contributes to the disparity in incidence between men and women and different socioeconomic statuses (5). Lower developed countries still show a higher rate of smoking in their population; the mortality rate in these countries is, unfortunately, significantly higher than in developed nations. The causes might be lack of or unequally distributed access to healthcare facilities leading to later diagnosis and treatment, polluted living conditions and barriers of sociocultural grounds (6). There is also evidence of lung cancers being caused by using biomass fuels for cooking indoors. This smoke has high levels of poly-cyclic-aromatic hydrocarbons, benzene and more carcinogenic compounds (7). Asbestos exposure is also recognized as a possible occupational cause of lung cancer (2).

1.1.2 Other risk factors

In addition to environmental factors, genetic factors must also be considered. People with a family history of lung cancer, as well as those suffering from Li-Fraumeni syndrome, are more likely to develop lung cancer. Recently, genome-wide association (GWA) studies have identified genetic polymorphisms which also modify a person's risk of lung cancer. It is

apparent from the observation that not all smokers will develop lung cancer, meaning that there is a genetic influence on the individual risk for lung cancer (8).

Gender not only plays a role in risk factors such as smoking, but also because of sex hormones. Mostly, they affect cancer development in nonreproductive organs, such as the lung (9). Unfortunately, the exact effect and its nature of possible influence on cancerous growth has yet to be studied adequately. Literature suggests though, that there might be an important link between tobacco smoke and the endocrine system (10). This effect can also be seen in the much higher number of postmenopausal women that have been diagnosed with lung cancer compared to men of the same age (10). Sex hormones also seem to have an influence on cancer development when administered exogenously. Lung cancer death in transgender women was shown to be much higher, as reported by Asschemann et al (11).

1.2. Non-small cell lung cancer

NSCLC is not just one disease, but a group of diseases with heterogenous genetic and cellular backgrounds. Pathological characteristics are the foundation for distinction between the different types of NSCLC, ADC and SSC. Additionally, large cell carcinoma and some types of neuroendocrine tumors are also classified as NSCLC (12).

1.3 EGFR mutation

EGFR mutations, the most common driver mutations found in NSCLC, are part of a larger group of mutations of receptor tyrosine kinases, ErbB. This group includes EGFR/erb-b2 receptor tyrosine kinase 1 (ERBB1), erb-b2 receptor tyrosine kinase 2 (HER2/ERBB2), erb-b2 receptor tyrosine kinase 3 (HER3/ERBB3), and erb-b2 receptor tyrosine kinase 4 (HER4/ERBB4) (13, 14).

Tyrosine kinases are transmembrane receptors, which function as the starting points of intracellular signaling pathways affecting cell proliferation, angiogenesis, and apoptosis (13).

The prevalence of EGFR mutations in NSCLC varies greatly. In Europe 14.1% of patients show an EGFR mutation, but the numbers are much higher in other parts of the world with Asia showing a prevalence of 38.4% and North and South America a prevalence of 24.4% prevalence (15). Routine testing for mutations in EFGR, ALK and ROS11 has been recommended by the European Society for Medical Oncology (ESMO), as well as corresponding agencies in Asia and America (16-18).

1.3.1 EGFR signaling pathway

The ErbB signaling pathway, which includes the EGFR pathway, is often very active in malignancies originating from epithelial cells. 80% to 90% of all cancer cases show ErbB signaling; most are due to gene amplification, point or deletion mutations, or gene fusion. This indicates that this pathway can be used as a target for therapy in many cancer patients (19, 20).

This discovery made it possible to develop therapeutic approaches using TKI and monoclonal antibodies. TKI therapy uses the receptor's kinase as a point-of-attack, impeding the function of its oncogenic form. Monoclonal antibody therapy focuses on the extracellular ligand-binding domain of the tyrosine kinase receptor. By this, it halts signaling in one of two possible ways: by upregulating the degradation of the receptor or by blocking its dimerization (20).

1.3.2 Effects of EGFR signaling

Activation of EGF receptor happens by a ligand binding to its extracellular module (20). As can be seen in Figure 1, this activation leads to various intracellular pathways and is a hallmark effect of tumor growth (21).

Its main action is via the PI-3K/AKT signaling pathway, which drives many distinctive features of cancer development such as autonomous growth signaling, continuous angiogenesis and an insensitivity of the cell to anti-growth signals (22). RAS and MAPKs are responsible for transcription factors regulating the growth and division of cells (21).

