Aus dem Zentrum für Innere Medizin der Universität zu Köln

Klinik und Poliklinik für Innere Medizin I

Direktor: Universitätsprofessor Dr. med. M. Hallek

Behandlung und Ergebnisse von Patienten mit nicht-kleinzelligem Lungenkarzinom im fortgeschrittenen Stadium in der routine ambulanten Versorgung

Inaugural-Dissertation zur Erlangung der Doktorwürde der Medizinischen Fakultät der Universität zu Köln

vorgelegt von

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For my darlings Jan, Piah and Raj

Be the change that you wish to see in the world*!*

Mahatma Gandhi

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3 Abbreviations

aaCCI	age adjusted charlson comorbidity index
Alk	Anaplastic lymphoma kinase
BRAF	B isoform of rapidly accelerated fibrosarcoma
ROS1	c-ROS oncogene 1
°C	degrees Celsius
CCI	Charlson comorbidity index
cm	centimeter
CO2	carbon dioxide
CTLA-4	Cytotoxic T lymphocyte antigen 4
DLCO	Diffusing capacity of the lungs for carbon monoxide
ECOG	Eastern cooperative oncology group
EGFR	Epidermal growth factor receptor
ESMO	European society of medical oncology
FEV1	Forced expiratory volume in 1 second
FISH	Fluorescence in situ hybridization
g	gram
Gy	gray
GEKID	Die Gesellschaft der Epidemiologischen Krebsregister in Deutschland Association of epidemiological-Cancer Registries in Germany
h	hour

HBV	Hepatitis-B virus
HGF	Hepatocyte growth factor
HER2	Human epidermal growth factor receptor 2
HIV	Human immunodeficient virus
IHC	immunohistochemistry
Ig	immunoglobulin
i.p.	intraperitoneal
i.v.	intravenous
KRAS	Kirsten rat sarcoma virus oncogene
LDCT	low-dose computer tomography
LN	lymph node
MET	mesenchymal epithelial transition
mg	milligram
MHC	major histocompatibility complex
min	minutes
mmol	millimole
mM	millimolar
ml	millilitre
mm	millimetre
µg	microgram
µl	microliter
ng	nanogram

NGS	next-generation sequencing
NLST	National lung cancer screening Trial
NRG	Neuregulin
NSCLC	Non-small cell lung cancer
NTRK	neurotrophic- tropomyosin- receptor kinase
OS	Overall survival
PD-L1	Programmed death-ligand 1
RCRI	revised cardiac risk index
RET	Receptor tyrosine kinase
RKI	Robert Koch Institute
ROS 1	c- ROS oncogene 1
RT	room temperature
RT-PCR	reverse transcription polymerase chain reaction
s.c.	subcutaneous
SCLC	Small cell lung cancer
SD	standard deviation
SEM	standard error of mean
SABR	stereotactic ablative radiotherapy
SBRT	stereotactic body radio therapy
TKI	Tyrosine kinase inhibitor
TNM staging	Tumour node metastases staging
VEGF	Vascular endothelial growth factor

4 Introduction

All malignancies arising from the lung parenchyma are collectively referred to as lung cancer. Prostate and breast cancer are the leading types of cancer in men and women respectively. Irrespective of gender, lung cancer is the second most common solid tumour worldwide and accounts for 13% of all cancers diagnosed (Siegel et al. 2022). It is responsible for the highest number of deaths secondary to cancer and accounts for almost a third of cancer related deaths in both men (28 %) and women (26%) (Global Burden of Disease Cancer et al. 2017).

4.1 Incidence

In 2019 approximately 23,500 women and 32,700 men were diagnosed with lung cancer in Germany (Association of Population-based Cancer Registries in Germany (GEKID);Robert Koch Institute (RKI) 2019). Bosetti et al reported an increase in the incidence in lung cancer in women in Europe in contrast to reports from the United States of America. (Bosetti et al. 2012). On the contrary the breast cancer incidence seems to be falling. The incidence of lung cancer is predicted to rise. Data from Quante et al projected over the next decade foresee lung cancer as the third important cause of cancer by 2030 maintaining its position as the leading cause of cancer related deaths (Quante et al. 2016). The projected incidence as well as projected deaths of the five most common types of cancers by 2030 in Germany are shown in Figure 4-1. If diagnosed early above 50% of patients with lung cancer survive more than 5 years. Unfortunately, the majority (>50%) of patients have advanced incurable disease at initial presentation. The median age at the time of diagnosis is 71 and these patients have a poor 5-year survival of 4% (Dela Cruz et al 2011; Torreet al. 2016).

4.2 Risk factors

Global statistics estimates that the majority of lung cancers (>90%) are secondary to smoking (Sun, Schiller, and Gazdar 2007). 10-15% of lung cancers are in non-smokers accounting for 15% of the men and 53% of the women who are diagnosed with this disease (Alberg and Samet 2003). The smoking related risk for lung cancer is calculated in pack years. This unit measures the amount smoked by multiplying the number of cigarettes smoked per day with the number of years the person smoked. 15 pack years increases the risk of lung cancer by 20 times (Doll et al. 2004). Other risk factors include radiation, polycyclic aromatic hydrocarbons, environmental factors such as smoke, asbestos, radon, heavy metals, ionizing radiation, HIV infection, pulmonary fibrosis, genetic factors, alcohol and dietary factors such as antioxidants and phytoestrogens (Hubbard et al. 2000; Alberg et al. 2003).

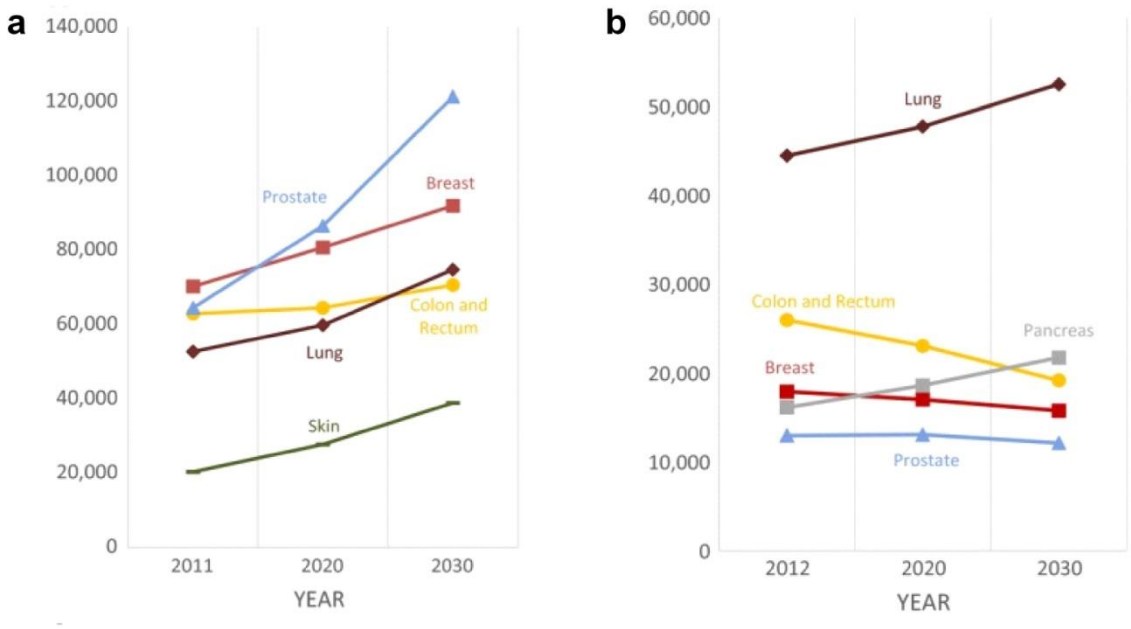


Figure 4-1 Projected incidence and mortality of cancer in Germany by 2030.

a. The projected incidence and b. the projected mortality due to common cancers. (Courtesy (Quante et al. 2016))

4.3 Staging

Lung cancers are classified by the Tumour, Node, Metastasis (TNM) staging system. This staging combines features of the tumour and classifies patients into different stages. Higher the stage, lower the 5-year survival chances of the patients (Goldstraw et al. 2016). The current classification is the 8th revised edition published by the international association for staging lung cancer (IASCL) (Goldstraw et al. 2016; Chansky et al. 2017). Table 4-1.shows the TNM descriptors and Table 4-2 the stage groupings for the current TNM classification. The classification is also an important prognosticator Figure 4-2.

T: Primary tumour	
Tx	Primary tumour cannot be assessed or tumour proven by presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumour
Tis	Carcinoma in situ
T1	Tumour ≤3cm in greatest dimension surrounded by lung or visceral pleura without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)
T1a (mi)	Minimally invasive carcinoma
T1a	Tumour ≤1 cm in greatest dimension
T1b	Tumour >1 cm but ≤2cm in greatest dimension
T1c	Tumour >2cm but ≤3cm in greatest dimension
T2	Tumour >3 cm but ≤5 cm or tumour with any of the following features
	Tumour >3 cm but ≤4 cm in greatest dimension
T2a	Tumour >4 cm but ≤5 cm in greatest dimension
T2b	
T3	Tumour >5 cm but ≤7 cm in greatest dimension or associated with separate tumour nodules in the same lobe as the primary tumour or directly invades any of the following structures: chest wall (including the parietal pleura and superior sulcus tumours), phrenic nerve and parietal pericardium.
T4	Tumour > 7cm in greatest dimension or associated with separate tumour nodules in a different ipsilateral lobe than that of the primary tumour or invades any of the following structures: diaphragm, mediastinum, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body and carina
N: Regional node involvement	
Nx	Regional lymph nodes not assessed
N0	No regional lymph node metastasis
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 nodes
N3	Metastasis in contralateral mediastinal, hilar or ipsi/contralateral scalene or supraclavicular lymph nodes
M: Distant Metastasis	
M0	No distant metastasis present
M1	Distant metastasis present
M1a	Separate tumour nodule(s) in a contralateral lobe, tumour with pleural or pericardial nodule(s) or malignant pleural or pericardial effusion
M1b	Single extrathoracic metastasis
M1c	Multiple extrathoracic metastasis in one or more organs

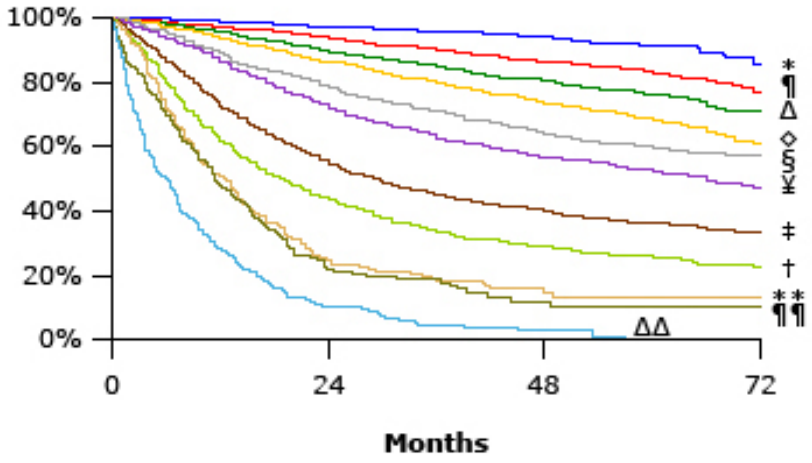
Table 4-1 T, N and M descriptors for the eighth edition of TNM classification of lung cancer

T- tumour, N- node and M- metastasis for the current TNM classification of lung cancer.

Stage groupings			
Occult carcinoma	**Tx**	**N0**	**M0**
Stage 0	**Tis (carcinoma in situ)**	**N0**	**M0**
Stage IA1	**T1a (mi) minimal invasive** **T1a**	**N0** **N0**	**M0** **M0**
Stage IA2	**T1b**	**N0**	**M0**
Stage IA3	**T1c**	**N0**	**M0**
Stage IB	**T2a**	**N0**	**M0**
Stage IIA	**T2b**	**N0**	**M0**
Stage IIB	**T1a to c** **T2a, T2b** **T3**	**N1** **N1** **N0**	**M0** **M0** **M0**
Stage IIIA	**T1a to c, T2a to c** **T3** **T4**	**N2** **N1** **N0 or N1**	**M0** **M0** **M0**
Stage IIIB	**T1a to c** **T2a to b** **T3** **T4**	**N3** **N3** **N2** **N2**	**M0** **M0** **M0** **M0**
Stage IIIC	**T3** **T4**	**N3** **N3**	**M0** **M0**
Stage IVA	**Any T**	**Any N**	**M1a/ M1b**
Stage IVB	**Any T**	**Any N**	**M1c**

Table 4-2 Stage groupings for the eighth edition of TNM classification of lung cancer

Tis carcinoma in situ, T1a (mi) minimal invasive adenocarcinoma



8th edition	Events / N	MST	24 month	60 month
* IA1	68 / 781	NR	97%	92%
¶ IA2	505 / 3105	NR	94%	83%
Δ IA3	546 / 2417	NR	90%	77%
◇ IB	560 / 1928	NR	87%	68%
§ IIA	215 / 585	NR	79%	60%
¥ IIB	605 / 1453	66.0	72%	53%
‡ IIIA	2052 / 3200	29.3	55%	36%
† IIIB	1551 / 2140	19.0	44%	26%
** IIIC	831 / 986	12.6	24%	13%
¶¶ IVA	336 / 484	11.5	23%	10%
ΔΔ IVB	328 / 398	6.0	10%	0%

Figure 4-2 Prognosis based on TNM staging

(Goldstraw et al. 2016)

4.4 Types

Non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) comprise the two main types of lung cancer and account for around 95% of all lung cancers. The majority of lung cancers (around 80-85%) are NSCLC which comprise mostly of adenocancer, squamous cell cancer and mixed types (Travis et al. 2015). Less than one fifth of the lung tumours are SCLC (Govindan et al. 2006). SCLC represent a very aggressive subgroup of tumours with a high growth fraction and a poor fiver year survival of 5-6% (Waqar et al. 2017; Gaspar et al. 2012; Farago et al.2018). Large cell cancers as well as sarcomatoid tumours are included in the remaining 5% of rare types of lung cancers.

4.5 Clinical signs and symptoms

The presenting signs and symptoms could be directly due to the tumour or due to its local or distant metastasis. Cough, shortness of breath, haemoptysis, chest pain or pleuritic pain as well as bone related pain and weight loss are the major symptoms these patients experience (Spiro et al. 2007). These are caused by the lung lesions or be secondary to metastases- in liver, bone, adrenal glands as well as brain. Patients can also rarely show manifestations which cannot be explained by the tumour primary or metastases, the paraneoplastic syndromes. Paraneoplastic syndromes include hypercalcemia, syndrome of inappropriate ADH secretion (SIADH), disseminated intravascular coagulation, hypercoagulability, Lambert- Eaton Syndrome and neurological changes.

4.5.1 Superior vena cava syndrome (SVC)

SVC syndrome includes the symptoms and signs secondary to occlusion of the superior vena cava by external compression, thrombosis or invasion. The most common cause for this syndrome is cancer of the lung (Cohen et al. 2008). The common symptoms include facial swelling, a feeling of head fullness, cough, shortness of breath and neck vein distension. The onset of symptoms and signs are dependent on the rate of disease progression which in turn leads to the partial or complete occlusion of this major vessel. In diseases with a slow progression venous collaterals are recruited reducing the severity of the symptoms. It is often a poor prognostic sign.

