OULU 2022
D 1665

ACTA UNIVERSITATIS OULUENSIS

Virve Tuisku

IMPROVING LUNG CANCER CARE USING REAL-WORLD DATA

UNIVERSITY OF OULU GRADUATE SCHOOL;
UNIVERSITY OF OULU,
FACULTY OF MEDICINE;
MEDICAL RESEARCH CENTER OULU

ACTA UNIVERSITATIS OULUENSIS
D Medica 1665

VIRVE TUISKU

IMPROVING LUNG CANCER CARE USING REAL-WORLD DATA

Academic dissertation to be presented with the assent of the Doctoral Training Committee of Health and Biosciences of the University of Oulu for public defence in Auditorium 7 of Oulu University Hospital, on 22 April 2022, at 12 noon

UNIVERSITY OF OULU, OULU 2022

Acta Univ. Oul. D 1665, 2022

Supervised by
Docent Jussi Koivunen

Reviewed by
Docent Tuula Toljamo
Doctor Eeva-Maija Nieminen

Opponent
Professor Panu Jaakkola

ISBN 978-952-62-3260-7 (Paperback)
ISBN 978-952-62-3261-4 (PDF)

ISSN 0355-3221 (Printed)
ISSN 1796-2234 (Online)

Cover Design
Raimo Ahonen

PUNAMUSTA
TAMPERE 2022

Tuisku, Virve, Improving lung cancer care using real-world data.
University of Oulu Graduate School; University of Oulu, Faculty of Medicine; Medical Research Center Oulu
Acta Univ. Oul. D 1665, 2022
University of Oulu, P.O. Box 8000, FI-90014 University of Oulu, Finland

Abstract

Lung cancer remains the leading cause of cancer incidence and mortality worldwide although the treatment of lung cancer has improved significantly over recent decades. Challenges to improve lung cancer survival still remain. One aspect is the early diagnostics of lung cancer by screening or detecting early-stage lung cancers rather than advanced stage, as the five-year survival rate is 40–80% for stage I lung cancer and only 2–6% for stage IV. Another aspect is the improvement of the treatments; major improvements have been made especially in NSCLC treatment with the advent of targeted therapies, like EGFR TKIs, and immunotherapies.

In this thesis, we wanted to investigate the association between lung cancer diagnostic delays and survival in a single Finnish cancer centre. In recent years, many centres have introduced fast-track diagnostic and treatment procedures for lung cancer, but it is uncertain whether they improve survival. In our study, shorter time intervals were not associated with improved survival, suggesting that fast-track approaches are unlikely to improve the survival of lung cancer patients.

EGFR TKIs have significantly improved progression-free survival of NSCLC patients with sensitizing EGFR mutations. However, TKIs are associated with significant and disabling side effects, like rash and diarrhoea, which adversely affect quality of life and treatment compliance. In turn, it has been shown that patients who develop skin rash are more likely to respond to treatment. Rash can be relieved with tetracycline antibiotics and topical corticosteroids. Prophylactic use of tetracyclines has been shown to inhibit the severity of TKI rash, but it is unknown whether prophylactic use of tetracyclines and topical corticosteroids can increase the survival of NSCLC patients treated with EGFR TKIs.

In this study, we present the results of a large nationwide cohort of patients treated with EGFR TKIs for NSCLC indication, using wide real-world registries. We found that prophylactic use of tetracyclines and topical corticosteroids can improve the survival of NSCLC patients treated with EGFR TKIs with high incidence of rash.

Keywords: diagnostic delays, EGFR mutation, lung cancer, tetracyclines, topical corticosteroids

Tuisku, Virve, Keuhkosyövän hoidon kehittäminen rekisteritietoja käyttäen.
Oulun yliopiston tutkijakoulu; Oulun yliopisto, Lääketieteellinen tiedekunta; Medical Research Center Oulu
Acta Univ. Oul. D 1665, 2022
Oulun yliopisto, PL 8000, 90014 Oulun yliopisto

Tiivistelmä

Keuhkosyövän hoidossa on otettu suuria edistysaskelia viime vuosikymmenten aikana. Siitä huolimatta keuhkosyöpä on edelleen useimmin diagnosoitu syöpä ja suurin syöpäkuolleisuuden aiheuttaja maailmassa. Haasteita keuhkosyövän ennusteen parantamisessa riittää edelleen. Yksi näkökulma on varhaisen diagnostiikan parantaminen keuhkosyöpää seulomalla ja löytämällä enemmän varhaisen vaiheen keuhkosyöpiä. Asteen I keuhkosyövän 5-vuotiselossaolo on 40–80 %, kun taas asteen IV keuhkosyövissä se on vain 2–6 %. Toinen näkökulma on hoitojen kehittyminen: merkittävää hyötyä on nähty erityisesti ei-pienisoluisen keuhkosyövän hoidossa täsmähoitojen, kuten EGFR-estäjien, sekä immunologisten hoitojen kehityksen myötä.

Tässä tutkimuksessa halusimme selvittää keuhkosyövän diagnostiikan viiveiden yhteyttä ennusteeseen suomalaisen syöpäkeskuksen potilailla. Monet syöpäkeskukset ovat kehittäneet nopean diagnostiikan ja hoidon polkuja keuhkosyöpäpotilaille, mutta on epävarmaa, voivatko ne parantaa ennustetta. Tässä tutkimuksessa nopea diagnostiikka tai hoidon aloitus ei parantanut ennustetta, joten nopeiden hoitopolkujen kehittäminen ei välttämättä tuo lisähyötyä keuhkosyöpäpotilaiden ennusteeseen.

EGFR-estäjät ovat merkittävästi parantaneet ei-pienisoluisen EGFR-mutatoituneen keuhkosyövän tautivapaata-aikaa, mutta niihin liittyy huomattavia elämänlaatua ja hoitomyöntyvyyttä heikentäviä haittoja, kuten ihottumaa ja ripulia. Ihottuman esiintymisen on toisaalta osoitettu korreloivan hoidon tehon kanssa. Ihottumaa voidaan hoitaa tetrasykliiniryhmän antibiooteilla ja kortisonivoiteilla. Tetrasykliinien ennakoiva käyttö vähentää vakavan ihottuman riskiä, mutta on ollut epävarmaa, voiko näiden hoitojen ennakoiva käyttö parantaa potilaiden ennustetta.

Tässä laajassa, kansallisessa tosielämän tietoja hyödyntävässä kohorttiaineistossa havaitsimme tetrasykliinien ja kortisonivoiteiden ennakoivan käytön parantavan ennustetta ei-pienisoluista keuhkosyöpää sairastavilla potilailla, jotka käyttävät suuren ihottumariskin EGFR-estäjiä.

Asiasanat: diagnostiikan viiveet, EGFR-mutaatio, keuhkosyöpä, kortisonivoiteet, tetrasykliinit

To my dear Family. You are my world.

Acknowledgements

The research for this thesis was carried out in the Department of Oncology and Radiotherapy at the University of Oulu during the years 2017–2021.

First, I want to express my deepest gratitude to my supervisor, Docent Jussi Koivunen, M.D., Ph.D. You introduced me to the interesting world of science. I am so grateful for your guidance and advice during these years. Despite your own busy work and life, you have always had time for me and my questions. Thank you, Jussi, for all the expert advice and support you have given me during this project; it has been indispensable.

I also express my special appreciation to my co-authors: Martti Arffman, MSocSc. for sharing your expertise in the statistic field, and Sanna Iivanainen, M.D., Ph.D., for your collaboration and guidance in the field of science, as well as being a friend outside science.

I am grateful to Docent Tuula Toljamo, M.D., Ph. D. and Eeva-Maija Nieminen, M.D., Ph.D. for your careful revision of this thesis and your valuable comments on it. Because of you, this thesis is more coherent and systematic.

I would like to thank my doctoral training follow-up group members, Hanne Kuitunen, M.D., Ph.D. and Heidi Jurvelin, MSc, Ph.D. Thank you for sharing your knowledge during this project. I especially wish to thank Hanne for your inspiring touch to medicine and your encouraging attitude and faith in me in this project, but also in everyday clinical work. I admire you as a person and as a colleague, and it is a privilege to work with you.

I am grateful to all my warm-hearted colleagues in the Department of Oncology and Radiotherapy. It is a pleasure to work with you and to be inspired daily by all of your intelligence and wisdom. I especially want to thank Johanna for your friendship and support in work, but particularly in life outside work. I truly appreciate our daily conversations. Susanna, I am grateful for all the help and support you have given me with this thesis, among many other things.

This study was financially supported by FICAN North, Orion Research Foundation sr, Oulu Medical Research Foundation and the University of Oulu, which I gratefully acknowledge.

I wish to thank all my friends outside the world of science for being there for me. Jaana, Kajsa and Mallu, you have known me for almost all my life, and with each passing year, our friendship becomes more and more valuable. Thank you Aino and Jonna for endless conversations and your wisdom of life. Thank you

Maria for your peer support in life. Thank you Marika and Tapani for all the memorable and funny moments we have had together.

I am deeply grateful to my dear family. My mother Aila and father Jorma – I have always been able to trust in your support and love in life. Your down-to-earth attitude grounds me. Without your help in everyday life and with my children, I would not be here. My dear siblings, Henri and Harri, it has been a privilege growing up with you. I can count on you no matter what.

My dear, beloved children, Alma, Jooa and Elsa, and my whole extended family: you are my world. You have taught me more about life than any school or education could. I am blessed to have you in my life. You are extraordinary – all of you. You can be whatever you want to be in life.

Finally, I owe my dearest gratitude and respect to my husband, Jaakko. You are the love of my life, my soulmate, my everything. Without you, life would be so much more boring and empty. Thank you for your unconditional support and understanding; you are always ready for a discussion and development, and I admire that. This would not be happening without your love and belief in me. Thank you for being You.

Oulu, January 2022 Virve Tuisku (née Alanen V)

Abbreviations

ADC	adenocarcinoma
AC	adjuvant chemotherapy
ALK	anaplastic lymphoma kinase
ATC	anatomical therapeutic chemical
ATM	ataxia-telangiectasia mutated
ASCL1	achaete-scute family BHLH transcription factor 1
BRAF	v-raf murine sarcoma viral oncogene homolog B1
BSC	best supportive care
CAV	chemotherapy combination
CT	computed tomography
CXCR2	CXC chemokine receptor type 2
CXR	chest radiograph
CYP1A1	cytochrome P450 family 1 subfamily A member 1
CYP2E1	cytochrome P450 family 2 subfamily E member 1
DFS	disease-free survival
DNA	deoxyribonucleic acid
EBUS	endobronchial ultrasound
ECOG	eastern cooperative oncology group
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
ER	emergency room
ErbB	family of tyrosine kinase receptors
ERCC1	excision repair cross-complementation group 1
ERCC2	excision repair cross-complementation group 2
FDA	U.S. Food and Drug Administration
FDG	fluorodeoxyglucose
FGFR4	fibroblast growth factor receptor 4
FISH	fluorescence in situ hybridisation
GP	general practitioner
Gy	Gray (J/kg)
HIV	human immunodeficiency virus
HER2	human epidermal growth factor receptor 2
HR	hazard ratio
H&E	haematoxylin and eosin
IASLC	The International Association for the Study of Lung Cancer

ICI	immune checkpoint inhibitors
IHC	immunohistochemistry
IMRT	intensity-modulated radiation therapy
LCC	large cell carcinoma
LDCT	low-dose computed tomography
LFT	liver function test
L858R	mutation
MET	hepatocyte growth factor receptor
MDT	multidisciplinary tumour board
mOS	median overall survival
MRI	magnetic resonance imaging
MYC	MYC proto-oncogene
NEUROD1	neuronal differentiation 1 gene
NGS	next generation sequencing
NICE	The National Institute for Health and Care Excellence
NLST	the national lung screening trial
NOS	not otherwise specified
NSCLC	non-small-cell lung cancer
NTRK	neurotrophic tyrosine receptor kinase
OS	overall survival
PCR	polymerase chain reaction
PD-L1	programmed death-ligand 1
PET	positron emission tomography
PFS	progression-free survival
PORT	post-operative radiotherapy
POU2F3	protein coding gene
RET	proto-oncogene
ROC	receiver operator characteristic
ROS1	proto-oncogene 1
R0	microscopically margin-negative resection
SCC	squamous cell carcinoma
SCLC	small-cell lung cancer
SOD2	superoxide dismutase 2
TERT	telomerase reverse transcriptase
TKI	tyrosine kinase inhibitor
TMB	tumour mutational burden
TNM	tumour, node, metastasis

TP53	tumour protein p53
TRAE	treatment-related adverse event
TTF-1	thyroid transcription factor 1
T790M	point mutation at position 790
UICC	The Union for International Cancer Control
WHO	World Health Organisation
YAP1	yes-associated protein 1

List of original publications

This thesis is based on the following publications, which are referred throughout the text by their Roman numerals:

I Alanen V, Koivunen JP. (2019). Association of diagnostic delays to survival in lung cancer: single center experience. *Acta Oncol. 2019 Jul;58*(7):1056-1061

II Alanen V, Iivanainen S, Arffman M, Koivunen JP. (2020). Tetracyclines increase the survival of NSCLC patients treated with EGFR TKIs: a retrospective nationwide registry study. *ESMO Open. 2020 Oct;5*(5):e000864.

III Alanen V, Iivanainen S, Arffman M, Koivunen JP. (2021). Purchase of prophylactic topical corticosteroids is associated with improved survival in NSCLCs treated with EGFR TKI: real-world cohort study. *Acta Oncologica*, DOI: 10.1080/0284186X.2021.1937309.

Contents

1 Introduction

Cancer incidence and mortality are highly growing worldwide. Population growth and aging, as well as socioeconomic development, are the main factors involved. When considering both sexes, lung cancer is the most commonly diagnosed cancer and the leading cause of cancer deaths worldwide. Breast cancer, prostate cancer and colorectal cancer follow in incidence and colorectal, stomach and liver cancer in mortality (Bray et al., 2018).

Studies in high-income countries indicate that 30–40% of new cancer cases could be avoided by eliminating or reducing exposure to known lifestyle and environmental risk factors such as smoking, excess body weight, alcohol intake, physical inactivity, ultraviolet radiation and environmental carcinogens (Islami et al., 2018) (Krstic, Mijac, Popovic, Pavlovic Markovic, & Milosavljević, 2019). Because more than 80% of lung cancers are attributed to cigarette smoking in Western countries, primary prevention is crucial for the reduction of lung cancer. The benefits of not starting to smoke and of stopping smoking have been clearly demonstrated in studies (Pirie, Peto, Reeves, Green, & Beral, 2013) (Vineis & Wild, 2014). Along with primary prevention, secondary prevention by CT screening has been shown to decrease lung cancer mortality, suggesting that early diagnosis leads to improved outcomes for smokers (National Lung Screening Trial Research Team et al., 2013).

Early diagnosis of cancer is usually related to less advanced stages and increased chance for curation. Delays in diagnostics and treatment initiation may worsen the outcomes for the cancer patient. The role of diagnostic and treatment delays in lung cancer have been studied, and the results are mixed: different studies have reported positive, negative and no associations across a range of time intervals, and the results are similar for all cancer types. It remains unclear whether more timely care improves outcomes (Neal et al., 2015) (Jensen, Mainz, & Overgaard, 2002) (Olsson, Schultz, & Gould, 2009).

Lung cancer can be broadly classified into two histologic types: non-small-cell lung cancer (NSCLC) and small-cell lung cancer (SCLC). NSCLC is the most common type of lung cancer and comprises approximately 80–85% of all lung cancers (Suster & Mino-Kenudson, 2020). The NSCLCs are further divided into adenocarcinomas, squamous cell carcinomas, and large-cell carcinomas.

SCLC is the most aggressive form of lung cancer. The systemic treatment for patients with SCLC has not changed significantly in the past several decades, but the frequency has recently been decreasing in many countries. The five-year

survival rate remains low at < 7% overall, and most patients survive for one year or less after diagnosis. Most patients have extensive-stage disease at the time of diagnosis, rather than limited-stage disease. The doubling time of cancer is rapid, and the patient's condition deteriorates quickly. Unlike NSCLC, in which major advances have been made using targeted therapies, there are still no approved targeted therapies for SCLC. Chemotherapy resistance to second-line and later treatments is also a major issue when considering the poor outcomes of SCLC (Byers & Rudin, 2015). However, research aimed at improving SCLC outcomes is ongoing, and immunotherapy and perhaps targeted therapy may, in the future, give some hope for this desperate disease (Yang, S., Zhang, & Wang, 2019).

Targeted therapy and immunotherapy have changed the treatment paradigm of non-small-cell lung cancer. Since the early 2000s, the identification of targetable mutations in NSCLC has allowed patients with advanced or metastatic disease to delay chemotherapy and instead be treated with medications, namely tyrosine kinase inhibitors (TKIs), designed to block the oncogenic driver (Hirsch et al., 2017). NSCLC shows a high degree of genomic complexity but clinically relevant molecular alterations with available targeted therapies is a smaller group. These clinically relevant molecular alterations include, for example, EGFR, ALK, ROS1 and NTRK (Suster & Mino-Kenudson, 2020). The use of these targeted therapies has led to unprecedented survival benefits in selected patients. Similarly, immune checkpoint inhibitors (ICIs) have dramatically changed the landscape of NSCLC treatment. Furthermore, the role of these novel agents and the patients that are more likely to benefit from the treatment remains unclear and needs to be studied to improve future clinical outcomes for lung cancer patients.

EGFR TKIs have dramatically improved survival in NSCLC, especially in patients with sensitizing EGFR mutations, but they are associated with significant and disabling side effects that adversely affect quality of life and treatment compliance. These effects include dermatological reactions, diarrhoea, hepatotoxicity, stomatitis, interstitial lung disease and ocular toxicity. On the other hand, many studies have reported better outcomes in patients with skin reactions compared with those without. Management of these side effects is vital, and pre-emptive treatment seems to be more effective than reactive treatment (Shah & Shah, 2019). Yet, EGFR TKIs are usually more tolerable treatments than chemotherapy for many patients, and the treatment can be continued longer – sometimes over a year.

The purpose of this thesis is to deepen the knowledge surrounding diagnostics and treatment of lung cancer in Finnish patients and to improve the outcome of the

disease. These studies aimed to examine lung cancer prognosis in two distinct aspects. One was the diagnostic pathway of lung cancer and the association of diagnostic delays with survival, and the other was the survival of NSCLC patients treated with EGFR TKIs and the management of TKI-induced side effects using tetracyclines and topical corticoids.

2 Review of the literature

2.1 Lung cancer

2.1.1 Epidemiology of lung cancer

Lung cancer is the leading cause of cancer incidence and mortality worldwide, with approximately 2.1 million new lung cancer cases and 1.8 million deaths per year. Incidence is higher in males than in females. The highest incidence rates among men are observed in Asia and in the majority of the European countries and among females in North America and Northern and Western Europe (Bray et al., 2018). According to the Finnish Cancer Registry, approximately 2,800 new cases are diagnosed every year in Finland. The incidence among men has been decreasing since the 1970s but has been increasing among women due to increased smoking (Suomen syöpärekisteri, 2019).