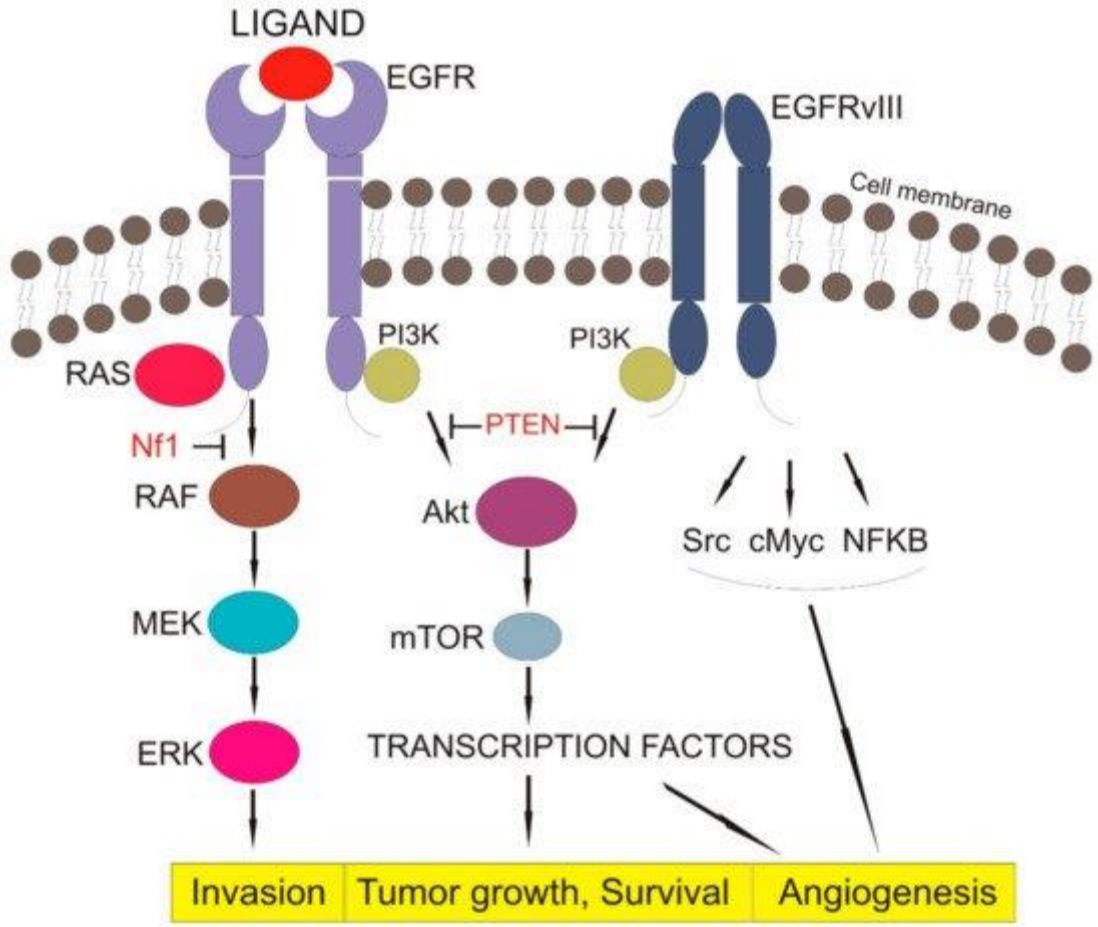

Figure 1: EGFR signaling pathway

(EGFR—epithelial growth factor receptor, EGFRvIII—Epidermal growth factor recep- tor variant III, Pi3K—Phosphoinositide 3-kinase, RAS—family of genes involving cellular signal transduction, PTEN— Phosphatase and tensin homolog, NF1—Neurofibromatosis type 1, RAF—serine/threonine-specific protein kinases, MEK— Mitogen-activated protein kinase, ERK—extracellular signal-regulated kinase, AkT—Protein kinase B, mTOR—mammalian target of rapamycin, Src—Proto-oncogene tyrosine-protein kinase, cMyc—c proto-oncogene, NFKB—nuclear factor kappa- light-chain-enhancer of activated B cells, Block arrow—inhibition activity, Point arrow—pathway flow

Source: Opitra, A et al. (21)

1.4 Treatment of NSCLC

1.4.1 Surgical resection

Tumor staging is done via computed tomography (CT), and positron emission tomography (PET), a step that is essential to ascertain further appropriate therapeutic measures. To this day, the most effective and consistent curative therapy remains surgical resection whenever reasonable (23).

1.4.2 Radiotherapy

Radiotherapy can be used as stereotactic radiosurgery by itself for early local NSCLC (Stage I-IIA), but also in conjunction with chemotherapy, as is the case for most patients with Stage III NSCLC. Unfortunately, it is generally considered that NSCLC in Stage IV is incurable (24). There is also evidence that high doses of radiation lead to better control of NSCLC tumors. Radiotherapy also has the advantage that it can be used as palliative treatment (25).

1.4.3 Chemotherapy

Chemotherapy and immunotherapy were thought to be antipathetic. Due many patients' experiences of not benefitting from mono-immunotherapy in Stage IV NSCLC, new significance has been given to chemotherapy as a treatment for cancer (26).

Adjuvant chemotherapy has been studied extensively and various regimens based on Cisplatin have been developed. Neoadjuvant therapy has not been studied as considerably, nevertheless it shows better tolerability, the possibility of down-staging the disease and quicker treatment of micrometastases (27).

1.4.4 Immunotherapy

Therapy with tyrosine kinase inhibitors is a patient-tailored therapy that has improved outcomes in many patients. It can be targeted towards cancerous driver mutations like EGFR mutations in NSCLC (25).

The first trial to show the benefits of TKI therapy in EGFR positive NSCLC was the IRESSA Pan-Asia Study. Compared to chemotherapy (47.3% response rate and 6.3 months of progression-free survival), patients receiving TKI therapy showed improved response (71.2%) and median progression-free survival (PFS) (9.5 months) (13).

This therapy is already being used in patients with Stage III disease that cannot have curative surgery. When combined with chemoradiotherapy, these patients show improved 2-year survival rates (26).

1.5 EGFR mutation's effect on the patients' prognosis

Plasma genotyping has made it possible to detect tumor DNA (ctDNA) circulating throughout the patients' bloodstream. This, in turn, enabled researches to more easily find gene mutations and target therapy specific mutations for individual patients (20).

Makoto M. et al. showed in their trial of 230 patients with metastatic NSCLC, without prior chemotherapeutic treatment, that treatment with first-line Gefitinib is preferable to standard chemotherapy. The toxicity measured in patients with advanced EGFR positive NSCLC was also deemed acceptable. Therefore, they recommended testing NSCLC patients for EGFR mutations (28).

EFGR mutation projects a better prognosis for the patients and sensitivity to tyrosine kinase inhibitors (TKIs), for example Erlotinib, Gefitinib, and Afatinib (29). For this reason, guidelines for clinical practice include testing NSCLC patients for those driver mutations to provide them with appropriate first-line treatment for their disease (30).

2. OBJECTIVES AND HYPOTHESIS

2.1 Aim of the study

The main purpose of this study was to evaluate if the presence of EGFR mutations in patients with NSCLC has an impact on the prognosis. The aim was also to determine whether there are more possible predictors of good outcome.

2.2 Hypothesis

1. EGFR-mutation can be shown to have a possible prognostic value in patients treated with radiotherapy and radiochemotherapy.
2. Patients harbouring a mutation of the EGFR-gene may have a significantly better survival rate than patients without this mutation.
3. The stage of disease at the time of diagnosis will have an impact on the 5-year survival rates of NSCLC patients in general.
4. The gender of patients with NSCLC influences their response to therapy and therefore the 5-year survival rate.

3. MATERIALS AND METHODS

3.1 Design and description of the study

This is a historical/retrospective cohort study using patient data and history from Regiomed Klinikum Coburg. Data was collected via patient records of the hospital over the course of several years; the data has been collected throughout the patients' treatment by the physicians of Klinikum Coburg and evaluated by me for the Thesis for the University of Split, School of Medicine.

3.2 Subjects and Methods

The sample will consist of all patients that received non-surgical treatment for non-small cell lung cancer at Regiomed Klinikum Coburg between the years of 2016 to 2020.

Exclusion criteria are concurrent other forms of cancer, patients having received surgical intervention for lung cancer, apart from patients with EGFR mutation, and patients, which, to our knowledge and paper trail, have not received a histological diagnosis according to WHO definition, or for which the date for a histological diagnosis was not noted in the patients' records. Additionally, patients receiving radiotherapy or chemotherapy for other types of cancer except non-small cell lung cancer were also excluded from the sample pool.

As this is a historical cohort study, no written or oral form of consent from the subjects is needed (see also ethical approval).

3.3 Independent variables

Independent variables are patient characteristics such as age, sex, comorbidities, and stage of disease.

3.4 Outcome measures

An important outcome is the incidence of EFGR-mutated compared to non-mutated non-small cell lung cancer, which will be measured in percentage. Additionally, I will look at the treatment the patients received, and the toxicity shown. Furthermore, the pattern of recurrence and mortality will be analyzed.

Important outcomes are the overall survival rate as well as the median survival time of patients with EGFR-mutations compared to patients without this mutation.

Furthermore, we will evaluate treatment- and patient-related variables and the treatment-related toxicity. The patterns of recurrences (local, regional, distant metastases) will be analyzed, as well.

3.5 Calculation of the minimal sample size

As a historical study with a limited pool of possible patients, the calculated sample size cannot be achieved in this study.

The calculated sample size is based on the assumption that 20% of the patients show EGFR mutations, compared to an estimated 40% prevalence among the population of non-small cell lung cancer patients. This would result in a sample size of 162 patients. The basis for this assumption is a literature search of meta-analyses about the prevalence of EGFR-mutated cancers among non-small cell lung cancer patients. The sample size was calculated with a type 1 error rate (alpha) of 0.05 and a power of 80%.