4.5.2 Pancoast syndrome

Pancoast syndrome is a characteristic sign of lung cancers arising in the upper lobe of the lung infiltrating the brachial plexus and other surrounding organs. Patients present with pain which could affect just the fingers or the whole arm till the scapula and accompanied with or without osteolytic lesions in the bone and atrophy of the musculature of the hand and or arm. Horner syndrome which includes miosis, ptosis and anhidrosis is also sometimes seen as part of the Pancoast syndrome.

4.6 Diagnosis

The most important diagnostic test is the bronchoscopy. The available diagnostic tools for lung cancer staging are listed in Table 4-3. The recommendation of European Society for Medical Oncology (ESMO) for the locoregional lymph node staging in patients with non-

metastatic NSCLC are used as baseline for the staging of patients (Postmus et al. 2017, Planchard, 2018 #180).

	Mandatory	**Optional**
General	Medical history, Physical examination, Comorbidity assessment, Performance status	
Imaging	X-ray thorax, CT of the thorax, PET-CT, MRI brain	Bone scintigraphy, Contrast enhanced Ct brain, US Abdomen, CT Abdomen and Pelvis
Laboratory	Blood cell counts, renal function, liver enzymes, Bone parameters	
Cardio-pulmonary function	FVC, FEV1, DLCO, ECG If needed CPET	Ejection fraction, CAG
Tissue procurement	Bronchoscopy, EBUS/ EUS mediastinal nodes, CT- guided biopsy	Mediastinoscopy

Table 4-3: **Diagnosis and staging work -up for lung cancer**

CT- Computed Tomography, PET- CT Positron emission tomography Computed Tomography, MRI magnetic resonance imaging, FVC Forced vital capacity, FEV1 Forced expiratory volume in 1 second, DLCO Diffusing capacity of the lungs for carbon monoxide, ECG electrocardiogram, CPET cardio pulmonary exercise testing, CAG coronary angiography, EBUS endoscopic bronchial ultrasound, EUS endoscopic ultrasound

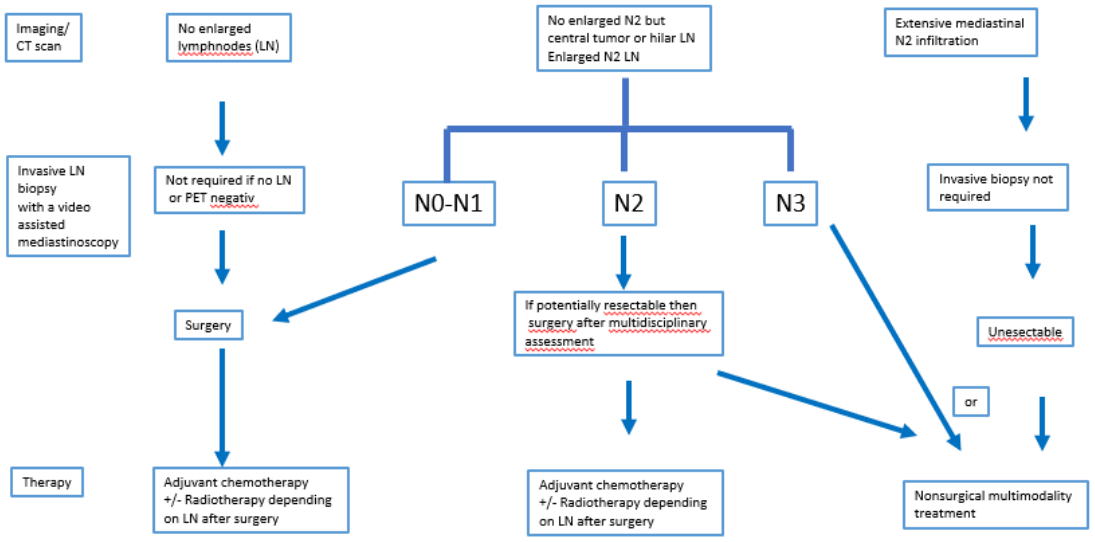


Figure 4-3 : Locoregional lymph node staging in patients with non-metastatic NSCLC adapted from ESMO recommendations

PET Positron Emission Tomography

4.7 Treatment

The staging diagnostics determine the stage of the disease. If the diagnostics reveal that the mediastinal lymph nodes are involved a video assisted mediastinoscopy is recommended to confirm the staging (Postmus et al. 2017). The decision to treat is made not only on the staging information but also on the fitness and comorbidities of the patients. Treatment decisions are made based on the staging investigations and the resulting stage as well as cardiopulmonary fitness and comorbidities of the patient.

4.7.1 Surgery

A cardiac and pulmonary assessment is mandatory prior to surgery. The standard screening lung function tests are FEV1 (forced expiratory volume in 1 second) and DLCO (Diffusing capacity of the lungs for carbon monoxide). Screening values above 80% of the normal value implies pulmonary fitness. An electrocardiogram, ECHO and cardiopulmonary testing provide information with regards to the cardiac fitness. Surgical resection should be considered in all patients with early-stage NSCLC i.e., stage I and II, once deemed fit after a cardiac and pulmonary assessment. The surgical approaches include wedge resection, segmentectomy, lobectomy or pneumonectomy. (Ginsberg and Rubinstein 1995; Veluswamy et al. 2015; Suzuki et al. 2019).

4.7.2 Radiotherapy

Post operative radiotherapy is not recommended in N0 or N1 disease (Burdett et al. 2016). In case it is administered it should be given post chemotherapy. If resection is not feasible in advanced stage III lung cancer, combined radio chemotherapy is the treatment of choice with an immune checkpoint inhibitor as maintenance therapy for up to one year after the combined chemoradiotherapy (Antonia et al. 2017).

A proportion of patients who have early-stage disease may not be assessed as fit for surgery. These patients can be offered a stereotactic ablative radiotherapy (SABR) as is another therapeutic alternative (Ezer et al. 2015). This treatment modality is not considered curative but could provide a local disease control for a considerable period of 5 years (Lindberg et al. 2015; Verstegen et al. 2015). It causes minimal acute side effects such as pneumonitis but needs to be advised with caution in patients with interstitial lung fibrosis (Louie et al. 2015; Chen et al. 2017). Rib fractures, persisting shortness of breath and cardiac arrythmias have been reported as late toxicities (Bahig et al. 2016; Timmerman, Herman, and Cho 2014).

4.7.3 Systemic therapy

4.7.3.1 *Neoadjuvant*

Pre-operative or neoadjuvant chemotherapy has no role in the current standard of practice as studies have not shown an advantage in overall survival (Lim et al. 2009; Group 2014; Gilligan et al. 2007). It may be beneficial in downstaging and thereby avoidance of an extensive resection. Recent studies highlight a role for neoadjuvant chemo-immunotherapy (Provencio et al. 2020; Jiang et al. 2022).

4.7.3.2 *Adjuvant*

Patients with stage II and III disease with a tumour size >4cm or N1 and N2 disease are offered an adjuvant chemotherapy. Treatment with three to four cycles of cisplatin doublets improved the absolute survival at 5 years by 4-5% (Artal Cortes, Calera Urquizu, and Hernando Cubero 2015). The chemotherapy should be commenced at least 8 weeks post surgery (Butts et al. 2010). Patients with earlier stage lung cancers failed to show an advantage with this treatment modality (Artal Cortes, Calera Urquizu, and Hernando Cubero 2015; Lim et al. 2009).

The trials with Erlotinib and Gefitinib in the adjuvant setting did not demonstrate a 5-year disease free survival benefit (Tanaka, Yoneda, and Takenaka 2020). The newer agent Osimertinib has now been shown to improve the overall survival of patients with an EGFR-mutation after adjuvant chemotherapy (Wu et al. 2022). Immune checkpoint inhibitors are currently recommended in patients with high PD-L1 expression in the early stages after initial surgery and chemotherapy (Felip et al. 2021). Patients with Stage III disease after curative radio chemotherapy who have a positive PD-L1 expression are also recommended a one-year maintenance treatment with an immune checkpoint inihibition.in the adjuvant setting has been established in patients (Antonia et al. 2018; Gray et al. 2020).

4.7.3.3 *Palliative*

Treatment decisions for patients with an advanced stage inoperable or metastatic NSCLC are made based on performance status (PS), PD-L1 expression and presence or absence of driver mutations. All these patients should have had a mutational analysis for oncogenic drivers as well as PD-L1 status by immunohistochemistry in order to offer a targeted therapy were possible. In the absence of a driver mutation a combined immune chemotherapy is the standard therapy of choice for these patients. Patients expressing PD-L1 >50% can be

offered an immune checkpoint inhibitor alone (Postmus et al. 2017; Planchard et al. 2018). The various therapy options for these patients have been shown in the algorithms

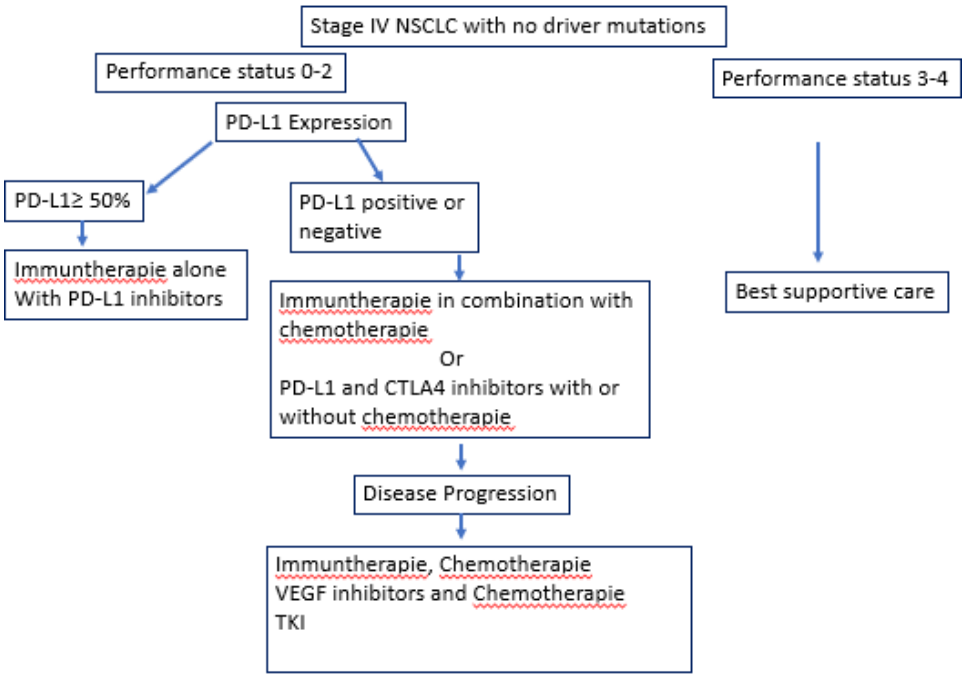


Figure 4-4 Recommendations for advanced stage IV non-small cell lung cancer in whom no driver mutations can be identified squamous cell carcinoma courtesy ESMO guidelines (Postmus et al. 2017)

PD-L1 Programmed death ligand 1, PS Performance status, CTLA-4 Cytotoxic T lymphocyte Antigen-4, VEGF Vascular endothelial growth factor, TKI Tyrosine kinase inhibitors.

4.7.3.3.1 Immunotherapy

Programmed cell death 1 (PD-1) is a transmembrane protein expressed on T- cells, B-cells and NK-cells. This protein binds to its ligands PD-L1 and PD-L2 expressed on tumour cells as well as hemopoietic cells. The interaction between the PD-1 and its ligand results in the inhibition of tumour cell apoptosis, peripheral T-cell exhaustion as well as their conversion to regulatory T-cells. (Francisco et al. 2009; Amarnath et al. 2011). Antibodies to PD-1 such as pembrolizumab and nivolumab and PD-L1 such as durvalumumab and atezolizumab are now standard first line therapy options for patients with advanced stage NSCLC with or without chemotherapy (Gadgeel et al. 2020; Reck et al. 2019). The level of PD-L1 expression is used to decide if the patient receives only immunotherapy or immunotherapy with chemotherapy.

Cytotoxic T lymphocyte antigen 4 (CTLA-4) has been shown to play a relevant role in the cancer immune surveillance by inhibiting CD4 and CD8 activation mediated by antigen presenting cells (Walker et al. 2011). CTLA-4 inhibitors such as ipilimumab and tremelimumab in combination with PD-L or PD-L1 inhibitors seem to enhance the responses resulting in prolonging the outcome of patients with advanced stage NSCLC (Hellmann et al. 2019).

4.7.3.3.2 Tyrosine kinase inhibitors

Approximately 20% of patients with an adenocarcinoma have driver mutations which offer a therapeutic option (Lindeman et al. 2018). Important driver mutations include mutations of epidermal growth factor receptors (EGFR), B isoform of rapidly accelerated fibrosarcoma (BRAF), anaplastic lymphoma kinase (Alk) translocations, c-ROS oncogene 1 (ROS1), neurotrophic- tropomyosin- receptor kinase (NTRK), receptor tyrosine kinase (RET) and Kirsten rat sarcoma virus oncogene (KRAS) mutations. The tumour material can be analysed by molecular methods to identify these changes and thereby identify targets for a personalised patient care. Patients with EGFR mutation were found to have better and more durable responses with tyrosine kinase inhibitors than with standard chemotherapy (Clinical Lung Cancer Genome and Network Genomic 2013), (Leighl et al. 2014). Non V600 BRAF-mutations, HER2-Amplifications, c-mesenchymal epithelial transition (MET)-alterations with c-MET Exon 14 skipping Mutations, Amplification und Fusions, Neuregulin (NRG)-Fusions, are other mutations which are being investigated with a potential for targeted therapy options.

Liquid biopsy is an alternative to tissue biopsy at to determine disease progression with a blood test. It allows the determination of circulation tumour cells in peripheral blood and thereby the mutations as well (Haber and Velculescu 2014). Fluorescence in situ hybridization (FISH), immunohistochemistry (IHC), reverse transcription polymerase chain reaction of cDNA (RT-PCR), or next-generation sequencing (NGS) are different techniques needed to identify the mutations.

The following mutations have approved targeted therapy options

1. EGFR mutations: 15-20% of patients with an adenocarcinoma could have an EGFR mutation. It is most commonly found amongst Asian women who are non-smokers (Kawaguchi et al. 2016). Tyrosine kinase inhibitors over 3 generations, erlotinib, gefitinib, afatinib, dacomitinib and osimertinib offer targeted therapy options for this small cohort of patients thereby significantly improving their prognosis. The landmark trial FLAURA showed how osimertinib as a first line therapy option significantly improves overall survival for this patient cohort (Soria et al. 2018). Combination therapies with dual TKI, TKI and vascular endothelial growth factor (VEGF) inhibitors, TKI and chemotherapy as well as combining TKI with Radiotherapy have shown to improve outcomes and have been included in the current therapy recommendations of ESMO (Planchard et al. 2018) Figure 4-5.
2. ALK rearrangements — The gene rearrangement is on the second chromosome. Approximately 4% of patients with NSCLC are young, non-smoking females with chromosomal rearrangements involving the ALK gene (Pikor et al. 2013). The oncogenic driver mutation as a result of the rearrangement between the 5' end of the echinoderm microtubule-associated protein-like 4 (*EML4*) gene and the 3' end of the *ALK* gene is the most common *ALK* rearrangement (Shaw et al. 2011). Crizotinib, ceritinib, alectinib, brigatinib and lorlatinib are TKIs targeting the ALK fusion gene and have improved survival of this small subgroup of patients with NSCLC (Hida et al. 2017; Katayama et al. 2011).
3. ROS1 rearrangements— 1-2 % of NSCLC patients have c-ROS oncogene 1 (*ROS1*) translocation (Bergethon et al. 2012). This patient subgroup is also characterized by young females who do not smoke. TKIs such as crizotinib, brigatinib and lorlatinib as well as entrectinib and cabozantinib are therapeutic options for this rearrangement (Chin et al. 2012; Drilon et al. 2020).

