UMEÅ UNIVERSITY

# FACTORS INFLUENCING MANAGEMENT AND OUTCOME IN NON-SMALL CELL LUNG CANCER

## The role of socioeconomic status, age, geographic region of origin and aspects of quality of life

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*To my mother and father*

*Education is the most powerful weapon*
*which you can use to change the world*
*-Nelson Mandela*

# List of scientific papers

This thesis is based on the following papers which are referred to in the text by their Roman numerals

I. **Willén L**, Berglund A, Bergström S, Bergqvist M, Öjdahl-Bodén A, Wagenius G, Lambe M. Educational level and management and outcomes in non-small cell lung cancer. A nationwide population-based study. Lung Cancer. 2019 May;131:40-46.

II. **Willén L**, Berglund A, Bergström S, Isaksson J, Bergqvist M, Wagenius G, Lambe M. Are older patients with non-small cell lung cancer receiving optimal care? A population-based study. Acta Oncol. 2022 Mar;61(3):309-317.

III. **Willén L**, Berglund A, Bergström S, Isaksson J, Bergqvist M, Wagenius G, Lambe M. Patterns of care and outcomes in immigrants with non-small cell lung cancer. A population-based study (Sweden). PLoS One. 2022 Dec 15;17(12): e0278706.

IV. **Willén L**, Berglund A, Bergström S, Isaksson J, Bergqvist M, Wagenius G, Lambe M. Depression, intoxication and suicide following a diagnosis of non-small cell lung cancer. A population-based study. *Manuscript*.

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Scientific papers not included in the thesis.

- Berglund A, **Willén L**, Grödeberg L, Skattum L, Hagberg H, Pauksens K. The response to vaccination against influenza A(H1N1) 2009, seasonal influenza and Streptococcus pneumoniae in adult outpatients with ongoing treatment for cancer with and without rituximab. Acta Oncol. 2014 Sep;53(9):1212-20.

- Holgersson G, Bergstrom S, Hallqvist A, Liv P, Nilsson J, **Willén L**, Nyman J, Ekman S, Henriksson R, Bergqvist M. The prognostic value of pre-treatment thrombocytosis in two cohorts of patients with non-small cell lung cancer treated with curatively intended chemoradiotherapy. Neoplasma. 2017;64(6):909-915.

- Isaksson J, Wennström L, Branden E, Koyi H, Berglund A, Micke P, Mattsson JSM, **Willén L**, Botling J. Highly elevated systemic inflammation is a strong independent predictor of early mortality in advanced non-small cell lung cancer. Cancer Treat Res Commun. 2022;31:100556.

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# Abstract

Yearly, 4,200 individuals in Sweden are diagnosed with lung cancer, of which 85 % are non-small cell lung cancer (NSCLC). The aims of this thesis were to investigate aspects of equality of care and outcomes in patients with NSCLC and to examine indicators of quality of life.

All studies used data in Lung Cancer Database Sweden (LCBaSe), a research database generated by record linkages between the National Lung Cancer Register and other population-based registers. We identified 40,000 patients with NSCLC diagnosed between 2002 and 2016.

**Paper I** examined influence of socioeconomic status. Patients with a high educational level were more often offered PET-CT, assessed in a multidisciplinary team setting, treated with stereotactic body radiotherapy and had better survival in early-, but not in late-stage disease.

**Paper II** investigated elderly NSCLC patients. No difference in stage was seen in patients ≤ 84 years, nor in diagnostic intensity <80 years. Treatment intensity was adapted according to age. Survival differed across age groups in early-, but not late-stage disease.

**Paper III** examined immigrants. We found evidence of a "healthy migrant effect". There were only small differences in management and outcome. If anything, non-Nordic immigrants had better survival in early-stage disease.

**Paper IV** assessed psychological impact following a NSCLC diagnosis. Higher rates of depression, anxiety, intoxication and suicide were seen in NSCLC patients compared to lung cancer free individuals. The risk of depression, anxiety and suicide decreased over time but the increased risk of intoxication remained throughout the follow-up period.

**In summary,** we found equal access of care and only minor differences in patterns of management and outcomes according to socioeconomic status, age and geographic region of origin. New diagnostics and treatment modalities need to be quickly introduced to enable equal access across socioeconomic groups. A careful assessment of older patients is important to avoid age-biased clinical decision-making. A diagnosis of NSCLC impacts psychological aspects of quality of life and active measures to identify and treat depression and anxiety as well as to identify patients at risk of intoxication and suicide is necessary.

*Keywords:* Lung neoplasms, NSCLC, Sweden, socioeconomic factors, educational level, aged, elderly, immigration, depressive disorder, dysthymic disorder, anxiety, suicide, survival, registries.

# Abbreviations

| | |
|---|---|
| AJCC | American Joint Committee on Cancer |
| ALK | Anaplastic Lymphoma Kinase |
| ATC | Anatomical Therapeutic Chemical Classification System |
| BRAF | V-raf Murine Sarcoma Viral Oncogene Homolog B |
| CCI | Charlson Comorbidity Index |
| CGA | Comprehensive Geriatric Assessment |
| CI | Confidence Interval |
| CIRS-G | Cumulative Illness Rating Scale for Geriatrics |
| CNS | Central Nervous System |
| CT | Computed Tomography |
| DANTE | The Detection and Screening of Early Lung Cancer with Novel Imaging Technology and Molecular Assays |
| DLCST | The Danish Lung Cancer Screening Trial |
| EBUS | Endobronchial Ultrasound |
| EGFR | Epidermal Growth Factor Receptor |
| ECOG | Eastern Cooperative Oncology Group |
| FDG | Fluorodeoxyglucose |
| GDPR | The General Data Protection Regulation |
| KRAS | Kirsten Rat Sarcoma Viral Oncogene Homolog |
| HER-2 | Human Epidermal Growth Factor 2 |
| HR | Hazard Ratio |
| IASLC | International Association for the Study on Lung Cancer |
| ICD | International Classification of Diseases |
| LCBaSe | Lung Cancer Database Sweden |
| LISA | Longitudinal Integration Database for Health Insurance and Labour Market Studies |
| MET | Mesenchymal-epithelial Transition |
| MILD | The Multicentric Italian Lung Detection Trial |

| | |
|---|---|
| MRI | Magnetic Resonance Imaging |
| NELSON | The Nederlands-Leuvens Longkanker Screenings Onderzoek Trial |
| NLST | The National Lung Screening Trial |
| NOS | Not Otherwise Specified |
| NRG | Neuregulin 1 |
| NSCLC | Non-Small Cell Lung Cancer |
| NTRK | Neurotrophin Receptor Tyrosine Kinase |
| OR | Odds Ratio |
| PET-CT | Positron Emission Tomography - Computed Tomography |
| PIN | Personal Identity Number |
| RATS | Robot-Assisted Thoracic Surgery |
| RCC | Regional Cancer Centre |
| RET | Rearranged during Transfection |
| ROS1 | ROS proto-oncogene 1 |
| RUT | Register Utiliser Tool |
| SCR | Swedish Cancer Register |
| SCLC | Small Cell Lung Cancer |
| SDI | Socio-Demographic Index |
| SES | Socioeconomic Status |
| SBRT | Stereotactic Body Radiotherapy |
| PS | Performance Status |
| TNM | Tumor,-Nodes-Metastasis |
| UHCS | Uniform Health Care System |
| UICC | The Union for International Cancer Control |
| VATS | Video-Assisted Thoracoscopic Surgery |
| VEGF | Vascular Endothelial Growth Factor Receptors |
| WHO | World Health Organization |

# Background

## General demographics

### Population numbers

In recent decades there has been a sharp increase in the size of the Swedish population that reached 10.45 million in 2021. The population has increased from a total of 8 million in 1969, 9 million in 2004 and 10 million in 2017. It is estimated that Sweden will have 11 million inhabitants in 2028 and 13 million in 2070 [1]. The increase reflects high birth rates and high levels of immigration.