3.6 Statistical tests

The results were analyzed using IBM SPSS Statistics for Windows (IBM Corp, 2022). Qualitative data were expressed as whole numbers and percentage while quantitative data were expressed as mean ± standard deviation or mean and interquartile range. First, the analysis of normality of data distribution will be done using the Kolmogorov Smirnov test. Survival rates were calculated according to the Kaplan-Meier method. The log-rank test was used to compare survival rates between different patient groups. Results will be displayed as tables and figures with a 95% confidence interval.

For categorical variables frequencies are shown. Pearson coefficients of correlation were computed between continuous variables and Phi coefficients of correlation were computed between categorical variables, as well as t-tests. The significance of all tests was set to 0.05.

3.7 Possible biases and confounding variables

Follow-up bias: Patients might have moved away or switched doctors. These patients will have to be eliminated from patient sample.

Recall bias: Data was collected by others. This cannot be avoided in this study.

Information bias: Not all information might be included in the patient records. This cannot be avoided in this study.

Study bias: Since this is a retrospective analysis, only explorative data can be derived from these results.

3.8 Ethical approval

Ethical approval was obtained from the Ethics-Committee of the University Hospitals of Erlangen (Report No 22-5-Br) on January 31, 2022.

4. RESULTS

4.1 CONSORT Flow Diagram

In order to accurately describe the process of inclusion and exclusions of patients from this study, a flow diagram was created.

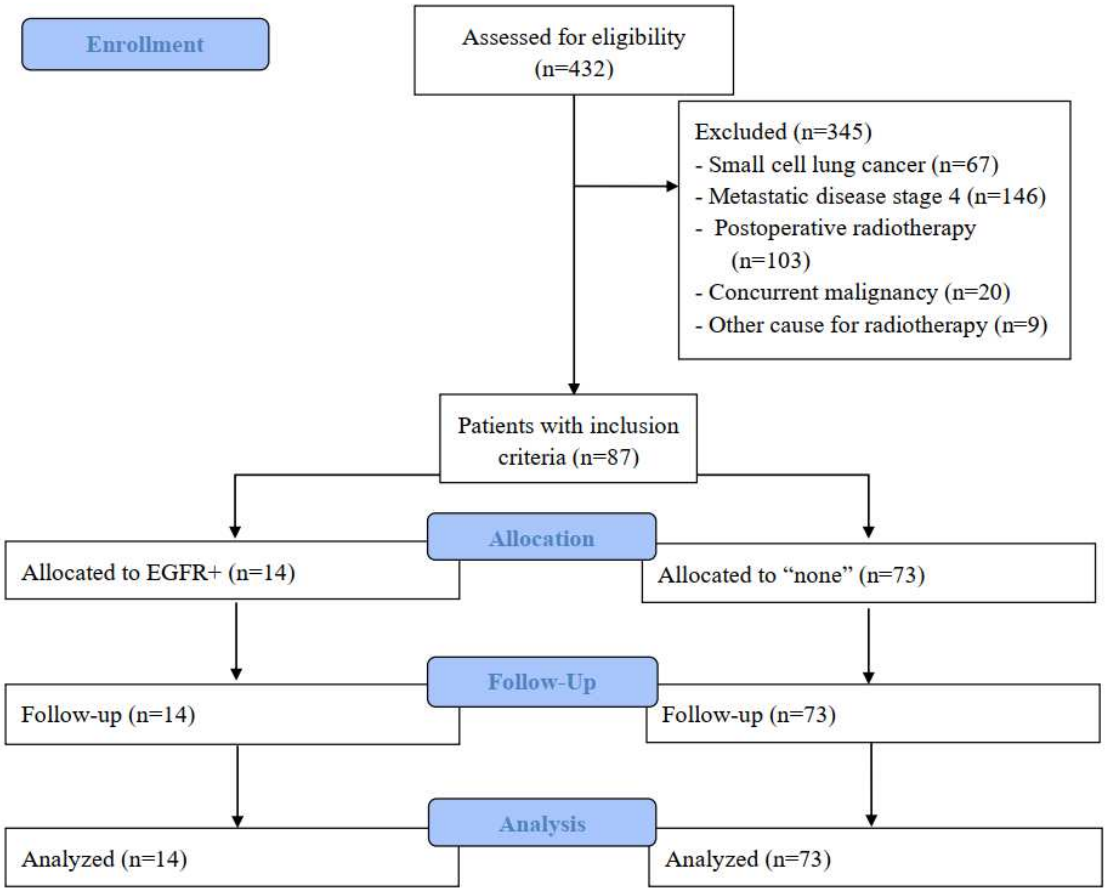

Figure 2: CONSORT Flow Diagram

432 patients with the diagnosis of lung cancer were identified between the years 2016 to 2020. 336 of these patients were excluded from this study because they did not meet the inclusion criteria. A further 35 patients were excluded due to conflicting or missing data in more than two criteria that were analyzed in this study. The remaining 87 patients were allocated according to their mutation status into EGFR + and "none" groups. Seeing as this is a retrospective study and no consent from the patients was needed, no patients dropped out of the follow-up.

4.2 Descriptive statistics of the sample (N=87)

After analyzing the data extracted from subjects' clinical reports, they were summarized and presented in Tables 1-3 and Figures 3-7. The data which were not available to us were classified as "unknown" in the tables.

There were 87 patients enrolled in the study, separated mainly into two groups by the presence or absence of EGFR mutation as reported by the histological analysis. 14 patients were shown to have the mutation, the 73 patients without the mutation were allocated the group “none”. The median age of the patients was 74 years (IQR: 65-82 years; 95% CI: 71-75 years). Patients showed an unequal gender distribution with 33 women (37.9%) and 54 men (62.1%).

Table 1: Patient characteristics (N=87)

		EGFR+ (N=14)	None (N=73)	Total (N=87)
Gender	Male	9 (64.3%)	45 (61.6%)	54 (62.1%)
	Female	5 (35.7%)	28 (38.3%)	33 (37.9%)
familial predisposition	No	10 (71.4%)	58 (79.4%)	68 (78.2%)
	Yes	4 (28.5%)	15 (20.5%)	19 (21.8%)
smoker	Non-smoker	9 (64.2%)	27 (36.9%)	36 (41.4%)
	Smoker	5 (35.7%)	46 (63.0%)	51 (58.6%)
Karnofsky Index	K 100	2 (14.2%)	7 (9.5%)	9 (10.3%)
	K 90-100	0 (0.0%)	1 (1.3%)	1 (1.1%)
	K 90	2 (14.2%)	8 (10.9%)	10 (11.5%)
	K 85	0 (0.0%)	1 (1.3%)	1 (1.1%)
	K 80-90	1 (7.1%)	3 (4.1%)	4 (4.6%)
	K 80	3 (21.4%)	19 (26.0%)	22 (25.3%)
	K 70-80	0 (0.0%)	2 (2,7%)	2 (2.3%)
	K 70	1 (7.1%)	5 (6.8%)	6 (6.9%)
	K 60	0 (0.0%)	4 (5.4%)	4 (4.6%)
	K 50	1 (7.1%)	0 (0.0%)	1 (1.1%)
	Unknown	3 (21.4%)	23 (31.5%)	26 (29.9%)
Grouped stages of disease	1-2B	1 (7.1%)	14 (19.1%)	15 (17.2%)
	3A	1 (7.1%)	20 (27.3%)	21 (24.1%)
	3B	3 (21.4%)	29 (39.7%)	32 (36.8%)
	3C-4	7 (50.0%)	8 (10.9%)	15 (17.2%)
	unknown	2 (14.2%)	2 (2.7%)	4 (4.6%)

The gender distribution in each group roughly corresponds to the overall distribution of the cohort. There are 9 male patients (64.2%) in the EGFR group and 45 (61.6%) in the group without the mutation.