4. MET abnormalities—Around 2-3% of patients with NSCLC have MET abnormalities (Awad et al. 2016). This mutation acts as an oncogenic driver and hampers the degradation of the MET protein. Capmatinib-and the now approved Tepotinib in the second line are good targeted therapies for patients with this mutation (Paik et al. 2015). Other MET- inhibitors being tested include glesatinib and savolitinib (Paik et al. 2020).
5. BRAF mutation—BRAF mutations are mostly found in smokers and account for 1-3% of NSCLC patients. The most common is the mutation at the V600 position of exon 15 (Paik et al. 2011; Litvak et al. 2014).These patients are recommended a combination with MEK and BRAF inhibitors such as dabrafenib und trametinib. (Planchard et al. 2016).
6. NTRK fusion — 1% of all NSCLC have a neurotrophic tropomycin receptor (NTRK) fusion or mutation. NTRK inhibitors such as larotrectinib or entrectinib have been approved therapeutic options for these mutations. (Hong et al. 2019; Doebele et al. 2020)

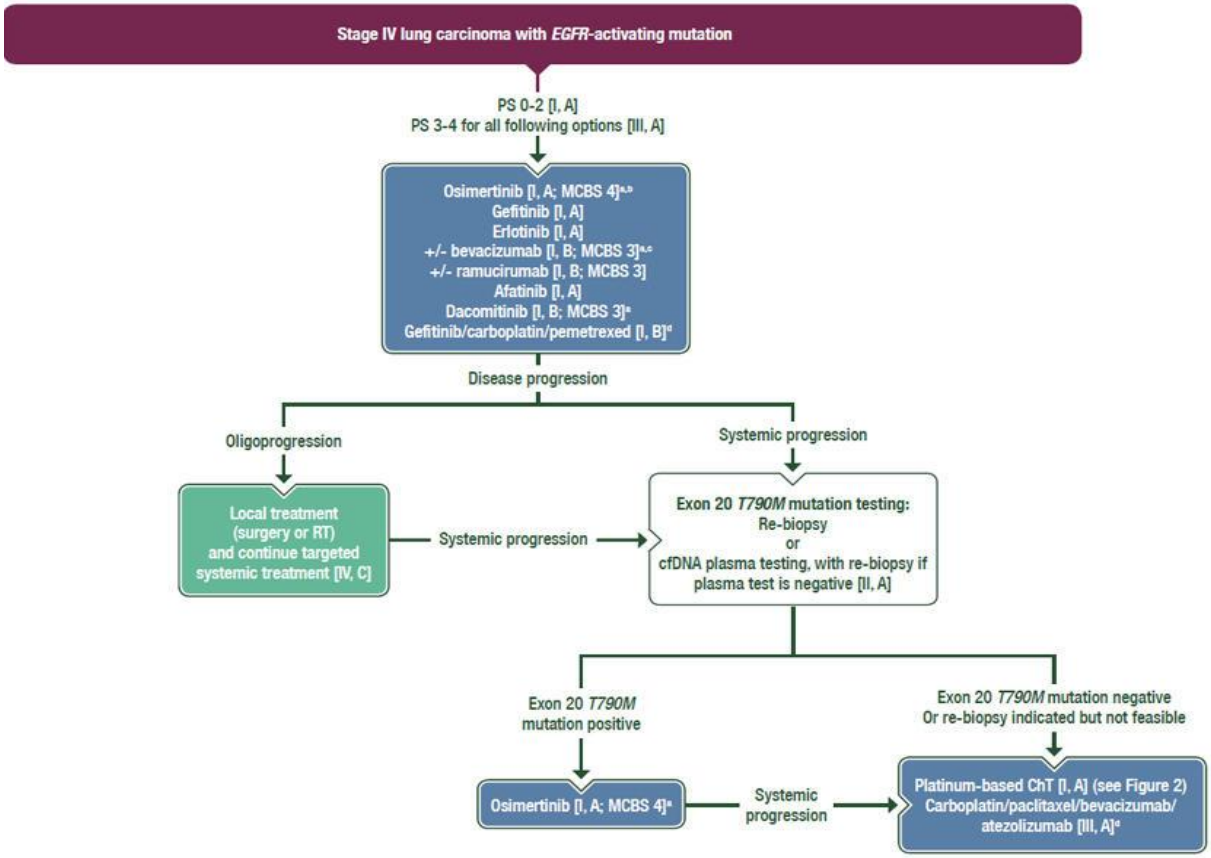


Figure 4-5 Treatment of patients with advanced stage NSCLC and an EGFR mutation (Courtesy ESMO guidelines)

(Postmus et al. 2017) cfDNA cell free DNA, ChT Chemotherapy, EGFR epidermal growth factor receptor, PS performance status, RT radiotherapy,

4.8 Prevention

Prevention is the best option to improve survival and reduce the lung cancer related deaths. Primary prevention aims to prevent the occurrence of the disease. The two main tools are prevention of smoking and early detection by means of screening.

4.8.1 Primary prevention

4.8.1.1 *Smoking*

The most important risk factor for a variety of cancers and around 80% of cancer related deaths is smoking. Cessation of smoking not only reduces the risk of developing lung cancer but also significantly reduces the cancer related morbidity and mortality (Anthonisen et al. 2005; Jha et al. 2013). Behavioural counselling and nicotine replacement therapy helps in smoking cessation.

4.8.1.2 *Screening*

Trials where chest X-ray or sputum cytology were the screening tools failed to show benefit hence these techniques are not recommended for lung cancer screening.

A recent trial in the United States showed that screening heavy smokers by means of a low dose computer tomography (LDCT) reduced the lung cancer related deaths by around 20%. Heavy smokers were defined as those aged between 55 and 74 years who smoked 30 pack years or former heavy smokers (≤15 years since cessation of smoking). (National Lung Screening Trial Research, Aberle, , et al. 2011; National Lung Screening Trial Research, Aberle, et al. 2011). The Dutch- Belgian Nelson trial recruited patients between 50 and 74 years of age and randomly screened them by CT at baseline, 1 ,3 and 5 years or not at all. The five-year follow- up data demonstrated a higher incidence of lung cancer in the intervention group and the resulting interventions significantly reduced the lung cancer related deaths in this arm (de Koning et al. 2020). The German Lung Cancer Screening Intervention Trial also demonstrated a reduction in lung-cancer mortality in a small subgroup of women (Becker et al. 2020). LDCT as screening tool for lung cancer will be routinely implemented in the coming years due to the above-mentioned trials which show a significant reduction in lung cancer related deaths. It is advisable to recruit these patients into a smoking cessation program as well. It is already recommended in the German S3 guidelines for patients between 55 and 74 years of age with a smoking history of ≥ 30 pack years and ≤15 pack year history of smoking cessation. Other patient risk groups such as those with COPD, lung fibrosis or asbestos exposure could also be offered a screening but this is not yet

recommended as routine practice. A large-scale screening program is not yet in practice in Germany.

4.8.2 Secondary prevention

The current S3 guidelines recommend regular thoracic imaging by means of a LDCT in patients who have received a curative therapy for a lung cancer every 3 months for the initial two years after diagnosis, then half yearly for three years and thereafter yearly. This helps in the early diagnosis of disease recurrence and enables early treatment.

4.9 Aims of this Project

More than half of the patients diagnosed with NSCLC are incurable at the time of diagnosis. All these patients are offered palliative treatments in an outpatient setting. Most clinical trials screen the patients based on their respective inclusion and exclusion criteria resulting in a skewed impression of the reality of treatment of these patients. The aim of this study was to analyse the treatment and outcome of all consecutive patients diagnosed with incurable advanced stage NSCLC in our community-based oncology group practice. The results would then reflect the day-to-day care of these patients and possibly highlight areas and help develop tools to improve the delivery of care. We reviewed our work previously between June 1995 to June 2006 and published our work in 2009. The overall survival of the patients was found to be 10 months in this analysis (Koeppler et al. 2009). A new analysis will help highlight the changes due to novel therapeutic agents and help us understand the current impact. Another aim of our project was to analyse the changes in outcome as well as the impact of new treatment strategies on the prognosis of patients.

5 Materials and methods

5.1 Patient samples

We retrospectively recruited patients with advanced stage NSCLC who were consecutively treated in our community-based oncology group practice between June 1995 and December 2016 into this study. The treatment and outcome of all patients were retrospectively analysed. Patients who were offered a curative therapy i.e., surgery or curative radio chemotherapy were not included. Locally advanced lung disease was defined as disease limited to one lung but inoperable or ineligible for a curative radio chemotherapy. Metastatic lung disease was defined as patients with a primary lung lesion and metastases. Advanced stage NSCLC was defined as all patients with locally advanced and or metastatic lung disease in whom a curative therapeutic option was not feasible. Patients with advanced stage NSCLC were consecutively identified and recruited into the study.

In our electronic file data system patients were identified by international coding for the classification of diseases (e.g., C34). Relevant data was extracted with a computerized data collection tool. Our cooperation partners i.e., hospitals and primary care physicians were approached for further relevant information related to the care of the patient. All patients gave informed consent. The primary end point was overall survival (OS) the response rates as well as toxicity secondary to treatment were the secondary endpoints.

The Eastern Cooperative Oncology Group (ECOG) criteria was used to evaluating the performance status (Oken et al. 1982). The National Cancer Institute common terminology criteria for serious adverse events version 3 was used to analysed the toxicity (Trotti et al. 2003). A widely used tool to study the effects on comorbidities on mortality rates is the Charlson comorbidity index (CCI) (Charlson et al. 1987). In this study the age adjusted Charlson comorbidity index (aaCCI) was used to analyse the influence of age as well as comorbidities on the disease specific outcome (Charlson et al. 1994).

5.2 Statistical analysis

A database was set up with the collated data and analysed. Statistical analysis was conducted by SPSS 19. The analyses were descriptive and no hypotheses were specifically tested. The Kaplan and Meier method was used to obtain survival curves.

6 Results

6.1 Patient demographics

Over the duration of the study 736 patients were identified. The demographic data is shown in

Table 6-1. All patients had an advanced stage NSCLC. Patients were mostly male (67%, n=490) and the median age at the time of presentation was 66 (range 37-88). Less than half the patients (46%, n=335) were under 65. Almost all patients had no communications problems due to language (96%, n=704). The majority of patients had a standard insurance (91%, n=670). More than half of the patients (52%, n=382) were retired and only 6% (n=37) were employed at the time of diagnosis. Data on employment was not available on approximately a third of the patients (27%, n=198).

Data on ECOG performance and the body mass index (BMI) was available on 52% (n=383) and 92% (n=680) of the patients respectively. 78% (297/383) of the patients had an ECOG performance status ≤1 and 46% (312/680) a normal BMI. Based on the aaCCI the patients could be divided into those with a score <8 and ≥8. 18% (136/736) had an aaCCI score was <8 and 82% (600/736) ≥8 respectively. In 11% (n=41) of patients an occupational hazard could be established. The authorities were informed in 83% (n=34) of these patients and an occupational hazard could be confirmed in 12% (n=5). Smoking history could be obtained on 84% (n=615) patients. More than half of these patients (53%) were smokers and despite the diagnosis of lung cancer 35% continued nicotine abuse. 13% of the patients never smoked. Table 6-2.

Surgery was the first therapeutic option in 21% (151/736) of the patients. 39% (59/151) of these patients received an adjuvant or neoadjuvant chemotherapy prior to enrolment in the study. Data on patients who received a radio chemotherapy with a curative intent prior to recruitment into the study was not available.

Age	Median (Range)	66 (37-88)
	Number	**%**
Age groups		
- <65 years	335	46
- 65-69 years	144	20
- 70-75 years	152	21
- >75 years	105	14
Gender		
- male	490	67
- female	246	33
Stage		
- metastatic	520	71
- locally advanced, non-operable	216	29
Year of diagnosis		
- 1995 – 2000	140	19
- 2001 – 2004	130	18
- 2005 – 2008	129	18
- 2009 – 2012	133	18
- 2013 – 2016	204	28
ECOG performance status *(n=383)*		
- ECOG ≤1	297	78
- ECOG ≥2	86	22

Table 6-1 Patient characteristics

(Chakupurakal et al. 2019) ECOG European cooperative oncology group

	Number	%
Age adjusted Charlson Comorbidity Index (aaCCI)		
- aaCCI <8	136	18
- aaCCI ≥8	600	82
Occupational hazard *(n=390)*		
- occupational hazard identified	41	11
Identified occupational hazard *(n=41)*		
- reported to the authorities	34	83
- confirmation of hazard	5	12
Marital status *(n=566)*		
- married or in a relationship	442	78
- widowed	46	8
- living alone	78	14
Body Mass Index		
- underweight	38	6
- normal	312	46
- overweight	251	37
- adipose	79	12
History of nicotine abuse		
- never smoked	78	13
- still smoking	214	35
- smoked prior	323	53

Table 6-2 Patient characteristics with comorbidities and smoking history

(Chakupurakal et al. 2019)

6.2 Tumour location

The majority of patients had an adenocarcinomatous cancer (61%, n=451). In 28% (n=205) of the patients the tumour had a squamous aetiology. In 48% (n=453) of the patients the tumour was located in the upper lobe. In 23% (n=166) and 10% (n=75) of the patients the tumour was located in the lower lobe and middle lobe respectively. Less than one third of the patients (29%, n=216) suffered from locally advanced disease whereas the 71% (n=520) had metastatic lung disease. Table 6-3.

Histology	**Number**	**%**
Adenocarcinoma	451	61
Squamous cell carcinoma	205	28
Other	69	9
Data not available	11	1
Stage of disease at the time of diagnosis		
Advanced stage inoperable	216	29
Metastatic disease	520	71
Tumour localization		
Main Bronchus, trachea or carina, Hilum	36	5
Upper lobe	353	48
Middle lobe	75	10
More than one lobe	36	5
Tumour location not defined	70	10

Table 6-3 Tumour characteristics

At the time of diagnosis or during the duration of the study 599 patients had or developed metastases. The most commonly involved organ was the lung (34%, n=200) followed by bone (27%, n=158) and brain (21%, n=127). Patients with metastatic lung disease had an average of 1.5 metastases (range 1-5). 26% (n=155) had metastases in sites other than lung, bone and brain. 8% (n=47) had involvement of all three sites i.e., lung, bone and brain. In 4% (n=24) only the lung and bone were involved. Figure 6-1.