Lung cancer is usually found in an advanced stage at the time of diagnosis. Fifty-seven percent of these patients have a metastatic disease, 22% regional and only 16% localized. Five-year survival rates are 4.7%, 29.7% and 56.3%, respectively (Schabath & Cote, 2019).

Several demographic factors have been identified to influence lung cancer development and outcomes, including gender, age, race, geography and socioeconomic status (Bade & Dela Cruz, 2020). Women tend to be diagnosed at a younger age, are more likely to be non-smokers and have more adenocarcinomas. The median age at lung cancer diagnosis is 70 years, and the median age at lung cancer death is 72 years (Bade & Dela Cruz, 2020). Lower socioeconomic status and education contribute to lung cancer risk and worse outcomes, particularly in men in Finland and worldwide (Suomen syöpärekisteri, 2019) (Bade & Dela Cruz, 2020). It appears that the individual's risk of developing and surviving lung cancer is the result of a complex relationship involving all of the aforementioned factors (Bade & Dela Cruz, 2020).

2.1.2 Etiology of lung cancer

Smoking is the leading risk factor of lung cancer. Globally, fifty-five percent of lung cancer deaths in women and over 70% in men are due to smoking. The relative risk of lung cancer in a smoker is estimated to be about twentyfold higher than that

of a never-smoker. The risk of smoking-related lung cancer increases according to the number of cigarettes smoked per day and the number of years smoked (Schabath & Cote, 2019) (O'Keeffe et al., 2018). Secondhand smoke exposure increases the risk of lung cancer as well; according to a meta-analysis published in 2018, the risk was 25% higher compared to non-exposure for non-smokers (Kim, Ko, Kwon, & Lee, 2018). In addition, there are numerous other exposures that are causally linked to lung cancer risk, including radon, asbestos, air pollution and some other carcinogenic agents. Infections like tuberculosis, HIV and chlamydia, pneumonia, pre-existing lung disease and inherited genetic susceptibility can also increase the risk of lung cancer (Schabath & Cote, 2019). It is estimated that the heritability of lung cancer is 18%, but many of the genetic components remain unidentified (Timofeeva et al., 2012). Genes like ATM, CXCR2, CYP1A1, CYP2E1, ERCC1, ERCC2, FGFR4, SOD2, TERT and TP53 exhibit significant associations with lung cancer susceptibility (Wang et al., 2017). Furthermore, linkage studies have identified an association of nicotine signalling–related genes to lung cancer incidence (Brennan, Hainaut, & Boffetta, 2011). Nicotine is responsible for maintaining smoking behaviour, and variation in nicotine metabolism is an important contributor to ethnic and individual differences in lung cancer risk. For example, many studies have reported an association between CYP2A6 variants and the risk of a smoker developing lung cancer (Murphy, 2021). In the future, it might be possible to target high-risk subgroups of lung cancer for specific interventions, including intensive efforts at smoking cessation, screening and prevention programs (Bade & Dela Cruz, 2020).

Globally, approximately 25% of lung cancer diagnoses are among never-smokers, and the aforementioned risk factors, smoking excluded, play a significant role for them, as well as advanced age. With never-smokers, the histology of cancer is most likely adenocarcinoma, and genetic alterations involving EGFR and ALK genes are frequent (Schabath & Cote, 2019).

2.1.3 Prevention of lung cancer

From a population health perspective, continued actions to promote tobacco smoking avoidance or cessation, protect workers from known inhaled carcinogens and maintain clean air are needed to decrease the risk of lung cancer. It is also likely beneficial to maintain a healthy body weight, increased physical activity, and a healthy diet (Bade & Dela Cruz, 2020).

2.1.4 Lung cancer screening

According to a meta-analysis from 2016, there was no benefit of chest radiology (CXR) screening, with or without sputum cytology (SC), for lung cancer mortality. Recent evidence instead showed that in selected high-risk individuals, low-dose computed tomography (LDCT) screening significantly reduced lung cancer mortality and all-cause mortality. The data from the National Lung Screening Trial (NLST) indicate that offering a LDCT screening program for patients aged 55–74 years with ≥ 30 pack-year history of cigarette smoking could provide as much as a 20% reduction in lung cancer mortality. Screening is also associated with notable harms, including over-diagnosis, false positives and consequences of false positives, like patients experiencing major complications as a result of invasive follow-up diagnostic procedures (Usman Ali et al., 2016) (Reduced lung-cancer mortality with low-dose computed tomographic screening, 2011).

The recently presented NELSON trial, a population-based, randomized, controlled trial initiated in 2000, found that lung cancer–related mortality was 24% lower among current and former smokers who underwent repeated computed tomographic (CT)–based screening than among those who underwent no screening at a 10-year follow-up. In that trial, the over-diagnosis rate was 19.7% at 10 years after randomization and only 8.9% at 11 years after randomization (de Koning et al., 2020).

Healthcare costs and cost effectiveness of screening should also be considered when evaluating benefits of screening. It is estimated that, according to NLST screening criteria, there would be approximately 125,100 people to be screened in Finland. It is suggested that a smoking cessation program and spirometry should be integrated as part of the screening program, as smoking cessation remains the most effective way to reduce lung cancer incidence (Pedersen et al., 2017).

2.2 Histology and molecular biology of lung cancer

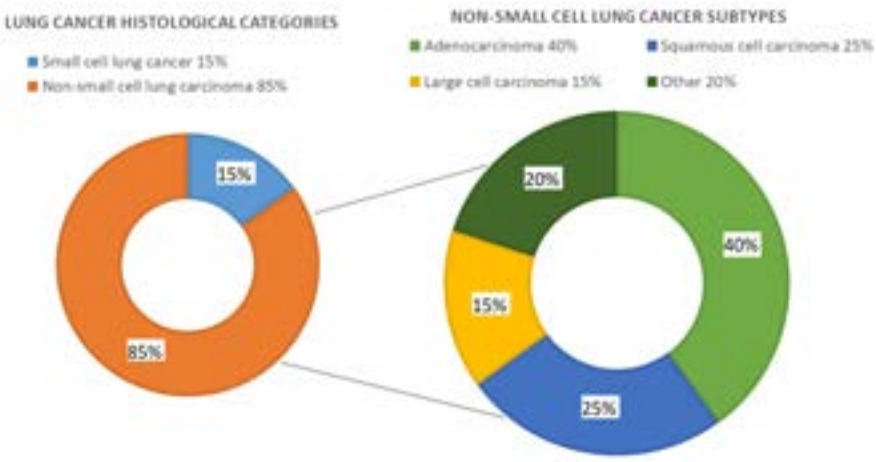

Fig. 1. Histological classification of lung cancer.

2.2.1 NSCLC

Of all lung cancers, 80–85% are non-small-cell lung carcinomas (NSCLC), which predominantly comprise adenocarcinoma (ADC), squamous cell carcinoma (SCC) and large cell carcinoma (LCC), along with smaller subtypes such as adenosquamous carcinoma, pleomorphic sarcomatoid carcinoma, large-cell neuroendocrine carcinoma and carcinoid tumour (Schabath & Cote, 2019). Adenocarcinomas tend to grow toward the periphery of the lung and have a greater tendency to metastasize than squamous cell carcinomas. Squamous cell carcinomas are the most likely to remain centrally located. Some types of NSCLC harbour specific genetic alterations that are amenable to targeted therapeutic agents (Suster & Mino-Kenudson, 2020).

EGFR-activating mutations

In 2004, Lynch et al. and Paez et al. reported the discovery of EGFR mutations in a selected subgroup of NSCLC patients. In the same year, the FDA approved erlotinib in unselected patients with advanced NSCLC after chemotherapy. Later, the superiority of EGFR TKIs in EGFR-mutated patients was found (Russo et al.,

2015). EGFR mutations occur in 10–20% of NSCLC patients (up to 40% for Asian patients) and mostly in adenocarcinoma, as well as in younger women, never-smokers and with lepidic or papillary histology.

EGFR is a transmembrane protein that stimulates intracellular protein-tyrosine kinase activity. Mutations in the tyrosine kinase domain of the EGFR gene lead to constitutive receptor activation, with its downstream signalling eventually leading to uncontrolled cell division. In-frame deletion on exon 19 (del 19) and L858R point mutation on exon 21 are the most common sensitizing mutations to TKIs (Suster & Mino-Kenudson, 2020). On the other hand, EGFR T790M point mutation on exon 20 confers resistance to older TKIs, but third-generation TKIs, such as osimertinib, are also effective for this mutation (Yi, Fan, Qian, Luo, & Zhang, 2019). There are also numerous other rare EGFR mutations which lead to constitutive activation of the receptor but have variable sensitivity to EGFR TKIs (such as ex20 insertion).

ALK rearrangements

Genetic alterations in the anaplastic lymphoma receptor kinase (ALK) occur in 2–7% of NSCLC patients. ALK rearrangement appears to be more common in younger patients and never- or light smokers diagnosed with adenocarcinoma or mucinous cribriform histology (Suster & Mino-Kenudson, 2020). ALK rearrangements create an oncogenic ALK tyrosine kinase that activates downstream signalling pathways resulting in increased cell proliferation and survival. ALK inhibitors (first-, second- and third-generation TKIs) are widely used for ALK-positive NSCLC (Thai & Solomon, 2018).

Other alterations

ROS1, BRAF, HER2, RET, MET and NTRK are other mutations and rearrangements that are clinically relevant, targetable or potentially targetable in NSCLC. There are also numerous other mutations and rearrangements that are currently clinically irrelevant but under investigation (Suster & Mino-Kenudson, 2020).

2.2.2 SCLC

Small-cell lung cancer (SCLC) is an aggressive disease that accounts for 13–15% of all lung cancer and has a tendency for early dissemination, resulting in 80–85% of patients being diagnosed with extensive disease. SCLC tends to originate in central locations and grow rapidly (Saltos, Shafique, & Chiappori, 2020).

SCLC is a highly complex disease at the molecular level, with a large number of mutations present in each tumour, and has in fact one of the highest tumour mutational burdens (TMB) of all cancers. Genomic profiling has identified a lack of functional p53 and Rb1 genes and amplification of the MYC oncogene in the vast majority of SCLC tumours. These defective tumour suppressor genes, along with aberrant expression of the MYC oncogene, lead to a rapid proliferation of tumour cells, while attempts to target these genomic alterations have repeatedly failed (Peifer et al., 2012) (Saltos et al., 2020) (Taniguchi, Sen, & Rudin, 2020). Recent gene expression profiling has led to the proposal of four different types of SCLC distinguished by four key transcriptional regulators – ASCL1, NEUROD1, POU2F3 and YAP1 – but the therapeutic options remain dismal for SCLC (Taniguchi et al., 2020) (Baine et al., 2020).

2.3 Diagnostics of lung cancer

2.3.1 Symptoms

There are no signs or symptoms that are specifically diagnostic to lung cancer. Symptoms typically appear late and indicate advanced disease. The most common symptoms are cough, dyspnoea, pain, weight loss, haemoptysis and fatigue. However, over 20% of lung cancers are diagnosed in asymptomatic patients (Cersosimo, 2002).

2.3.2 Radiology

The first test to evaluate a patient suspected of lung cancer is usually chest radiography (CXR). The results may reveal a mass, lymph node enlargement, pleural effusion or lung collapse. CXR is a basic examination and should be performed whenever a patient has symptoms that could indicate lung cancer, although a normal CXR does not rule out lung cancer (Cersosimo, 2002).

A contrast-enhanced CT scan of the chest and upper abdomen or the whole body should be carried out as a baseline imaging. Imaging of the central nervous system by CT scan or MRI is most relevant for patients with neurological symptoms or signs, with MRI being more sensitive and more expensive than CT (Planchard et al., 2018). Bone imaging is required if bone metastases are clinically suspected and can be done by bone scan (Chang et al., 2012). Bone metastases can, however, be seen in a CT scan or FDG-PET-CT; and if so, a bone scan is not needed.

FDG-PET-CT scan has a high sensitivity for the evaluation of solitary pulmonary nodules, intrathoracic pathological lymph nodes and distant metastasis, and the combined use of FDG-PET with CT imaging has a major impact on diagnosis and staging of NSCLC. The advantage of FDG-PET-CT imaging is a high sensitivity for detecting pulmonary lesions (90%), metastases in normal-sized hilar and/or mediastinal lymph nodes (74–85%) and distant metastases (93%). This permits better selection of patients eligible for surgery or definitive radiotherapy with curative intent (Grootjans et al., 2015). Limitations to FDG-PET-CT use include nonmalignant inflammatory disorders that can demonstrate FDG uptake and the low sensitivity of this exam in small tumour lesions, as well as limited availability (Planchard et al., 2018).

2.3.3 Microscopic diagnosis

Most patients with suspected lung cancer require a tissue-based diagnosis. Tissue and cytological specimens are needed to confirm the diagnosis, elucidate the histologic type of lung cancer and determine the extent of the cancer, as well as increasingly for the molecular biological investigations required for drug therapy planning.

Molecular profiling (primarily in non-squamous cancers) has become standard in clinical practice in NSCLC. The least invasive method possible for accurate diagnosis should be used. However, minimally invasive approaches often yield only small biopsy specimens and can lead to additional approaches (Rivera, Mehta, & Wahidi, 2013) (Dietel et al., 2016). A histological sample provides better conditions for accurate diagnosis than a cytological sample (Robertson, Steliga, Siegel, & Arnaoutakis, 2014). Cytological samples can be taken by fine needle aspiration from a tumour or metastasis, sputum or pleural fluid, or cytological wash and brushing in bronchoscopy, while histological samples are obtained by core needle biopsy or surgical biopsy. A biopsy can also be taken via bronchoscopy when the tumour is intrabronchial (Rivera et al., 2013).

Sputum cytology is one method of establishing a diagnosis of lung cancer, but the sensitivity is very low and varies by location of the lung cancer; moreover, it should not be used as a single method unless other samples are unavailable and findings refer to SCLC or SCC only (Rivera et al., 2013). Sputum cytology is rarely used in lung cancer diagnostics today.

One of the most common diagnostic tests for lung cancer is fibreoptic bronchoscopy. For central endobronchial lesions, the overall sensitivity of bronchoscopy for diagnosing lung cancer is 88%, but for peripheral lesions the sensitivity is much lower, especially for lesions < 2 cm in diameter (Rivera et al., 2013). Endobronchial ultrasound (EBUS) is helpful for lymph node staging of the mediastinum and is not as invasive as mediastinoscopy (Sampsonas, Kakoullis, Lykouras, Karkoulias, & Spiropoulos, 2018). EBUS has a diagnostic yield of 93% and a specificity of 100% (Rivera et al., 2013).

CT scan–guided transthoracic biopsy is a sensitive method (sensitivity approximately 90%) and usually gives enough tissue for tumour sampling, but patients' risk of complications, such as pneumothorax and haemothorax, must be taken into account. Biopsy can sometimes be taken by thoracoscopy as well as from a metastatic lesion through ultrasound or CT scan guidance (Rivera et al., 2013).

When tumour tissues are difficult to reach, or when multiple analyses are necessary to monitor tumour progression and treatment response, liquid biopsy is a valid noninvasive alternative. In liquid biopsy, circulating tumour DNA (ctDNA) is extracted from plasma samples and analysed through, for example, PCR or NGS-based methods. Critically, not all tumours shed sufficient amounts of DNA into peripheral circulation for detection, and even the most sensitive of assays appear to achieve approximately 85% sensitivity in advanced stage disease. Liquid biopsy is not by far used in primary diagnostics (Rolfo et al., 2018).

2.3.4 Pathology and molecular characterization

The pathological classification at diagnosis may influence initial treatment decisions such as the initial surgical approach. As much tumour tissue as possible enables better diagnosis and classification as early as possible in the trajectory to therapeutic decisions. The rate of not otherwise specified (NOS) diagnosis after the complete diagnostic workup should be < 10% (Postmus et al., 2017).

Table 1. Diagnostics of lung cancer.

Method	Findings
Imaging	
Chest radiography	Primary tumour
CT scan	Primary tumour, nodes, metastasis
Cranial CT/MRI	Intracranial metastasis
Bone scan	Bone metastasis
FDG-PET-CT	Primary tumour, nodes, metastasis
Sampling	
Sputum cytology	Cytological samples
Pleural fluid sample	Cytological samples
Bronchoscopy	Cytological or histological samples
EBUS	Fine needle biopsy
Mediastinoscopy	Surgical tumour specimen
CT-guided biopsy	Core or fine needle biopsy
Performance status	
Spirometry and diffusion capacity	Respiratory functions
Exercise test	Cardiorespiratory capacity

The majority of NSCLC cases can be subclassified based on histomorphological examination using haematocyclin and eosin staining, but, quite often, immunohistochemistry (IHC) is needed for diagnosis and determination of the tumour subtype. The most commonly used IHC markers for the classification of NSCLCs are TTF-1, Napsin A, CK5/6, P63 and P40 (Osmani, Askin, Gabrielson, & Li, 2018).

EGFR mutations are generally identified with the use of gene sequencing methodologies and real-time polymerase chain reaction (PCR)-based assays, and both methods have demonstrated high performance and sensitivity (Villalobos & Wistuba, 2017). Detecting ALK fusion genes and their results includes break-apart fluorescence in situ hybridization (FISH) and IHC, and when combining these two tests, the results are optimized. Other methods, like reverse-transcription PCR (RT-PCR) and next-generation sequencing (NGS), are also in use. Other alterations (ROS1, KRAS, BRAF, NTRK, etc.) can be identified using different methods, for example, NGS assays (Villalobos & Wistuba, 2017).

Immunotherapy with anti–PD-L1 or anti–PD-1 antibodies stimulates the innate immune system to react to the tumour growth. PD-L1 protein expression can be detected by IHC analysis, and it seems to be the main predictive biomarker explored for response to anti–PD-1/PD-L1 immunotherapy. In NSCLC, PD-L1 is

recommended to be scored by the percentage of positive tumour cells (Yu, Boyle, Zhou, Rimm, & Hirsch, 2016).

SCLC is an aggressive, poorly differentiated and high-grade neuroendocrine carcinoma, and it is typically diagnosed in small biopsies or cytology specimens, with routine immunostaining only. The histological diagnosis is based mostly on haematoxylin and eosin (H&E) specimens, but IHC can sometimes be helpful in the differential diagnosis setting. Nevertheless, cytology is a highly reliable method to establish a SCLC diagnosis (Raso, Bota-Rabassedas, & Wistuba, 2021). In SCLC, a lack of adequate tissue for molecular profiling is a major issue. This is due to rare surgical resections in SCLC, small diagnostic biopsies and the absence of a validated biomarker for treatment selection. Because of this, molecular profiling in SCLC is not in clinical use (Byers & Rudin, 2015).