21.8% of all patients reported having a familial predisposition, in this case defined as at least one blood relative of first- or second-degree suffering or having suffered from a malignancy, and 58.6% disclosed to having smoked or smoking at the time of diagnosis. Interestingly, only 35.7% of patients with EGFR mutation reported smoking compared to 63.0% of those without mutation.

Unfortunately, in 29.9% no Karnofsky Index (K) noted in the patients' files. 22 patients (25.3%) were marked as K 80, 10 (11.5%) were marked K 90, 9 (10.3%) were marked K 100, with the remaining 19 patients being distributed among the remaining 7 levels noted.

Stage 3B is the most common stage of disease in this cohort (36.8%), followed by stage 3A (24.1%). Early stages 1-2B and late stages of disease 3C-4 show an equal distribution of 17.2% each. In 4 patients (4.6%) the stage at the time of diagnosis was not recorded in the patients' files. The majority of patients with EGFR mutation were diagnosed at stages 3B (21.4%) and 3C-4 (50%), among patients without the mutation the majority was noted as stages 3A (27.3%) and 3B (39.7%).

Table 2: Treatment characteristics of patients with and without EGFR mutation (N=87)

Variable		EGFR+ (N=14)	None (N=73)
Radiotherapy	No[1]	1 (7.1%)	2 (2.7%)
	Yes[2]	13 (92.8%)	70 (95.8%)
	Unknown[3]	0 (0.0%)	1 (1.3%)
Chemotherapy	No	6 (42.8%)	28 (38.3%)
	Yes	8 (57.1%)	43 (58.9%)
	Unknown	0 (0.0%)	2 (2.7%)
TKI[4]-Therapy	No	6 (42.8%)	70 (95.8%)
	Yes	8 (57.1%)	1 (1.3%)
	Unknown	0 (0.0%)	2 (2.7%)
recurrence	No	11 (78.5%)	54 (73.9%)
	Yes	3 (21.4%)	17 (23.2%)
	Unknown	0 (0.0%)	2 (2.7%)
Local recurrence	No	12 (85.7%)	63 (86.3%)
	Yes	2 (14.2%)	7 (9.5%)
	Unknown	1 (7.1%)	3 (4.1%)
Distant recurrence	No	13 (92.8%)	69 (94.5%)
	Yes	0 (0.0%)	1 (1.3%)
	Unknown	1 (7.1%)	3 (4.1%)
Regional recurrence	No	13 (92.8%)	70 (95.8%)
	Yes	0 (0.0%)	0 (0.0%)
	Unknown	1 (7.1%)	3 (4.1%)
Exitus letalis	No	6 (42.8%)	31 (42.4%)
	Yes	8 (57.1%)	42 (57.5%)

[1] Patient has received therapy / has been found to have recurrence
[2] Patient has not received therapy / has not been found to have recurrence
[3] Patient is unknown to have received therapy / is unknown to have been found to have recurrence
[4] Tyrosine Kinase Inhibitor Therapy

In total, 83 patients (95.4%) received radiotherapy. Only 1 patient (7.1%) with EGFR mutation and 2 patients (2.7%) without mutation did not receive radiotherapy. 58.6% of the patients were treated using chemotherapy showing similar distribution between the patients with EGFR mutation and those without. In the EGFR group, 8 patients (57.1%) received TKI therapy, whereas only 1 patient (1.3%) without the mutation did.

A recurrence of the disease was noted in some cases, though the distribution between the groups was very similar; 21.4% of patients with EGFR mutation and 23.2% of patients without the mutation were reported to have recurring disease. 2 (14.2%) cases of recurring

disease in the EGFR mutated group were reported to be local. Unfortunately, nothing more could be found in the files concerning the locations in the last patient in the last patient to have shown recurrence of disease. Of the patients without the mutation 9.5% reported local recurrence and 1.3% distal recurrence; in 4.1% of cases no further information could be found in the files.

Survival of patients in the group with EGFR mutation and the group without the mutation was very similar with 42.8% and 42.2%, respectively.

Table 3: Maximal toxicity shown by patients after therapy according to CTCAEv4 (N=87)

		none	mild	moderate	severe	Total
Radio-therapy	No[1]	3 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (3.4%)
	Yes[2]	53 (65.1%)	11 (13.3%)	17 (20.5%)	1 (1.2%)	83 (95.4%)
	Unknown[3]	1 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Chemo-therapy	No	25 (73.5%)	3 (8.8%)	6 (17.6%)	0 (0.0%)	34 (39.1%)
	Yes	31 (60.8%)	8 (15.7%)	11 (21.6%)	1 (2.0%)	51 (58.6%)
	Unknown	2 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.3%)
TKI[4] therapy	No	50 (65.8%)	11 (14.5%)	14 (18.4%)	1 (1.3%)	76 (87.4%)
	Yes	6 (66.7%)	0 (0.0%)	3 (33.3%)	0 (0.0%)	9 (10.3%)
	Unknown	2 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.3%)
Total		57 (66.7%)	11 (12.6%)	17 (19.5%)	1 (1.1%)	87 (100.0%)

[1] Patient has received therapy / has been found to have recurrence
[2] Patient has not received therapy / has not been found to have recurrence
[3] Patient is unknown to have received therapy / is unknown to have been found to have recurrence
[4] Tyrosine Kinase Inhibitor Therapy

The majority of patients (65.1%) that received radiotherapy showed no symptoms attributed to the toxicity of the treatment. However, 13.3% showed mild and 20.5% moderate adverse effects of therapy. 60.8% of chemotherapy patients also have not reported any toxicity. In this group, 15.7% described mild and 21.6% moderate adverse effects.

In both patient groups, radiotherapy as well as chemotherapy, one patient reported having severe adverse effects due to their therapy, 1.2% and 2.0% respectively. 66.7% of patients treated with TKI therapy described no adverse effects, 33.3% noted moderate toxicity.

Disregarding the type of therapy specified in the patients' files, 12.6% showed mild, 19.5% moderate and 1.1% severe toxicity. The majority of patients (66.7%) did not complain of any adverse effects.

4.2 Survival date and prognostic factors (N=87)

The survival of patients was analyzed with Kaplan-Meier and displayed in Figures 3-7 and summarized in Table 4.