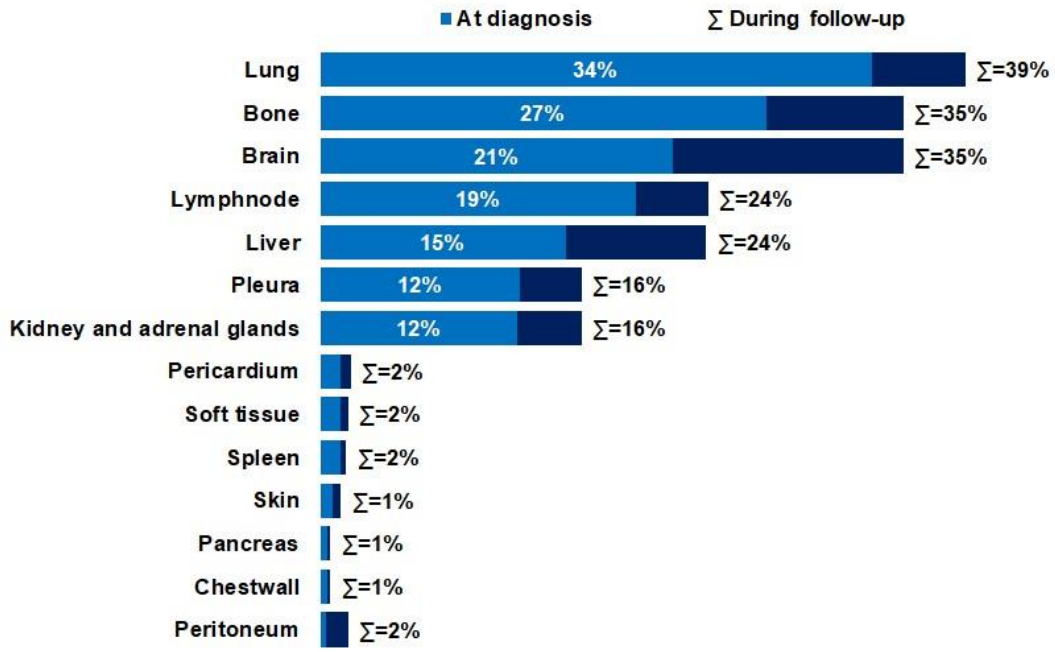


Figure 6-1 Sites of metastases at the time of diagnosis as well as metastases developed during follow-up

(Chakupurakal et al. 2019)

6.3 Treatment

Almost all patients in the study (93%, n=685) were considered to be suitable for a palliative chemotherapy. Only a small proportion of frail or unfit patients (7%, n=51) were offered best supportive care. The majority of patients who were offered a palliative treatment received chemotherapy with or without radiotherapy (95%) and a small cohort (5%) got radiotherapy alone. 650 patients were administered 1622 chemotherapy lines (mean 2.5 per patient; range 1-11). The most common chemotherapy was a platin doublet therapy (524/650, 81%). Platin doublet therapy was the first (72%, n=468), second (33%, n=144) and third line (22%, n=56) therapeutic option. More than half of the patients (67%, n=433) received a second line and treatment and 40% (n=260) were given a third line treatment. More than 3 lines of chemotherapy was administered to more than a fifth of the patient cohort (22%, n=146). A small cohort of patients, 8% (50/650) received a triple therapy. a combination of a platin, a taxane or pemetrexed and bevacizumab. A single agent was the treatment of choice in 23% (n=147) as first line. Only 7% (n=46) patients received an immunotherapy with nivolumab or pembrolizumab Table 6-4.

	N	%
Palliative treatment		
- received palliative treatment	685	93
- received best supportive care only	51	7
Treatment modalities *(n=685)*		
- medical treatment +/- radiation	650	95
- radiation only	35	5
Number of medical therapy lines *(n=650); median: 2 lines (1-11)*		
- 1 line	217	33
- 2 lines	173	27
- 3 lines	114	18
- 4 or more lines	146	22
1st line therapy *(n=650)*		
- platin doublet	411	63
- platin triplet	49	8
- platin mono	8	1
- chemotherapy mono	107	16
- chemotherapy combination	43	7
- TKI mono	31	5
- PD-1 inhibitor	1	0.2
2nd line therapy *(n=433)*		
- platin doublet	124	29
- platin triplet	14	3
- platin mono	6	1
- chemotherapy mono	149	34
- chemotherapy combination	46	11
- TKI mono	62	14
- PD-1 inhibitor	20	5
- bevacizumab mono	12	3
3rd line therapy *(n=260)*		
- platin doublet	44	17
- platin triplet	7	3
- platin mono	5	2
- chemotherapy mono	118	46
- chemotherapy combination	28	11
- TKI mono	41	16
- PD-1 inhibitor	11	4
- bevacizumab mono	5	2

Table 6-4 Treatment characteristics

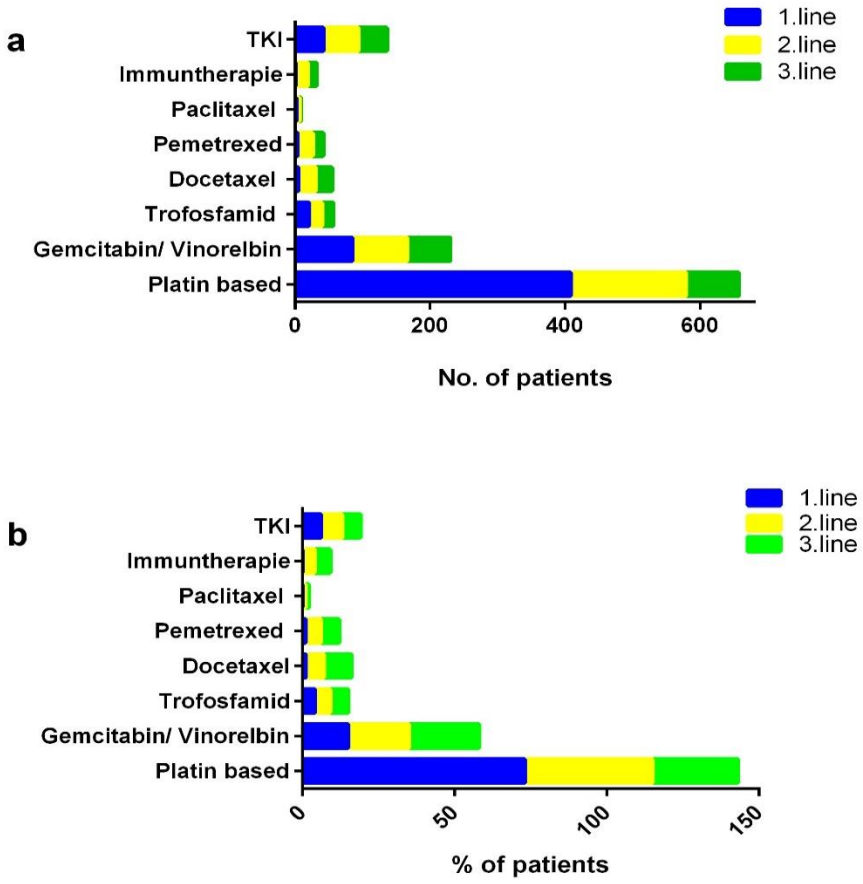


Figure 6-2 Therapy regimens used as first, second or third line

The preferred first, second- or third-line therapies are shown in number of patients (a) and percentage (b)

650, 433, 260 patients received one, two or three lines of therapy respectively Figure 6-2. A platin based therapy was the preferred therapy of choice as first and second line. Very few patients received immunotherapy or triple immunochemotherapy the current standard. Docetaxel which is the current second line of choice was also not as popular. Instead, gemcitabine or vinorelbine mono was used more often in the second line. The treatment was tolerated very well by the majority (93%). Toxicities were observed in <10% of all chemotherapies administered and in <20% of the patients treated. Most grade 3-4 toxicities were directly related to chemotherapy such as neutropenia, anaemia or thrombocytopenia.

6.3.1 Patients with driver mutations

Genomic analysis for the presence of possible mutations or translocations in the EGFR, ROS-1, ALK or BRAF genes were conducted. 29% (n=214), 8% (n=61), 18% (n=129) and 6% (n=42) of the total number of patients had the analysis done for the EGFR, ROS-1, ALK or

BRAF genes respectively Figure 6-3. Of the 60% (n=446) of the patients tested, 10% (n=44) were identified to have a therapy relevant genetic change. The data on PD-L1 expression was not obtained as this immunohistochemistry staining was routinely performed only after 2016. 39 patients were diagnosed with a mutation (ALK; ROS; EGFR) and received a targeted therapy Figure 6-3.

OS of this patient subgroup was 15.6 months (range 0.4 – 186 months). Contrary to the current evidence patients without a driver mutation (amongst those tested) survived longer (10.8 months, range 0.5– 112.8 months) (P=0.135) Figure 6-14. Best supportive care was offered for 4 patients (9%) due to reduced performance status and comorbidities. The driver mutation was identified in these patients shortly after or before they died. One patient had a BRAF mutation and a concomitant ALK-translocation. At the time of the study a targeted therapy was only available for the ALK translocation resulting in a therapy with crizotinib.

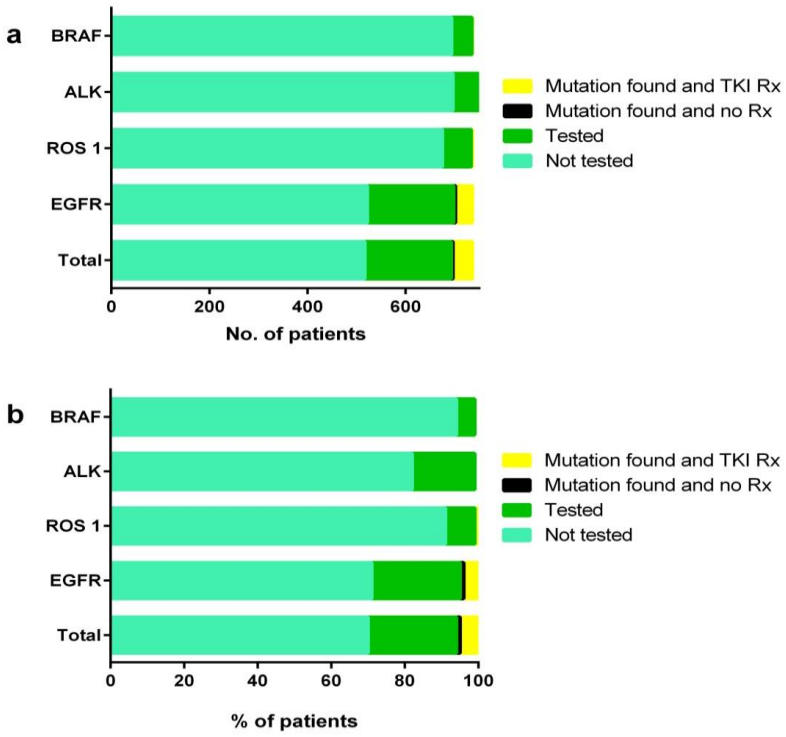


Figure 6-3 Number and percentage of patients tested for driver mutations

EGFR Epidermal growth factor, ALK- Anaplastic lymphoma kinase, ROS - c-ROS oncogene 1, BRAF - B isoform of rapidly accelerated fibrosarcoma, K- RAS Kirsten rat sarcoma virus oncogene

6.3.2 Supportive therapy and toxicity

A significant number of patients (n=532, 72%) required pain management. Following chemotherapy supportive agents were used to avoid sepsis related to neutropenia and the symptoms due to anaemia, thrombocytopenia or neutropenia. The agents commonly administered were blood and blood products, erythropoietic stimulating agents and or granulocyte stimulating colony factor. In this study 41% (n=303), 17% (n=127) and 11% (n=81) patients received these three agents respectively. Bone metastases increase the risk of bone fractures. Bone strengthening agents are the current standard of management for these patients to reduce the risk of fractures. Almost a fifth of the patients received a bisphosphonate or a monoclonal antibody directed against RANKL [24% (n=178)]. Figure 6-4a.

In addition to chemo or radiotherapy 86% (n=633) were offered a palliative supportive therapy. These included surgical options such as kyphoplasty or resection of a metastasis (n=58,8%) patients. Four (0.5%) patients received radiofrequency ablation and an intraperitoneal chemotherapy whereas two (0.2%) were offered chemoembolization. Figure 6-4b.

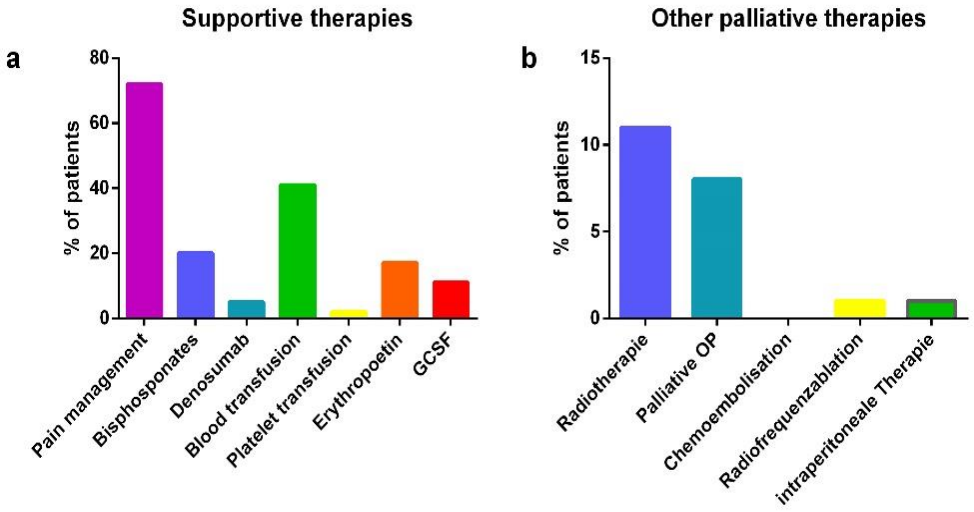


Figure 6-4 Palliative treatment options and supportive therapy

a shows supportive treatment options the patients received and b shows the additional palliative therapeutic options offered. GCSF Granulocyte colony stimulating factor. OP operation