2.3.5 Staging

TNM (tumour, node, metastasis) staging of lung cancer is important for defining the extent of disease, consequently assigning prognosis and guiding treatment. TNM stage remains the most valuable prognostic factor in predicting recurrence rates and survival times, followed by tumour histologic grade and patient sex, age and performance status. Molecular prognostication in lung cancer is an exploding area of research, yet no molecular prognostic marker has been adopted into clinical use so far. Future prognostication of outcomes in lung cancer will likely be based on a combination of TNM stage and molecular tumour profiling and yield more precise, individualized survival estimates and treatment algorithms (Detterbeck, Boffa, Kim, & Tanoue, 2017).

The eighth edition of TNM in lung cancer was published in 2017 by the Union for International Cancer Control (UICC). TNM classification has three components: size of the primary tumour (T), regional lymph node(s) involvement (N) and distant metastases (M) (Brierley, Gospodarowicz, & Wittekind, 2017) (Table 2). The overall stage grouping (I–IV) is determined by the combination of T, N and M descriptors and is published by the International Association for the Study of Lung Cancer (IASLC) (Goldstraw et al., 2016) (Hwang et al., 2020) (Table 3).

Table 2. TNM classification of lung cancer.

TNM	Characteristics
T1	≤ 3 cm, not involving main bronchus
T1a(mi)	Minimally invasive carcinoma
T1a	≤ 1 cm
T1b	> 1 to ≤ 2 cm
T1c	> 2 to ≤ 3 cm
T2	> 3 to ≤ 5 cm or involvement of main bronchus
T2a	> 3 to ≤ 4 cm
T2b	> 4 to ≤ 5 cm
T3	> 5 to ≤ 7 cm or smaller tumour, with involvement of chest wall or pericardium
T4	> 7 cm or invasion of mediastinum, diaphragm, heart, great vessels, etc.
N	Nodal involvement
N1	Ipsilateral peribronchial and/or hilar nodes
N2	Ipsilateral mediastinal and/or subcarinal nodes
N3	Contralateral mediastinal or hilar nodes
M	Metastasis
M1a	Tumour in contralateral lung or malignant effusion
M1b	Single extrathoracic metastasis
M1c	Multiple extrathoracic metastases in one or more organs

Modified from Brierley et al., 2017

Table 3. Staging in lung cancer.

T/M	N0	N1	N2	N3
T1	IA	IIB	IIIA	IIIB
T2a	IB	IIB	IIIA	IIIB
T2b	IIA	IIB	IIIA	IIIB
T3	IIB	IIIA	IIIB	IIIC
T4	IIIA	IIIA	IIIB	IIIC
M1a	IVA	IVA	IVA	IVA
M1b	IVA	IVA	IVA	IVA
M1c	IVA	IVA	IVA	IVA

Modified from Hwang et al., 2020

2.3.6 Multidisciplinary team

Changes in the therapeutic scenario in the last 15 years have emphasized the need for a multidisciplinary approach to lung cancer. Treatment decisions should ideally be discussed within a multidisciplinary tumour (MDT) board consisting of specialists like a radiologist, respiratory physician, thoracic surgeon, oncologist and sometimes pathologist. MDT meetings enable patient management plans to be based on a board range of expert knowledge, and all aspects of treatment options can be considered. MDT meetings also provide a forum for discussion of patient dilemmas, cross-specialty education and development of peer-reviewed management plans (Ung, Campbell, Duplan, Ball, & David, 2016).

Several studies have demonstrated the benefits of the MDT approach, and results indicate that it is associated with changes in the staging and diagnosis of cancer, initial management plans, higher rates of treatment, shorter time to treatment after diagnosis, better survival and adherence to clinical guidelines (Pillay et al., 2016). In lung cancer, the data indicate improved patient outcomes with an MDT program compared to the standard model of care (Nemesure, Albano, & Bilfinger, 2020).

2.4 Diagnostic pathway and delays

In lung cancer, the diagnostic workup from the onset of symptoms to the time of diagnosis is often lengthy, with delays resulting from ongoing investigations and fragmented care. The interval between the discovery of symptoms and the time the patient is diagnosed and receives therapy can be divided roughly into patient delay and doctors' delay. A stage shift can occur while awaiting diagnostic investigations (Jensen et al., 2002). It is likely that earlier diagnosis leads to better clinical outcomes, as the five-year survival rate for stage I lung cancer is 40–80%, for stage II disease 26–42%, for stage III disease 9–20% and just 2–6% in stage IV lung cancer (Hwang et al., 2020).

Consensus-based standards for maximum acceptable waiting times for referral, diagnosis and treatment for lung cancer have been established. For example, the United Kingdom's National Institute for Health and Care Excellence (NICE) recommends 14 days to diagnosis and 28 days to treatment (National Collaborating Centre for Cancer, [UK], 2011) (Jacobsen et al., 2017). These recommendations are largely based on expert opinion with little evidence to guide them; meanwhile, these standards are not always upheld, and significant delays in lung cancer care

persist. A 2017 literature review estimated that 15–63% of patients do not receive treatment within 31 days of diagnosis (Jacobsen et al., 2017).

Timely lung cancer diagnosis and treatment requires quick and effective coordination across multiple disciplines, including primary care, radiology, pulmonology, oncology and surgery (Jacobsen et al., 2017). Some countries have developed rapid access programs or diagnostic assessment programs to improve diagnostic workup. They have been able to reduce the timelines for diagnostic procedures and decisions to treat and increase patient satisfaction. However, the impact of rapid access programs on survival is controversial. While timely care may contribute substantially to patients' quality of life and emotional well-being, it remains unclear whether timely care also improves patient outcomes, and the results are mixed and even paradoxical (Olsson et al., 2009) (Mullin et al., 2020) (Habbous et al., 2021) (Pattison et al., 2020).

There are several factors associated with timeliness of care. In many studies, patients with lower-stage lung cancer had the longest diagnosis-to-treatment intervals, presumably because patients with more advanced disease are more likely to have symptoms, which can prompt diagnostic workup. Patients with better performance status had longer times to treatment, which may be due to patients with poorer performance status being less likely to receive curative therapies, resulting in faster commencement of palliative care. Patients undergoing curative treatment may require additional cardiorespiratory workup to assess fitness prior to surgery or complex radiotherapy planning for curative radiotherapy, both of which can lengthen the time interval to the beginning of treatment (Vinod, Chandra, Berthelsen, & Descallar, 2017).

2.5 Treatment of early-stage NSCLC

When planning lung cancer treatment, many things must be taken into consideration: tumour histology, molecular pathology and stage, as well as the factors of the patient, such as age, performance status, comorbidities and cardiorespiratory functions. In non-metastatic lung cancer, the cardiopulmonary fitness of the patient will determine the choice of treatment. Preoperative diagnostic workup with PET-CT and invasive mediastinal staging (EBUS or mediastinoscopy) may identify patients at higher risk for the presence of regional lymph node metastases and should be done properly before choosing the treatment method for each patient.

Surgery is the recommended treatment for patients with stage I–II NSCLC (Hirsch et al., 2017). Surgical options include lobectomy, segmentectomy or wedge resection, and surgery can be done through standard open thoracotomy or video-assisted thoracoscopic surgery (VATS), which is most commonly used today. R0 resection is the main goal of the surgery with margin clearance and nodal dissection (Postmus et al., 2017).

For patients with clinical stage I NSCLC, who have medical contraindications, who refuse surgery or whose tumour is inoperable, high-dose stereotactic body radiation therapy (SABR) is an option and has resulted in high local tumour control and low toxicity. SABR is mainly used for tumours up to 5 cm and is recommended especially for peripheral tumours. Stereotactic body radiation uses highly sophisticated planning and delivery technology and is usually delivered in three fractions of 18 Gy to the target volume (Hirsch et al., 2017). Local control rates of SABR are 80–90% at five years (Lindberg et al., 2015). SABR is not appropriate for ultracentral tumours, as increased toxicity has been reported for this subgroup (Postmus et al., 2017).

One systematic review and meta-analysis assessed overall survival in matched and unmatched patient cohorts with NSCLC undergoing SBRT or surgery. The current evidence suggests that surgery is superior to SBRT in terms of mid- and long-term clinical outcomes. SBRT is associated with lower perioperative mortality. However, the long-term clinical outcomes favouring surgery may result from an imbalance in baseline patient characteristics, preoperative comorbidities or tumour characteristics, rather than treatment efficacy (Cao et al., 2019).

2.5.1 Adjuvant therapy

Nonetheless, even after an apparently complete resection, the risk of recurrence in lung cancer remains substantial. Most patients relapse in the form of distant rather than local disease. Adjuvant chemotherapy (AC) after surgery has been demonstrated to significantly improve median survival: 4–5% absolute increase in five-year survival, according to a published meta-analysis, when cisplatin-based regimens are used for patients with pathologic stages II and III after surgery with curative intent. AC is not recommended for stages IA and IB (TNM 8th). The dose of cisplatin should be at least 300 mg/m^2 in three to four cycles, and the interval between surgery and the start of adjuvant chemotherapy is restricted to 6–8 weeks in most studies (Artal Cortés, Calera Urquizu, & Hernando Cubero, 2015).

Postoperative radiotherapy for patients with completely resected NSCLC is not recommended. The combined results of a PORT meta-analysis revealed a significant adverse effect of postoperative radiotherapy on survival and a 21% relative increase in the risk of death. The results for stage III and N2 patients were slightly in favour of postoperative radiotherapy, and postoperative radiotherapy after an R1 resection appears reasonable, but it is not supported by high-quality evidence (Postoperative radiotherapy in non-small-cell lung cancer: Systematic review and meta-analysis of individual patient data from nine randomized controlled trials, PORT meta-analysis trialists group, 1998) (Postmus et al., 2017).

The role of targeted therapies in the adjuvant setting is not defined. At present, the choice of adjuvant therapy should not be guided by molecular analyses, and targeted agents should not be used in the adjuvant setting. Results from the placebo-controlled RADIANT study revealed no benefit from the use of adjuvant EGFR TKI erlotinib, either for the whole population or for the EGFR mutant subgroup (Kelly et al., 2015). Some other, more recent studies have shown a disease-free survival (DFS) advantage for adjuvant TKI-treated patients, but data on overall survival is still missing (Yue et al., 2018) (Wu et al., 2020). According to an ADAURA trial (Wu et al., 2020), in patients with completely resected stage IB to IIIA EGFR mutation–positive NSCLC, disease-free survival was significantly longer among those who received osimertinib than among those who received the placebo. Osimertinib has recently been approved in this indication by the FDA and EMA.

2.6 Treatment of locally advanced NSCLC

All NSCLC patients with stage III disease that are planned for definitive treatment should undergo a PET-CT and brain MRI/CT to rule out detectable extrathoracic, extra- or intracranial metastasis and to assess potential mediastinal lymph node involvement. Furthermore, invasive mediastinal staging may provide an additional benefit in verifying or excluding mediastinal lymph node involvement of the cancer. It is recommended that single PET-positive distant lesions should be pathologically confirmed (Postmus et al., 2017). Locally advanced diseases should especially be discussed within a multidisciplinary tumour board, as treatment options are manifold and dependent on tumour staging.

Stage III NSCLC might be resectable if there are only single-station N2 disease or T3-4N0-1 tumours when a R0 resection is considered to be feasible. The role of neoadjuvant chemotherapy in this setting is controversial. Neoadjuvant

chemotherapy can potentially downstage the disease, thereby improving the feasibility of complete resection, but complete resection rates were generally similar in patients receiving neoadjuvant chemotherapy versus upfront surgery in several randomized trials (Myall & Das, 2020).

Patients with stage IIIA/B unresectable NSCLC and with good performance status should be treated with concurrent platinum-based doublet chemoradiotherapy, with two to four cycles of concomitant platinum doublet chemotherapy (Postmus et al., 2017) (Senan et al., 2016). The recommended total radiotherapy dose is 60–66 Gy, with CT-based planning and three-dimensional planning, and delivery or intensity-modulated radiation therapy should be used (Bradley et al., 2015). Five-year survival for these patients is approximately 15–20% (Hirsch et al., 2017).

Consolidation therapy

In the PACIFIC trial, phase 3 and placebo-controlled, stage IIII NSCLC patients treated with concurrent chemoradiotherapy were given consolidation therapy with durvalumab up to 12 months, and significant improvements in overall survival (OS) and progression-free survival (PFS) were observed when PD-L1 expression was > 1% (Paz-Ares, Spira et al., 2020). An estimated 49.6% of patients randomized to durvalumab remained alive at four years, compared to the placebo at 36.3% (Faivre-Finn et al., 2021). Consolidation therapy with durvalumab up to 12 months is recommended for patients who have received concurrent chemoradiotherapy, have no disease progression afterward and have a performance status of 0–1 (Ettinger et al., 2021).

2.7 Treatment of advanced NSCLC

Stage I–III patients, who are not suitable for definitive treatment, and stage IV patients are treated less intensively. Performance status, age and comorbidities of the patient, as well as tumour molecular biology and the patient's preferences, dictate the choice of treatment. The purpose of the treatment is to ease lung cancer symptoms and to improve quality of life and survival.

2.7.1 Chemotherapy

Chemotherapy with platinum doublets should be considered in all stage IV NSCLC patients without an actionable oncogenic driver, without major comorbidities and with performance status 0–2. Benefits of chemotherapy versus best supportive care (BSC) have been demonstrated in meta-analyses, with hazard ratio (HR) 0.77 (Non-Small Cell Lung Cancer Collaborative Group, 2010). Four to a maximum of six cycles of chemotherapy are recommended. Carboplatin is as effective as cisplatin, as there seems to be no difference in OS (Planchard et al., 2018). According to a PARAMOUNT trial, patients with non-squamous NSCLC might benefit from continued maintenance with pemetrexed after induction therapy with platinum doublet. There was a significant reduction in the risk of disease progression over the placebo group, HR = 0.62 (Paz-Ares et al., 2012).

Docetaxel and pemetrexed (pemetrexed for non-squamous NSCLC only) are confirmed treatment options in second-line chemotherapy for NSCLC, with comparable efficacy (Hanna et al., 2004).

2.7.2 Immunotherapy

Immune checkpoint inhibitors (ICIs) have been shown to improve survival in advanced NSCLC. ICIs work by boosting the body's natural tumour killing response by modulating T-cell function. These agents may also promote T-cell attack on self-antigens, which can lead to toxicities labelled as immune-related adverse events, like colitis, hypophysitis, pneumonitis, thyroiditis and inflammatory arthritis (Assi, Kamphorst, Moukalled, & Ramalingam, 2018). Patients with severe preexisting autoimmune disorders should not be treated with ICIs because they can cause autoimmune disease flare-ups, and these patients might be more sensitive to immune-related adverse events in general. Nevertheless, the data on this is limited because patients with autoimmune disease are typically excluded from immunotherapy clinical trials (Brahmer et al., 2018).

The efficacy of PD-1 checkpoint inhibition for NSCLC has been correlated with smoking history, tumour mutational load and neoantigen burden. Several studies have demonstrated that PD-L1 expression in the tumour microenvironment may increase the likelihood of clinical benefit, but it is neither fully sensitive nor a specific biomarker. Testing for tumour mutational burden is not currently in clinical use but might be in the future. Finding a good predictive biomarker for immunotherapy would be essential to identify patients who will most likely benefit

from therapy. Immunotherapy is expensive, and the optimal use of treatment is not yet clear (Brahmer et al., 2018).

Pembrolizumab or atezolizumab should be considered as standard first-line options for patients with advanced NSCLC and PD-L1 expression ≥ 50% and who do not have contraindications for ICIs. In studies (KEYNOTE-042, Impower110), the OS benefit was driven by patients with ≥ 50% PD-L1 expression, and the median OS (mOS) nearly doubled by immunotherapy compared to chemotherapy, with pembrolizumab 30 versus 14 months and atezolizumab 20 versus 13 months, respectively (Reck et al., 2019) (Herbst et al., 2020).

Patients with non-squamous cell NSCLC without actionable mutations and PD-L1 < 50% should be considered for combination therapy with pembrolizumab and pemetrexed plus carboplatin. In a KEYNOTE-189 study, combination therapy demonstrated better OS and PFS compared to the placebo-combination group, with HR 0.56 and 0.48. In this study, patients received combination therapy for four cycles, followed by pemetrexed maintenance plus pembrolizumab or placebo for up to a total of 35 cycles. Costs and toxicity are apparently greater in combination therapy (Gadgeel et al., 2020).

Analogously to non-squamous histology, patients with squamous cell NSCLC without actionable mutations and PD-L1 < 50% should be considered for combination therapy with pembrolizumab and carboplatin plus nab-paclitaxel/paclitaxel. In a KEYNOTE-407 study, combination therapy showed a clinically meaningful improvement over placebo plus chemotherapy in OS and PFS, with HR 0.71 and 0.57 (Paz-Ares, Vicente et al., 2020). Furthermore, first-line nivolumab plus ipilimumab combined with two cycles of chemotherapy compared to chemotherapy only yielded improved overall survival in patients with advanced NSCLC, with HR 0.66 (Paz-Ares et al., 2021) The position of this quadruplet therapy remains to be settled since it may have greater side effects and costs compared to pembrolizumab-based combinations.

Second-line immunotherapy with nivolumab, pembrolizumab and atezolizumab remains a therapeutic option in advanced NSCLC. This treatment should be reserved for those patients who were previously treated with chemotherapy and have no contraindications for immunotherapy, irrespective of PD-L1 expression (Planchard et al., 2018).

2.7.3 EGFR TKIs

EGFR is a receptor tyrosine kinase within the ErbB family consisting of four members: EGFR (ErbB1, HER1), ErbB2 (HER2), ErbB3 (HER3) and ErbB4 (HER4). Activation and expression of the epidermal growth factor receptor leads to cell proliferation, differentiation and survival. In cancer, EGFR signalling is often deregulated and leads to treatment resistance of the tumour and poor survival of patients. EGFR TKIs inhibit the EGFR signalling and prevent EGFR expression and dimerization (Jutten & Rouschop, 2014).

The EGFR receptor can be constitutively activated in the tumours by mutations in the tyrosine kinase domain of the receptor. The most common of the activating EGFR mutations are exon 19 deletion and L858R, which construct 90% of all and predict sensitivity to EGFR TKIs. Other mutations, such as the EGFR T790M point mutation on exon 20 or exon 20 insertions, confer resistance to TKIs (Suster & Mino-Kenudson, 2020).