### Life expectancy

In the 18th century, only one in three inhabitants reached an age of 60 years compared to one in two in the 19th century. In 2018, every fifth person in Sweden was 65 years or older and it is predicted that one fourth of the population will be older than 65 years in 2070 [1]. Between 1970 and 2021, the average life expectancy increased from 77.1 years to 84.8 years in women and from 72.2 to 81.2 years in men [2, 3]. Today, only 9 % of women and 14 % of men die before the age of 65 [4]. Yearly, 92,000 deaths are recorded; the most common cause of death is cardiovascular disease followed by cancer [5].

### Immigration

Immigration to Sweden was very low prior to the 1930s, instead Swedes emigrated. Between 1860 and 1930 1.4 million Swedes emigrated, mainly to the USA. Of Swedes born between 1850 and 1900, 20 % of men and 15 % of women emigrated [6]. Immigration to Sweden began to increase in the 1930s and was up to the 1970s mainly labor related because of booming industries in Sweden and poor economies in Finland and other European countries. In the 1970s a peak of refugees arrived from Iran and in the 1990s from former Yugoslavia. In more recent decades, there has been a shift from labor immigration to immigration of refugees due to wars or political conflicts (**Figure 1**).

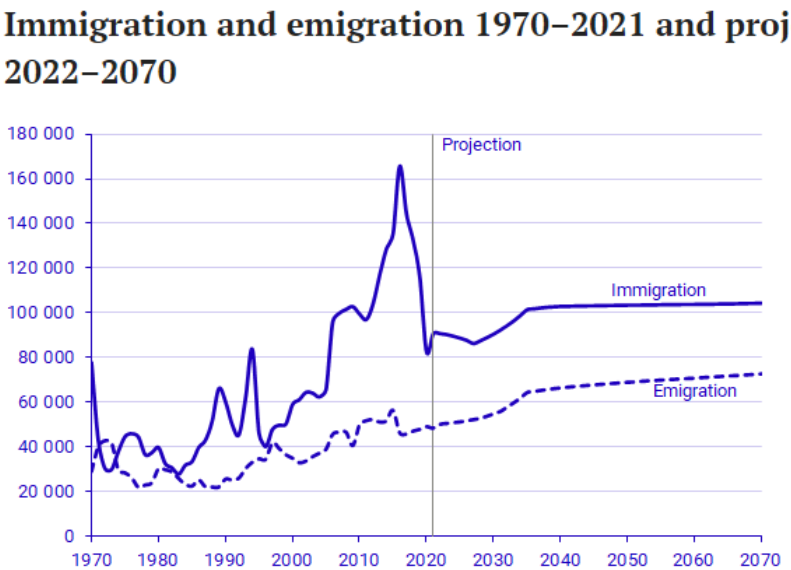


***Figure 1**. Data from Statistics Sweden on immigration and emigration in Sweden in absolute numbers between 1970-2021 as well as a projection for 2022-2070 [7].*

In 2000 Sweden had 1 million foreign born residents but this has since increased to 2 million inhabitants in 2021 thus representing 20 % of the Swedish population [2]. In 2016 immigration peaked with 163 000 new arrivals but numbers has since declined and 90 000 immigrants entered Sweden in 2021 [8]. Re-emigrating Swedes were the most common immigrant entering Sweden in 2021, followed by individuals born in India, Syria, Germany, Pakistan, Poland, Iran, Iraq, Turkey, China and Afghanistan [8]. The most common age at immigration is 25-34 years [8].

In 2021, the largest foreign born population group in Sweden was individuals from Syria with approximately 196,000 individuals followed by Iraq 147,000, Finland 137,000, Poland 95,000 and Iran 83,000 individuals. Of the Nordic immigrants, Finland is the most common country of origin with 137,000 individuals followed by Norway 41,000, Denmark 38,000 and Iceland 6,000 individuals [9]. To a high extent, immigrants reside in urban areas in Sweden; mainly in the regions of Stockholm, Skåne and Västra Götaland [10].

Emigration is defined as individuals taking residence in a country outside of Sweden for more than 12 months. In 2001, 32 000 individuals emigrated compared to 55 000 in 2015 and 48 000 in 2021. Emigration is most common in foreign-born individuals, primarily among those that came to Sweden for work or education as opposed to refugees or immigration due to family-ties [6]. However, in absolute numbers the ten most common countries of birth in emigrants 2021 was Sweden, Finland, India, Poland, Iraq, Denmark, Germany, Norway, Syria and the USA. Similar to the age distribution in immigrants, the most common age for emigration is 25-34 years [6].

## Educational level

There has been a shift in educational level. In 1990, one in 10 individuals obtained a higher education corresponding to three or more years of post-secondary schooling (University or University College). Today, 52 % of women and 39 % of men continues their schooling beyond 12 years with 30 % obtaining a higher educational degree. Individuals with a high education are more often women, with highly educated parents and living in the larger regions of Sweden with proximity to centers of higher education [1, 11]. Correspondingly, the proportion of individuals with a low education ≤ 9 years is declining. In 2000, 21 % of Swedes had a low level of education compared to 10 % in 2021.

## Depression and deaths due to suicide and intoxication

The definition of quality of life according to the WHO is “an individual’s perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns”[12]. One aspect of quality of life is psychological wellbeing. Worldwide, approximately 350 million individuals suffers from depression making it the ninth most common cause of disability and death [13]. The global point prevalence of major depressive disorders is estimated to 4.7 % (95% CI 4.4-5.0) [14]. Being diagnosed with cancer is, for most individuals, a stressor and for some a trauma. The diagnosis will inevitably lift existential thoughts on life and death. Depressive symptoms may also precede a cancer diagnosis, an increased risk of depressive symptoms was seen already five years prior to hospitalization due to cancer [15]. Many symptoms of cancer can limit psychological and physical reserves and therefore limit life and cause psychological damage but the cancer symptoms can also mimic depression and be misinterpreted. A meta-analysis found depression and anxiety to be associated with an increase in incidence of lung cancer and several other cancer types [16]. In stage IV NSCLC, the prevalence of moderate or severe

depressive symptoms have been reported to be 36 % [17]. Also malnutrition, commonly seen in lung cancer patients, is associated with depression [18]. A major depression is associated with worse survival in cancer patients overall (HR 1.41; 95 % CI 1.29-1.54) but also specifically for lung cancer (HR 1.39; 95% CI 1.24-1.56) [19]. Interestingly, the use of and adherence to antidepressant medications have been found to improve lung cancer survival, especially norepinephrine-dopamine reuptake inhibitors and tricyclic antidepressants [20, 21].

In Sweden, approximately 1.200 deaths due to suicide are reported yearly [22]. Suicide is more common in men, in individuals with a low level of education in both sexes, in elderly, in widowed/unmarried and in patients with a substance abuse, a severe somatic diagnosis i.e. stroke or cancers with a poor prognosis or a history of psychiatric disorders or previous suicide attempts [23-26]. In 2021, the age standardized suicide death rate in men with ≤9 years of schooling was 33.9 compared to 18.0 per 100,000 in men with ≥12 years of schooling. The corresponding rates in women were 19.1 vs 8.7 per 100,000 [27]. Death due to intoxication of medical or narcotic drugs are rare with 822 recorded deaths in 2020. Of these, about half were attributed to accidental intoxications and 25 % to suicide. While accidental intoxications are more common in men, suicidal intoxications are more common in women of which around 50 % has a previous diagnosis of depression or anxiety. Anxiolytics and sedatives are the dominating drugs in suicidal intoxications and opioids in accidental deadly intoxications. The most common substances overall involved in deadly intoxications are methadone, zopiclone, buprenorphine and heroin. For suicidal intoxications the most common drugs are zopiclone, propiomazine and oxycodone, all of which are commonly prescribed to cancer patients [28].