6.4 Hospitalisation and death

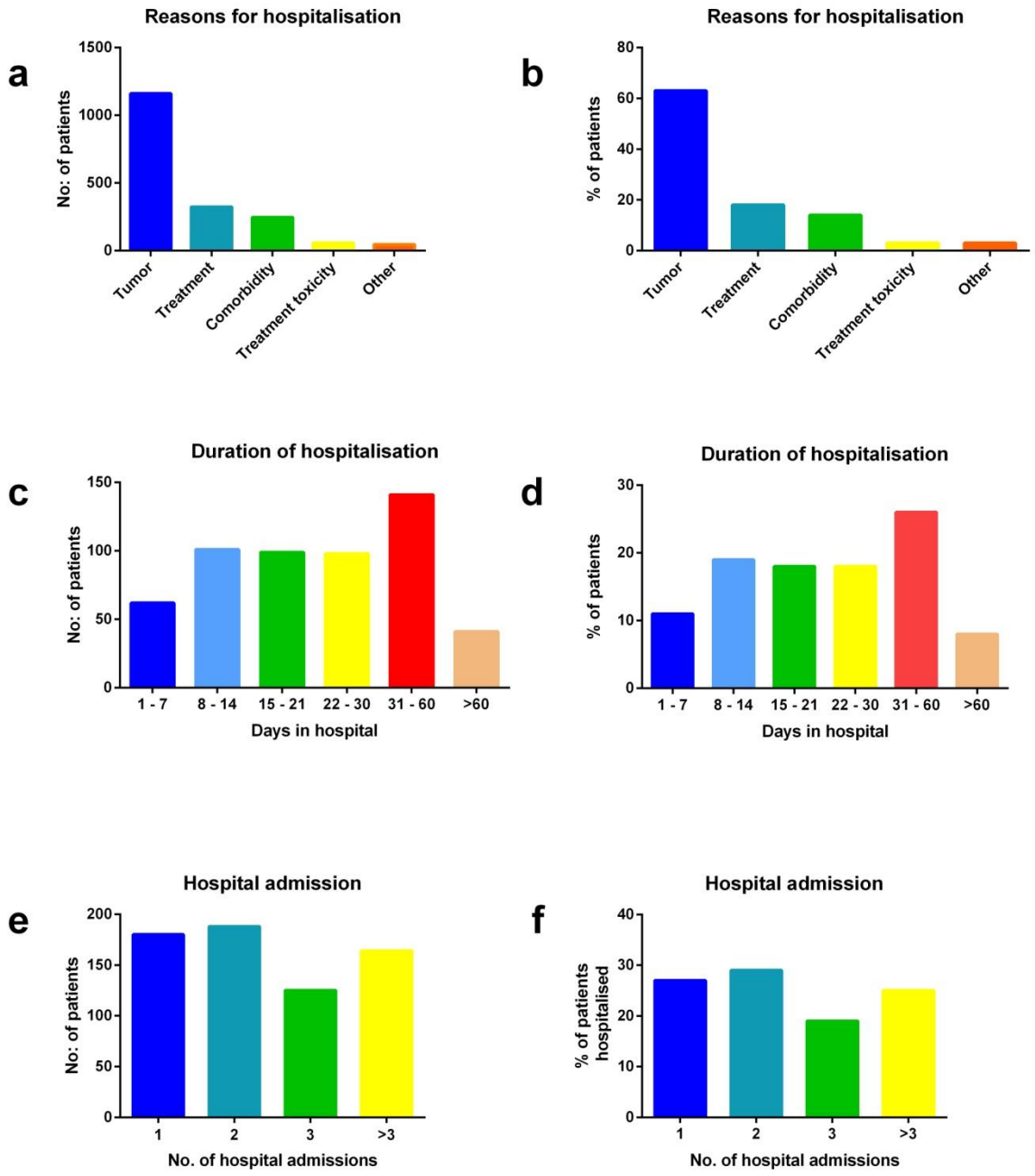


Figure 6-5 Hospitalisation

Demonstrates the number and percentages for reasons of hospitalisation (a and b), duration of hospitalisation in days (c and d) and number of hospital admissions during follow-up (e and f) respectively

89% (n=657) of the patients required an admission into hospital after the onset of chemo and/or radiotherapy. The cause of hospitalisation was mostly tumour related problems (63%, n=1,160 hospitalisations), Treatment related toxicities led to hospital admission in only 3% (n=57 hospitalisations). Hospital admissions were mostly following chemotherapy or for the delivery of palliative supportive therapies such as radiofrequency ablation, intraperitoneal chemotherapy and chemoembolization. Patients had to be admitted on average 3 times (range 1-17). The median duration of hospital stay was 22 days (range 1-179 days). Figure 6-5.

Data with regards to the place of death was available in 79% (n=493). 40% (198/493) of these patients died at home. Half of the patients (50%;245/493) died in hospital and almost a tenth (10%; 50/493) in a hospice or old age home Figure 6-6.

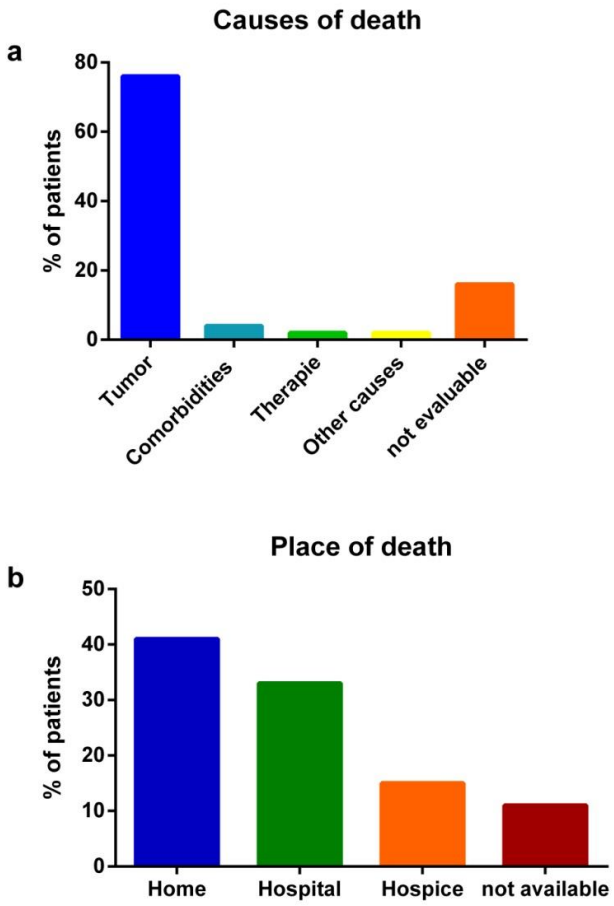


Figure 6-6 Death of patients with lung cancer.

the causes of death and b the place of death.

6.5 Survival analyses

A total of 53 patients (7%) from the study population were alive at the end of the study. The OS of the whole cohort, 736 patients, was a median of 13.5 months (range 0.4 – 195) Figure 6-7.

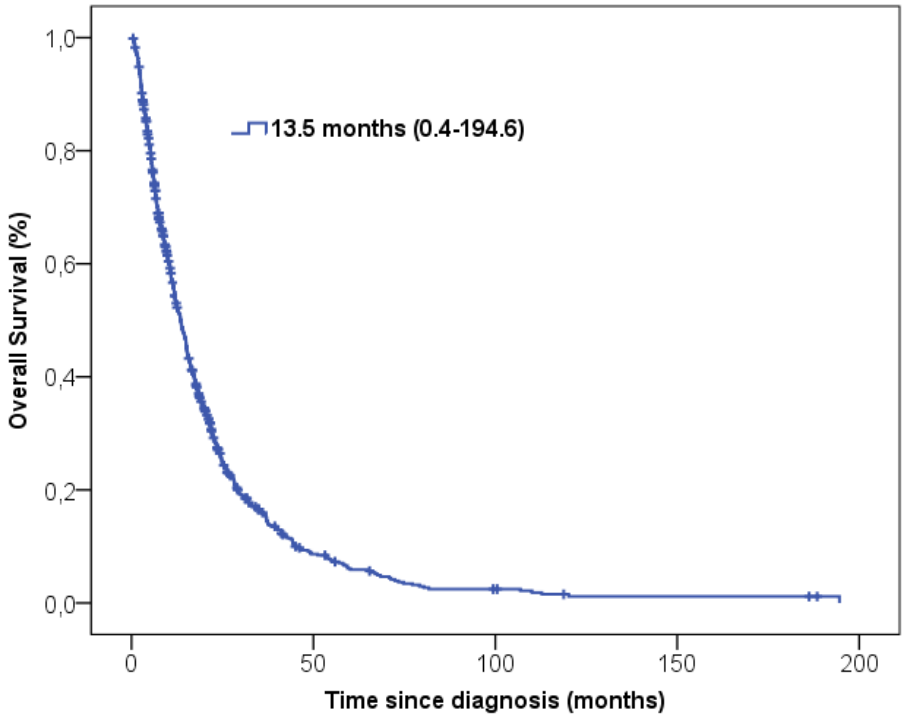


Figure 6-7 Overall survival analyses of patients with advanced stage lung cancer.

All 736 patients were analysed here.

OS based on age was analysed. 364 patients ≤65 years and 372 patients ≥66 years were analysed. The median survival of the group ≤65 was 15 months (range 0.4-194.6). The median survival of the latter group ≥66 years was 12 months (range 0.7-77.2). Younger age, ≤65, was associated with a statistically significant OS (P=<0.001) Figure 6-8.

OS was also analysed with sex as the confounding variable. Data on 490 men and 260 women was available. The median OS for men was 12.5 months (range 0.7-194.6) and for women was 15.4 months (range 0.4-188.5), suggesting an inferior OS for men (P=0.012) Figure 6-9.

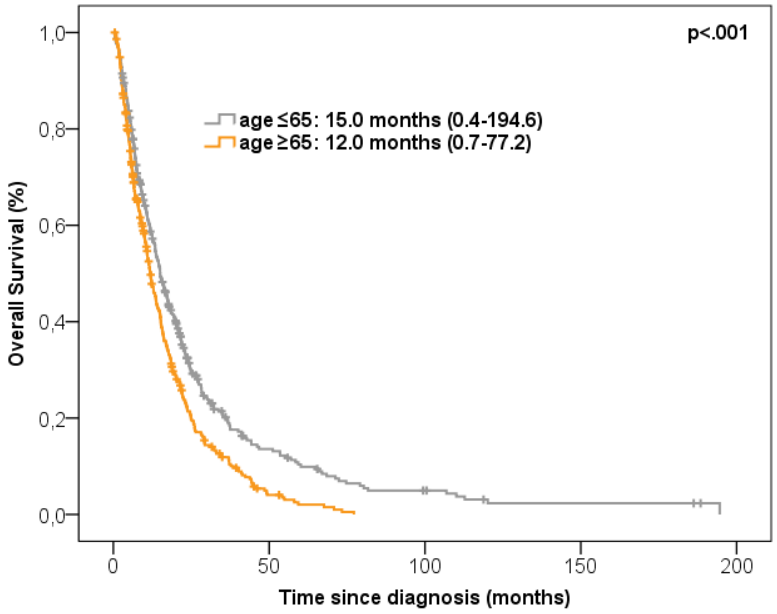


Figure 6-8 OS based on age

364 patients ≤65 years and 372 patients ≥66 years were analysed. The median survival of the group ≤65 was 15 months (range 0.4-194.6). The median survival of the latter group ≥66 years was 12 months (range 0.7-77.2). The difference was statistically significant (P=<0.001).

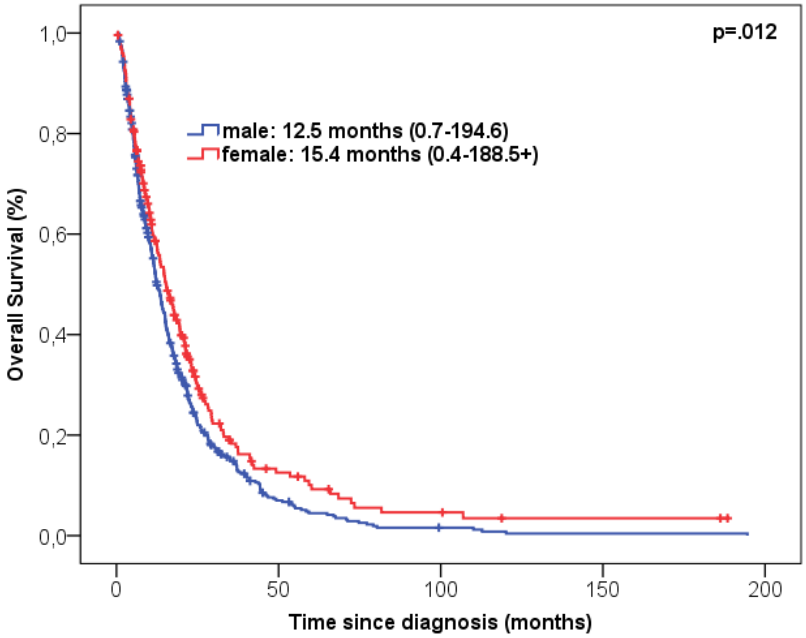


Figure 6-9 OS based on sex

490 men and 260 women were analysed. Median OS for men was 12.5 months (range 0.7-194.6) and for women was 15.4 months (range 0.4-188.5). The P value is 0.012.

Smoking history was available on 78 non-smokers, 214 smokers and 323 ex-smokers. The median survival of non-smokers, smokers and ex-smokers was 17.7 months (range 0.9-77.2), 12.4 months (range 0.4-188.5) and 12.9 months (range 0.7-194.6) respectively. The difference was not statistically significant (P=0.086) Figure 6-10.

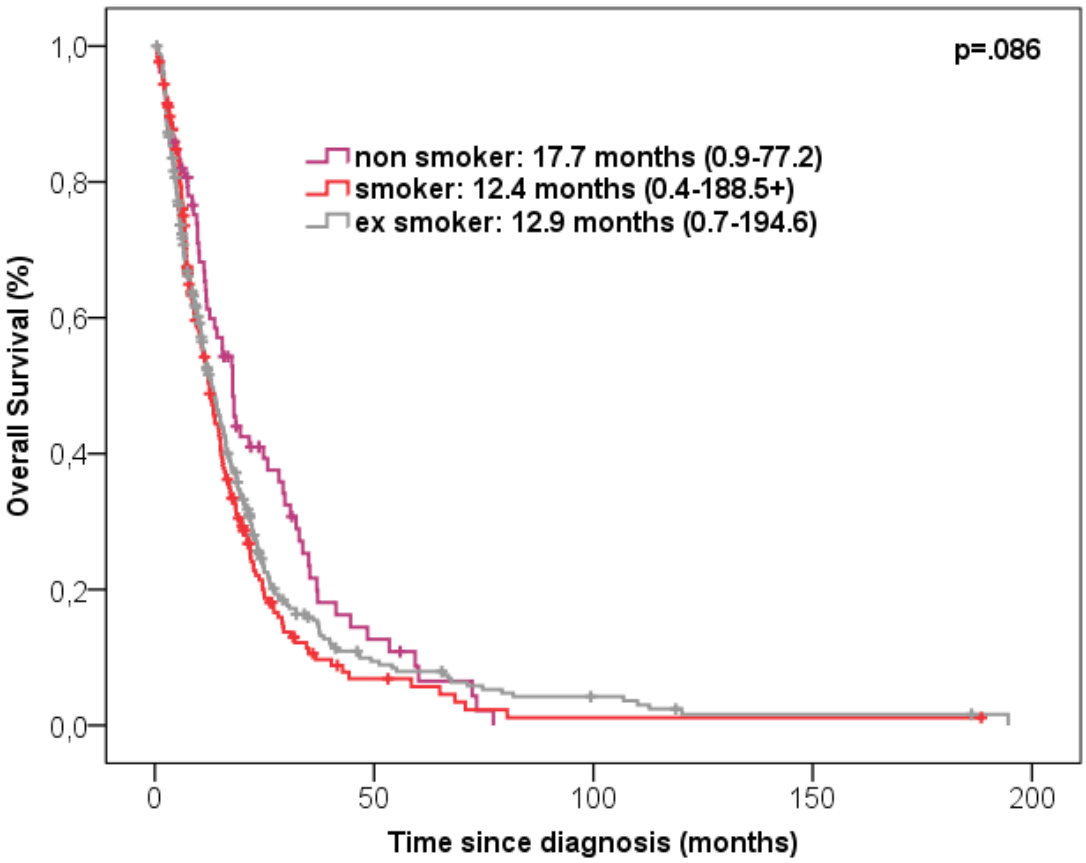


Figure 6-10 OS based on smoking history

78 non-smokers, 214 smokers and 323 ex-smokers were analysed. The median survival of non-smokers, smokers and ex-smokers was 17.7 months (range 0.9-77.2), 12.4 months (range 0.4-188.5) and 12.9 months (range 0.7-194.6) respectively. The difference was not statistically significant (P=0.086).

6.5.1 Influence of time of relapse after initial curable disease stage

As mentioned earlier 21% of the patients had a curative therapy and were in a follow-up program. These patients were compared to those who had no prior curative therapies. OS of patients with curative treatment was 20.6 months (0.7-194.6 months) compared to 12.5 months (0.4-188.5 months) if they had no curative therapy. The difference was statistically different (P=<0.001) Figure 6-11. Patients who were in the follow-up program had a significantly longer

survival from diagnosis of advanced stage disease than those diagnosed with advanced stage disease de novo.