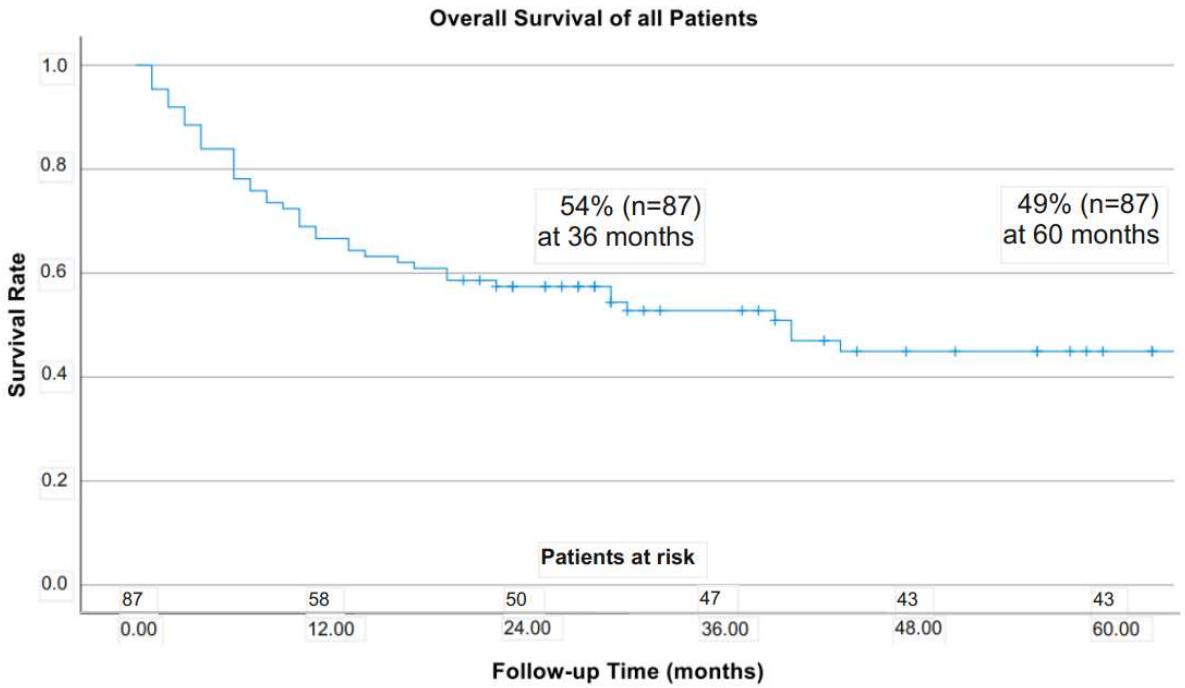

Figure 3: Overall Survival of All Patients

At 36 months follow-up, the cohort showed a survival rate of 54%. After 60 months of follow-up time, survival rate was 49% of all 87 patients, disregarding any other factors but being treated for NSCLC. Their median survival time was 40 months (95% CI: 20-59 months; SD±9). The survival ranged from a minimum of one month to a maximum of 205 months.

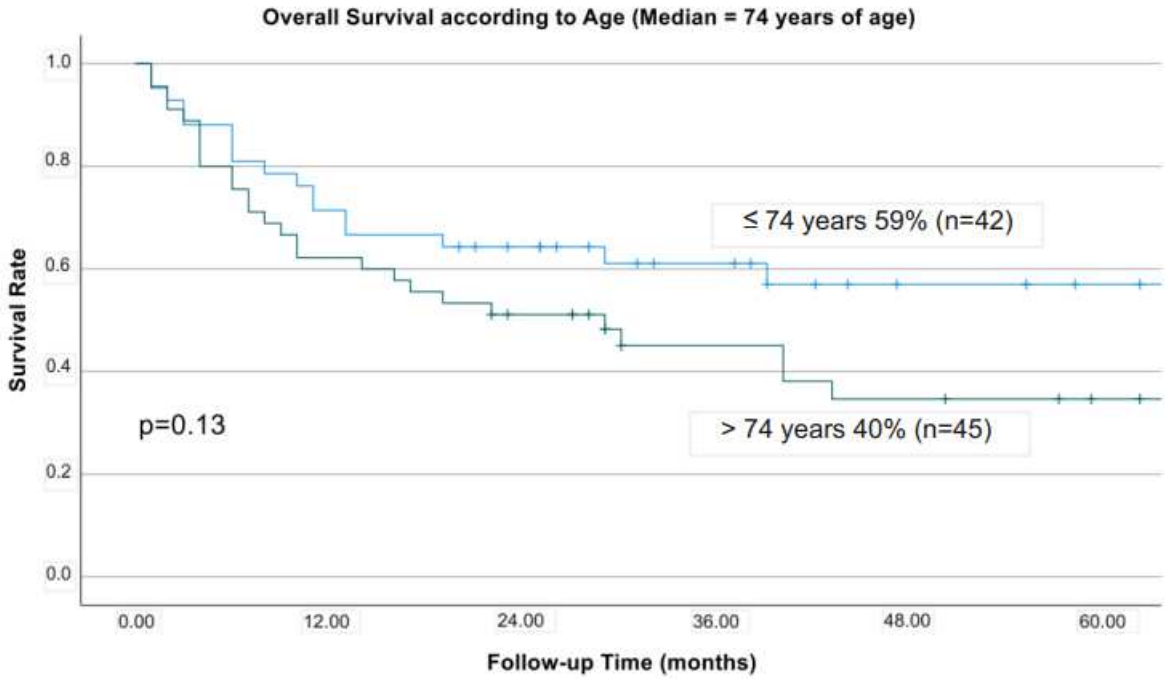

Figure 4: Overall Survival according to Age

There was no statistically significant improvement in survival time of patients under the age of 74 years compared to patients above that age (*P*=0.13). The median age of patients was 74±11 years. Eighteen (59%) of the patients 74 years or younger were recorded as "alive" 60 months after their diagnosis. In this age group, the minimal survival was one month, the maximum was 85 months. Their median survival was 68 months (95% CI: 13-122 months; SD±28). In patients above the age of 74 years, 18 (40%) patients survived for 60 months. The minimal survival was one month, the maximum was 205 months. Median survival was 29 months (95% CI: 9-48 months; SD±9).