The first-generation reversible EGFR TKIs, erlotinib and gefitinib, were developed before the identification of mutations and were first studied in an unselected patient population. They improved OS (erlotinib) and had a tendency toward improved survival (gefitinib) compared to BSC (Shepherd et al., 2005) (Thatcher et al., 2005). It was later found that EGFR mutation is the most important predictor of the benefit of response to therapy with an EGFR TKI. In a 2015 meta-analysis, in patients with exon 19 deletions, the pooled HR for PFS was 0.24, and in patients with exon 21 L858R substitution, the pooled HR for PFS was 0.48 compared to platinum doublet therapy. It was also observed that never-smokers and women received greater benefits from the treatment than smokers and men (Lee et al., 2015). There is limited evidence for increased OS for the TKIs when compared with standard chemotherapy, but most trials have allowed participants to switch treatments on disease progression, which will have a confounding effect on any OS analysis (Greenhalgh et al., 2021).

The second-generation irreversible TKIs afatinib and dacomitinib have shown improved PFS compared to gefitinib (Paz-Ares et al., 2017) (Wu et al., 2017).

Osimertinib is a third-generation EGFR TKI that selectively inhibits both EGFR–TKI–sensitizing and T790M resistance mutations. T790M point mutation is detected in 50% or more of the patients who have disease progression after first- or second-generation TKIs. Osimertinib was first tested in a T790M+ setting, where it improved PFS compared to chemotherapy (Mok et al., 2017). In the FLAURA study, the median progression-free survival was 18.9 months in the osimertinib

group and 10.2 months in the standard EGFR TKI group in a first-line setting. In addition, patients with known or treated CNS metastases were included in the trial, and the objective response rate and median duration of response were in line with the values in the overall population (Soria et al., 2018). The median overall survival was better in the osimertinib group, with HR 0.80 compared to the standard EGFR TKI group and the median exposure for treatment was 20.7 months and 11.5 months, respectively. (Ramalingam et al., 2020).

Patients who benefit from EGFR TKI treatment may continue to receive the same therapy beyond initial radiological progression as long as they are clinically stable. Almost all patients who benefit from EGFR TKIs will eventually develop clinical resistance. If first- or second-generation TKIs were used in the first-line setting, osimertinib can be used in second-line therapy, if there is a proven T790M mutation at the time of progression (Planchard et al., 2018).

Table 4. EGFR TKIs.

Generation	EGFR inhibition	Drug	Molecular targets	Adverse event
1st	Reversible	Gefitinib	EGFR del19, L858R	Rash, abnormal LFT
1st	Reversible	Erlotinib	EGFR del19, L858R	Rash, diarrhoea
2nd	Irreversible	Afatinib	EGFR del19, L858R, uncommon mutations, HER2, HER4	Diarrhoea, paronychia, rash
2nd	Irreversible	Dacomitinib	EGFR del19, L858R, HER2, HER4	Diarrhoea, rash
3rd	Irreversible	Osimertinib	EGFR mutations, T790M	Diarrhoea, rash

Modified from Wu et al., 2018

Adverse events of EGFR TKIs

The safety profile for EGFR TKIs is manageable and predictable, indicating that proactive supportive treatment and dose modification are adequate managements for the side effects associated with EGFR inhibition. EGFR TKIs are usually well tolerated and are rarely discontinued because of treatment-related adverse events (TRAEs). The risk for discontinuation because of TRAEs is approximately 7–8% (Ding et al., 2017).

The most common adverse events for EGFR TKIs are rash (66%), diarrhoea (53%), stomatitis, paronychia, dry skin, liver dysfunction, and interstitial lung disease. There are differences between different TKIs' adverse events. Afatinib has

the greatest probability of causing rash, diarrhoea and stomatitis; dacomitinib is associated with the highest risk of paronychia, dry skin and interstitial lung disease; and gefitinib has the greatest risk of liver dysfunction. Afatinib is associated with the most adverse events of grade 3 or higher, compared with other EGFR TKIs. Osimertinib is well tolerated among all TKIs (Zhao et al., 2019).

EGFR TKI–induced rash

Many studies have reported better outcomes in patients with skin reactions compared with those without. EGFR is widely expressed by epithelial cells in skin, where it stimulates epidermal growth and accelerates wound healing. Inhibition of EGFR has negative impacts for skin, such as premature differentiation, inducing inflammation and apoptosis, skin atrophy, telangiectasia and photosensitivity. The most common manifestation is an acneiform rash. Rash usually appears within two to four weeks of initiating therapy but can also be earlier or delayed, and it can have a major impact on the quality of life for these patients (Petrelli, Borgonovo, Cabiddu, Lonati, & Barni, 2012) (Liu et al., 2013) (Table 5).

Skin reactions following EGFR TKIs are believed to result from an effect on wild-type EGFR, and their efficacy is related to effects on mutant variants of EGFR. Third-generation EGFR TKIs that spare wild-type EGFR are associated with fewer dermatological reactions (Shah & Shah, 2019).

For severe dermatological reactions, it is recommended to discontinue the use of EGFR TKI. For less severe toxicity, therapeutic options include the use of moisturizers and avoidance of sun exposure and irritants. Many studies have reported that pre-emptive treatment is more effective than reactive treatment by limiting the incidence and severity of dermatological reactions (Hofheinz et al., 2016) (Melosky et al., 2016). The prophylactic use of antibiotics, like tetracyclines, may reduce the relative risk of severe rash associated with EGFR-targeted agents by 42–77% (Ocvirk, Heeger, McCloud, & Hofheinz, 2013). Furthermore, topical treatments like sunlight protection, skin care with hydrophilic cream and topical corticosteroids can be recommended for prophylactic and reactive use (Hofheinz et al., 2016) (Petrelli et al., 2016).

Table 5. EGFR TKI–induced dermatological toxicity.

Organ site	Clinical manifestation	Onset from the start of TKI
Skin		
	Acneiform rash (papulopustular rash)	~2 weeks
	Erythema	~2 weeks
	Photosensitivity	~2 weeks
	Pruritus	~2 weeks
	Xerosis	2-3 weeks
	Fissures and cracks	2-3 months
Nail		
	Paronychia	2-3 months
Hair		
	Alopecia	2-3 months
	Hypertrichosis	2-5 months
Eye		
	Conjunctivitis, blepharitis	2-5 months
	Xerotic	2-3 weeks

Modified from Ocvirk et al., 2013

2.7.4 Other targeted therapy

Alectinib is the first-line treatment in ALK-rearranged advanced NSCLC, with a superior survival rate of 62.5% compared to crizotinib (45.5%) (Mok et al., 2020). Brigatinib also appears to be more effective than crizotinib in a first-line setting (Camidge et al., 2020). If crizotinib has been used in first line, alectinib or brigatinib can be used as a second-line therapy. Lorlatinib is a next-generation TKI that seems to be effective after first- or second-generation ALK TKIs (Solomon et al., 2018).

Crizotinib is recommended in the first-line setting or as a second line in patients with stage IV NSCLC with ROS1 rearrangement. Trials of other TKIs in this setting are ongoing. BRAF/MEK inhibition using dabrafenib with trametinib can be used in patients with stage IV NSCLC with BRAF V600E mutation. Several other, more rare, molecular targets have been identified harbouring somatic variants with therapeutic potential, including RET, MET, HER2 and NTRK, and several trials are performing ongoing investigations (Planchard et al., 2018).

2.8 Treatment of SCLC

2.8.1 Treatment of limited-stage SCLC

Surgery does not play a significant role in the management of stage I–III SCLC, but after extensive diagnostic workup, surgery may be considered in patients with clinical stages I and II disease. Concurrent chemoradiotherapy is a preferred treatment for patients with limited-stage (stage I–III) SCLC. Cisplatin or carboplatin plus etoposide are preferred chemotherapy regimens, and four cycles are typically used. Recommended radiotherapy doses are 60–66 Gy in 30–33 fractions, and intensity-modulated radiation therapy (IMRT) should be used (Wakeam et al., 2017) (Dingemans et al.).

2.8.2 Treatment of extensive SCLC

In the extensive stage, chemotherapy is the mainstay treatment in the first-line setting and has been for decades. Platinum plus etoposide are the preferred regimens with a median OS of 9–10 months, PFS of 5–6 months and 1-year OS of ~35% (Dingemans et al.). Maintenance or continuation treatment has not demonstrated improved outcomes compared with four to six cycles of a platinum plus etoposide (Rossi et al., 2010). SCLC is usually sensitive to the initial treatment; however, most patients develop recurrent disease after initial treatment. Topotecan is a standard second-line choice with modest efficacy; overall survival is only 26 weeks versus 14 weeks in patients managed with BSC alone. CAV is an alternative option (Dingemans et al.).

In recent years, targeted therapy and immunotherapy have been actively tested for SCLC, with many disappointments. Immunotherapy seems to be the most promising future SCLC treatment, perhaps combined with radiotherapy or chemotherapy. Nivolumab is an approved third-line treatment for SCLC, and atezolizumab and durvalulmab in combination with chemotherapy as a first-line treatment also demonstrated improved efficacy in the IMpower133 study (Yang et al., 2019).

2.9 Palliative care

Early palliative care has been shown to improve quality of life, decrease symptom burden and help patients better understand their illness. One randomized controlled trial studied early palliative care integrated with standard oncologic care, compared with standard oncologic care alone, and resulted in survival that was prolonged by approximately two months, while clinically meaningful improvements in quality of life and mood were observed as well. Early palliative care resulted in greater documentation of resuscitation preferences in the outpatient electronic medical record, as well as less aggressive care at the end of life, which did not adversely affect survival in this trial (Temel et al., 2010). The World Health Organization (WHO) recommends early palliative care soon after the diagnosis of advanced cancer (Temel et al., 2017). Patients with metastatic lung cancer often have a substantial symptom burden and poor quality of life. Pain, dyspnoea and fatigue are the most frequently reported symptoms and affect at least 65% of patients with advanced lung cancer. Symptom burden and high mortality of lung cancer leads to the need for support among patients and their families. Palliative care can provide this comprehensive support and should be integrated into the wholeness of treatment early on (Kapo & Akgün, 2015).

3 Aims of the present study

Lung cancer remains the leading cause of cancer incidence and mortality worldwide, although the treatment of lung cancer has improved significantly over recent decades. Nevertheless, challenges to improve survival remain. Diagnostic workup in lung cancer is often lengthy, and rapid diagnostics and treatment approaches have been applied in many countries to improve patient satisfaction, but it is unknown whether it leads to improved survival.

EGFR TKIs are widely used in the treatment of NSCLC, and these TKIs are especially effective in patients whose tumours harbour activating mutations in the EGFR gene. It has been demonstrated that patients who develop skin rash with EGFR TKIs are more likely to respond to treatment, and skin rash has been found to be an independent predictive factor for survival. Rash can be relieved with tetracycline antibiotics and topical corticosteroids, and prophylactic use of tetracyclines has been shown to inhibit the severity of TKI rash, but it is unknown whether the use of prophylactic tetracyclines and topical corticosteroids can increase survival of NSCLC patients treated with EGFR TKIs.

These studies aimed to examine prognosis of lung cancer in two different aspects. One aim was to evaluate the optimal diagnostic workup in lung cancer, and the other was to investigate the correlation of prophylactic use of tetracyclines and topical corticosteroids with survival among EGFR-mutated NSCLC patients in real life. More specifically, the objectives were as follows:

1. To analyse the diagnostic methods used in lung cancer diagnostics
2. To analyse diagnostic delays in lung cancer and their correlation with survival
3. To evaluate the use of prophylactic tetracyclines and topical corticoids in conjunction with the use of EGFR TKIs
4. To correlate the use of prophylactic measures with survival and treatment duration among NSCLC patients treated with EGFR TKIs

4 Materials and methods

4.1 Patient cohorts

Two different patient cohorts were formed for use in this doctoral thesis. These cohorts are elucidated in the following subsections.

4.1.1 Diagnostic delays (1)

The study population

Patient cohort 1 consisted of all new lung cancer diagnoses that were assessed at the pulmonary medicine clinic or at the multidisciplinary tumour board (MDT) for lung cancer at Oulu University Hospital between the years 2015 and 2016 (n = 221). Patients with cancer recurrence were excluded. The patient's age, gender, smoking status, ECOG status, date of GP visit and referral to hospital, initiation of symptoms referring to lung cancer, dates of diagnostic methods and radiographic tests, date of diagnosis (either radiological, histological or cytological), TNM staging, histology, EGFR or ALK status, and treatment modalities were collected from the electronic patient records. TNM classification (tumour size and lymph node or metastasis involvement) and the stage of the disease were determined according to the 7th edition of the International Association for the Study of Lung Cancer (IASLC) Lung Cancer Staging (Mirsadraee, Oswal, Alizadeh, Caulo, & van Beek, 2012). Patient demographics are detailed in Table 6.

Diagnostic methods

All the diagnostic methods used for lung cancer diagnostics were collected from the electronic patient records. We collected all the radiographic tests linked with lung cancer that were performed during the diagnostic workup. We also wanted to know which investigations for tissue diagnostics were done to obtain histological diagnosis and what the sensitivity of the investigations was. We also wanted to identify the role of PET-CT in the diagnostics and whether it would change the stage of the disease.

Table 6. Patient demographics in cohort 1.

Demographics	n (%)
Age (median)	69
Male	145 (65.6)
Female	76 (34.4)
Smoking	
Yes	195 (88.8)
No	20 (9)
Unknown	6 (2.7)
Symptoms before diagnosis	
Yes	156 (70.6)
No	65 (29.4)
Performance status (ECOG 0-4)	
0	62 (28.1)
1	85 (38.5)
2	37 (16.7)
3	30 (13.1)
4	8 (3.6)
Clinical stage at diagnosis	
I	54 (24.4)
II	36 (16.3)
III	44 (19.9)
IV	87 (39.4)
Histology	
Adenocarcinoma	88 (39.8)
Squamous cell carcinoma	71 (32.1)
Small-cell carcinoma	21 (9.5)
Other carcinoma	21 (9.5)
No histopathology	20 (9)
Multidisciplinary Tumour Board	
Yes	200 (90.5)
No	21 (9.5)

Modified from Study I

Diagnostic time intervals

Different time intervals were evaluated from electronic patient records, including intervals from symptoms to treatment, symptoms to GP visit and referral, referral to diagnostic procedures and diagnosis, and diagnosis to treatment. The whole clinical pathway was assessed from initiation of symptoms to treatment (Fig. 2).

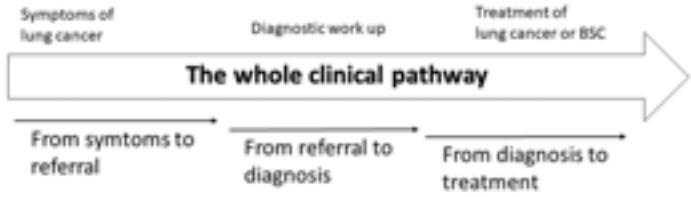

Fig. 2. Figure of the different time intervals.

Survival

Survival was analysed from the cytological/histological diagnosis of lung cancer to death or end of follow-up, the first of which counting as an event. Survival analyses were conducted according to the stage of the disease in the entire population and according to, for example, smoking, ECOG status and treatment. We also analysed the associations of the clinical pathway time intervals with survival. To this end, we grouped the patient population with time intervals above or below the median in specific components of the clinical pathway. We conducted survival analyses in the whole population and stratified by stage. We also carried out ROC analyses according to delay of time in specific components to determine whether there were cut points with improved survival prediction compared to median times alone in the stratification factors studied.

4.1.2 EGFR TKI patients (2)

The study population

For patient cohort 2, we collected all the patients who had received entitlement to special reimbursement for EGFR TKIs (gefitinib, erlotinib and afatinib) in Finland between 2011 and 2016 (n = 1541) using the Special Reimbursement Register of Social Insurance Institution of Finland. We combined data for these patients from the National Drug Purchase Registry (purchases of EGFR TKIs, antibiotics and topical corticosteroids), National Cancer Registry (cancer-related data) and Statistics Finland (survival) from 2011–2017 based on their social security numbers. The data were linked using personal identity codes, and anonymization was carried out before the data analysis. Of this population, final analysis was carried out with

patients (n = 1271) who had purchased EGFR TKIs and also had data available on the nationwide population-based Finnish Cancer Registry. Drug purchases and survival data were collected until 31.12.2017. Patient demographics are presented in Table 7.

Table 7. Patient demographics in cohort 2.

Demographics	n (%)
All patients	1271 (100)
Male	681 (53.6)
Female	590 (46.4)
EGFR TKI	
Gefitinib	169 (13.3)
Erlotinib	1073 (84.4)
Afatinib	29 (2.3)
Histology	
Adenocarcinoma	838 (65.9)
Other	433 (34.1)
-14 to 200d (overall use)	
Tetracyclines	447 (35.2)
Topical corticosteroids	270 (21.2)
No purchases	696 (54.8)
-14 to +14d (prophylactic use)	
Tetracyclines	188 (14.8)
Topical corticosteroids	196 (15.4)
No purchases	997 (78.4)
+15 to +200d (later use)	
Tetracyclines	259 (20.4)
Topical corticosteroids	176 (13.8)
No purchases	824 (64.8)

Modified from Studies II and III

Drug purchases

Data on drug purchases were collected from the Prescription database of the Special Reimbursement Register of Social Insurance Institution and included the date of purchase and the strength and number of purchased units. Reimbursement for gefitinib and afatinib is based only on advanced disease and the presence of activating tumour EGFR mutations in Finland. For erlotinib, reimbursement is based on advanced disease setting with either progression on the first-line chemotherapy or the EGFR activating mutation status, and these patients are

registered under the same reimbursement number and cannot be separated by mutational status. The registries that were used do not have information on the treatment line.

The purchase of antibiotics (all) was collected by Anatomical Therapeutic Chemical (ATC) class J01, tetracyclines by ATC J01AA and topical corticosteroids by ATC D07. The timing of the topical corticosteroid and tetracycline purchases were also collected.

The patients were stratified according to the purchase of the first EGFR TKI, the purchase of antibiotics and topical corticosteroids and their ATC class, and the timing of purchases. The timing of antibiotics and topical corticosteroid purchases were analysed from the first EGFR TKI purchase date and grouped into overall use (-14 to 200d), prophylactic use (-14 to +14d) or later use (+15d to 200d). EGFR TKI dose reduction was characterized by the purchase of TKI with a lower dose compared to the initial purchased dose within 200 days from the first EGFR TKI purchase. An EGFR TKI treatment break was characterized as a break of treatment for more than 30 days during the first 200 days of TKI use defined by the TKI purchase dates and the quantity of tablets purchased. The EGFR TKI treatment length was analysed from the date of the first EGFR TKI purchase to the last purchase date plus days on the treatment according to the number of tablets in the last purchase. Treatment discontinuation before 31.12.2017 was counted as an event, but a gap of 10 days between purchases was allowed and not counted as a discontinuation of treatment.

Survival

Survival was analysed from the first EGFR TKI purchase to the date to death or end of follow-up, and death was counted as an event. We analysed the survival of the cohort in different categories: by the timing of the antibiotic or topical corticosteroid purchases from the time of the first EGFR TKI purchase, by the ATC class of antibiotic (all), tetracycline and non-tetracycline, and by the ATC class of topical corticosteroids.