# Cancer incidence

Demographic shifts with increased life expectancy, advances in health care and improved social conditions will influence cancer incidence and survival. European estimates suggest that 50 % of the population will develop cancer at some point during their lifetime and the overall incidence of cancer in 2040 may increase with 18 % compared to current incidence rates [29]. Cancer incidence increases with age and in Europe about 60 % of new cancer cases and more than 70 % of cancer deaths occur in patients older than 64 years [29]. Therefore, an increase in the demand of cancer care is expected. Hence, there is a need to intensify cancer prevention efforts. Up to 40 % of cancers are estimated to be linked to modifiable lifestyle factors such as diet, obesity, smoking and alcohol [29]. The same factors are also associated with tolerance to cancer treatment. Government actions on tobacco control, programs for cancer screening and HPV-virus vaccinations will also have an influence on future cancer incidence trends.

# The Swedish health care system

The tax financed universal health care system in Sweden is regulated by law with healthcare offered to all permanent residents in Sweden. Emergency care is available to all individuals from the European Union and some other countries based on special agreements. Asylum seekers receive care that cannot be deferred. Interpreter services are offered free of charge.

Sweden is divided into 21 County Councils, each responsible for the organization and funding of regional health care (**Figure 2**). The 290 municipalities in Sweden are responsible for the organization and funding of care for the elderly and disabled i.e. retirement homes or home based services. Private health care providers are also available, some with and some without contract agreements with the National Health Care Services [30]. Approximately 5 % of the Swedish population has a private healthcare insurance, often provided by an employer.

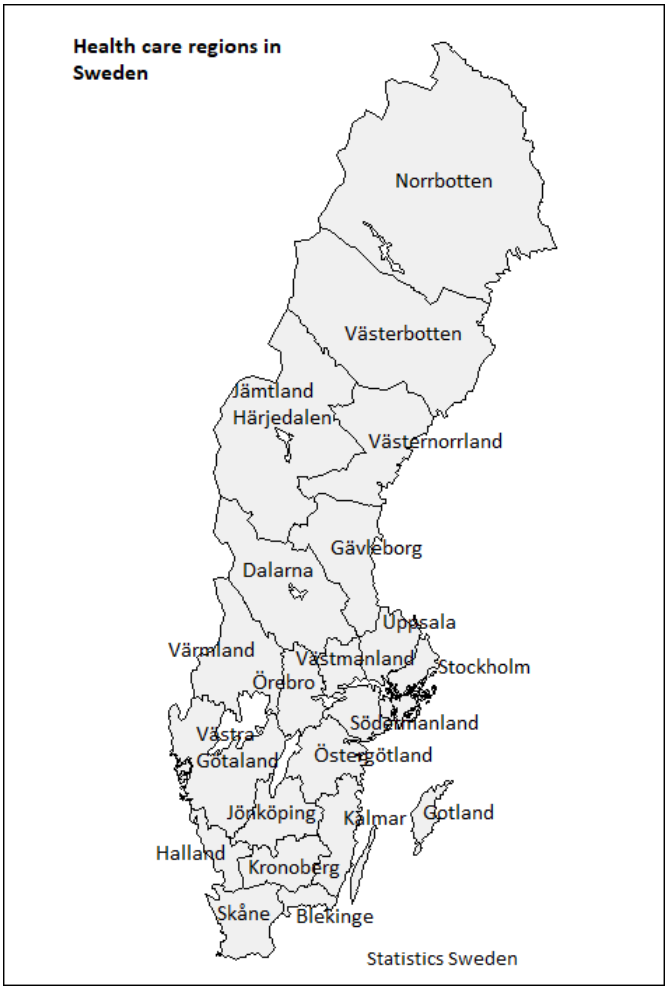


***Figure 2**. The health care regions in Sweden, map provided by Statistics Sweden.[31]*

# Research on population-based registers in Sweden

Since the 17th century, population-based data have been available in Sweden. Parish registers on baptisms, weddings and deaths were kept by the Church of Sweden for census purposes, tax collection and recruitment of soldiers. Initially data was entered by hand in church books but data was digitalized in the late 1960's [32]. The responsibility for civil registration on private individuals in Sweden was transferred from the church to the Swedish Tax Agency in 1991 [33]. Updates are reported five times per week to other Swedish government agencies and Statistics Sweden.

Since 1947, a personal identity number (PIN) is assigned to all residents in Sweden at birth or time of permanent residency [34]. The PIN is a unique personal identifier with birth date and a birth number where gender is encoded. The use of PIN in registries enables follow-up over time and cross-linkage between databases.

The Swedish registries can be sub-grouped into four main categories: National Government Registries, National Quality Registries, biobanks and research generated datasets (**Figure 3**).

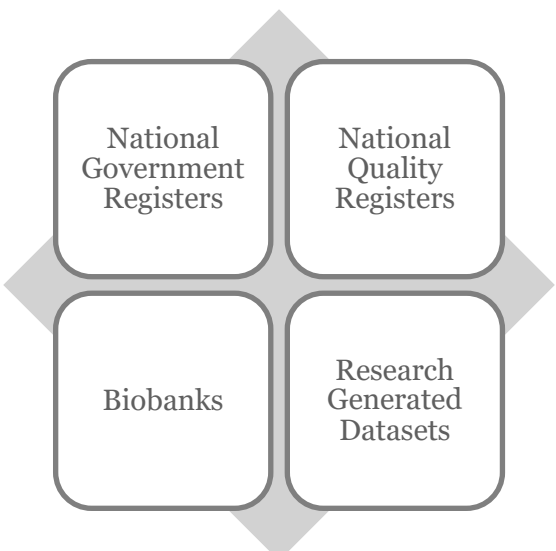


***Figure 3.*** *The four main categories of Swedish registers.*

The Swedish health registries are administered by the Swedish Board of Health and Welfare and contain information on in- and outpatient hospital care, cancer, prescription of medical drugs and cause of death.

Statistics Sweden administers registers with information on births and deaths, migration in and out of Sweden and socioeconomic factors (education, income, marital status, employment)[35]. The National Quality Registries provides individualized clinical data from the health care system, including information on diagnostics, disease characteristics, treatment and outcome. The National Quality Registries are administered by six Register Centers. Approximately 100 certified quality registries are available covering many disease areas, for example bipolar affective disorders, hip surgery, pregnancy, corneal transplant, HIV, heart failure, intensive care, pain rehabilitation and cancer. The approximately 30 National Quality Registries in the field of cancer are supported by six Regional Cancer Centers [36]. Biobank data in Sweden are mainly collected and stored by health care centers (90%), but also by private providers of healthcare and laboratory services. Yearly, approximately 3-4 million samples are included in biobanks [37]. The Swedish Research Council provides information on Swedish register data available for research. To explore accessible information, information on data available in registers and also biobanks, are pooled in the Register Utiliser Tool (RUT) [35].

The use of data from Swedish population and health registers is regulated under Swedish law by The Public Access and Secrecy Act (Offentlighets- och sekretesslagen, the Ethical Review Act (Etikprövningslagen), the Personal Data Act (Personuppgiftslagen) and the General Data Protection Regulation (GDPR) (Dataskyddsförordningen). Before accessing data, an ethics approval from the Swedish Ethical Review Authority is mandatory [38]. The data is usually delivered de-identified with name and PIN replaced with a unique sequence ID. The individuals included in the registers are not informed of the sharing of data for a specific project and individual prior patient informed consent is not necessary according to law.[39] However, as opposed to the National Government Registers, inclusion in a Quality Register is not mandatory and patients are informed that data may be used for research purposes.