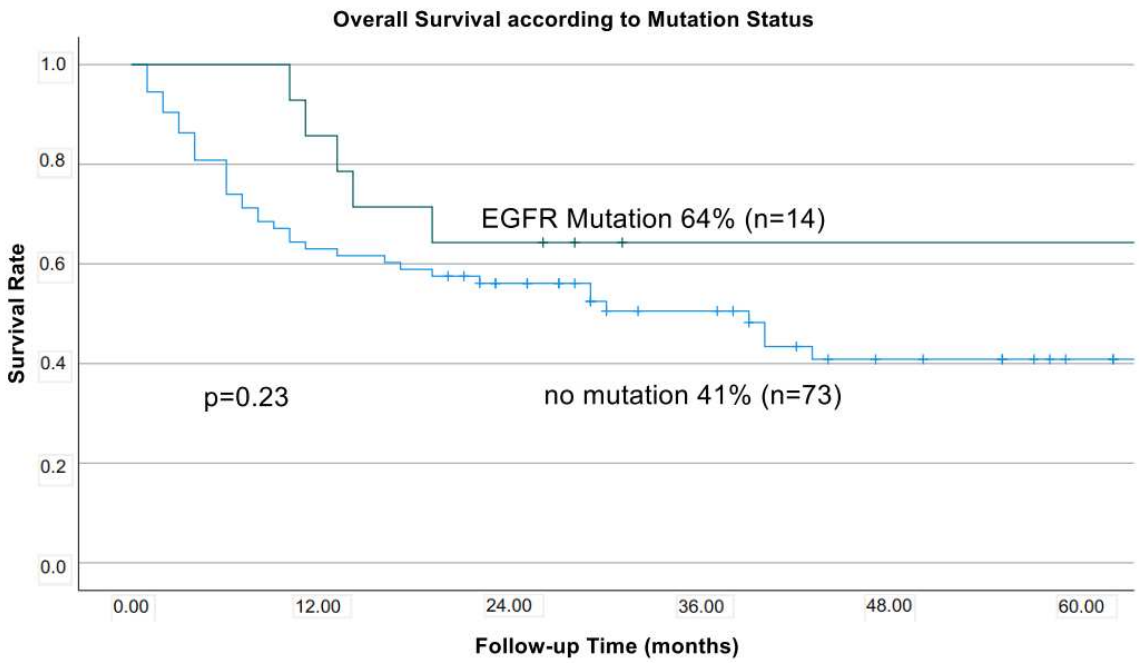

Figure 5: Overall Survival according to Mutation Status

There was no statistically significant improvement in survival time of patients with EGFR mutation compared to patients without the mutation (*P*=0.23). In the patient group with EGFR mutation, 9 (64%) patients had survived until the 60-month follow-up time. For this patient group minimum survival was 10 months and maximum survival 117 months; their median survival was 96 months (95% CI: 0-230; SD±69).

In the group without mutation, only 34 (41%) patients had survived 60 months. Their minimum survival was one month, the maximum 205 months; median survival in this group was 39 months (95%CI: 21-56 months; SD±8).

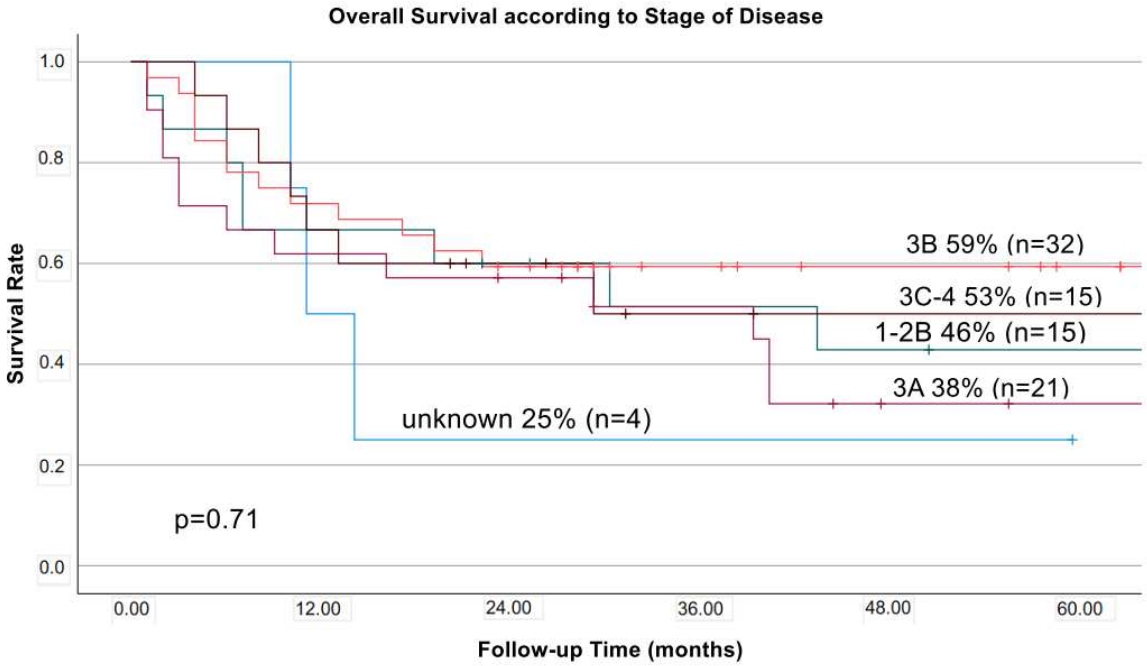

Figure 6: Overall Survival according to Stage of Disease

There was no statistically significant improvement in survival time in case of early diagnosis when comparing the reported stages of disease at diagnosis (*P*=0.71). Only 8 (38%) patients with stage 3A at diagnosis were reported to have survived for 60 months. Their minimum and maximum survival was one month to 205 months; median survival was 39 months (95% CI: 0-81months; SD±21). A total of 7 (46%) patients with stages 1-2B were found to have survived 60 months. The minimum survival was also one month, the maximum survival in this group was 96 months. Median survival of patients with stages 1-2B at diagnosis was 43 months (95% CI: 5-80months; SD±19).

Interestingly, more patients with more advanced stages 3B and 3C-4 survived until the 60-month follow-up, namely 59% and 53% respectively. The minimum and maximum survival for patients with stage 3B was one month to 95 months; median survival was 95 months; a 95% confidence interval could not be generated. For patients with stages 3C-4 minimum and maximum survival was 4 months to 117 months. Patients with stages 3C-4 had a median survival of 29 months (95% CI: 0-76 months; SD±24).

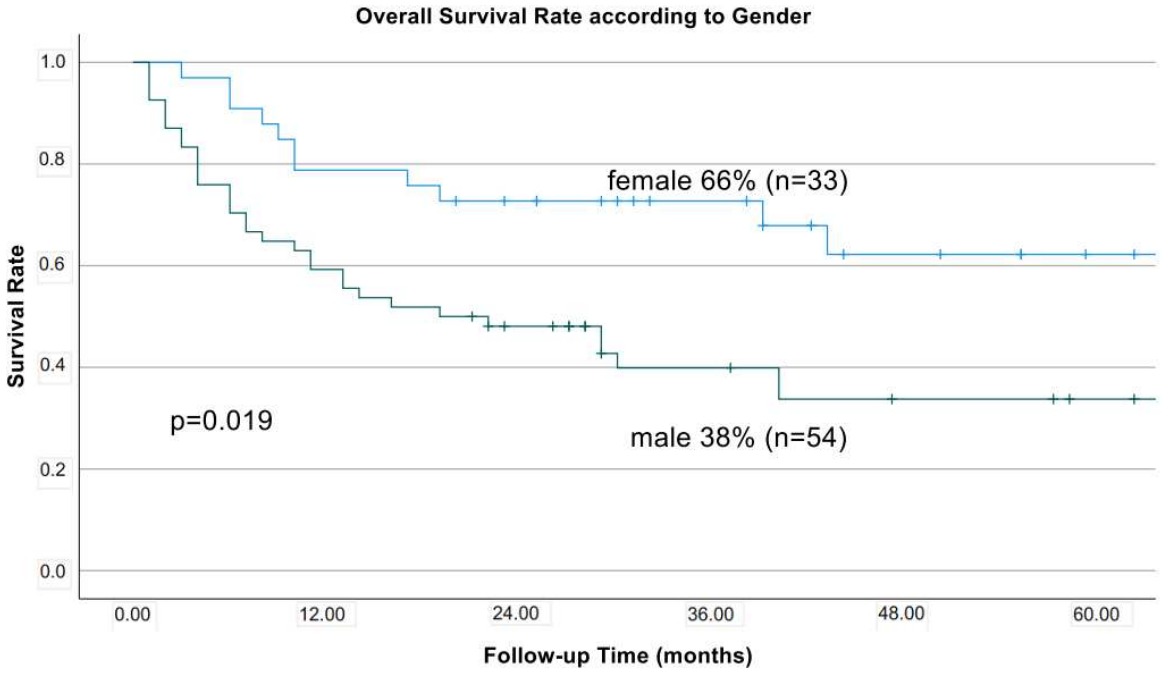

Figure 7: Overall Survival according to Gender

There was statistically significant improvement in survival time when comparing the different genders (*P*=0.019). 21 (38%) males survived the 60-month follow-up time, with a minimum survival of one month and a maximum of 205 months. The median survival was 19 months (95% CI: 2-35 months, SD±8). 22 (66%) female patients survived until the 60-month follow-up time. The minimum survival was three months, the maximum 117 months. The median survival of women in this study was 68 months (95%CI: 27-108 months, SD±20).