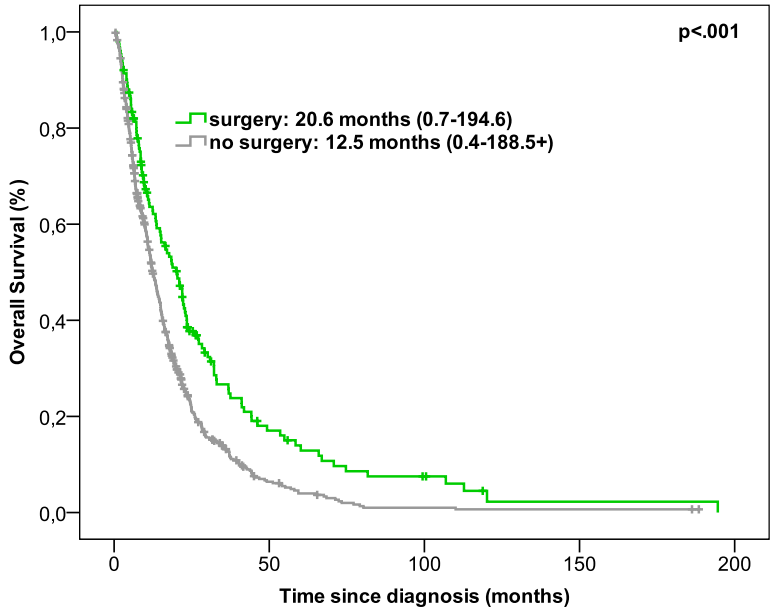


Figure 6-11 OS of patients who were identified with advanced stage lung cancer during follow-up

Patients who were in routine follow-up after curative resection and hence diagnosed with an advanced stage lung cancer (surgery +/- chemotherapy) were compared with those who had no prior curative therapy (no surgery). Patients with curative treatment had an OS of 20.6months (0.7-194.6 months) compared to 12.5months (0.4-188.5 months). The difference was statistically different (P=<0.001).

OS based on the time to relapse after initial curative therapy was analysed. The OS for patients diagnosed with an advanced stage lung disease ≤12 months after the initial therapy was 13.4 months (0.4-188.5). Patients with a relapse > 12 months had an OS of 20 months (0.7-194.6). The difference was statistically significant (P=0.010) favouring patients who had a delayed relapse i.e., more than one year after the initial therapy Figure 6-11. The analysis based on the tumour type showed no statistically significant difference (data not shown).

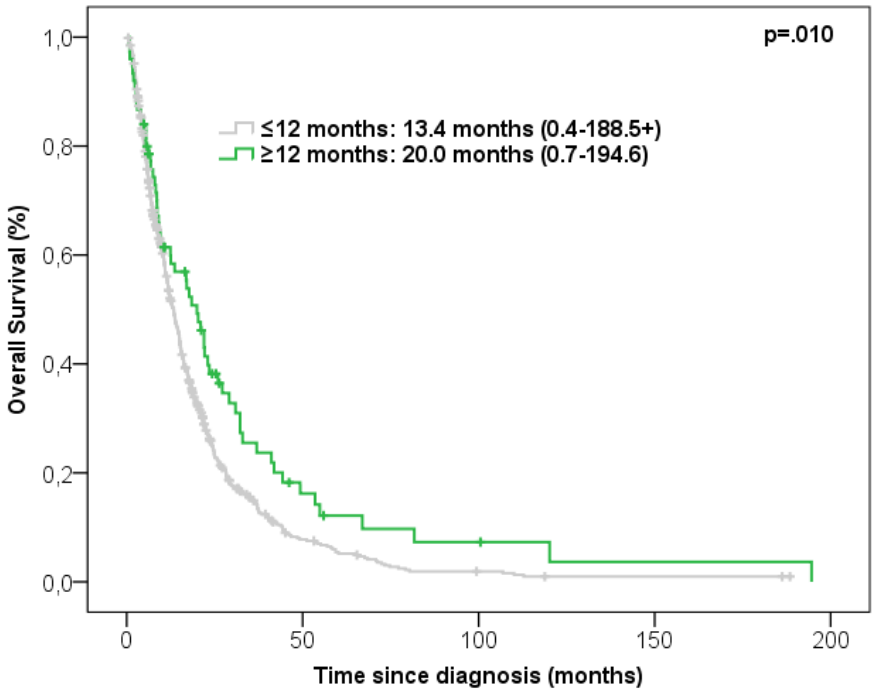


Figure 6-12 OS difference based on the time from diagnosis of advanced stage disease after curative treatment

Diagnosis of advanced stage disease ≤12 months or > 12 months after the curative treatment showed an overall survival 13.4 months (0.4-188.5) or 20 months (0.7-194.6) respectively. The difference was statistically significant (P=0.010).

6.5.2 Influence of metastases and lines of treatment

OS was also analysed based on the presence or absence of metastases. In the absence of metastases, the OS of patients with advanced stage disease was 16.9 months (range 1,2-188.5 months) compared to 11.6 months (range 0.4-194.6 months). The difference was statistically significant (P=0.003) favouring patients who had no confirmed metastases (Figure 6-13). Patients with brain metastases had an inferior (10.2 months versus 14.4 months) (P=0.002) (data not shown). No significant difference in OS was shown on analysis of the patient groups with and without liver metastases (data not shown).

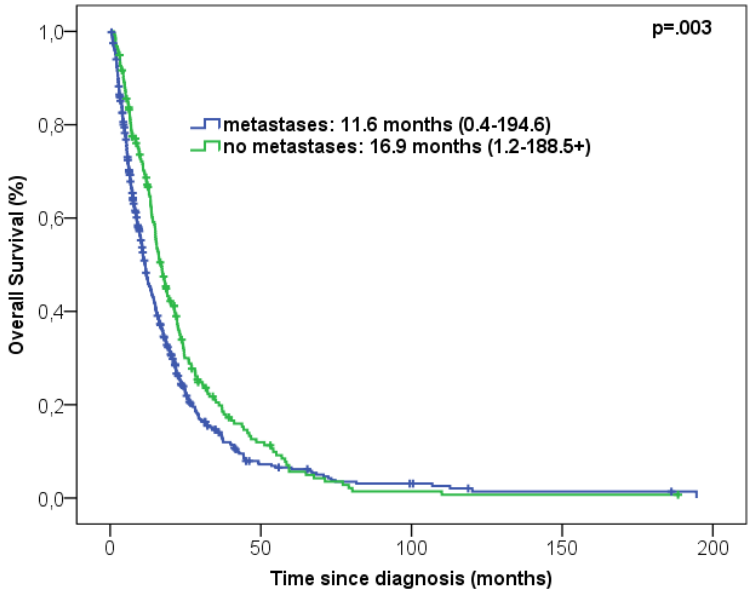


Figure 6-13 OS differences between patients with and without metastases

520 patients with advanced stage lung cancer with metastases and 216 patients without metastases were analysed. The median survival was 11.6 months (range 0.4-194.6) for patients with metastases and 16.9 months (1.2-188.5) for those without metastases. The difference was statistically significant (P=0.003) (Chakupurakal et al. 2019)

An analysis was also performed based on the number of therapy lines patients received. The median OS of patients who were given 1,2 or more therapy lines was 5.4 months (range 0.5-100), 11.0 months (1.3-195) or 20.4 months (range 2.6-188) respectively. The difference was statistically significant (P<0.001) (Chakupurakal et al. 2019). (Data not shown).

Patients who received best supportive care only had a shortened OS of 5.1 months (0.4 - 120) (data not shown).

6.5.3 OS of patients with driver mutations

366 patients had no molecular genetic analysis for the presence of driver mutations. In 53 patients where a mutation was identified the median OS was 15.6 months (range 0.4-186.3 months). The OS of patients lacking a driver mutation was 10.8 months (range 0.5-112.8 months). The analysis between patients with driver mutations and no driver mutations (tested or not tested) showed no statistically significant difference (P=0.136) Figure 6-14.

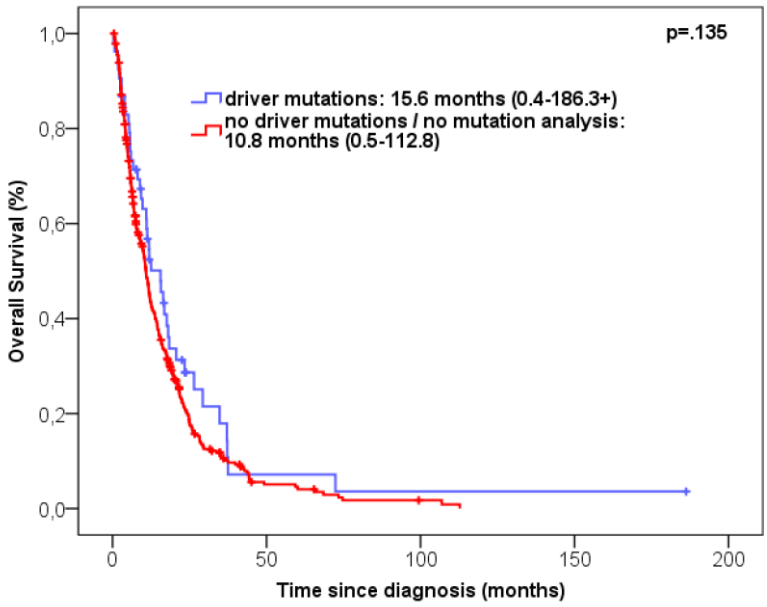


Figure 6-14 OS of patients with and without driver mutations

Mutations were identified in 53 patients. The differences between the groups- driver mutations tested versus those who were tested but no mutation was identified versus driver mutations not tested was not statistically significant

6.5.4 Influence of comorbidities and performance on overall survival

Performance score is a good prognostic marker hence the ECOG performance score was used as a variable. Data was available on 383 patients. 297 patients had a score ≤1 and a smaller group, 86 patients had a score ≥2. Patients with an ECOG performance score ≤1 had a statistically significant OS 13.0 months (range 0.4 – 195 months) in comparison to those with an ECOG score≥2 median of 8.0 months (0.7 - 189months) (P=0.004) Figure 6-15.

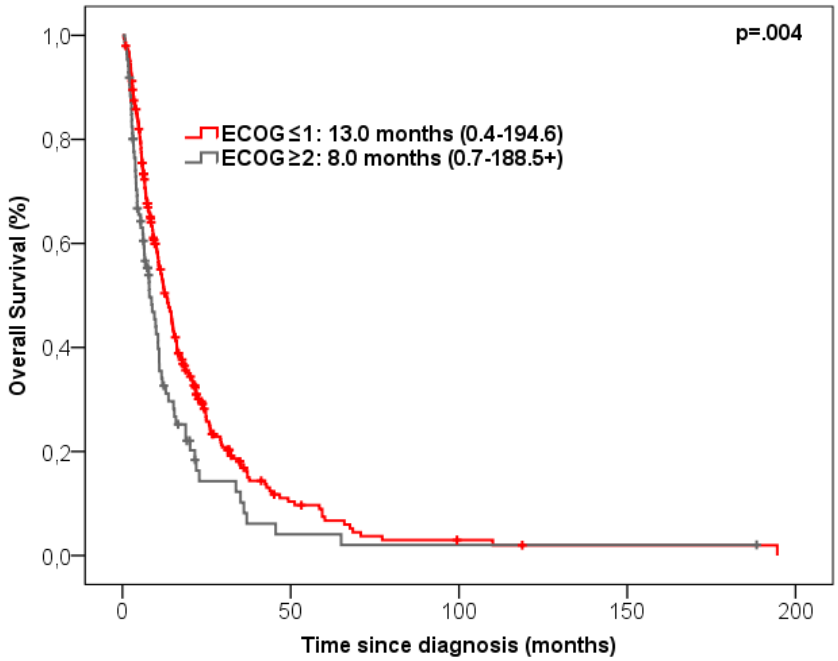


Figure 6-15 OS differences based on the ECOG performance score.

297 patients with ≤1 ECOG performance score and 86 patients with ≥2 ECOG performance score was analysed. The OS was 13 months (0.4-194.6) and 8 months (0.7-188.5) respectively. The difference was statistically significant (P=0.004). ECOG- eastern cooperative oncology group

CCI and aaCCI score is a good parameter to assess the relevance of comorbidities on disease survival. The cohort had a minimum score of 6 which was very high. In the initial analysis 4 different subgroups were identified CCI ≤7, 8, 9 and ≥ 10 with 136, 137, 151 and 312 patients respectively. The OS of patients in these groups were 17.2 months (range 0.4-188.5), 13.4 months (0.8-194.6), 12.2 months (0.6-80.4) and 12.3 months (0.5-79.2) respectively. The difference was statistically significant (P=<0.001) (data not shown). Patients were then analysed based on the aaCCI score in two groups, those with a score <8 or ≥8. The OS of patients with an aaCCI score <8 was 17.2 months (range 0.4-189 months) and ≥8 was 12.5 months (range 0.5-195 months). The differences in OS were statistically significant favouring the cohort with a lower score (P<.001) Figure 6-16.

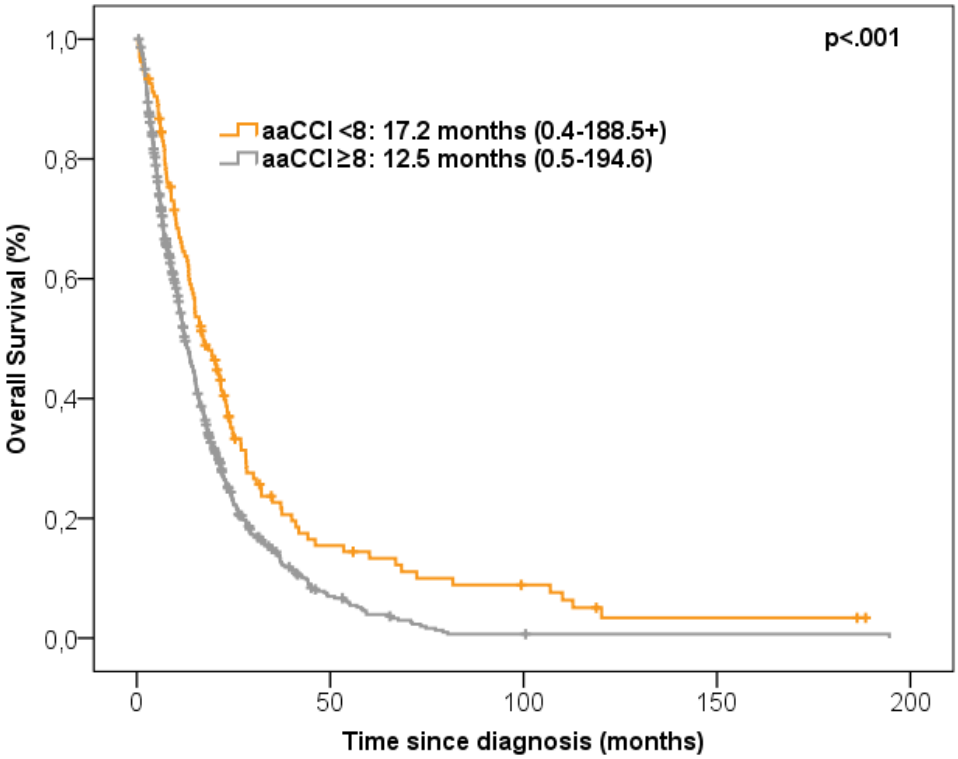


Figure 6-16 OS differences based on aaCCI

136 patients with aaCCI<8 600 patients with aaCCI>8 was analysed. The OS were 17.2 months (0.4-188.5) and 12.5 months (0.5-194.6) respectively. aaCCI- age adjusted charlson comorbidity index (Chakupurakal et al. 2019)

7 Discussion

In the last 5 years a variety of therapeutic options have become available for patients with advanced lung cancer. Nevertheless, it remains the leading cause for cancer related mortality. In a previous analysis, the OS of the patients treated in our community group practice, from the months of June 1995 to June 2006, was 10 months. (Koeppler et al. 2009). This study has three times more patients, 736 patients versus 212 patients, than the study published in 2009. The proportion of patients with metastatic disease is also higher in this study 71% versus 51%, An interesting observation is the increasing aging population who develop the disease. Patients ≥70 amount to 35% of the total patient population in comparison to 26% in the previous study. Increasing age did not imply deterioration in the performance score as patients with an ECOG score ≥2 made up 22% of this study cohort versus 43% in the study by Koeppler et al. Though all these factors have had a relevant impact on outcome the increase in OS is also due to the improvement in the therapeutic and supportive care options now-a-days. In this study very few patients received triple immunotherapy or immunotherapy alone. The impact of the advent of tyrosine kinase inhibitors cannot be assessed as well. 60% of patients had a genomic mutation analysis for one or the other known driver mutation. Of these patients 10% were identified to have a driver mutation 6.3.1.