Strengths of register-based research in Sweden include the availability at low cost of nationwide population data of generally high quality and completeness. By means of record linkages, comprehensive research data sets can be created to address a wide variety of research questions. Limitations include delayed reporting to some health registers, incomplete data, changes in coding and disease classifications over time as well as rapid developments in diagnostics and treatment. Also, the information at hand may not be applicable or suited for all research aims.

# Lung cancer

## Epidemiology

Globally, cancer is the leading cause of death with approximately 10 million deaths in 2020. Lung cancer is the second most commonly diagnosed malignancy with 2.21 million cases yearly [40]. Lung neoplasms are the leading cause of cancer related deaths with 1.8 million deaths yearly, almost twice as high compared to the second most common cause of cancer death; colorectal cancer [40]. In Europe, cancers of the lung represent 20.4 % of all cancer deaths [41].

In the Nordic countries, higher overall age-standardized incidence rates for both men and women are seen in Denmark. Sweden has the lowest incidence rates in the Nordic countries with the exception of Finnish females. (**Table 1**) [41, 42].

***Table 1.*** *Age standardized lung cancer incidence rates in the Nordic countries. Data accessed from the Association of the Nordic Cancer registries (NORDCAN) [43]*

| Age standardized incidence rates for lung cancer in the Nordic countries | | |
|---|---|---|
| **Country** | **Male** | **Female** |
| Denmark | 75.8 | 68.7 |
| Norway | 65.2 | 54.5 |
| Iceland | 57.0 | 60.3 |
| Finland | 56.3 | 28.0 |
| Sweden | 35.3 | 36.6 |

In Sweden, lung cancer is the fourth and seventh most common cancer site in women and men, respectively [44]. Each year, approximately 4,200 individuals are diagnosed with lung cancer of which 52 % are women. Lung cancer is predominantly diagnosed in the elderly and only rarely in patients below 40 years of age [45, 46]. The median age at diagnosis is 69 years and only 10 % are diagnosed in individuals 60 years or younger [47]. Most cases of lung cancer are diagnosed in age group 70-79 years followed by age group 60-69 years [47]. Future incidence and death rates of lung cancer are likely to be influenced by increasing and aging populations, changes in the prevalence of smoking and the introduction of novel

treatment options. For time trends in lung cancer incidence in the Nordic countries see **Figure 4.**

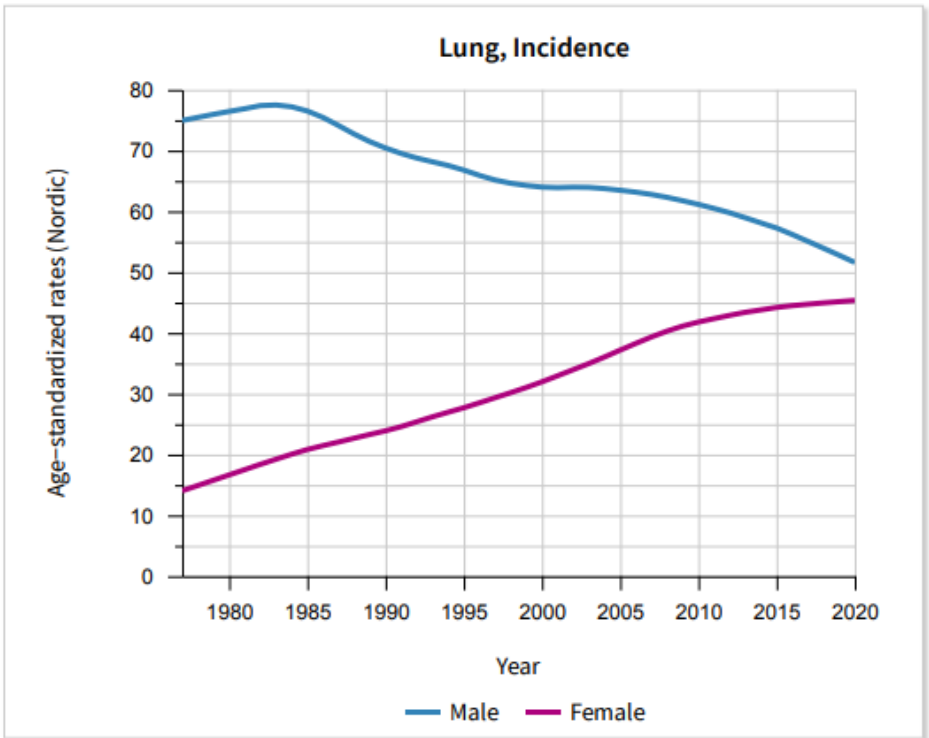


***Figure 4.*** *Lung cancer age-standardized incidence rates by year and gender in the Nordic countries. Data accessed from the Association of the Nordic Cancer registries (NORDCAN) [43].*

Tobacco smoke is a well-established risk factor for lung cancer, containing 55 carcinogens of which 20 have been found to induce lung tumors, and estimated to cause 80-90 % all incident lung cancers [48, 49]. The risk associated with smoking is dose related, with relative risks increasing with early age at smoking initiation, amount of tobacco consumed and duration of smoking [50]. Even after smoking cessation, an increased risk of lung cancer remains up to 30 years in ex-smokers compared to never smokers [51]. Other factors increasing the risk of lung cancer includes exposures to radon (especially in combination with smoking), metals: arsenic, chromium and nickel and previous irradiation to the chest [46]. In

Sweden, only 17 % of female and 12 % of male patients diagnosed in 2021 were never smokers [47].

Worldwide, incidence as well as age-standardized death trends are decreasing in men and increasing in women reflecting historical trends in smoking prevalence [52, 53]. However, the reduction in lung cancer mortality in men is mainly seen in middle or high socio-demographic index (SDI) countries. In low SDI countries smoking, exposure to asbestos and exposure to ambient particulate matter pollutions remains high [52]. A reduction in the smoking prevalence among women may not influence death rates to the same extent as in men due to sex differences in histological subtypes and susceptibility to tobacco carcinogens [51, 54-56]. For trends in Lung cancer mortality in the Nordic countries see **Figure 5.**

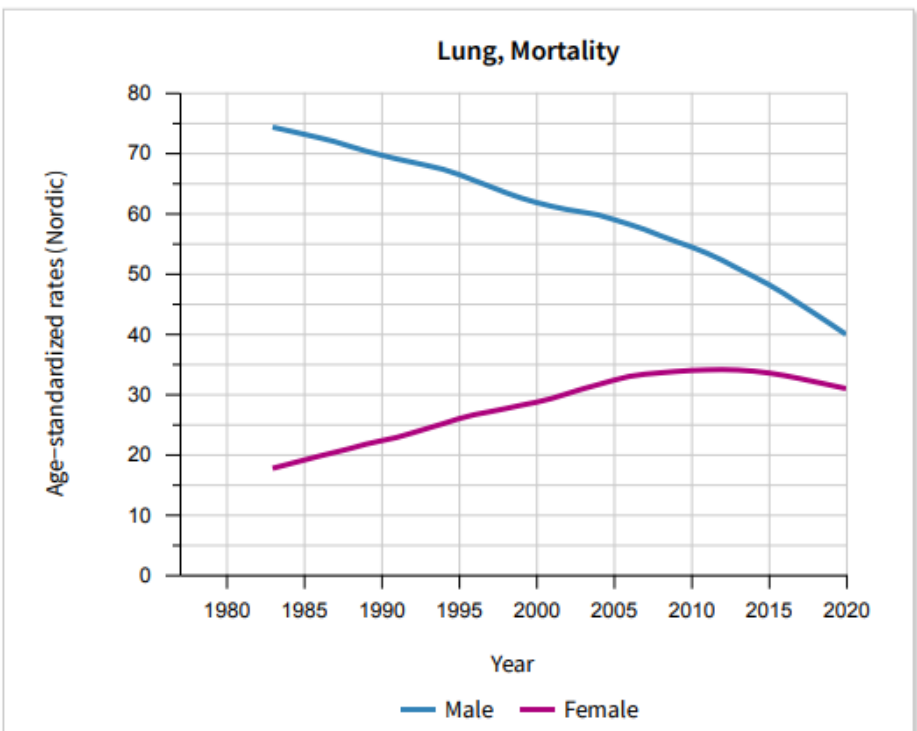


***Figure 5****. Lung cancer age-standardized mortality rates by year and gender in the Nordic countries. Data from the Association of the Nordic Cancer registries (NORDCAN) [43].*