We conducted survival analyses on the benefits of tetracycline and topical corticosteroids among different EGFR TKIs, because they have different risks for rash. We also conducted a survival analysis between topical corticosteroids and tetracycline prophylaxis in erlotinib users to determine whether there was a synergy when both prophylaxes were used. Erlotinib was chosen because the benefit of prophylaxis was limited to erlotinib users only. The effects of prophylactic

tetracycline and topical corticosteroid use were analysed for treatment breaks and dose reductions in erlotinib users using Fisher's test.

Progression-free survival (PFS) could not be analysed using this data because the date of progression on EGFR TKI was unavailable in our registries. However, the registry data enabled an analysis of EGFR TKI treatment duration, and because permanent treatment discontinuations are mostly related to cancer progression, the endpoint of treatment duration closely reflects PFS.

4.1.3 Statistical methods

For cohort 1, IBM SPSS Statistics V.22.0–25.0 for Windows was applied for statistical analysis. Survival was analysed using the Kaplan-Meier method with the log-rank test. The reported p values were from two-sided $\chi 2$ tests and the Mann-Whitney test. Probability values below 0.05 were considered significant.

For cohort 2, IBM SPSS Statistics 24.0.0.0 for Windows was applied for statistical analysis. Comparisons between groups were assessed using Chi-Square analysis. Survival was analysed using the Kaplan–Meier method with the log-rank test. In univariate and multivariate analyses, Cox regression was used, and the results were reported with 95% confidence level. In multivariate analyses, Cox proportional hazard models were used to adjust for sex, initial stage (local, advanced or unknown), tumour histology (adenocarcinoma or other) and the use of prophylactic tetracycline or topical corticosteroids. Patients with no purchases were used as a reference category. Probability values below 0.05 were considered significant.

Permits and ethical aspects

Informed consent from patients was not required due to the register nature of the studies. Data collection was carried out according to national legislation. The collection of cohort 1 was done under a permit from the medical director of Oulu University Hospital (314/2017). The collection of cohort 2 was carried out under permits from the Oulu University Hospital ethics committee (43/2017), Social Insurance Institution of Finland (48/522/2017), Finnish Institute of Health and Welfare (THL/1391/5.05.00/2017), and Statistics Finland (TK-53-1277-17). Anonymization was carried out before data analysis.

5 Results

5.1 Diagnostic methods (Study I)

5.1.1 Patients of cohort 1

Over 70% of the patients in cohort 1 had symptoms of lung cancer. Most of the patients came to the hospital with outpatient referral (75.1%), and 18.1% came through the emergency room (ER). Of the patients, 6.8% had no referral, among whom lung cancer was mostly an incidental finding. Ninety percent of the patients were evaluated by multidisciplinary tumour board at some point during the diagnostic workup.

Almost 40% had clinical stage IV disease at the time of diagnosis, and 44.4% of the patients had stage I–II disease. Of the patients, 46.6% had histological diagnosis of cancer, 25.3% cytological and 28.1% radiological. Adenocarcinoma was the most common histology (39.8%), followed by squamous cell cancer (32.1%) and small-cell cancer (9.5%). Only 2.3% had EGFR-mutated NSCLC, but this was due to the low number of tests performed; tests were limited to patients with metastatic adenocarcinoma by institutional policy.

Of all the patients, 36.7% were treated with surgery, 5% with chemoradiotherapy/radiotherapy with curative intent, 37% with palliative oncological treatment and 21% with BSC only.

A Kaplan-Mayer analysis for survival was done by tumour stage in the whole population. As expected, patients were grouped statistically significantly ($p < 0.00001$) by stage. Excellent long-term survival of stage I patients was observed in the cohort; survival was over 90% at 40 months of follow-up. Stage II patients exhibited decreased survival of 35% compared to what has been seen in IASLC staging (approximately 50–60%) (Goldstraw et al., 2016).

5.1.2 Sensitivity of diagnostic tests

CT scan was performed on all of the patients, and sensitivity to detect lung cancer was 100%. Chest x-ray was done in 89% of the cases and had a sensitivity of 88%. PET-CT was done on 32.1% of the patients and had a sensitivity of 95.8% to detect lung cancer. PET-CT changed the stage of the disease compared to CT alone for

over 50% of the patients; it resulted in downstaging of 23.9% and upstaging of 29.6% among the patients compared to conventional CT.

The most common tissue tests carried out for diagnosis were bronchoscopy with sampling, CT-directed core-needle biopsy, sputum test and pleural effusion sampling, and they had sensitivities of 35.1, 90.9, 17.4 and 39.1%, respectively (Table 8).

Table 8. Sensitivity of diagnostic methods for cancer diagnosis.

Method	n (%)
Chest X-ray	
Positive	174 (88.3)
Negative	23 (11.7)
CT scan	
Positive	221 (100)
Negative	0 (0)
PET scan	
Positive	68 (95.8)
Negative	3 (4.2)
Bronchoscopy with sampling	
Positive	65 (35.1)
Negative	120 (64.9)
Sputum test	
Positive	22 (17.4)
Negative	104 (82.6)
Pleural effusion cytology	
Positive	9 (39.1)
Negative	14 (60.9)
CT-guided biopsy	
Positive	70 (90.9)
Negative	7 (9.1)

Modified from Study I

5.2 Diagnostic time intervals

The median time of the whole clinical pathway, from symptom initiation to treatment, was 130.5 days. The median time from referral to diagnosis was 33 days and from diagnosis to treatment 27 days. There were no delays from referral to CT scan, specialist appointment or bronchoscopy, but times for CT-directed core needle biopsy and PET scan were more delayed with a median of 36 and 47 days from referral. The longest diagnostic delay was from symptom initiation to referral to

hospital, with a median time of 58 days. Median time from diagnosis to surgery was 36 days and to oncologist appointment 20.5 days. Median time from oncologist appointment to treatment (surgery excluded) was 7 days.

5.2.1 Association of the clinical pathway time intervals with survival

The patients of the cohort were grouped by time interval above or below median time intervals in specific components of the clinical pathway. In addition, ROC analyses were carried out according to time delay in specific components, but these analyses did not show any improved cut-offs for survival prediction compared to median times; therefore, median time intervals were used for grouping.

In the analysis for the whole clinical pathway, there was no statistical survival difference in the whole population or the population stratified by stage. However, there was a tendency for improved survival in stage I patients with shorter whole clinical pathway intervals (Figure 3). Results were similar in the interval from symptoms to referral.

Survival analyses revealed that there was improved survival in patients with longer interval from referral to diagnosis in the whole population ($p = 0.03$) (Figure 4) but not when stratified by stage. Similar findings were seen in survival for the patients with longer time interval from diagnosis to treatment in the whole population ($p = 0.000013$) (Figure 5) and in stage IV ($p = 0.00002$).

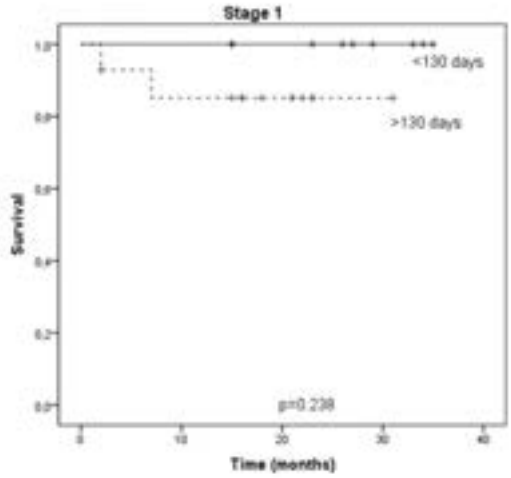

Fig. 3. Survival analysis for the whole clinical pathway in stage I. Reprinted from study I with permission from © 2019 Taylor & Francis.

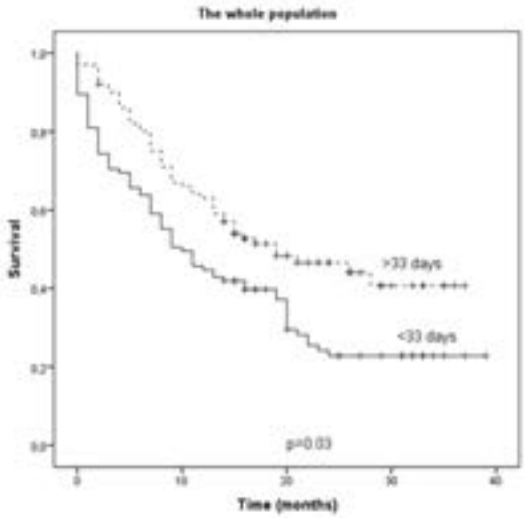

Fig. 4. Survival analysis for referral to diagnosis in the whole population. Reprinted from study I with permission from © 2019 Taylor & Francis.

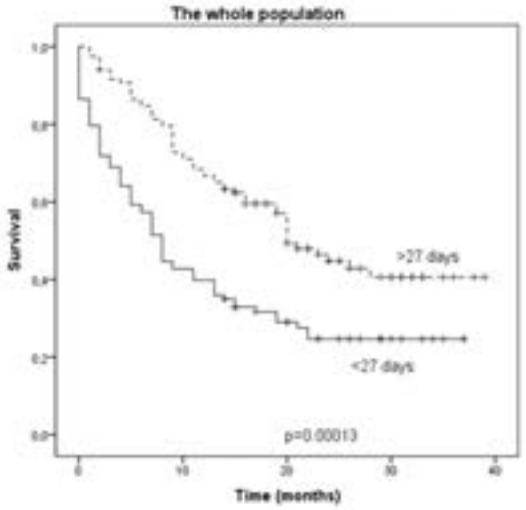

Fig. 5. Survival analysis for diagnosis to treatment in the whole population. Reprinted from study I with permission from © 2019 Taylor & Francis.

5.3 Tetracyclines among EGFR TKI users (Study II)

In cohort 2, 63.1% (n = 802) of the patients had antibiotic purchases up to 200 days from the first EGFR TKI purchase. Of these purchases, 55.7% were tetracyclines. Meanwhile, 25.3% of the patients had purchased antibiotics for prophylactic use (-14 to +14d) from the first EGFR TKI purchase, and most of these (58.3%) were tetracyclines.

5.3.1 Antibiotic purchases and survival

Purchase of antibiotics was associated with improved survival (HR 0.81, 95% CI 0.71-0.91) in the whole cohort. The survival benefit was limited to tetracycline purchases (HR 0.72, 95% CI 0.64-0.82), and the largest survival benefit was seen with prophylactic use compared to later use (+15 to +200d) (Figure 6A-B). Most beneficial was when tetracyclines were used for both prophylaxis and later (Figure 6C). Purchases of other ATC class antibiotics were associated with worsen survival (HR 1.14, 95% CI 0.99-1.30) (Figure 7).

Survival analyses were conducted with different TKIs separately, and the benefit of tetracyclines was limited to erlotinib only (HR 0.68, 95% CI 0.58-0.78). There was an even greater benefit observed for afatinib, but it was non-significant due to the small sample size (n = 29). Among gefitinib users, there was no difference in survival.

Moreover, multivariate analyses were conducted with statistically significant baseline factors, including gender, initial stage and tumour histology, and the results revealed a beneficial effect of tetracyclines for the whole population and for erlotinib users.

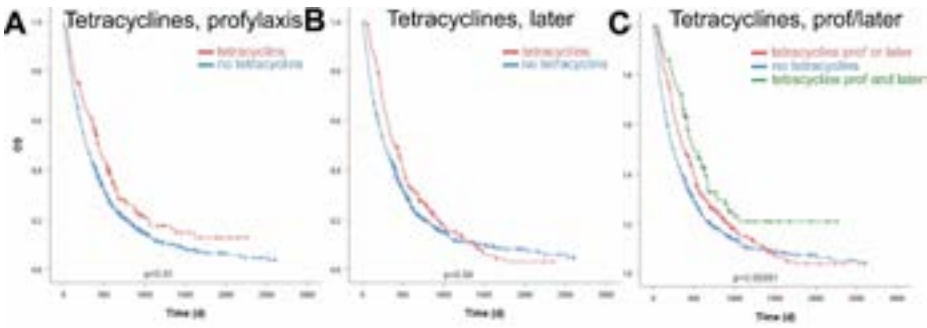

Fig. 6. Survival in the whole cohort according to the timing of tetracycline purchase from 1st EGFR TKI purchase. Reprinted from study II with permission from 2020 CC BY NC license.

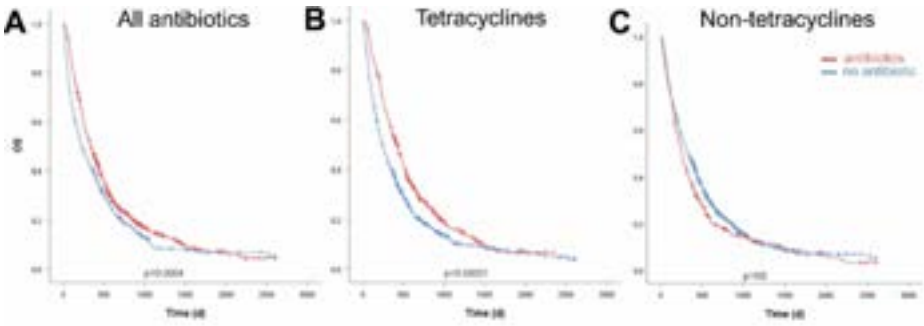

Fig. 7. Survival in the whole cohort according to use of antibiotics. Reprinted from study II with permission from 2020 CC BY NC license.

5.4 Topical corticosteroids among EGFR TKI users (Study III)

In cohort 2, 21.2% (n = 270) of the patients made purchases of topical corticosteroids up to 200 days from the first EGFR TKI purchase. Of them, 15.4% had prophylactic purchases (-14 to +14d) and 13.8% later purchases (+15 to +200d).

5.4.1 Topical corticosteroid purchases and survival

The overall purchase (-14d to 200d) of topical corticosteroids was associated with improved survival compared to those with no purchases (HR 0.64, 95% CI 0.55-0.74). The survival benefit was also observed with prophylactic purchases (HR 0.78, 95% CI 0.66-0.92).

Survival analyses were conducted with different TKIs separately, and the benefit of topical corticosteroids was limited to erlotinib only (HR 0.62, 95% CI 0.52-0.73) (Figure 8), similar to tetracyclines. There was no survival benefit among gefitinib users, and afatinib users were excluded because of the low patient number (n = 29). In the univariate analysis, survival improvements for erlotinib users were seen among the overall and prophylactic purchasers of topical corticosteroids compared to patients without purchases. The effect of topical corticosteroids on survival was observed in multivariate analyses for the whole population and for the erlotinib users regardless of the corticosteroid purchase times.

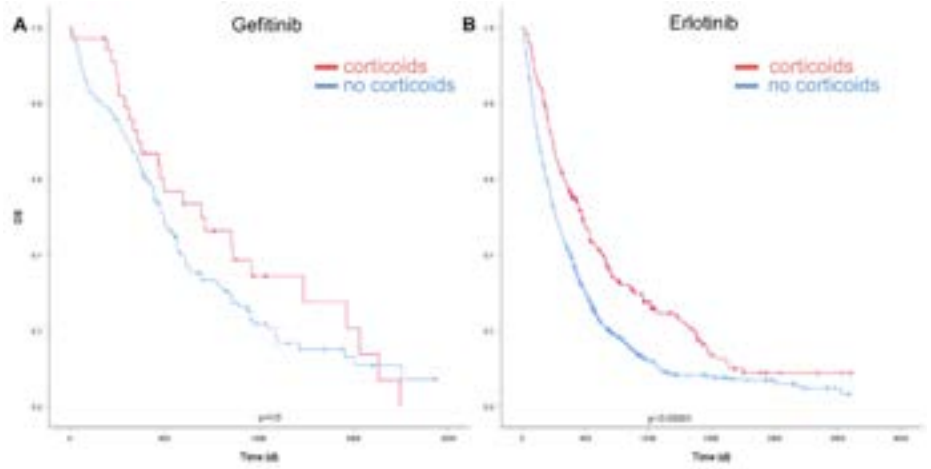

Fig. 8. Survival according to the purchases of topical corticosteroids and erlotinib or gefitinib. Reprinted from study III with permission from © 2021 Taylor & Francis.

5.5 Effect of tetracycline and topical corticoid prophylaxis on erlotinib breaks, dose reductions and treatment duration

The effect of the prophylactic tetracyclines and topical corticosteroids were analysed for dose reductions and treatment breaks among the erlotinib users using Fisher's test. Prophylactic use of tetracyclines was not associated with treatment breaks for more than 30 days or with dose reductions during the first 200 days. For topical corticosteroid prophylaxis, there was no association with erlotinib dose reductions, but there was a slightly higher frequency of erlotinib treatment breaks, 19.4% versus 11.3%.

The results revealed that the use of prophylactic tetracyclines and topical corticosteroids were associated with longer treatment duration compared to no prophylaxis. For tetracyclines, a median treatment duration was 120 days versus 90 days with no prophylaxis (HR 0.81, 95% CI 0.68-0.95). For topical corticosteroids, a median treatment duration was 135 days (HR 0.75, 95% CI 0.64-0.90). The use of both topical corticosteroids and tetracycline prophylaxis was associated with an even longer erlotinib treatment duration, with a median of 164 days (HR 0.60, 95% CI 0.42-0.86).

5.6 Topical corticosteroids, different EGFR TKIs and synergy with tetracyclines (Study III)

We also aimed to determine whether there was a synergy between topical corticosteroids and tetracycline prophylaxis in erlotinib users. In the cohort, 24% of the patients (n = 257) had prophylactic purchases of either corticosteroids or tetracyclines, and 3.5% of the patients (n = 38) had purchases of both drugs. There was a significant survival benefit for purchasers of both drugs (HR 0.51, 95% CI 0.35-0.75) and single agents (HR 0.78, 95% CI 0.66-0.90) compared to non-purchasers (Figure 9).

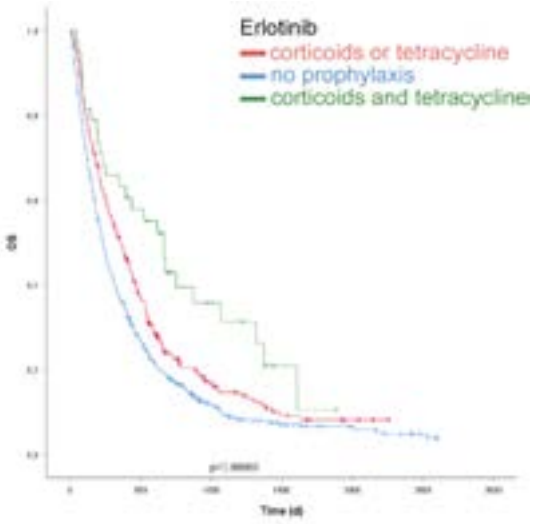

Fig. 9. Survival in erlotinib users according to the prophylactic purchases of corticosteroids or tetracyclines, both, or no prophylactic purchases. Reprinted from study III with permission from © 2021 Taylor & Francis.