Table 4: Prognostic factors with impact on overall survival

		5-year survival	P-value
Overall		49%	
Age			0.13
	Below Median	59%	
	Above Median	40%	
Mutation status			0.23
	EGFR +	64%	
	None	41%	
Stage of disease			0.71
	1-2B	46%	
	3A	38%	
	3B	59%	
	3C-4	53%	
	Unknown	25%	
Gender			0.019
	Female	66%	
	Male	38%	

5. DISCUSSION

Due to the limited number of participants in this study, the two groups, with and without EGFR mutation, were of very different sizes. Unfortunately, that means that just one patient has a much greater impact in the group with EGFR mutation than in the other group; due to this the results can be skewed.

The median age of 74 years and the IQR of 65 to 82 years also means that the cohort was on average much older than the population of the county (median age 46,3 years) and therefore, the results cannot be applied to the population in large (31).

Usually, smoking is considered one of the major risk factors for lung cancer in developed countries. (8) Looking at the cohort, over half of them reported a history of smoking. However, smoking seems to be much less prevalent in patients with EGFR mutation at only 35.7%, though this can be skewed due to the small sample size. Although, this also seems to be in concordance with the global incidence of never smokers developing lung cancer (5).

The Karnofsky Index is used to determine how independent and capable of mastering everyday life patients are (32). Unfortunately, there is quite a significant number of patients in this study whose records did not note this score. Of those that did note it, the majority were recorded with an index of 80 or higher. This shows that the patients were able to perform activities of everyday life, albeit with some effort. They also showed some signs and symptoms of disease at the time of diagnosis (33).

95.4% of patients in this study had received radiotherapy. This large number can be traced back to the cohort data being taken from a radiotherapy center. Nevertheless, radiotherapy for NCSLC is an established method for postoperative and palliative treatment (34). Over half of the participants in the study have received chemotherapy. This is standard treatment for NSCLC of stage 3B or higher and whenever surgery cannot be performed (35). In this study, the exclusion of all patients without EGFR mutation except those having received surgery means that the percentage of patients with radiotherapy, chemotherapy or TKI therapy might be higher than usual. Only 10.3% of patients received therapy with TKI. This small percentage is most certainly due to the small number of participants in general, but this, in turn, has led to only a small number of patients with NSCLC and EGFR mutation. All but one of the patients receiving TKI therapy had a histological diagnosis of EGFR mutation. However, there were still 6 patients (42.6%) with the mutation that did not receive TKIs. Unfortunately, we cannot really be sure why they did not receive this therapy, because nothing was noted in the patients' files.

Any recurrences analyzed depend on them having been documented in the patient files. In both groups, over 70% of patients were not reported to have suffered from recurrences. Of

those patients with EGFR mutation, most recurrences, two out of three, were noted as local recurrences; the last recurrence was, unfortunately, not specified. Of course, the small number of patients in this group makes any single recurrence seem much more noticeable. Nevertheless, the percentage of recurrences is roughly the same in the patient group without EGFR mutation. In this group, most recurrences are also reported as local and there is also a small percentage of unknown recurrences. The frequency of recurrence in this study was much higher than that detected by a larger study in the USA, which showed a 25% to 35% recurrence rate for patients with lung cancer in their region (36). This, however, cannot be absolutely transferred to this cohort, because it did not distinguish between different types of lung cancer. The low rate of recurrence in this study could have one simple reason. The files noting the patients' progression were, as previously stated, not always complete and therefore, it might just be missing from the files. Additionally, their study came to a different conclusion about the location of recurrences, namely that most were cases of distant, rather than local, disease (36).

The analysis of toxicity shown by patients due to their treatment for NSCLC is, in this case, difficult. Most patients in this study received two different kinds of treatment. Therefore, it was impossible to determine which of the treatments was responsible for the adverse effects the patients had reported. Fortunately for the patients, most of them did not report any toxicity as far as was noted in the files; those that did mostly showed mild toxicity. The fact that most adverse effects of therapy can be seen in patients that have received radiotherapy can be attributed to the fact that all but three patients were treated with radiotherapy. Therefore, a statement about which form of therapy might lead to more toxicity cannot be made. Common toxic side effects of TKI therapy range from diarrhea, skin rashes to stomatitis or erosions of the cornea. Their severity depends on the drugs' potency (37). Other side effects, such as interstitial lung disease cannot be correlated to the drugs' strength. These types of toxic effects often lead to a complete stop in treatment with TKI therapeutic agents (38).

The survival of the patients was analyzed in regard to their age, their mutation, the stage of disease at the time of diagnosis and their gender. The follow-up time was 60 months. Overall, just over half of patients (57.5%) survived 5 years after their diagnosis. The median age of the study's participants was 74 years. This could be a reason for the lower 5-year survival rate in patients above 74 years. Though their median survival might look quite different at first glance, the small sample size of the study makes this result insignificant.

The presence of EGFR mutation in NSCLC is generally regarded as a point of intervention for therapeutic measures (39). The mutation has a major impact on disease treatment and prognosis. Due to this, a better disease outcome has been shown (40). Even

though patients with EGFR mutation did survive longer in this study, the difference to that of patients without the mutation was not significant.

It was also implied that the stage of the disease at the time of diagnosis might make a difference in the 5-year survival of patients with NSCLC, notwithstanding the presence of EGFR mutation. However, the results did not show any significant difference between groups of patients with early disease and those with advanced disease. A small review of patients and treatment of stage 3 NSCLC in the United Kingdom, though, has placed the 5-year survival of patients at only 6%, which they attributed to most patients not receiving radical treatment (41). When transferring their conclusion to this study, which showed a 5-year survival rate of 38% to 59% depending on the stage of disease, it would be reasonable to assume that patients in this study survive longer, in part at least due to their treatment.

The only significant difference in 5-year survival rate in this study could be found when comparing male and female patients with NSCLC. Although, even this result is unreliable, as can be seen by the overlapping confidence intervals of these cohorts. The effect of gender on the disease outcome has been studied with several different cancer types, mostly in relation to their response to different forms of treatment (42). A meta-analysis by Pinto and Coll on NSCLC treatment showed that female patients benefited less from certain chemotherapeutic agents than males. Females in their study had a higher risk of disease progression (43). However, there needs to be much further study into the effects of gender on cancer therapy and therefore also on gender-based survival (42).