Overall survival	**1 year**	**3 years**	**5 years**
Praxis Klinik Koblenz (06/1995 - 12/2016)	47%	10%	4%
Cancer registry Munich	31%	8%	4%
Cancer registry Rhineland-Palatinate	-	-	4%
SEER, USA	-	-	4%
Cancer Research UK (www.cancerresearchuk.org)	30%	-	

Table 7-1: Comparison of survival indices of lung cancer patients with advanced incurable disease.

SEER -Surveillance, Epidemiology or end results program of United states of America, UK United Kingdom (Chakupurakal et al. 2019)

We compared our data with results available from different data registries such as Munich, the state of Rhineland-Palatinate, the SEER (Surveillance, Epidemiology or End Results program) registry USA or NHS England Table 7-1. The differences in our 1-, 3- and 5-year survival data in comparison to other data registries is probably due to the possibility to obtain first hand on the patients we treated. Registries in contrast to our own database rely on a variety of sources for data input. The encouraging results highlight that good quality care can be successfully delivered in a community practice.

This study is also an observation of the different treatment practices of two decades. Immunotherapy with or without chemotherapy is the current first line standard of treatment for patients with advanced stage lung disease (Reck et al. 2016; Paz-Ares et al. 2018; Gandhi et al. 2018). The tumour responses to immunotherapy are significantly superior than the standards of treatment during this study. Immunohistochemistry testing for PD-L1 expression was not standard and no patient received immunotherapy in the first line or triple immunochemotherapy at all. An immunotherapy as second- or third-line treatment was administered only in 9% of the patients. The most common therapy option after platin doublet therapy was gemcitabine or vinorelbine monotherapy Figure 6-2. Immunotherapies have changed the prognosis of NSCLC dramatically. For the first time in the history of advanced stage NSCLC last year 5-year survival data was published on this patient cohort (Garon et al. 2019). Hence the prognosis of advanced stage NSCLC will significantly change in the next decade.

The same observation can be made of the patients screened for driver mutations. The current aim is to test all patients with an advanced stage adenocarcinomatous NSCLC for driver mutations. All patients who have a mutation should be treated with the appropriate tyrosine kinase inhibitor (Hirsch et al. 2016). This study was conducted during a time period where next generation sequencing was not available as standard. This explains the poor OS of patients with advanced stage NSCLC and driver mutations contrary to expectations.

Brain tumours are mostly (50%) lung cancer associated metastases (Schouten et al. 2002; Dawe, Greenspoon, and Ellis 2014). The presence of brain metastases alters the prognosis of advanced stage lung disease and less than 10% of the patients with palliative stage lung cancer develop brain metastases during the course of the disease (Goncalves et al. 2016). Patients with advanced stage lung cancer with brain and or liver metastases have a poor prognosis. We could

show a poor OS for patients with brain metastases Figure 6-13. In this study the proportion of patients with liver metastases was very small, probably the reason why a significance difference in OS was not observed for this group of patients (Riihimaki et al. 2014).

21% of the patients were in follow-up after a curative surgery with or without chemotherapy. This possibly resulted in the early diagnosis of advanced lung disease before the patients' developed symptoms. This subgroup of patients showed an improved OS in comparison to patients who had no curative treatment, 20.3 months versus 12.5 months, ($p<.001$) Figure 6-11. This highlights the necessity of a viable follow-up program. Patients with disease relapse can be identified earlier, before the onset of symptoms and have a better outcome. This is the same advantage observed by lung cancer screening programs (Toumazis et al. 2020). Implementation of counselling and behavioural therapy to stop nicotine abuse is another important tool which could reduce the number of patients who struggle to stop smoking despite the lung cancer diagnosis and treatment. Data on patients who received radio chemotherapy with a curative intention was unfortunately unavailable. This drawback in the collected data possibly has had an impact on decisions to treat as well as the ability to tolerate subsequent treatments.

More than a third of the patients had bone metastases but only 25% of these patients received a bone protecting agent. In order to protect the patients from potential fractures the awareness to deliver a bisphosphonate or RANK-Ligand antibody has to be increased so that more patients may be offered this supportive treatment in the future (Landherr et al.2017). 40% of the patients profited from transfusion of blood and or platelets 40% Figure 6-4. These data also highlight the importance of supportive therapy in addition to chemo and or radiotherapy.

Age, sex, ECOG performance status and metastases, especially brain metastases are factors which influence the outcome of lung cancer patients (Pinto et al. 2018). The impact of these variables on OS could be confirmed in our study. A small cohort of patients were above 80 (n=29, 4%). The proportion of patients above 75 increased from 8% (n=11) to 17 % (n=46) on a comparison between the first half of this study between 1995-2000 with the second half from2011-2016. The aging population with a lower ECOG performance (see 6.5.4) that makes them unsuitable for the standard therapeutic options which have not been studied in a similar cohort. Another observation is the increase in the number of patients in the last 5 years of the

study Table 6-1. This could be because of an increase in incidence or because patients feel comfortable with an outpatient treatment.

Currently limited data is available on suitable therapy options for elderly patients with comorbidities as they are not included routinely in clinical trials. Figure 6-16. Highlights how important comorbidities are in influencing outcome in cancer care. Patients with comorbidities are not recruited into clinical studies routinely resulting in a lack of data on the management of these patients. Clinical studies should target elderly patients with multiple comorbidities thereby reflecting the day-to-day clinical practice. Such studies will in return help understand the dose limiting toxicities of different therapies relevant to this patient cohort (Alexander et al. 2017). Recent studies have concentrated on factors affecting outcomes in the elderly and suggested screening tools to aid the use of chemotherapies (Quoix et al. 2011; Corre et al. 2016; Hurria et al. 2016). These may help alleviate the possible treatment related toxicities if incorporated into our day-to-day practice.

The majority of our study cohort (93%) were offered a chemo and or radiotherapy. Though a small subgroup of patients had an ECOG status of ≥2 in 22% (n=86), the majority tolerated the treatment with minimal toxicity Figure 6-15. Treatment related grade 3 or 4 toxicity was minimal and resulted in 3% of the overall number of hospital admissions. We were unable to obtain data on grade 1 and 2 toxicities. The major cause for multiple hospital admissions (63%, 1,160 hospitalizations) in the majority of the patients (89%, n=657) was the tumour itself Figure 6-5. The majority of the patients died in hospital or in a hospice. In a significant proportion (40%, n=198) death could be facilitated at home. The infrastructure for palliative end of life care at home has to be strengthened further so that more patients and their families can be adequately supported at the time of maximum need (Gomes et al. 2013). The value of multidisciplinary teams is of utmost importance for the appropriate management of this patient cohort.

8 Conclusions

In conclusion, the changes in cancer therapy over the last decade has further improved the outcome of patients with advanced stage lung cancer. In the outpatient setting, the relevant palliative therapies, both therapeutic as well as supportive treatments, can be delivered successfully. The patients enjoy good treatment close to home and the outcomes are comparable to randomised controlled trials as well as data available from regional and international registry data. Patients diagnosed with early-stage lung cancer should be enrolled in a follow-up program after their initial curative treatment. This allows the early detection of relapse prior to the onset of symptoms and hence improves their survival outcomes. This cohort of patients with multiple comorbidities can be efficiently managed with a comprehensive multidisciplinary team which in turns improves patient care. Expansion of ambulatory palliative care teams allows the support of patients and their families facing their ends of life.

9 Summary

Advanced stage lung cancer remains the leading cause for cancer related mortality. A significant proportion of these patients are managed in Germany in the outpatient setting. We studied the management and outcomes of patients with advanced stage lung cancer treated in our outpatient setting. Patients diagnosed and treated with advanced incurable non-operable non-small cell lung cancer (NSCLC) between June 1995 and December 2016 were consecutively recruited into the study and their data was then analysed.

736 patients with a median age of 66 (37–88) could be evaluated. Locally advanced disease was diagnosed in all patients and metastatic disease was confirmed in 71%. Adenocarcinoma (61%) was the predominant histological subtype followed by squamous cell cancer (28%). At least one line of chemotherapy was delivered in the majority (93%) with patients receiving a mean of 2.5 lines of treatment (range 1-11). The most common type of therapy was platin doublet chemotherapy (524/650; 81%). The most common cause of death was tumour progression (76%) and 93% of the patients died during the observation period. Patients enjoyed a median OS of 13.5 months (0.4–195 months). Metastases reduced the OS. Patients with metastatic lung disease had an inferior OS of 11.6 months (0.4–195 months) compared to patients with locally advanced disease 16.9 months (1.2–189 months) (P = 0.003).

The changes in cancer therapy over the last decade has further improved the outcome of patients with advanced stage lung cancer. Palliative therapies, both therapeutic as well as supportive treatments, can be delivered successfully in the outpatient with the help of a comprehensive multidisciplinary team. The patients enjoy good treatment close to home and the outcomes are comparable to randomised controlled trials as well as data available from regional and international registries. Patients diagnosed with early-stage lung cancer should be enrolled in a follow-up program after their initial curative treatment. This allows the early detection of relapse prior to the onset of symptoms and hence improves their survival outcomes. Expansion of ambulatory palliative care teams allows the support of patients and their families at the end of life at home.

10 Zusammenfassung

Lungenkrebs im fortgeschrittenen Stadium ist eine der Haupttodesursachen im Zusammenhang mit Krebs. Ein erheblicher Teil dieser Patienten wird in Deutschland ambulant behandelt. Wir wollten die Ergebnisse von Patienten mit Lungenkrebs im fortgeschrittenen Stadium, die ambulant behandelt wurden, analysieren und untersuchen. Alle konsekutiven Patienten mit fortgeschrittenem unheilbarem nicht operierbarem nicht-kleinzelligem Lungenkrebs (NSCLC), die zwischen Juni 1995 und Dezember 2016 behandelt wurden, wurden retrospektiv analysiert.

736 Patienten mit einem medianen Alter von 66 Jahren (37–88 Jahre) konnten untersucht werden. Alle Patienten hatten zum Zeitpunkt der Präsentation eine lokal fortgeschrittene Erkrankung und 71% hatten eine metastasierte Erkrankung. Das Adenokarzinom (61%) war der häufigste histologische Subtyp, gefolgt von Plattenepithelkarzinomen (28%). Die Mehrheit (93%) erhielt mindestens eine Chemotherapie. Im Mittel wurden 2,5 Behandlungslinien pro-Patient (1–11) verabreicht, wobei die Platin-Dubletten-Chemotherapie die häufigste Behandlungsart war (524/650; 81%). 93% der Patienten starben während des Beobachtungszeitraums, hauptsächlich aufgrund des Tumour‘s (76%). Das mediane Gesamtüberleben (OS) betrug 13.5 Monate (0,4–194.6). Patienten mit lokal fortgeschrittener Erkrankung hatten ein OS von 16.9 Monaten (1.2–188.5 +) im Vergleich zu 11,6 Monaten (0.4–194.6) bei Patienten mit Metastasen (P= 0.003).

Die Fortschritte in der Krebstherapie haben das Ergebnis von Patienten mit fortgeschrittenem Lungenkrebs verbessert. Diese Patientengruppe profitiert von einer palliativen Chemotherapie, die ambulant erfolgreich durchgeführt werden kann. Die Ergebnisse sind vergleichbar mit randomisierten kontrollierten Studien und aktuellen Daten aus regionalen und internationalen Registern. Die Nachsorge von Patienten mit Lungenkrebs, die eine kurative Therapie erhalten haben, führt zur Früherkennung eines Rezidivs und damit zu einem längeren Überleben. Ein kompetentes multidisziplinäres Team ist für die Versorgung dieser Patientenkohorte mit mehreren Komorbiditäten obligatorisch. Der Ausbau der ambulanten Palliativversorgungsteams ermöglicht die Unterstützung von Patienten und ihren Familien am Lebensende in deren zu Hause.

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12 Related publication

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Research Article Open Access

Treatment and Outcome of Patients with Palliative Non-small Cell Lung Cancer (NSCLC) in Routine Outpatient Care Over Two Decades

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Abstract

Objectives: We evaluated the practice in our outpatient setting to analyze and study the outcomes of patients with palliative lung cancer.

Methods: All consecutive patients with palliative non-small cell lung cancer (NSCLC) treated between June 1995 and December 2016 were analyzed retrospectively.

Results: 736 patients with a median age of 66 (37-88) could be evaluated. All patients had a primary lesion in the lung and 71% metastatic disease at the time of presentation. Adenocarcinoma (61%) was the most common histological subtype followed by squamous cell cancer (28%). The majority (93%) received at least one line of chemotherapy. A mean of 2.5 lines of treatment per patient (1-11) was delivered with platin doublet chemotherapy being the most common therapeutic choice (479/650; 74%). 93% of patients died, mostly due to tumor (76%) during the observation period.. The median overall survival (OS) was 13.5 months (0.4-194.6). Patients with disease limited to the lungs without metastases had an OS of 16.9 months (1.2–188.5+) compared with 11.6 months (0.4-194.6) for patients with metastases (p=0.003).

Conclusions: Good quality care can be delivered closer to home in an outpatient setting with the help of a competent multidisciplinary framework. Our results are comparable to that of clinical trial and cancer registry data.

Keywords: Non-small cell lung cancer; Palliative treatment; Chemotherapy; Carcinoma; Metastasis

Introduction

Lung cancer is the second most common solid tumor and the leading cause of cancer related deaths across both genders worldwide [1,2]. Unfortunately, the majority of patients are diagnosed at an advanced stage where a curative option is not feasible. Lung cancer mainly comprises of two different subtypes small cell and non-small cell; the latter accounting for around 85% of all lung cancers. The recent advent of immunotherapy agents has further revolutionized the available therapeutic options [3]. The knowledge of driver mutations and the availability of tyrosine kinase inhibitors targeting these mutations has significantly improved the prognosis of this small sub-cohort of NSCLC patients [4-6].