6 Discussion

Despite all the major advancements, improving lung cancer survival remains a challenge and seems to be a result of many components.

Preventing lung cancer through smoking avoidance and cessation and maintaining clean air and a healthy lifestyle are important preemptive factors. Early detection of lung cancer by LDCT screening has demonstrated to significantly reduce lung cancer mortality in selected high-risk populations (Usman Ali et al., 2016), and these trials have suggested that early diagnosis can improve survival.

Accurate diagnostics and staging of lung cancer are important as they contribute to treatment options and prognosis. Better access to PET-CT scanning and EBUS for mediastinal lymph node sampling have increased the accuracy of staging for lung cancer. In our study, we found that longer time for diagnostic workup or lung cancer treatment delays do not worsen survival, suggesting that the diagnostic workup should be done accurately rather than focusing on the diagnostic time.

Evolving therapies are dramatically changing the lung cancer survival rates. Therapies, especially for NSCLC, have revolutionized over recent years, and treatment is becoming increasingly more targeted and individually tailored to each patient based on identification of driver genetic mutations. In our study, we have provided the results of a large, nationwide cohort of patients treated with EGFR TKIs for NSCLC indication and found that prophylactic use of tetracyclines and topical corticosteroids can improve the survival of NSCLC patients treated with EGFR TKIs with high incidence of rash.

6.1 Diagnostic methods

In this study, we evaluated diagnostic investigations performed on lung cancer patients. Chest x-ray is a good basic examination, and when it shows suspicion of lung cancer, it should be supplemented with a CT scan. When stage IV disease is evident, PET-CT does not necessarily provide any additional information, but, particularly when treatment with curative intent is considered, PET-CT is helpful for accurate staging and treatment planning.

Bronchoscopy was routinely done for the majority of the patients (84%) according to local clinical practice, regardless of the radiological stage, but it yielded a positive cytological or histological sample only for less than a third of the patients. For the stage I patients, positivity was as low as 10%. Most of the

diagnoses by bronchoscopy were cytological and, therefore, not suitable for modern molecular biology analysis. Nevertheless, CT-guided needle biopsy yielded positive results in 91% of the patients, and most of them were core-needle biopsies with tumour material suitable for molecular biology analysis. In our study, EBUS was used only for 4.1% of the patients, but it should be used more widely to improve the selection of surgical candidates and to yield improved patient outcomes (Sampsonas et al., 2018).

We suggest that bronchoscopy should not be done routinely when lung cancer is suspected due to its low sensitivity, especially in peripheral tumours. For patients with peripheral tumour and stage IV disease, bronchoscopy is often useless and might cause excessive distress for patients and delays in their diagnostic pathway.

6.2 Diagnostic time intervals and survival

Many institutions have developed rapid access programs or diagnostic assessment programs for lung cancer diagnostics, and they have been able to reduce the timelines in diagnostic procedures and increase patient satisfaction. However, the effect of rapid access programs to survival is controversial. Nordic countries aside from Finland have integrated fast-track pathways for diagnostics and treatment of lung cancer (Christensen, Jekunen, Heinonen, Dalton, & Rasmussen, 2017), and five-year survival rates of lung cancer have improved in all the other Nordic countries but not in Finland. Finland, in fact, has the worst survival numbers of the Nordic countries, with 13%, compared to Sweden (19.5%), Norway (19%) and Denmark (16.6%) (Bray et al., 2018) (Lundberg et al., 2020). A similar trend has not been seen among other cancers. We hypothesized that rapid diagnostics applied in other Nordic countries would play a role in improved survival compared to Finland, and, therefore, our cohort could illustrate the link between rapid diagnostics and improved survival.

In this study, we investigated time intervals between symptoms, referral, diagnosis and treatment and their relation to survival among Finnish lung cancer patients. To our surprise, shorter time intervals were not associated with improved survival. In fact, longer intervals from referral to diagnosis and diagnosis to treatment were associated with improved survival. Findings were similar to some other studies, where a longer time to treatment was associated with better overall survival (Habbous et al., 2021) or where no statistically significant association between the length of the diagnostic interval and mortality was seen (Tørring, Frydenberg, Hansen, Olesen, & Vedsted, 2013). One previous Finnish study also

demonstrated that long specialist treatment delays were not correlated with worse prognosis in patients with advanced disease. In that study, in patients with more limited disease, the delay time was thought to be more critical when curative treatment was the goal, and for them, the diagnostic process was suggested to proceed without delay to avoid a situation in which curable disease becomes incurable (Salomaa et al., 2005).

According to these findings, it is likely that the fast-track diagnostic pathways are unable to improve survival. Instead, other factors are more important for that matter, such as accurate diagnostics, larger numbers of patients receiving treatment with curative intent, more modern treatment approaches, and perhaps the implementation of national cancer plans that are currently used in many countries. These national cancer plans have been developed with a focus on the patient perspective and include components such as uniform national cancer care guidelines, contact nurses, multidisciplinary treatment decisions, individualized management plans, centralization of treatment to fewer centres, structured care processes and standardized pathways aiming at reducing waiting times (Lundberg et al., 2020). Fast-track diagnostics are likely to improve patient satisfaction, which is also an important factor in healthcare and could be another aspect behind their implementation even though they might not improve survival.

In this cohort, invasive mediastinal staging was likely underused, as it was only done for 12.7% of the patients even though 36.7% were treated with surgery. This could reflect the low survival of the stage II patients in this cohort, who are likely to be under-staged when staging is done only by radiological evaluation of mediastinum. However, PET-CT was performed for 32.1% of the patients in the cohort, but its accuracy in detecting metastatic lymph nodes is about 80%, whereas it is highly sensitive for detecting extra-thoracic metastasis (Schmidt-Hansen et al., 2014).

In this study population, only a small number of patients (5%) received definitive concurrent chemoradiotherapy with curative intent, even though almost 20% of the patients had stage III disease, concluding 25% of these patients received curative-intent therapy. Stage III NSCLC is a highly heterogeneous group of patients, but unlike patients with stage IV, patients with stage III disease should be evaluated for curative-intent therapy. To improve outcomes for patients with stage III unresectable NSCLC, it is therefore important to evaluate the multidisciplinary care pathway for these patients, including consultation with thoracic surgeons, radiation oncologists, and medical oncologists. It is also crucial to consider how navigation through the pathway can be improved to facilitate optimal treatment

delivery as it is critical to identify those patients who may be eligible for curative-intent therapy.

The association of longer time intervals with improved survival might be explained by the confounding effect of patients with advanced lung cancer eligible for palliative or BSC only. Patients with advanced disease are diagnosed more rapidly, and BSC is initiated within shorter time frames. Patients who are candidates for curative or more active treatments are likely to undergo more investigations, resulting in increased length of the clinical pathway.

Limitations of study I

The retrospective nature of the study created limitations and restrictions compared to prospective trials. The rather small quantity of patients from a single institution was a limitation as well. A prospective, nationwide study would give more precise information on lung cancer diagnostics and its effects on survival in Finnish lung cancer patients. Furthermore, our study did not consider patient satisfaction and quality of life, and these factors could not be investigated in the cohort.

6.3 EFGR TKIs

EGFR TKIs are the standard of care in the first-line treatment of advanced EGFR mutated non-small-cell lung cancer and can also be used for unselected NSCLC patients in later settings. Rash is known to be the most common side effect of EGFR TKIs, especially in first and second-generation TKIs, and has been found to be an independent predictive factor for survival (Petrelli et al., 2012). Side effects can lead to discontinuation of treatment and dose reductions and can have a negative impact on quality of life. Rash can be alleviated with the use of moisturizers and tetracyclines, as well as the avoidance of sun exposure and irritants (Hofheinz et al., 2016). Tetracyclines can decrease the severity of rash, but it is unknown whether they can also improve the survival of NSCLC patients treated with EGFR TKIs.

In the present study, we provided the results of a large, nationwide cohort of patients treated with EGFR TKIs for NSCLC indication. In Finland, large numbers of registries are available, and data can be combined with social security numbers. The current study reveals the possibilities of using large real-world registries to investigate clinically important issues, which are out of scope for commercially funded clinical trials.

6.3.1 EGFR TKIs and tetracyclines

The hypothesis of the study was that prophylactic use of tetracyclines could improve survival and TKI treatment duration and decrease the number of EGFR TKI dose reductions and treatment breaks. The major finding of our study was that tetracycline prophylaxis increased the survival and TKI treatment duration of NSCLC patients treated with erlotinib. A similar trend was seen with afatinib users, but it was non-significant due to the small sample size. The same benefit was not seen among gefitinib users.

The pharmacokinetics of erlotinib and gefitinib differ, and when administered at their recommended doses, the plasma concentration of erlotinib is seven times higher than that of gefitinib, which has led to the assumption that erlotinib is both more effective and associated with more adverse events than gefitinib. However, a meta-analysis has shown that the efficacies of these two drugs are comparable regardless of EGFR mutation status. Gefitinib is associated with fewer grade 3-4 rashes than erlotinib, which could be explained by pharmacokinetics: the bioavailability of erlotinib 150 mg/day (equal to the maximum tolerated dose) is threefold higher than that of gefitinib 250 mg/day (one-third of the maximum tolerated dose). Dose reductions have been seen significantly more frequently with erlotinib than gefitinib users, while efficacy remains comparable, suggesting that erlotinib might be administered at a lower-than-standard dose to reduce adverse events while retaining its efficacy (Yang, Z. et al., 2017).

Some previous moderate-size studies have shown that tetracycline prophylaxis reduces the number and severity of TKI-induced rash, but the effect on survival has not previously been demonstrated (Melosky et al., 2016) (Arrieta et al., 2015). Our study had a significant number of patients (n = 1271), and approximately 15% had received tetracycline prophylaxis. We hypothesized that national registries with large numbers of patients could enable a study of the effect of tetracyclines on survival. To our knowledge, this is the first study to provide evidence that tetracyclines can affect the survival of EGFR TKI-treated NSCLC patients. Based on these results, prophylactic tetracyclines should be considered when initiating an EGFR TKI treatment with high incidence for rash such as erlotinib, afatinib or dacomitinib.

6.3.2 EGFR TKIs and topical corticosteroids

Our aim was to explore whether topical corticosteroids have a similar effect on survival and whether their effect is synergistic with tetracyclines. The results of the current study suggest that prophylactic use of topical corticosteroids is related to better survival of NSCLCs treated with EGFR TKIs. The benefit was limited to erlotinib only, as was seen with tetracyclines. An explanation could be the difference in pharmacokinetics, as previously described. The prophylactic use of corticosteroids was also associated with a longer erlotinib treatment duration, suggesting that there might also be a benefit in progression-free survival (PFS). There seemed to be a synergistic effect on survival and treatment duration when both prophylactic measures, tetracyclines and topical corticosteroids, were used simultaneously.

Limitations of studies II and III

There are limitations to be considered when evaluating the results of these studies. They were retrospective studies that held confounding factors compared to prospective randomized clinical trials, but with a large number of subjects, they provide important clinical information. One aspect to consider is purchases compared to the use of drugs, as the use of medication cannot be identified from the registries that were used. However, there is a high level of patient adherence concerning cancer care, and it is likely that the purchased drugs were highly used. We feel that the data on prophylactic use of tetracyclines or topical corticosteroids (−14 to +14 days of the first EGFR TKI purchase) provided an estimate with the least confounding factors since TKI-induced rash rarely begins within the first two weeks of use. For the later use of tetracyclines and topical corticosteroids (+15 to 200d), there are more factors creating bias. For example, patients who develop rash and need related management are generally considered to have a better prognosis, and many patients do not survive to 200 days and, therefore, have less time to be exposed to tetracyclines and topical corticosteroids.

One limitation specific to topical corticosteroids is that exposure to topical agents is difficult to investigate since they do not have a standard dose or dosing frequency, and it could not be further investigated within the cohort. Both corticosteroids and tetracyclines can also be used for indications other than TKI-induced rash and that could not be ruled out in this cohort.

The synergistic effect on survival was seen in the study when tetracyclines and topical corticosteroids were used simultaneously, although the population was rather small (n = 38). It would be interesting to observe the results in a large population, especially with prophylactic use of both measures.

The FLAURA trial demonstrated superior efficacy with osimertinib compared to first- or second-generation EGFR TKIs, with lower rates of serious adverse events (Soria et al., 2018). As a result, osimertinib is now widely used as first-line treatment for advanced EGFR-mutated NSCLC, but older EGFR TKIs are still used when osimertinib cannot be used for toxicity, availability or reimbursement reasons. In the FLAURA trial, prophylactic measures were not allowed in the comparator arm, and it can be questioned whether the results of the trial would have been similar if prophylactic tetracyclines and corticosteroids were permitted in the comparator arm.

7 Conclusions

The conclusions are summarized as follows:

1. CT-guided needle biopsy should be used as a preferred method for tumour sampling when diagnostic tumour sampling is needed.
2. Bronchoscopy should not be done routinely on all lung cancer patients but merely when it can help the diagnostic workup.
3. Longer time for diagnostic workup or lung cancer treatment delays does not worsen survival, suggesting that fast-track approaches might not improve lung cancer outcomes.
4. Prophylactic use of tetracyclines can improve the survival of NSCLC patients treated with EGFR TKIs with high incidence of rash.
5. Prophylactic use of topical corticosteroids can improve the survival of NSCLC patients treated with EGFR TKIs with a high incidence of rash.
6. Tetracyclines and topical corticosteroids should be considered as a prophylaxis for all patients treated with EGFR TKIs with a high incidence of rash.

References

Arrieta, O., Vega-González, M. T., López-Macías, D., Martínez-Hernández, J. N., Bacon-Fonseca, L., Macedo-Pérez, E. O., . . . de la Garza-Salazar, J. (2015). Randomized, open-label trial evaluating the preventive effect of tetracycline on afatinib induced-skin toxicities in non-small cell lung cancer patients. *Lung Cancer (Amsterdam, Netherlands), 88*(3), 282-288. doi:S0169-5002(15)00171-3 [pii]

Artal Cortés, Á, Calera Urquizu, L., & Hernando Cubero, J. (2015). Adjuvant chemotherapy in non-small cell lung cancer: State-of-the-art. *Translational Lung Cancer Research, 4*(2), 191-197. doi:10.3978/j.issn.2218-6751.2014.06.01 [doi]

Assi, H. I., Kamphorst, A. O., Moukalled, N. M., & Ramalingam, S. S. (2018). Immune checkpoint inhibitors in advanced non-small cell lung cancer. *Cancer, 124*(2), 248-261. doi:10.1002/cncr.31105 [doi]

Bade, B. C., & Dela Cruz, C. S. (2020). Lung cancer 2020: Epidemiology, etiology, and prevention. *Clinics in Chest Medicine, 41*(1), 1-24. doi:S0272-5231(19)30080-2 [pii]

Baine, M. K., Hsieh, M. S., Lai, W. V., Egger, J. V., Jungbluth, A. A., Daneshbod, Y., . . . Rekhtman, N. (2020). SCLC subtypes defined by ASCL1, NEUROD1, POU2F3, and YAP1: A comprehensive immunohistochemical and histopathologic characterization. *Journal of Thoracic Oncology : Official Publication of the International Association for the Study of Lung Cancer, 15*(12), 1823-1835. doi:S1556-0864(20)30755-3 [pii]

Bradley, J. D., Paulus, R., Komaki, R., Masters, G., Blumenschein, G., Schild, S., . . . Choy, H. (2015). Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): A randomised, two-by-two factorial phase 3 study. *The Lancet.Oncology, 16*(2), 187-199. doi:S1470-2045(14)71207-0 [pii]

Brahmer, J. R., Govindan, R., Anders, R. A., Antonia, S. J., Sagorsky, S., Davies, M. J., . . . Herbst, R. S. (2018). The society for immunotherapy of cancer consensus statement on immunotherapy for the treatment of non-small cell lung cancer (NSCLC). *Journal for ImmunoTherapy of Cancer, 6*(1), 75. doi:10.1186/s40425-018-0382-2

Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R. L., Torre, L. A., & Jemal, A. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians, 68*(6), 394-424. doi:10.3322/caac.21492 [doi]

Brennan, P., Hainaut, P., & Boffetta, P. (2011). Genetics of lung-cancer susceptibility. *The Lancet Oncology, 12*(4), 399-408. doi:https://doi.org/10.1016/S1470-2045(10)70126-1

Brierley, J. D., Gospodarowicz, M. K., & Wittekind, C. (2017). *TNM classification of malignant tumours* (8th ed.). Chicester: John Wiley & Sons, Incorporated. Retrieved from https://ebookcentral.proquest.com/lib/[SITE_ID]/detail.action?docID=4792667

Byers, L. A., & Rudin, C. M. (2015). Small cell lung cancer: Where do we go from here? *Cancer, 121*(5), 664-672. doi:10.1002/cncr.29098 [doi]

Camidge, D. R., Kim, H. R., Ahn, M. J., Yang, J. C. H., Han, J. Y., Hochmair, M. J., . . . Popat, S. (2020). Brigatinib versus crizotinib in advanced ALK inhibitor-naive ALK-positive non-small cell lung cancer: Second interim analysis of the phase III ALTA-1L trial. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology, 38*(31), 3592-3603. doi:10.1200/JCO.20.00505 [doi]

Cao, C., Wang, D., Chung, C., Tian, D., Rimner, A., Huang, J., & Jones, D. R. (2019). A systematic review and meta-analysis of stereotactic body radiation therapy versus surgery for patients with non-small cell lung cancer. *The Journal of Thoracic and Cardiovascular Surgery, 157*(1), 362-373.e8. doi:S0022-5223(18)32347-X [pii]

Cersosimo, R. J. (2002). Lung cancer: A review. *American Journal of Health-System Pharmacy : AJHP : Official Journal of the American Society of Health-System Pharmacists, 59*(7), 611-642. doi:10.1093/ajhp/59.7.611 [doi]

Chang, M. C., Chen, J. H., Liang, J. A., Lin, C. C., Yang, K. T., Cheng, K. Y., . . . Kao, C. H. (2012). Meta-analysis: Comparison of F-18 fluorodeoxyglucose-positron emission tomography and bone scintigraphy in the detection of bone metastasis in patients with lung cancer. *Academic Radiology, 19*(3), 349-357. doi:10.1016/j.acra.2011.10.018 [doi]

Christensen, N. L., Jekunen, A., Heinonen, S., Dalton, S. O., & Rasmussen, T. R. (2017). Lung cancer guidelines in sweden, denmark, norway and finland: A comparison. *Acta Oncologica (Stockholm, Sweden), 56*(7), 943-948. doi:10.1080/ 0284186 X.2017.1315172 [doi]

de Koning, H. J., van der Aalst, C. M., de Jong, P. A., Scholten, E. T., Nackaerts, K., Heuvelmans, M. A., . . . Oudkerk, M. (2020). Reduced lung-cancer mortality with volume CT screening in a randomized trial. *The New England Journal of Medicine, 382*(6), 503-513. doi:10.1056/NEJMoa1911793 [doi]