Unfortunately, some limitations of this study have to be addressed. This study mostly relies on patient's files collected since 2016 in just one hospital. The patients were not obligated to be treated in this hospital for any complications or other diseases or events they suffered leaving their records incomplete. In order to as accurately as possible group these patients by several different characteristics, some assumptions had to be made.

Whenever the exact date of the patient's histological diagnosis, i.e., day, month, and year, could not be found in the records, it was assumed to have been on the fifteenth of the month. This was done, so that the "time to exitus" could be calculated. The same was done for "time to first progression". If the patient's hospital file listed the patient as "living", or if there was no evidence of death, or if obituaries in a public death registry could not be located on April 13, 2022, I used this date to calculate survival time for these patients.

The patients were also grouped according to the stage of their disease. When the patient's records listed them as in-between two different stages, the higher stage was used to assign them to a group.

On the basis of the side effects recorded during the patients' radiotherapy, chemotherapy or TKI treatment - or a combination of these - the patients were grouped according to the highest toxicity they experienced during treatment. In the case of patients whose files did not list toxicity, consequently being categorized as "unknown" for the presence of toxicity, it was assumed, in order to also group these patients, that they did not have any adverse reactions during their treatment.

6. CONCLUSIONS

1. Although literature strongly suggests that EGFR-mutations in NSCLC have a positive prognostic value, there was no significant difference in prognosis seen in this retrospective study.

2. With 64% vs 41%, the 5-year survival rate of patients with EGFR mutation was not significantly higher in this study as compared to non-mutated patients (p=0.23). This may be attributed to the small patient number.

3. The stage of disease (UICC stages 1-2A vs 3A vs 3B vs 3C-4) at the time of diagnosis was not shown to significantly influence survival rates of patients with NSCLC treated by combined radiochemotherapy.

4. With 66% vs 54% female patients had significantly increased 5-year survival rates compared to male patients (p=0.019)

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8. SUMMARY

Objectives: The goal of this study was to evaluate whether the presence of EGFR (Epidermal Growth Factor Receptor) mutations in patients with NSCLC treated by radiochemotherapy, would have an impact on the disease prognosis and survival.

Materials and methods: This was a historical/retrospective cohort study using data and history from patients treated at Regiomed Klinikum Coburg between 2016 and 2020, based on specific and predefined inclusion and exclusion criteria. Out of 432 patients with lung cancer, 336 patients were excluded for various reasons (small cell histology, prior surgery, metastatic or recurrent disease, stereotactic radiosurgery). 87 patients were included in this study, 14 of these patients harboring EGFR mutations. Patient characteristics analyzed were familial predisposition, Karnofsky-performance status, history of smoking, type of therapy received, any recurrence and its location, as well as possible toxicity due to the therapy. Using the Kaplan-Meier method, overall survival rates of patients was analyzed according to the mutation status, age, stage of disease at time of diagnosis and gender and compared by the logrank-test, The statistical data was analyzed with IBM SPSS Statistics for Windows 26 (IBM Corp, 2019). Patient data was supplemented from public databases whenever possible.

Results: The median age of patients was 74±11 years. Five-year overall survival rate (5y-OS) for all 87 patients was 49%, 5y-OS of patients older than 74 years was 40%, for those being younger 59% (P=0.13). Patients with EGFR mutation (n=14) and patients without the mutation (n=73) had a 5y-OS of 64% and 41%, respectively (P=0.23). 5-year-survival was 46% in patients with stages 1-2B, 38% in patients with stage 3A, 59% in stage 3B and 53% in patients with stages 3C-4 (P=0.71). This study did show a significant increase in survival for female patients compared to male patients, with 66% vs 38%, respectively (P=0.019).

Conclusions: In patients with (mainly) stage 3 non-small cell lung cancer treated by definitive radiochemotherapy, excellent overall 5-year-survival rates around 50% were obtained. Patients with EGFR-mutated tumors (n=14) had a better survival rate as compared to patients without EGFR-mutated tumors (n=73), albeit reaching no statistical significance. This may be attributed to the small patient number with EGFR-positive tumors.

9. CROATIAN SUMMARY

Naslov: Retrospektivna analiza podataka o preživljenju bolesnika s karcinomom pluća nemalih stanica (NSCLC) nakon zračenja i kemoterapije: Utjecaj mutacije receptora epidermalnog faktora rasta (EGFR)

Ciljevi: Cilj ovog istraživanja bio je procijeniti hoće li prisutnost EGFR mutacija u bolesnika s NSCLC, a koji su liječeni radio kemoterapijom, imati utjecaja na prognozu bolesti i preživljenje.

Materijali i metode: Ovo je bila povijesna/retrospektivna kohortna studija u kojoj su se koristili podaci i povijest pacijenata liječenih u Regiomed Klinikum Coburg u periodu od 2016. do 2020. godine, na temelju specifičnih i unaprijed definiranih kriterija uključivanja i isključivanja. Od 432 pacijenta s karcinomom pluća, 336 pacijenata bilo je isključeno iz različitih razloga (histologija malih stanica, prethodni kirurški zahvat, metastatska ili rekurentna bolest, stereotaktička radiokirurgija).

U ovu studiju bilo je uključeno 87 pacijenata od kojih je 14 pacijenata imalo EGFR mutacije. Analizirane karakteristike pacijenata bile su: obiteljska predispozicija, status Karnofsky-jevog učinka, povijest pušenja, vrsta primljene terapije, svaki recidiv i njegova lokacija, kao i moguća toksičnost zbog terapije. Koristeći Kaplan-Meierovu metodu analizirane su ukupne stope preživljavanja pacijenata prema statusu mutacije, dobi, stadiju bolesti u trenutku dijagnoze i spolu te su uspoređene logrank testom. Statistički podaci analizirani su pomoću IBM SPSS Statistike za Windows 26 (IBM Corp, 2019.). Podaci o pacijentima dopunjavani su iz javnih baza podataka kad god je to bilo moguće.

Rezultati: Srednja dob pacijenata bila je 74±11godina. Petogodišnja ukupna stopa preživljavanja (5y-OS) za svih 87 pacijenata bila je 49%, 5y-OS pacijenata starijih od 74 godine bila je 40%, za one mlađe 59% (P=0,13). Pacijenti s mutacijom EGFR (n=14) i pacijenti bez mutacije (n=73) imali su 5y-OS od 64% odnosno 41% (P=0,23). Petogodišnje preživljenje bilo je 46% u bolesnika sa stadijima 1-2B, 38% u bolesnika sa stadijem 3A, 59% u stadiju 3B i 53% u bolesnika sa stadijima 3c-4 (P=0,71). Ova studija je pokazala značajno povećanje preživljenja za žene u usporedbi s muškim pacijentima, i to 66% u odnosu na 38% (P=0,019).

Zaključci: U pacijenata s (uglavnom) stadijem III karcinoma pluća nemalih stanica, liječenih definitivnom radiokemoterapijom, postignute su izvrsne ukupne stope petogodišnjeg preživljenja od oko 50%. Pacijenti s EGFR-mutiranim tumorima (n=14) imali su bolju stopu preživljavanja u usporedbi s bolesnicima bez EGFR-mutiranih tumora (n=73), iako nisu postigli statističku značajnost. To se može pripisati malom broju pacijenata s EGFR-pozitivnim tumorima.