Despite the advances in the treatment options, only 4% of the patients diagnosed with palliative NSCLC survive more than 5 years [7]. Data obtained from clinical trials do not reflect the day-to-day reality of older patients, with multiple comorbidities deemed unfit as per inclusion and exclusion criteria. We retrospectively analyzed data on patients with palliative NSCLC in our community-based outpatient practice over the last two decades. The aim of our study was to analyze the impact of various treatment modalities on an unselected, unbiased population. We demonstrate the importance of a multidisciplinary team in the treatment of this patient cohort and the impact of changing therapeutic options on day-to-day clinical practice.

Methods

The treatment and outcome of all consecutive patients diagnosed with palliative NSCLC in our community-based oncology group practice between June 1995 and December 2016 was retrospectively analyzed. No patient could be offered a curative therapy i.e. surgery or curative radiochemotherapy. Patients with disease limited to one lung but inoperable or ineligible for a curative radiochemotherapy were defined as having locally advanced lung disease. Patients with a primary lesion in the lung and metastases were defined as having metastatic lung disease. All patients with locally advanced lung disease and metastatic lung disease were identified as having advanced stage palliative NSCLC and included in the study. The primary endpoint was OS and the secondary endpoints were response rates and toxicity. Informed consent was obtained from all patients. Patients were identified by searching the practice's electronic files for relevant codes of the international classification of diseases. A computerized data collection tool was used to extract the relevant data. In addition to data from our personal files, information was also obtained from our cooperation partners involved in the care of the patient i.e. hospitals and primary care physicians.

Performance status was evaluated using the Eastern Cooperative Oncology Group (ECOG) criteria [8]. Toxicity was analyzed based on the National Cancer Institute CTC version 3 [9]. The Charlson comorbidity index (CCI) has been widely used to predict the mortality rate based on the comorbidities [10]. We used the age adapted Charlson comorbidity index (aaCCI) to analyze the influence of age as well as comorbidities on the disease specific outcome [11]. The anonymized data were collected from patient files into a database and analyzed statistically using SPSS 19. Statistical analyses were descriptive, specific hypotheses were not tested. Survival analyses were performed according to the method of Kaplan and Meier.

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Results

Patient demographics

736 patients with advanced stage palliative NSCLC were identified during the study duration. Patient demographic data is shown in Table 1. The majority were male (n=490, 67%) with a median age of 66 (range 37-88) at the time of diagnosis. 46% of the patients (n=335) were under 65. Language posed no barrier to good communication in the majority of patients (96%, n=704).

ECOG performance status and body mass index (BMI) was available for 383 patients and 680 respectively (52%; 92%). The majority (297/383, 78%) had an ECOG performance status ≤ 1 and around half (312/680, 46%) a normal BMI (18.5-24.9). History of nicotine abuse could be obtained on the majority of patients (n=615, 84%); of these 53% were smokers and 35% continued to smoke despite the diagnosis. 13% never smoked. An occupational hazard could be established in 11% (n=41) of patients. Based on the available documented evidence, 83% (n=34) of these patients were reported to the respective authorities and in 12% (n=5) an occupational hazard could be confirmed. In our patient cohort, the aaCCI was <8 and ≥ 8 in 18% (136/736), and 82% (600/736) respectively Table 1.

151/736 (21%) had surgery as first line therapy and 59/151 (39%) adjuvant or neoadjuvant chemotherapy prior to recruitment into this study and were in a follow-up program. Information on patients who received curative radio chemotherapy was not available.

Tumor location

61% (n=451) of patients had an adenocarcinoma whereas 28% (n=205) had a squamous etiology. Majority of the tumors were located in the upper lobe (48%, n=353) followed by lower lobe (23%, n=166) and middle lobe (10%, n=75). 216 patients (29%) suffered from locally advanced lung disease. 520 (71%) had metastatic lung disease. 27%, 20% and 15% (n=138, n=106, n=76) of patients with metastasis had only lung, bone or brain metastases respectively at the time of diagnosis. Patients with metastatic disease had on average 1.5 metastases (range 1-5). 8% had brain and bone +/- lung metastases (n=42), 4% had lung and bone metastases (n=21) and 26% (n=137) had metastases in other sites such as adrenal glands and liver.

Treatment

The majority of patients (93%, n=685) were considered fit for a palliative therapy whereas 7% (n=51) of the patients were offered best supportive care alone. Therapy consisted of chemotherapy with or without palliative radiation in 95% of patients, 5% had radiation only. 1,622 chemotherapy lines were administered to 650 patients (mean 2.5 per patient; range 1-11). A platin doublet chemotherapy was the most common therapeutic option in 479/650 patients (74%) and in 619/1,622 (38%) therapy lines respectively. 433 patients (67%) received a second and 260 (40%) a third line treatment. A platin doublet was administered as first, second and third line treatment in 411 (63%), 124 (29%) and 44 (17%) lines respectively Figure 1. 146 (22%) received more than 3 lines of chemotherapy. 8% (50/650) of patients were offered a triple therapy with a platin, a taxane or pemetrexed in combination with bevacizumab. 23% (n=147) received a single agent treatment as first line. Immunotherapies with nivolumab or pembrolizumab were offered to 46 (7%) patients.

Supportive therapy and toxicity

Supportive therapy played a major role in the treatment. 633 patients (86%) were offered a palliative support therapy in addition to chemotherapy or radiotherapy. 58 (8%) patients received a palliative surgery such as kyphoplasty or resection of a metastasis, 2 (0.3%) received chemoembolization, 4 (0.5%) radiofrequency ablation and 4 (0.5%) an intraperitoneal chemotherapy. 24% (n=178) received a bisphosphonate or a monoclonal antibody directed against RANKL. 72% (n=532) required pain management. 41% (n=303), 17% (n=127) and 11% (n=81) were given blood and blood products, erythropoietic stimulating agent and or a granulocyte stimulating colony factor following chemotherapy. 93% of the patients tolerated the treatment very well. In 9% of all applied chemotherapies and in 19% of patients grade 3-4 neutropenia, thrombocytopenia and anaemia could be observed.

Age	Median (Range)	66 (37-88)
	N	%
Age groups		
- <65 years	335	46
- 65-69 years	144	20
- 70-75 years	152	21
- >75 years	105	14
Gender		
- male	490	67
- female	246	33
Stage		
- metastatic disease	520	71
- advanced stage disease	216	29
Year of diagnosis		
- 1995 - 2000	140	19
- 2001 - 2004	130	18
- 2005 - 2008	129	18
- 2009 - 2012	133	18
- 2013 - 2016	204	28
ECOG performance status *(n=383)*		
- ECOG ≤1	297	78
- ECOG ≥2	86	22
Age adjusted Charlson Comorbidity Index (aaCCI)		
- aaCCI <8	136	18
- aaCCI ≥8	600	82
Occupational hazard *(n=390)*		
- occupational hazard identified	41	11
Identified occupational hazard *(n=41)*		
- reported to the authorities	34	83
- confirmation of hazard	5	12
Marital status *(n=566)*		
- married or in a relationship	442	78
- widowed	46	8
- living alone	78	14
Body Mass Index		
- underweight	38	6
- normal	312	46
- overweight	251	37
- adipose	79	12
History of nicotine abuse		
- never smoked	78	13
- still smoking	214	35
- smoked prior	323	53

Table 1: Demographic data.

89% (n=657) of the patients required hospitalization following the onset of therapy. On average patients were hospitalized 3 times (range 1-17). The majority of hospitalizations (63%, 1,160 hospitalizations) were due to tumor related problems with only 57 (3%) admissions resulting from treatment related toxicities. The remaining patients were hospitalized for the delivery of chemotherapy or palliative procedures such as radiofrequency ablation, intraperitoneal chemotherapy and chemoembolization. The median duration of hospitalization was 22 days (range 1-179 days). In patients for whom the information was available (79%, n=493); 50% (245/493) died in hospital, 40% (198/493) at home and 10% (50/493) of patients in a hospice or old age home.

Survival analyses

The median OS of the whole cohort was 13.5 months (range 0.4 – 195). 7% (n=53) of the patients are still alive. Men had an inferior median OS in comparison with women 12.5 *versus* 15.4 months (p=0.12). Younger age was associated with a better OS; 15 months if ≤ 65 *versus* 12 months if >65 (p<0.001). The OS of patients who received best supportive care only was 5.1 months (0.4 - 120). Patients with advanced lung disease had a better OS of 16.9 months compared to 11.6 months in patients with metastatic lung disease (p=0.003) (Figure 2). Amongst the patients with metastatic disease, those who had brain metastases had an inferior OS compared to those without (10.2 months *versus* 14.4 months) (p=0.002). A statistically significant difference in survival was not observed between the patients with or without liver metastases.

Patients who received more therapy lines had a better prognosis which was statistically significant (p<0.001). The median OS varied from 5.4 months (range 0.5-100) to 11.0 months (1.3-195) to 20.4 months (range 2.6-188) in patients who received 1, 2 or more than 2 therapy lines respectively.

Survival analysis of patients with aaCCI scores <8 and ≥ 8 show a significantly different outcome (17.2 months vs. 12.5 months; p<.001) (Figure 3). Patients with an ECOG performance score ≤ 1 survived 13.0 months (0.4 - 195) in comparison to a median of 8.0 months (0.7 - 189+) if the ECOG was ≥ 2 (p=0.004).

Patients with driver mutations

In the last decade, tyrosine kinase inhibitors became available for patients with driver mutations. Molecular genetic analysis for possible mutations or translocations on EGFR, ROS-1, ALK or BRAF genes were performed in 29% (n=214), 8% (n=61), 18% (n=129) and 6% (n=42) of the total number of patients. 10% of the patients tested (44/446) had a genetic aberration in the analysis. PD-L1 expression was not analyzed until 2016 and hence the data on PD-L1 testing was not obtained.

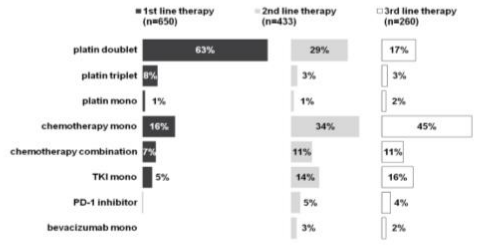

Figure 1: Administered therapies in 1st, 2nd and 3rd line treatment.

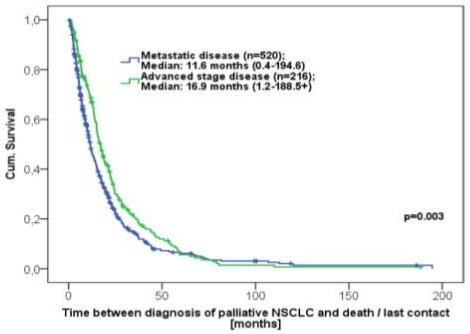

Figure 2: Overall Survival - comparison of patients with metastatic disease *vs.* advanced stage disease.

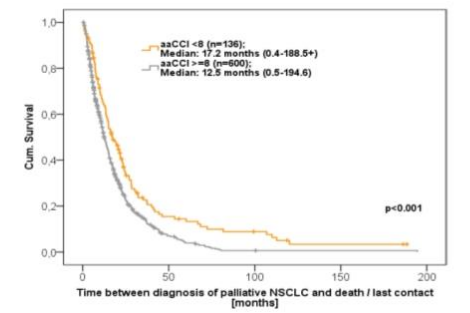

Figure 3: Overall Survival - comparison of patients with an age adapted Charlson comorbidity index (aaCCI) ≥8 *vs.* aaCCI <8.

39 patients were diagnosed with a mutation (ALK; ROS; EGFR) and received a targeted therapy. OS of this patient subgroup was not significantly longer than patients without a driver mutation, 16.5 months (1.8 - 186+) *versus* 13.4 months (0.4 - 195) (p=0.342). 4 patients (9%) had best supportive care only as they died shortly after or before the driver mutations were established or had radiation or chemotherapy mostly due to comorbidities and a reduced performance status. The patient with BRAF mutation had an ALK-translocation as well and hence was commenced on crizotinib.

Discussion

Lung cancer remains the most important cause of cancer related deaths despite the advances in the available therapeutic options. Our own previous analysis from June 1995 to June 2006 published in 2009 showed a median OS of 10 months [12]. In comparison with the analysis published in 2009, the current study comprises a bigger cohort (736 *versus* 212) with metastatic disease in a bigger proportion (71% *versus* 51%). The current study had a greater subgroup of elderly patients 70 or above (35% *versus* 26%) but a smaller proportion with an ECOG of 2-4 (22% *versus* 43%). Even after taking these factors into account the improvement in OS in our current study is probably due to the improvement in the therapeutic options and supportive care provided.

Our 1, 3- and 5-year OS data surpasses the data obtained from the Rhineland-Palatinate or Munich, SEER or NHS England cancer registries. This suggests that the advent of new therapeutic options has resulted in an improvement in the OS of this patient cohort and that we can successfully deliver this care in a community practice.

Around one fifth of the patients had a curative therapy with surgery and or adjuvant chemotherapy prior to enrolment in the study, implying that these patients were possibly identified prior to the onset of symptoms during the follow-up period. This cohort of patients might have contributed to our admirable results. We analyzed this cohort with the rest of the subset which had no prior surgery and found as expected an improved OS (20.3 months *versus* 12.5 months, p<.001). The lack of data on patients who received curative radio chemotherapy is also a drawback of our study with respect to the possible influence of this treatment on subsequent therapeutic decisions as well as their tolerability and also the prognosis of this subset of patients.

Age, gender, ECOG performance status and metastases, especially brain metastases, are established risk factors which influence the outcome of patients with lung cancer [13]. Our own experience confirmed the impact of these confounding variables on survival outcome. 4% (n=29) of the patients were above 80. In the time period between 1995-2000 8% (n=11) of the patient cohort were above 75 whereas between 2011-2016 they accounted for 17% (n=46) of the study group. We need more clinical studies which recruit elderly patients in order to understand the dose limiting toxicities in this cohort of patients [14]. The statistically significant impact of aaCCI on outcome highlights the influence of comorbidities. The recently suggested tools to predict chemotherapy toxicities should be incorporated into our day-to-day practice to alleviate the impact of comorbidities on outcome [15-17].

Despite the ECOG status of ≥ 2 in 22% (n=86) of patients, 93% could be offered a chemo or radiotherapy and the majority tolerated the treatment with minimal toxicity. Our data shows minimal limitation with respect to grade 3 and 4 toxicity secondary to chemotherapy. A drawback of our study is the lack of grade 1 and 2 toxicity data. A significant proportion (89%, n=657) of the patients required multiple hospital admissions and mostly (63%, 1,160 hospitalizations) due to tumor related events. In many patients (40%, n=198) death at home could be facilitated highlighting the value of multidisciplinary teams in the community setting. In the future we should invest in resources to facilitate end of life care at home [18].

Conclusion

We conclude that with the advances in cancer therapy the outcome of patients with palliative lung cancer has improved. This patient group benefits from palliative chemotherapy which can be accomplished successfully in an outpatient setting with outcomes comparable to randomized controlled trials and contemporary data available from regional and international cancer registries. Appropriate follow-up of patients with lung cancer who have received a curative therapy results in the early detection of relapse and hence improved outcome. A good comprehensive multidisciplinary team is mandatory in the delivery of care for this patient cohort with multiple comorbidities.

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13 Lebenslauf

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2012-2015: Fachärztin, Innere Medizin I, Universitätsklinikum Köln bei Prof. Dr. M. Hallek
2014: Zusatzweiterbildung in Palliativmedizin
2016: Qualifikation zur fachgebundenen genetischen Beratung
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