Detterbeck, F. C., Boffa, D. J., Kim, A. W., & Tanoue, L. T. (2017). The eighth edition lung cancer stage classification. *Chest, 151*(1), 193-203. doi:S0012-3692(16)60780-8 [pii]

Dietel, M., Bubendorf, L., Dingemans, A. M., Dooms, C., Elmberger, G., García, R. C., . . . von Laffert, M. (2016). Diagnostic procedures for non-small-cell lung cancer (NSCLC): Recommendations of the european expert group. *Thorax, 71*(2), 177-184. doi:10.1136/thoraxjnl-2014-206677 [doi]

Ding, P. N., Lord, S. J., Gebski, V., Links, M., Bray, V., Gralla, R. J., . . . Lee, C. K. (2017). Risk of treatment-related toxicities from EGFR tyrosine kinase inhibitors: A meta-analysis of clinical trials of gefitinib, erlotinib, and afatinib in advanced EGFR-mutated non-small cell lung cancer. *Journal of Thoracic Oncology : Official Publication of the International Association for the Study of Lung Cancer, 12*(4), 633-643. doi:S1556-0864(16)33582-1 [pii]

Dingemans, A. -. C., Früh, M., Ardizzoni, A., Besse, B., Faivre-Finn, C., Hendriks, L. E., . . . Reck, M.Small-cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up☆. *Annals of Oncology,* doi:10.1016/j.annonc.2021.03.207

Ettinger, D. S., Wood, D. E., Aisner, D. L., Akerley, W., Bauman, J. R., Bharat, A., . . . Hughes, M. (2021). NCCN guidelines insights: Non-small cell lung cancer, version 2.2021. *Journal of the National Comprehensive Cancer Network : JNCCN, 19*(3), 254-266. doi:jnccnGLINS1903 [pii]

Faivre-Finn, C., Vicente, D., Kurata, T., Planchard, D., Paz-Ares, L., Vansteenkiste, J. F., . . . Antonia, S. J. (2021). Four-year survival with durvalumab after chemoradiotherapy in stage III NSCLC-an update from the PACIFIC trial. *Journal of Thoracic Oncology : Official Publication of the International Association for the Study of Lung Cancer, 16*(5), 860-867. doi:S1556-0864(21)00022-8 [pii]

Gadgeel, S., Rodríguez-Abreu, D., Speranza, G., Esteban, E., Felip, E., Dómine, M., . . . Garassino, M. C. (2020). Updated analysis from KEYNOTE-189: Pembrolizumab or placebo plus pemetrexed and platinum for previously untreated metastatic nonsquamous non-small-cell lung cancer. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology, 38*(14), 1505-1517. doi:10.1200/JCO.19.03136 [doi]

Goldstraw, P., Chansky, K., Crowley, J., Rami-Porta, R., Asamura, H., Eberhardt, W. E., . . . International Association for the Study of Lung Cancer Staging and Prognostic Factors Committee Advisory Boards and Participating Institutions. (2016). The IASLC lung cancer staging project: Proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer. *Journal of Thoracic Oncology : Official Publication of the International Association for the Study of Lung Cancer, 11*(1), 39-51. doi:S1556-0864(15)00017-9 [pii]

Greenhalgh, J., Boland, A., Bates, V., Vecchio, F., Dundar, Y., Chaplin, M., & Green, J. A. (2021). First-line treatment of advanced epidermal growth factor receptor (EGFR) mutation positive non-squamous non-small cell lung cancer. *The Cochrane Database of Systematic Reviews, 3*(3), CD010383. doi:10.1002/14651858.CD010383.pub3 [doi]

Grootjans, W., de Geus-Oei, L. F., Troost, E. G., Visser, E. P., Oyen, W. J., & Bussink, J. (2015). PET in the management of locally advanced and metastatic NSCLC. *Nature Reviews.Clinical Oncology, 12*(7), 395-407. doi:10.1038/nrclinonc.2015.75 [doi]

Habbous, S., Khan, Y., Langer, D. L., Kaan, M., Green, B., Forster, K., . . . Holloway, C. M. B. (2021). The effect of diagnostic assessment programs on the diagnosis and treatment of patients with lung cancer in ontario, canada. *Annals of Thoracic Medicine, 16*(1), 81-101. doi:10.4103/atm.ATM_283_20 [doi]

Hanna, N., Shepherd, F. A., Fossella, F. V., Pereira, J. R., De Marinis, F., von Pawel, J., . . . Bunn, P. A.,Jr. (2004). Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology, 22*(9), 1589-1597. doi:JCO.2004.08.163 [pii]

Herbst, R. S., Giaccone, G., de Marinis, F., Reinmuth, N., Vergnenegre, A., Barrios, C. H., . . . Spigel, D. R. (2020). Atezolizumab for first-line treatment of PD-L1-selected patients with NSCLC. *The New England Journal of Medicine, 383*(14), 1328-1339. doi:10.1056/NEJMoa1917346 [doi]

Hirsch, F. R., Scagliotti, G. V., Mulshine, J. L., Kwon, R., Curran, W. J.,Jr, Wu, Y. L., & Paz-Ares, L. (2017). Lung cancer: Current therapies and new targeted treatments. *Lancet (London, England), 389*(10066), 299-311. doi:S0140-6736(16)30958-8 [pii]

Hofheinz, R. D., Deplanque, G., Komatsu, Y., Kobayashi, Y., Ocvirk, J., Racca, P., . . . Jatoi, A. (2016). Recommendations for the prophylactic management of skin reactions induced by epidermal growth factor receptor inhibitors in patients with solid tumors. *The Oncologist, 21*(12), 1483-1491. doi:theoncologist.2016-0051 [pii]

Hwang, J. K., Page, B. J., Flynn, D., Passmore, L., McCaul, E., Brady, J., . . . Fong, K. M. (2020). Validation of the eighth edition TNM lung cancer staging system. *Journal of Thoracic Oncology : Official Publication of the International Association for the Study of Lung Cancer, 15*(4), 649-654. doi:S1556-0864(19)33846-8 [pii]

Islami, F., Goding Sauer, A., Miller, K. D., Siegel, R. L., Fedewa, S. A., Jacobs, E. J., . . . Jemal, A. (2018). Proportion and number of cancer cases and deaths attributable to potentially modifiable risk factors in the united states. *CA: A Cancer Journal for Clinicians, 68*(1), 31-54. doi:10.3322/caac.21440 [doi]

Jacobsen, M. M., Silverstein, S. C., Quinn, M., Waterston, L. B., Thomas, C. A., Benneyan, J. C., & Han, P. K. J. (2017). Timeliness of access to lung cancer diagnosis and treatment: A scoping literature review. *Lung Cancer (Amsterdam, Netherlands), 112*, 156-164. doi:S0169-5002(17)30472-5 [pii]

Jensen, A. R., Mainz, J., & Overgaard, J. (2002). Impact of delay on diagnosis and treatment of primary lung cancer. *Acta Oncologica (Stockholm, Sweden), 41*(2), 147-152. doi:10.1080/028418602753669517 [doi]

Jutten, B., & Rouschop, K. M. (2014). EGFR signaling and autophagy dependence for growth, survival, and therapy resistance. *Cell Cycle (Georgetown, Tex.), 13*(1), 42-51. doi:10.4161/cc.27518 [doi]

Kapo, J. M., & Akgün, K. M. (2015). Integrating palliative care into the care of patients with advanced lung cancer. *Cancer Journal (Sudbury, Mass.), 21*(5), 434-439. doi:10.1097/PPO.0000000000000149 [doi]

Kelly, K., Altorki, N. K., Eberhardt, W. E., O'Brien, M. E., Spigel, D. R., Crinò, L., . . . Shepherd, F. A. (2015). Adjuvant erlotinib versus placebo in patients with stage IB-IIIA non-small-cell lung cancer (RADIANT): A randomized, double-blind, phase III trial. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology, 33*(34), 4007-4014. doi:10.1200/JCO.2015.61.8918 [doi]

Kim, A. S., Ko, H. J., Kwon, J. H., & Lee, J. M. (2018). Exposure to secondhand smoke and risk of cancer in never smokers: A meta-analysis of epidemiologic studies. *International Journal of Environmental Research and Public Health, 15*(9), 1981. doi: 10.3390/ijerph15091981. doi:10.3390/ijerph15091981 [doi]

Krstic, M. N., Mijac, D. D., Popovic, D. D., Pavlovic Markovic, A., & Milosavljević, T. (2019). General aspects of primary cancer prevention. *Digestive Diseases (Basel, Switzerland), 37*(5), 406-415. doi:10.1159/000497191 [doi]

Lee, C. K., Wu, Y. L., Ding, P. N., Lord, S. J., Inoue, A., Zhou, C., . . . Yang, J. C. (2015). Impact of specific epidermal growth factor receptor (EGFR) mutations and clinical characteristics on outcomes after treatment with EGFR tyrosine kinase inhibitors versus chemotherapy in EGFR-mutant lung cancer: A meta-analysis. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology, 33*(17), 1958-1965. doi:10.1200/JCO.2014.58.1736 [doi]

Lindberg, K., Nyman, J., Riesenfeld Källskog, V., Hoyer, M., Lund, J. Å, Lax, I., . . . Lewensohn, R. (2015). Long-term results of a prospective phase II trial of medically inoperable stage I NSCLC treated with SBRT - the nordic experience. *Acta Oncologica (Stockholm, Sweden), 54*(8), 1096-1104. doi:10.3109/0284186X.2015.1020966 [doi]

Liu, H. B., Wu, Y., Lv, T. F., Yao, Y. W., Xiao, Y. Y., Yuan, D. M., & Song, Y. (2013). Skin rash could predict the response to EGFR tyrosine kinase inhibitor and the prognosis for patients with non-small cell lung cancer: A systematic review and meta-analysis. *PloS One, 8*(1), e55128. doi:10.1371/journal.pone.0055128 [doi]

Lundberg, F., Andersson, T., Lambe, M., Engholm, G., Mørch, L., Johannesen, T., Virtanen, A., ... Lambert, P. (2020). Trends in cancer survival in the Nordic countries 1990–2016: the NORDCAN survival studies. *Acta Oncologica, 59:11,* 1266-1274, DOI: 10.1080/0284186X.2020.1822544 [doi]

Melosky, B., Anderson, H., Burkes, R. L., Chu, Q., Hao, D., Ho, V., . . . Laskin, J. J. (2016). Pan canadian rash trial: A randomized phase III trial evaluating the impact of a prophylactic skin treatment regimen on epidermal growth factor receptor-tyrosine kinase inhibitor-induced skin toxicities in patients with metastatic lung cancer. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology, 34*(8), 810-815. doi:10.1200/JCO.2015.62.3918 [doi]

Mirsadraee, S., Oswal, D., Alizadeh, Y., Caulo, A., & van Beek, E.,Jr. (2012). The 7th lung cancer TNM classification and staging system: Review of the changes and implications. *World Journal of Radiology, 4*(4), 128-134. doi:10.4329/wjr.v4.i4.128 [doi]

Mok, T., Camidge, D. R., Gadgeel, S. M., Rosell, R., Dziadziuszko, R., Kim, D. W., . . . Peters, S. (2020). Updated overall survival and final progression-free survival data for patients with treatment-naive advanced ALK-positive non-small-cell lung cancer in the ALEX study. *Annals of Oncology : Official Journal of the European Society for Medical Oncology, 31*(8), 1056-1064. doi:S0923-7534(20)39796-9 [pii]

Mok, T. S., Wu, Y. -., Ahn, M. -., Garassino, M. C., Kim, H. R., Ramalingam, S. S., . . . AURA3 Investigators. (2017). Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. *The New England Journal of Medicine, 376*(7), 629-640. doi:10.1056/NEJMoa1612674 [doi]

Mullin, M. L. L., Tran, A., Golemiec, B., Stone, C. J. L., Noseworthy, C., O'Callaghan, N., . . . Digby, G. C. (2020). Improving timeliness of lung cancer diagnosis and staging investigations through implementation of standardized triage pathways. *JCO Oncology Practice, 16*(10), e1202-e1208. doi:10.1200/JOP.19.00807 [doi]

Murphy, S. (2021). Biochemistry of nicotine metabolism and its relevance to lung cancer. *Journal of Biological Chemistry, 296, 100722.* doi:10.1016/j.jbc.2021.100722 [doi]

Myall, N. J., & Das, M. (2020). Advances in the treatment of stage III non-small cell lung cancer. *Clinics in Chest Medicine, 41*(2), 211-222. doi:S0272-5231(20)30010-1 [pii]

National Collaborating Centre for Cancer, (UK). (2011). The diagnosis and treatment of lung cancer. doi:NBK99021 [bookaccession]

National Lung Screening Trial Research Team, Church, T. R., Black, W. C., Aberle, D. R., Berg, C. D., Clingan, K. L., . . . Baum, S. (2013). Results of initial low-dose computed tomographic screening for lung cancer. *The New England Journal of Medicine, 368*(21), 1980-1991. doi:10.1056/NEJMoa1209120 [doi]

Neal, R. D., Tharmanathan, P., France, B., Din, N. U., Cotton, S., Fallon-Ferguson, J., . . . Emery, J. (2015). Is increased time to diagnosis and treatment in symptomatic cancer associated with poorer outcomes? systematic review. *British Journal of Cancer, 112 Suppl 1*(Suppl 1), 92. doi:10.1038/bjc.2015.48 [doi]

Nemesure, B., Albano, D., & Bilfinger, T. (2020). Lung cancer recurrence and mortality outcomes over a 10-year period using a multidisciplinary team approach. *Cancer Epidemiology, 68*, 101804. doi:S1877-7821(20)30138-7 [pii]

Non-Small Cell Lung Cancer Collaborative Group. (2010). Chemotherapy and supportive care versus supportive care alone for advanced non-small cell lung cancer. *The Cochrane Database of Systematic Reviews, (5):CD007309. doi*(5), CD007309. doi:10.1002/14651858.CD007309.pub2 [doi]

Ocvirk, J., Heeger, S., McCloud, P., & Hofheinz, R. D. (2013). A review of the treatment options for skin rash induced by EGFR-targeted therapies: Evidence from randomized clinical trials and a meta-analysis. *Radiology and Oncology, 47*(2), 166-175. doi:10.2478/raon-2013-0014 [doi]

O'Keeffe, L. M., Taylor, G., Huxley, R. R., Mitchell, P., Woodward, M., & Peters, S. A. E. (2018). Smoking as a risk factor for lung cancer in women and men: A systematic review and meta-analysis. *BMJ Open, 8*(10), e021611-021611. doi:10.1136/bmjopen-2018-021611 [doi]

Olsson, J. K., Schultz, E. M., & Gould, M. K. (2009). Timeliness of care in patients with lung cancer: A systematic review. *Thorax, 64*(9), 749-756. doi:10.1136/thx.2008.109330 [doi]

Osmani, L., Askin, F., Gabrielson, E., & Li, Q. K. (2018). Current WHO guidelines and the critical role of immunohistochemical markers in the subclassification of non-small cell lung carcinoma (NSCLC): Moving from targeted therapy to immunotherapy. *Seminars in Cancer Biology, 52*(Pt 1), 103-109. doi:S1044-579X(17)30097-4 [pii]

Pattison, A., Jeagal, L., Yasufuku, K., Pierre, A., Donahoe, L., Yeung, J., . . . Czarnecka-Kujawa, K. (2020). The impact of concordance with a lung cancer diagnosis pathway guideline on treatment access in patients with stage IV lung cancer. *Journal of Thoracic Disease, 12*(8), 4327-4337. doi:10.21037/jtd-20-157 [doi]

Paz-Ares, L., Ciuleanu, T. E., Cobo, M., Schenker, M., Zurawski, B., Menezes, J., . . . Reck, M. (2021). First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): An international, randomised, open-label, phase 3 trial. *The Lancet.Oncology, 22*(2), 198-211. doi:S1470-2045(20)30641-0 [pii]

Paz-Ares, L., de Marinis, F., Dediu, M., Thomas, M., Pujol, J. L., Bidoli, P., . . . Gridelli, C. (2012). Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): A double-blind, phase 3, randomised controlled trial. *The Lancet.Oncology, 13*(3), 247-255. doi:10.1016/S1470-2045(12)70063-3 [doi]

Paz-Ares, L., Spira, A., Raben, D., Planchard, D., Cho, B. C., Özgüroğlu, M., . . . Faivre-Finn, C. (2020). Outcomes with durvalumab by tumour PD-L1 expression in unresectable, stage III non-small-cell lung cancer in the PACIFIC trial. *Annals of Oncology : Official Journal of the European Society for Medical Oncology, 31*(6), 798-806. doi:S0923-7534(20)36374-2 [pii]

Paz-Ares, L., Tan, E. H., O'Byrne, K., Zhang, L., Hirsh, V., Boyer, M., . . . Park, K. (2017). Afatinib versus gefitinib in patients with EGFR mutation-positive advanced non-small-cell lung cancer: Overall survival data from the phase IIb LUX-lung 7 trial. *Annals of Oncology : Official Journal of the European Society for Medical Oncology, 28*(2), 270-277. doi:10.1093/annonc/mdw611 [doi]

Paz-Ares, L., Vicente, D., Tafreshi, A., Robinson, A., Soto Parra, H., Mazières, J., . . . Halmos, B. (2020). A randomized, placebo-controlled trial of pembrolizumab plus chemotherapy in patients with metastatic squamous NSCLC: Protocol-specified final analysis of KEYNOTE-407. *Journal of Thoracic Oncology : Official Publication of the International Association for the Study of Lung Cancer, 15*(10), 1657-1669. doi:S1556-0864(20)30500-1 [pii]

Pedersen J., Sørensen J., Zaghir J., Fløtten Ø., Brustugun O. . . . . (2017). Implementation of lung cancer CT screening in the Nordic countries. *Acta Oncologica, 56:10*, 1249-1257, doi: 10.1080/0284186X.2017.1329592 [doi]

Peifer, M., Fernández-Cuesta, L., Sos, M. L., George, J., Seidel, D., Kasper, L. H., . . . Thomas, R. K. (2012). Integrative genome analyses identify key somatic driver mutations of small-cell lung cancer. *Nature Genetics, 44*(10), 1104-1110. doi:10.1038/ng.2396 [doi]

Petrelli, F., Borgonovo, K., Cabiddu, M., Coinu, A., Ghilardi, M., Lonati, V., & Barni, S. (2016). Antibiotic prophylaxis for skin toxicity induced by antiepidermal growth factor receptor agents: A systematic review and meta-analysis. *The British Journal of Dermatology, 175*(6), 1166-1174. doi:10.1111/bjd.14756 [doi]