In Sweden, the incidence of lung cancer follow global trends with decreasing incidence in men and increasing incidence in women. The lung cancer incidence has more than doubled in women between 1997-1999 and 2017-2019 [44]. Every year in Sweden, 3,600 deaths are attributed to lung cancer making it the most common cause of cancer related death in women and the second most common in men [57].

## Cardinal symptoms at diagnosis

Early-stage lung cancer gives few or no symptoms and is often an accidental finding on radiology examinations performed due to other symptoms or illnesses. Early symptoms of lung cancer are usually vague and this may explain why 51 % of patients are diagnosed with advanced stage IV disease [58]. Although many symptoms are considered unspecific, less than 10 % of lung cancer patients are completely asymptomatic at time of diagnosis [59]. The most common symptom is a persistent cough, present in 50-75 % of patients [46, 60]. Other symptoms may derive from the primary tumor, including hemoptysis (13 %), bronchial obstruction with dyspnea (4 %), thoracic pain due to tumor infiltration of the brachial plexus (Pancoast tumor), pleura or the thoracic wall (3 %) and Horner's syndrome due to infiltration of sympathic nerves [60, 61]. Regional metastasis may lead to dyspnea due to pleural effusion, swelling of the face secondary to a superior vena cava syndrome or a vocal cord paresis as a result of recurrent laryngeal nerve paralysis. Distant metastasis is associated with general symptoms such as fatigue, weight loss, cachexia (up to 60 %), skeletal pain (up to 25 %), subcutaneous metastasis palpable as nodules (rare), and vertigo, confusion, headache, nausea or seizures as a consequence of cerebral metastasis (up to 10 %) [61]. Also para-malignant symptoms are common; thromboembolic events, syndrome of inappropriate ADH secretion (SIADH), hypercalcemia (10-20 %), gynecomastia and neurological symptoms [61].

## Diagnostics

Following patient interview, physical examination, spirometry and blood samples; diagnostic work-up to determine a correct clinical cancer stage often include $^{18}$F-fluorodeoxyglucose (FDG) - positron emission tomography - computed tomography (PET-CT) or computed tomography (CT) of the thorax and upper abdomen. In locally advanced disease, or if symptoms of central nervous system (CNS) metastasis are present, a magnetic resonance imaging (MRI) or CT of the brain is performed. To obtain tumor biopsies, bronchoscopy, transthoracic biopsies and/or endobronchial ultrasound (EBUS) are performed [62]. For schematic overview of diagnostic modalities see **Figure 6.**

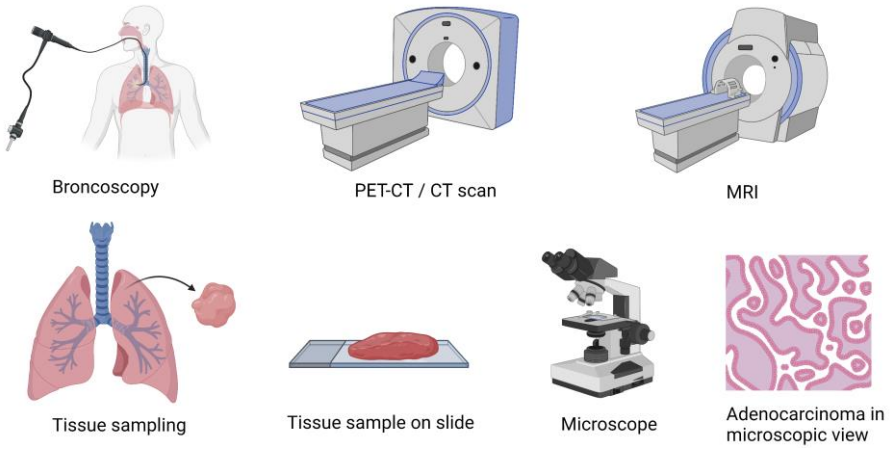


***Figure 6**. Schematic overview of diagnostic modalities in lung cancer. Illustration created in BioRender.com.*

A correct and adequate sampling of tumor tissue is necessary to determine the histological type, PD-L1 status and the possible presence of targetable mutations in EGFR (Epidermal growth factor receptor), BRAF (V-raf murine sarcoma viral oncogene homolog B), MET (mesenchymal-epithelial transition) and KRAS (Kirsten rat sarcoma viral oncogene homolog), as well as rearrangements in ALK (anaplastic lymphoma kinase), ROS1 (ROS proto-oncogene 1), RET (Rearranged during Transfection) and NTRK (neurotrophin receptor tyrosine kinase). The combined results of these tests serve as predictive markers and dictates the optimal treatment decision tailored for each patient [63]. Although biopsies with tissue samples are still considered standard of care due to high specificity and sensitivity, liquid biopsies on plasma, serum, urine or cerebrospinal fluid are emerging with testing of circulating tumor DNA, micro-RNA and circulating tumor cells [64]. In Sweden 2019-2021, a vast majority of all lung cancer patients (72.6 %) obtained their diagnosis based on tumor biopsies, 21.1 % based on cytology and a mere 6.3 % based on clinical and radiological findings alone (**Figure 7**) [65].

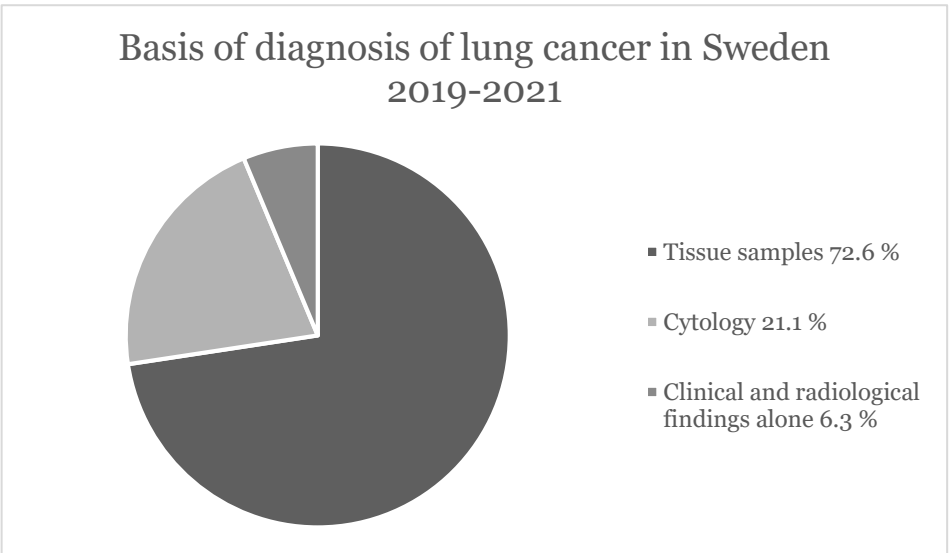


***Figure 7****. Basis of diagnosis of lung cancer in Sweden 2019-2021. Data obtained from the National Lung Cancer Register [65].*

## Histopathology

To ensure a global standard, the histology of lung cancer is based on the 2015 WHO Lung cancer classification of tumors of the Lung, Pleura, Thymus and Heart [66]. Lung cancer can be divided into two main entities; small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) accounting for approximately 15 % and 85 % of all lung cancer respectively [67]. NSCLC is further subdivided into three main histopathological categories: Adenocarcinomas, Squamous cell carcinomas and NSCLC NOS (not otherwise specified) (**Figure 8**) [68]. Additional data on immunohistochemistry and mutational profile enables further subdivisions within each histopathological category.