Petrelli, F., Borgonovo, K., Cabiddu, M., Lonati, V., & Barni, S. (2012). Relationship between skin rash and outcome in non-small-cell lung cancer patients treated with anti-EGFR tyrosine kinase inhibitors: A literature-based meta-analysis of 24 trials. *Lung Cancer (Amsterdam, Netherlands), 78*(1), 8-15. doi:S0169-5002(12)00390-X [pii]

Pillay, B., Wootten, A. C., Crowe, H., Corcoran, N., Tran, B., Bowden, P., . . . Costello, A. J. (2016). The impact of multidisciplinary team meetings on patient assessment, management and outcomes in oncology settings: A systematic review of the literature. *Cancer Treatment Reviews, 42*, 56-72. doi:S0305-7372(15)00224-8 [pii]

Pirie, K., Peto, R., Reeves, G. K., Green, J., & Beral, V. (2013). The 21st century hazards of smoking and benefits of stopping: A prospective study of one million women in the UK. *The Lancet, 381*(9861), 133-141. doi:https://doi.org/10.1016/S0140-6736(12)61720-6

Planchard, D., Popat, S., Kerr, K., Novello, S., Smit, E. F., Faivre-Finn, C., . . . ESMO Guidelines Committee. (2018). Metastatic non-small cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Annals of Oncology : Official Journal of the European Society for Medical Oncology, 29*(Suppl 4), iv192-iv237. doi:10.1093/annonc/mdy275 [doi]

Postmus, P. E., Kerr, K. M., Oudkerk, M., Senan, S., Waller, D. A., Vansteenkiste, J., . . . ESMO Guidelines Committee. (2017). Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Annals of Oncology : Official Journal of the European Society for Medical Oncology, 28*(suppl_4), iv1-iv21. doi:10.1093/annonc/mdx222 [doi]

Postoperative radiotherapy in non-small-cell lung cancer: Systematic review and meta-analysis of individual patient data from nine randomised controlled trials. PORT meta-analysis trialists group. (1998). *Lancet (London, England), 352*(9124), 257-263. doi:S0140673698063417 [pii]

Ramalingam, S. S., Vansteenkiste, J., Planchard, D., Cho, B. C., Gray, J. E., Ohe, Y., . . . FLAURA Investigators. (2020). Overall survival with osimertinib in untreated, EGFR-mutated advanced NSCLC. *The New England Journal of Medicine, 382*(1), 41-50. doi:10.1056/NEJMoa1913662 [doi]

Raso, M. G., Bota-Rabassedas, N., & Wistuba, I. I. (2021). Pathology and classification of SCLC. *Cancers, 13*(4), 820. doi: 10.3390/cancers13040820. doi:10.3390/cancers13040820 [doi]

Reduced lung-cancer mortality with low-dose computed tomographic screening. (2011). *N Engl J Med, 365*(5), 395-409. doi:10.1056/NEJMoa1102873

Reck, M., Rodríguez-Abreu, D., Robinson, A. G., Hui, R., Csőszi, T., Fülöp, A., . . . Brahmer, J. R. (2019). Updated analysis of KEYNOTE-024: Pembrolizumab versus platinum-based chemotherapy for advanced non-small-cell lung cancer with PD-L1 tumor proportion score of 50% or greater. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology, 37*(7), 537-546. doi:10.1200/JCO.18.00149 [doi]

Rivera, M. P., Mehta, A. C., & Wahidi, M. M. (2013). Establishing the diagnosis of lung cancer: Diagnosis and management of lung cancer, 3rd ed: American college of chest physicians evidence-based clinical practice guidelines. *Chest, 143*(5 Suppl), e142S-e165S. doi:S0012-3692(13)60293-7 [pii]

Robertson, W. W., Steliga, M. A., Siegel, E. R., & Arnaoutakis, K. (2014). Accuracy of fine needle aspiration and core lung biopsies to predict histology in patients with non-small cell lung cancer. *Medical Oncology (Northwood, London, England), 31*(6), 967-7. Epub 2014 Apr 29. doi:10.1007/s12032-014-0967-7 [doi]

Rolfo, C., Mack, P. C., Scagliotti, G. V., Baas, P., Barlesi, F., Bivona, T. G., . . . Gandara, D. R. (2018). Liquid biopsy for advanced non-small cell lung cancer (NSCLC): A statement paper from the IASLC. *Journal of Thoracic Oncology : Official Publication of the International Association for the Study of Lung Cancer, 13*(9), 1248-1268. doi:S1556-0864(18)30680-4 [pii]

Rossi, A., Garassino, M. C., Cinquini, M., Sburlati, P., Di Maio, M., Farina, G., . . . Torri, V. (2010). Maintenance or consolidation therapy in small-cell lung cancer: A systematic review and meta-analysis. *Lung Cancer (Amsterdam, Netherlands), 70*(2), 119-128. doi:10.1016/j.lungcan.2010.02.001 [doi]

Russo, A., Franchina T., Ricciardi G., Picone A., Ferraro G., Zanghi M. (2015). A decade of EGFR inhibition in EGFR-mutated non small cell lung cancer (NSCLC): Old successes and future perspectives. *Oncotarget, 6(29)*: 26814–26825. doi: 10.18632/oncotarget.4254 [doi]

Salomaa, E., Sällinen S., Hiekkanen, H., Liippo, K. (2005) Delays in the diagnosis and treatment of lung cancer. *Chest, 128(4)* :2282-8. doi: 10.1378/chest.128.4.2282 [doi]

Saltos, A., Shafique, M., & Chiappori, A. (2020). Update on the biology, management, and treatment of small cell lung cancer (SCLC). *Frontiers in Oncology, 10*, 1074. doi:10.3389/fonc.2020.01074 [doi]

Sampsonas, F., Kakoullis, L., Lykouras, D., Karkoulias, K., & Spiropoulos, K. (2018). EBUS: Faster, cheaper and most effective in lung cancer staging. *International Journal of Clinical Practice, 72*(2), 10.1111/ijcp.13053. Epub 2018 Jan 3. doi:10.1111/ijcp.13053 [doi]

Schabath, M. B., & Cote, M. L. (2019). Cancer progress and priorities: Lung cancer. *Cancer Epidemiology, Biomarkers & Prevention : A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology, 28*(10), 1563-1579. doi:10.1158/1055-9965.EPI-19-0221 [doi]

Schmidt-Hansen, M., Baldwin, D. R., Hasler, E., Zamora, J., Abraira, V., & Roqué I Figuls, M. (2014). PET-CT for assessing mediastinal lymph node involvement in patients with suspected resectable non-small cell lung cancer. *The Cochrane Database of Systematic Reviews, 2014*(11), CD009519. doi:10.1002/14651858.CD009519.pub2 [doi]

Senan, S., Brade, A., Wang, L. H., Vansteenkiste, J., Dakhil, S., Biesma, B., . . . Vokes, E. (2016). PROCLAIM: Randomized phase III trial of pemetrexed-cisplatin or etoposide-cisplatin plus thoracic radiation therapy followed by consolidation chemotherapy in locally advanced nonsquamous non-small-cell lung cancer. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology, 34*(9), 953-962. doi:10.1200/JCO.2015.64.8824 [doi]

Shah, R. R., & Shah, D. R. (2019). Safety and tolerability of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors in oncology. *Drug Safety, 42*(2), 181-198. doi:10.1007/s40264-018-0772-x [doi]

Shepherd, F. A., Rodrigues Pereira, J., Ciuleanu, T., Tan, E. H., Hirsh, V., Thongprasert, S., . . . National Cancer Institute of Canada Clinical Trials Group. (2005). Erlotinib in previously treated non-small-cell lung cancer. *The New England Journal of Medicine, 353*(2), 123-132. doi:353/2/123 [pii]

Solomon, B. J., Besse, B., Bauer, T. M., Felip, E., Soo, R. A., Camidge, D. R., . . . Shaw, A. T. (2018). Lorlatinib in patients with ALK-positive non-small-cell lung cancer: Results from a global phase 2 study. *The Lancet.Oncology, 19*(12), 1654-1667. doi:S1470-2045(18)30649-1 [pii]

Soria, J. C., Ohe, Y., Vansteenkiste, J., Reungwetwattana, T., Chewaskulyong, B., Lee, K. H., . . . FLAURA Investigators. (2018). Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *The New England Journal of Medicine, 378*(2), 113-125. doi:10.1056/NEJMoa1713137 [doi]

Suomen syöpärekisteri. (2019).

Suster, D. I., & Mino-Kenudson, M. (2020). Molecular pathology of primary non-small cell lung cancer. *Archives of Medical Research, 51*(8), 784-798. doi:S0188-4409(20)31460-0 [pii]

Taniguchi, H., Sen, T., & Rudin, C. M. (2020). Targeted therapies and biomarkers in small cell lung cancer. *Frontiers in Oncology, 10*, 741. doi:10.3389/fonc.2020.00741 [doi]

Temel, J. S., Greer, J. A., El-Jawahri, A., Pirl, W. F., Park, E. R., Jackson, V. A., . . . Ryan, D. P. (2017). Effects of early integrated palliative care in patients with lung and GI cancer: A randomized clinical trial. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology, 35*(8), 834-841. doi:10.1200/JCO.2016.70.5046 [doi]

Temel, J. S., Greer, J. A., Muzikansky, A., Gallagher, E. R., Admane, S., Jackson, V. A., . . . Lynch, T. J. (2010). Early palliative care for patients with metastatic non-small-cell lung cancer. *The New England Journal of Medicine, 363*(8), 733-742. doi:10.1056/NEJMoa1000678 [doi]

Thai, A. A., & Solomon, B. J. (2018). Treatment of ALK-positive nonsmall cell lung cancer: Recent advances. *Current Opinion in Oncology, 30*(2), 84-91. doi:10.1097/CCO.0000000000000431 [doi]

Thatcher, N., Chang, A., Parikh, P., Rodrigues Pereira, J., Ciuleanu, T., von Pawel, J., . . . Carroll, K. (2005). Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: Results from a randomised, placebo-controlled, multicentre study (iressa survival evaluation in lung cancer). *Lancet (London, England), 366*(9496), 1527-1537. doi:S0140-6736(05)67625-8 [pii]

Timofeeva, M. N., Hung, R. J., Rafnar, T., Christiani, D. C., Field, J. K., Bickeböller, H., . . . Transdisciplinary Research in Cancer of the Lung (TRICL) Research Team. (2012). Influence of common genetic variation on lung cancer risk: Meta-analysis of 14 900 cases and 29 485 controls. *Human Molecular Genetics, 21*(22), 4980-4995. doi:10.1093/hmg/dds334 [doi]

Tørring, M. L., Frydenberg, M., Hansen, R. P., Olesen, F., & Vedsted, P. (2013). Evidence of increasing mortality with longer diagnostic intervals for five common cancers: A cohort study in primary care. *European Journal of Cancer (Oxford, England : 1990), 49*(9), 2187-2198. doi:S0959-8049(13)00088-9 [pii]

Ung, K. A., Campbell, B. A., Duplan, D., Ball, D., & David, S. (2016). Impact of the lung oncology multidisciplinary team meetings on the management of patients with cancer. *Asia-Pacific Journal of Clinical Oncology, 12*(2), 298. doi:10.1111/ajco.12192 [doi]

Usman Ali, M., Miller, J., Peirson, L., Fitzpatrick-Lewis, D., Kenny, M., Sherifali, D., & Raina, P. (2016). Screening for lung cancer: A systematic review and meta-analysis. *Preventive Medicine, 89*, 301-314. doi:S0091-7435(16)30070-6 [pii]

Villalobos, P., & Wistuba, I. I. (2017). Lung cancer biomarkers. *Hematology/Oncology Clinics of North America, 31*(1), 13-29. doi:S0889-8588(16)30120-4 [pii]

Vineis, P., & Wild, C. P. (2014). Global cancer patterns: Causes and prevention. *Lancet (London, England), 383*(9916), 549-557. doi:S0140-6736(13)62224-2 [pii]

Vinod, S. K., Chandra, A., Berthelsen, A., & Descallar, J. (2017). Does timeliness of care in non-small cell lung cancer impact on survival? *Lung Cancer (Amsterdam, Netherlands), 112*, 16-24. doi:S0169-5002(17)30420-8 [pii]

Wakeam, E., Acuna, S. A., Leighl, N. B., Giuliani, M. E., Finlayson, S. R. G., Varghese, T. K., & Darling, G. E. (2017). Surgery versus chemotherapy and radiotherapy for early and locally advanced small cell lung cancer: A propensity-matched analysis of survival. *Lung Cancer (Amsterdam, Netherlands), 109*, 78-88. doi:S0169-5002(17)30308-2 [pii]

Wang, J., Liu, Q., Yuan, S., Xie, W., Liu, Y., Xiang, Y., . . . Li, Y. (2017). Genetic predisposition to lung cancer: Comprehensive literature integration, meta-analysis, and multiple evidence assessment of candidate-gene association studies. *Scientific Reports, 7*(1), 8371. doi:10.1038/s41598-017-07737-0

Wu, Y. L., Cheng, Y., Zhou, X., Lee, K. H., Nakagawa, K., Niho, S., . . . Mok, T. S. (2017). Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): A randomised, open-label, phase 3 trial. *The Lancet.Oncology, 18*(11), 1454-1466. doi:S1470-2045(17)30608-3 [pii]

Wu, Y. L., Tsuboi, M., He, J., John, T., Grohe, C., Majem, M., . . . ADAURA Investigators. (2020). Osimertinib in resected EGFR-mutated non-small-cell lung cancer. *The New England Journal of Medicine, 383*(18), 1711-1723. doi:10.1056/NEJMoa2027071 [doi]

Yang, S., Zhang, Z., & Wang, Q. (2019). Emerging therapies for small cell lung cancer. *Journal of Hematology & Oncology, 12*(1), 47-3. doi:10.1186/s13045-019-0736-3 [doi]

Yang, Z., Hackshaw, A., Feng, Q., Fu, X., Zhang, Y., Mao, C., & Tang, J. (2017). Comparison of gefitinib, erlotinib and afatinib in non-small cell lung cancer: A meta-analysis. *International Journal of Cancer, 140*(12), 2805-2819. doi:10.1002/ijc.30691 [doi]

Yi, L., Fan, J., Qian, R., Luo, P., & Zhang, J. (2019). Efficacy and safety of osimertinib in treating EGFR-mutated advanced NSCLC: A meta-analysis. *International Journal of Cancer, 145*(1), 284-294. doi:10.1002/ijc.32097 [doi]

Yu, H., Boyle, T. A., Zhou, C., Rimm, D. L., & Hirsch, F. R. (2016). PD-L1 expression in lung cancer. *Journal of Thoracic Oncology : Official Publication of the International Association for the Study of Lung Cancer, 11*(7), 964-975. doi:S1556-0864(16)30340-9 [pii]

Yue, D., Xu, S., Wang, Q., Li, X., Shen, Y., Zhao, H., . . . Wang, C. (2018). Erlotinib versus vinorelbine plus cisplatin as adjuvant therapy in chinese patients with stage IIIA EGFR mutation-positive non-small-cell lung cancer (EVAN): A randomised, open-label, phase 2 trial. *The Lancet.Respiratory Medicine, 6*(11), 863-873. doi:S2213-2600(18)30277-7 [pii]

Zhao, Y., Liu, J., Cai, X., Pan, Z., Liu, J., Yin, W., . . . He, J. (2019). Efficacy and safety of first line treatments for patients with advanced epidermal growth factor receptor mutated, non-small cell lung cancer: Systematic review and network meta-analysis. *BMJ (Clinical Research Ed.), 367*, l5460. doi:10.1136/bmj.l5460 [doi]

Original articles

I Alanen V, Koivunen JP. (2019). Association of diagnostic delays to survival in lung cancer: single center experience. *Acta Oncol. 2019 Jul;58*(7):1056-1061

II Alanen V, Iivanainen S, Arffman M, Koivunen JP. (2020). Tetracyclines increase the survival of NSCLC patients treated with EGFR TKIs: a retrospective nationwide registry study. *ESMO Open. 2020 Oct;5*(5):e000864.

III Alanen V, Iivanainen S, Arffman M, Koivunen JP. (2021). Purchase of prophylactic topical corticosteroids is associated with improved survival in NSCLCs treated with EGFR TKI: real-world cohort study. *Acta Oncologica*, DOI: 10.1080/0284186X.2021.1937309.

Original publications are not included in the electronic version of the dissertation.

1649. Nortunen, Minna (2021) Carbonic anhydrases II, IX, and XII in esophageal and duodenal diseases

1650. Lohi, Venla (2021) Hearing impairment among ageing adults in Northern Finland : prevalence, incidence and risk factors

1651. Khatun, Masuma (2021) The endometrium in disease : studies on endometrial stem cells, polycystic ovary syndrome, and stanniocalcin-1

1652. Hannonen, Juuli (2021) Humerus fractures in children : treatment trends and surgical techniques

1653. Parkkila, Karri (2021) Biomarkers and clinical parameters in comprehensive cardiovascular risk estimation

1654. Korkalainen, Noora (2022) Long-term neurologic and cardiovascular outcome in fetal growth restriction : a longitudinal study from prenatal period to early school age

1655. Kiiskilä, Jukka (2022) Association of mitochondrial DNA haplogroups with endurance performance

1656. Kyrklund, Mikael (2022) Antibody response to oxidized epitopes and oral bacteria in atherosclerosis

1657. Salin, Janne (2022) Luokkahuoneen sisäilman mikrobien ja pölyn toksisuudet lisäävät opettajien työympäristöön liittyvien oireiden riskiä : poikkileikkaustutkimus

1658. Kanavakis, Georgios (2022) Associations of facial profile and occlusion in the Northern Finland Birth Cohort 1966

1659. Khakpour, Shahab (2022) Multi-component finite element analysis of low-energy acetabular fracture : computational study of pelvic girdle fracture mechanism

1660. Tapio, Joona (2022) Role of HIF-P4H inhibition and hemoglobin levels in metabolic diseases

1661. Pihlaja, Toni (2022) Varicose vein disease : postoperative care and treatment of venous ulcers

1662. Heula, Anna-Leena (2022) Meningeal protein synthesis in chronic subdural hemorrhagies : analysis of proteins and evaluation of their clinical significance

1663. Erikson, Kristo (2022) The brain as an end organ in sepsis?

1664. Karvonen, Elina (2022) Glaucoma screening in the Northern Finland Birth Cohort Eye Study

Book orders:
Virtual book store
http://verkkokauppa.juvenesprint.fi

UNIVERSITY OF OULU P.O. Box 8000 FI-90014 UNIVERSITY OF OULU FINLAND

ACTA UNIVERSITATIS OULUENSIS

ISBN 978-952-62-3260-7 (Paperback)
ISBN 978-952-62-3261-4 (PDF)
ISSN 0355-3221 (Print)
ISSN 1796-2234 (Online)

UNIVERSITY OF OULU