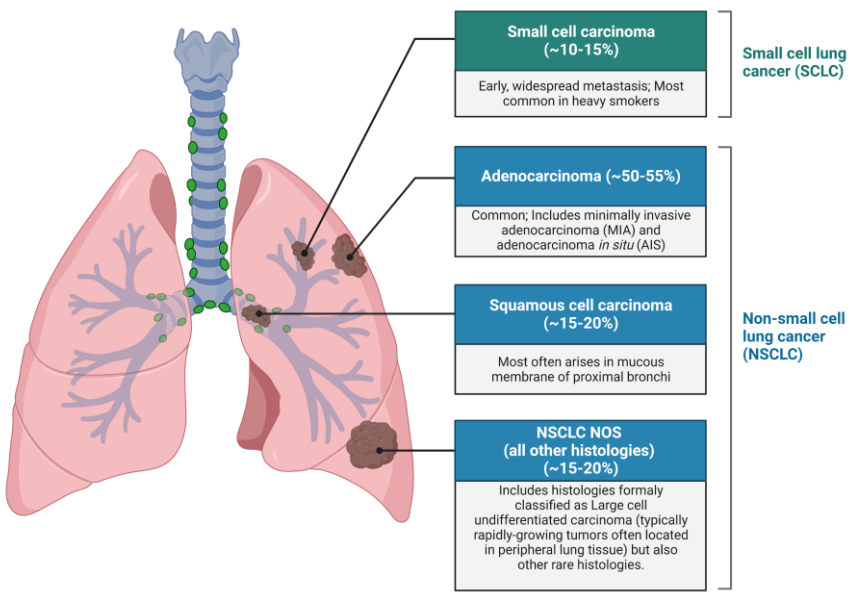


***Figure 8:*** *The two main entities of lung cancer; small cell lung cancer and non-small cell lung cancer with description of typical location and characteristics, and the distribution of histology in Sweden adapted from data in the Swedish National Lung Cancer Register 2017-2021. Illustration created with BioRender.com [69].*

Small cell lung cancer is a very aggressive malignant tumor, with neuroendocrine differentiation and has several similarities in clinical presentation and treatment options with other high grade neuroendocrine

tumors. Since SCLC more often is disseminated at time of diagnosis, curative treatment with surgical resection or radiotherapy is less common in SCLC. Despite declining smoking trends, incidence rates of SCLC have declined at a slower rate compared to NSCLC [42].

The incidence trends of the main histopathological categories of NSCLC are closely linked to historical habits of cigarette consumption and possibly also variations in cigarette design and manufacturing i.e. the addition of filters and the introduction of low-tar products [70]. Low-tar cigarettes appear not to have reduced the overall incidence or lung cancer, but has been suggested to have contributed to a shift from squamous cell carcinomas to adenocarcinomas [71]. Since the 70s, the incidence of adenocarcinomas has increased from 8.9/100,000 person years 1973 rising to 20.3/100,000 in 2015. In contrast, the incidence of squamous cell carcinomas fell from 13.3/100,000 in 1973 to 9.8/100,000 in 2015 [42, 67]. Today, the most common histopathology in Sweden is adenocarcinoma representing 55 % of all lung cancers [47].

## Staging

Tumor staging is a standardized classification method to uniformly describe the anatomical extent of a malignancy. Correct staging is essential for reliable communication between clinicians, choice of optimal treatment and assessment of prognosis [72-75]. Staging is based on the tumor-node-metastasis (TNM)-system; T describing the extent of the primary tumor, N the spread to lymph nodes and M the existence of distant metastases. The TNM classification may be based on solely clinical data such as clinical presentation, radiology, imaging and biopsies (cTNM) or on pathological stage following surgical resection (pTNM). Following resection, tumors may be further classified; R0 with no identifiable residual tumor macro- or microscopically, R1 with macroscopically negative, but microscopically residual disease and R2 with gross residual tumor. Furthermore, TNM may be based on restaging i.e. after treatment (yTNM), at time of recurrence (rTNM) or following autopsy (aTNM). By combining the T, N and M classifications, a tumor stage ranging from IA-IVB is obtained. Stage is used when choosing optimal treatment and is also the most important prognostic tool to predict recurrence and survival [76]. In response to technological and medical developments, revisions and refinements of the TNM-system are performed periodically by The Union for International Cancer Control (UICC) and American Joint Committee on Cancer (AJCC) [72]. The first edition was published in 1974 and the current 8$^{th}$ edition is in use since January 1, 2017 [77].

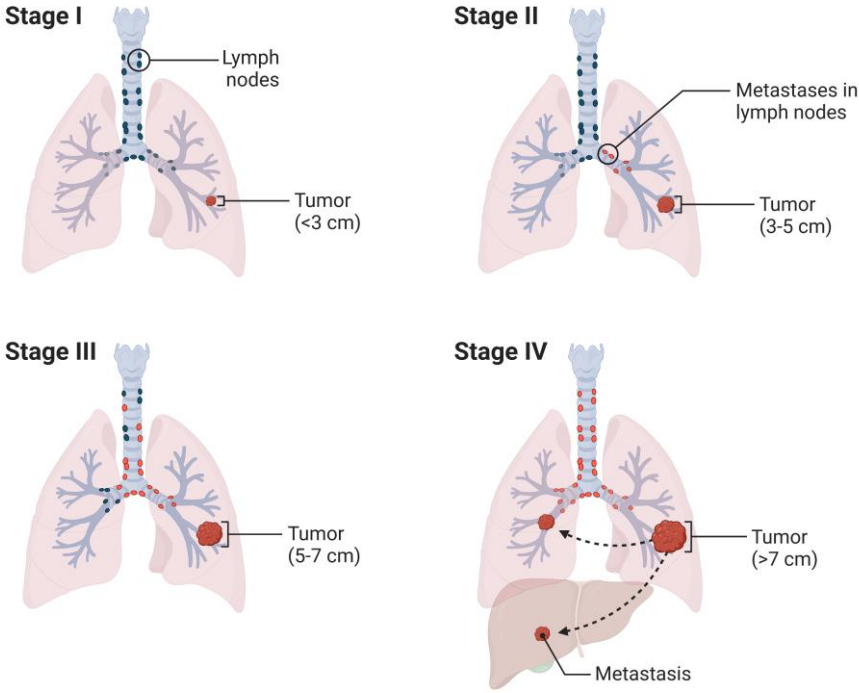


***Figure 9.*** *Schematic image of the four tumor stages of lung cancer, Stage I-IV. Illustration created with BioRender.com [78].*

For TNM- and stage classifications of lung cancer see **Figure 9** and **Table 2-3**. The staging classification is established on the International Association for the Study on Lung Cancer (IASLC) database; a global database consisting of more than 90,000 patients from more than 19 countries, mainly in Europe and Asia [72, 73, 75, 77]. The TNM classification of lung cancer has been externally validated [74, 75, 79]. In Sweden, a majority (50 %) of patients with NSCLC have advanced stage IV disease at time of diagnosis, 25 % have stage I, 5 % stage II and 20 % stage III. Metastatic disease is even more common in SCLC; 70 % of patients are diagnosed with stage IV disease, 22 % with stage III and a mere 2 % and 4 % with stage II and I disease, respectively [47].

***Table 2:*** *Definitions for the T, N and M descriptors according to the 8th edition of the TNM-staging for lung cancer reproduced from Goldstraw et al [77].*

| **T:Primary Tumor** | |
|---|---|
| **Tx** | Primary tumor cannot be assessed or tumor proven by presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy |
| **T0** | No evidence of primary tumor |
| **Tis** | Carcinoma in situ |
| **T1** | Tumor ≤3 cm in greatest dimension surrounded by lung or visceral pleura without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e. not in the main bronchus) |
| **T1a(mi)** | Minimally invasive adenocarcinoma |
| **T1a** | Tumor ≤1 cm in greatest dimension |
| **T1b** | Tumor >1 cm but ≤2 cm in greatest dimension |
| **T1c** | Tumor >2 cm but ≤3 cm in greatest dimension |
| **T2** | Tumor >3 cm but ≤5 cm or tumor with any of the following features. – involves main bronchus regardless of distance from the carina but without involvement of the carina. –Invades visceral pleura – Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung. |
| **T2a** | Tumor >3 cm but ≤4 cm in greatest dimension |
| **T2b** | Tumor >4 cm but ≤5 cm in greatest dimension |
| **T3** | Tumor >5 cm but ≤7 cm in greatest dimension or associated with separate tumor nodule(s) in the same lobe as the primary tumor or directly invades any of the following structures: chest wall (including the parietal pleura and superior sulcus tumors), phrenic nerve, parietal pericardium. |
| **T4** | Tumor >7 cm in greatest dimension or associated with separate tumor nodule(s) in a different ipsilateral lobe than that of the primary tumor or invades any of the following structures: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, and carina. |
| **N: Regional lymph node involvement** | |
| **Nx** | Regional lymph nodes cannot be assessed |
| **N0** | No regional lymph node metastasis |
| **N1** | Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension. |
| **N2** | Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s) |
| **N3** | Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s) |
| **M: Distant metastasis** | |
| **M0** | No distant metastasis |
| **M1** | Distant metastasis present |
| **M1a** | Separate tumor nodule(s) in a contralateral lobe; tumor with pleural or pericardial nodule(s) or malignant pleural or pericardial effusion |
| **M1b** | Single extrathoracic metastasis |
| **M1c** | Multiple extrathoracic metastases in one or more organs |

***Table 3:*** *Lung cancer stage grouping according to the 8th edition of lung cancer staging reproduced from Goldstraw et al [77].*

| T/M | Label | N0 | N1 | N2 | N3 |
|---|---|---|---|---|---|
| **T1** | T1a | IA1 | IIB | IIIA | IIIB |
| | T1b | IA2 | IIB | IIIA | IIIB |
| | T1c | IA3 | IIB | IIIA | IIIB |
| **T2** | T2a | IB | IIB | IIIA | IIIB |
| | T2b | IIA | IIB | IIIA | IIIB |
| **T3** | T3 | IIB | IIIA | IIIB | IIIC |
| **T4** | T4 | IIIA | IIIA | IIIB | IIIC |
| **M1** | M1a | IVA | IVA | IVA | IVA |
| | M1b | IVA | IVA | IVA | IVA |
| | M1c | IVB | IVB | IVB | IVB |

## Screening

Screening may lead to earlier detection of tumors and thus reduce mortality. However, the benefits of lung cancer screening have, despite an established risk group in smokers, been debated since the results from early screening trials failed to show evidence of improved survival. The Detection and Screening of Early Lung Cancer with Novel Imaging Technology and Molecular Assays (DANTE) study in 2007 found a similar lung cancer mortality in the screening (543 lung cancer cases per 100,000 person-years) and control arm (544 per 100.000 person-years), but had limited statistical power [80]. The same year, the Danish Lung Cancer Screening Trial (DLCST) reported twice as many cancer cases in the screening group with more early-stage tumors detected, but could not prove significant reductions in mortality [81]. The Multicentric Italian Lung Detection trial (MILD) followed by the National Lung Cancer Screening Trial (NLST) and Nederlands-Leuvens Longkanker Screenings Onderzoek trial (NELSON) were the first studies to report survival benefits with a reduction of lung cancer mortality between 20 and 33 % [82-84]. Enrolled patients in these studies had a high adherence to screening at around 90 % without an increase in depression or anxiety

[85]. Estimates from The Swedish Lung Cancer Study Group indicate that 320 screenings need to be performed to prevent one lung cancer death. This can be compared to 665-1700 screenings needed to prevent one breast cancer death and 864 screenings to prevent on death in colorectal cancer. However, screening must be carefully introduced to minimize ionizing radiation and the risk of false-positive results and over diagnosis [86]. Evaluations on the value of the introduction of lung cancer screening in Sweden are ongoing. A major challenge will be how to correctly identify risk groups as no register of smokers is available. In the previously mentioned trials on lung cancer screening, inclusion criteria regarding smoking was a smoking history of >15-30 pack years. Several obstacles remain such as costs, allocation of resources and ethical considerations. A remaining challenge following an introduction of screening, is how to improve early detection of lung cancers in non-smokers that represent approximately 10-15 % of all lung cancer cases with an overrepresentation in young women [87].

## Treatment of non-small cell lung cancer

The main treatment options for lung cancer include, alone or in combination, surgery, radiotherapy and medical treatment including chemotherapy, targeted therapies and checkpoint inhibitors. **Figure 10.**

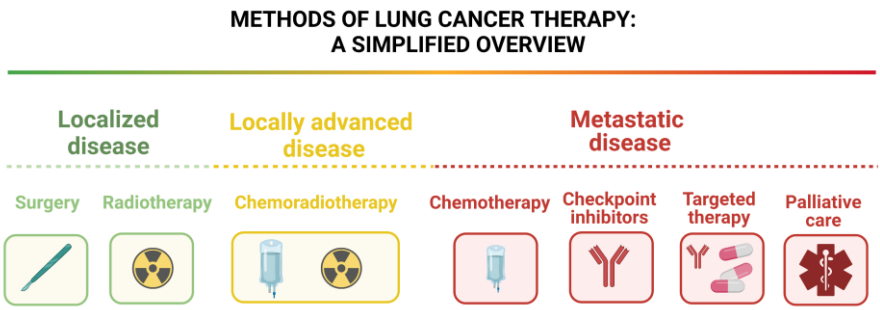


***Figure 10:*** *A simplified overview of NSCLC treatment. Illustration created with BioRender.com.*

The choice of treatment is based on both patient and tumor related factors. In recent years, significant advances have been made with a number of new therapies made accessible for patients with NSCLC both in an adjuvant and a palliative setting [46]. For detailed overview of treatments see **Figure 11.**

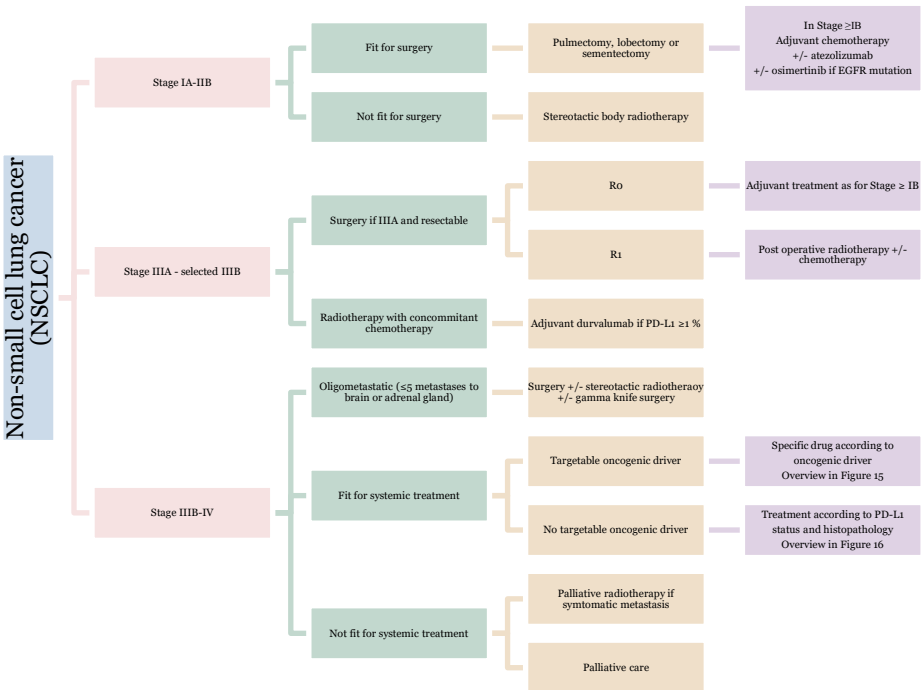


***Figure 11:*** *Overview of NSCLC treatment according to tumor stage adapted from ESMO guidelines and Swedish clinical guidelines [88].*

## Treatment in early-stage disease

In early-stage IA-IIIA NSCLC, surgery is the preferred treatment modality if the tumor is resectable and the patient is considered fit for surgery following assessment of performance status, lung function and exercise capacity [46]. Surgery is more common in patients with NSCLC compared to SCLC; a study in the USA on surgery 1973-2015 found surgical rates of 37 % for adenocarcinomas, 31 % for squamous cell carcinomas, 26 % for large cell carcinomas and a mere 6 % for SCLC [67]. Previously, open thoracotomy as well as minimally invasive surgery were standard but the introduction of video-assisted thoracoscopic surgery (VATS) has been found to limit bleeding, duration of hospital stay and complications.[89] Developments with robot-assisted thoracic surgery (RATS) may additionally improve perioperative outcomes.[90] An overview of surgical techniques is presented in **Figure 12.** Lobectomy is the standard operating technique, however in small T1aN0-tumors limited surgical resections with segmentectomy or even wedge resections are possible [91]. Trends for surgery are stable, but the introduction and extended use of stereotactic body radiotherapy (SBRT) enables treatment also in older and less fit patients with early-stage disease [67, 92, 93].

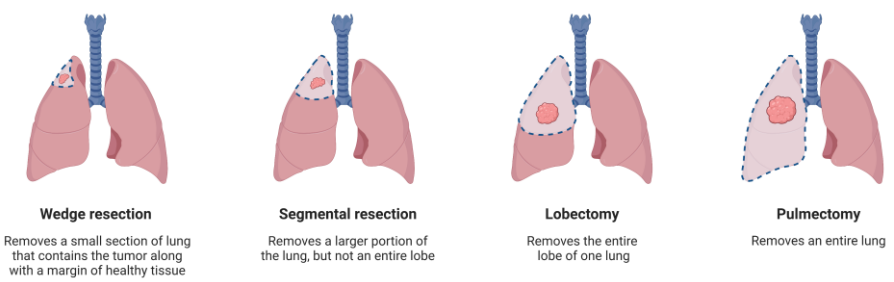


***Figure 12:*** *Schematic images of techniques of lung cancer surgical techniques. Illustration created with BioRender.com [94].*

SBRT is a radiotherapy technique where radiation is delivered in very high doses in a few fractions with high precision and therefore with limited doses to surrounding tissues (**Figure 13**). This limits toxicity to surrounding tissue and treatment time and thus enable treatment also for unfit patients. It is typically administered with 15 Gy per fraction every other day, three times, to a total dose of 45 Gy but several other fractionations are available. A retrospective follow-up study on SBRT to stage I-II NSCLC found rates of recurrence to be 21.5 % after 2 years and 30.0 % after 5 years. Distant metastasis was more common than local and

regional recurrence [95]. There are no prospective randomized controlled studies comparing surgery and SBRT in medically fit patients eligible for surgery, several previous studies closed due to difficulties to recruit patients [96, 97].

***Figure 13:*** *Image of dose-planning of stereotactic body radiotherapy (SBRT) of lung cancer. @Linda Willén*

In studies examining the addition of chemotherapy in early-stage disease, no survival advantages were seen for neoadjuvant chemotherapy but the addition of 3-4 cycles of adjuvant cisplatin-based chemotherapy following surgery has been found to improve both the survival rate (39.4 % vs 34.3 %, HR 0.86 95 % CI 0.76-0.98) and the disease-free survival rate (39.4% vs 34.3%, HR 0.83 95 % CI 0.74-0.94) at five years in patients with stage IB or higher [98-100].

Further intensified treatment in especially stage IIIA with adjuvant radiotherapy following adjuvant chemotherapy has been studied, but the prospective LungART study found no survival benefits [101]. Postoperative radiotherapy with sequential or concomitant chemotherapy can be offered to patients with stage II-III N0-2 with R1 margins [102].

In stage IB-IIIA tumors with PD-L1 ≥1 %, adjuvant atezolizumab following adjuvant chemotherapy has in the IMpower-010 study been found to improve disease-free survival compared to best supportive care

[103]. The benefit of treatment was higher in patients with a high PD-L1 expression and in Sweden atezolizumab is recommended to patients with tumors without EGFR and ALK driver alterations expressing PD-L1 ≥50 % following surgery and adjuvant chemotherapy. Adjuvant tyrosine kinase inhibitors (TKI) have been shown to improve disease-free survival in a postoperative adjuvant setting for patients with an EGFR mutated NSCLC. Osimertinib is now offered for up to three years in this patient cohort following adjuvant chemotherapy but data are not yet mature for assessment of the effect on overall survival [104, 105].

### Treatment in locally advanced disease

In patients with stage IIIA and selected stage IIIB NSCLC, concurrent chemoradiotherapy is standard of care in surgically unresectable tumors [106]. Chemoradiotherapy includes a combination of radiotherapy combined with a platinum-based chemotherapy, commonly cisplatin or carboplatin with vinorelbin. The chemotherapy is administered with three to four doses, often in three week cycles. The radiotherapy generally commences at dose two and is administered with photons 2 Gy per fraction, 5 days per week, 34 times to a total of 68 Gy. Internationally other chemotherapy combinations and radiotherapy fractionations are used. For a picture of a linear accelerator used to deliver radiotherapy see **Figure 14.**

The results of the PACIFIC-study made addition of adjuvant treatment with the immune checkpoint inhibitor durvalumab standard of care in patients without disease progression following concurrent chemoradiotherapy. In the 5-year follow-up a survival of 47.5 months was seen with durvalumab compared to 29.1 months with placebo [107, 108]. In the study, treatment with durvalumab was offered regardless of PD-L1-expression, but in post-hoc analyses patients with a PD-L1-expression <1% had improvements in PFS but not OS [108].

***Figure 14.*** *A linear accelerator used to administer radiotherapy treatment in the Department of Oncology, Gävle Hospital, Sweden. ©Linda Willén.*

## Treatment in late-stage disease

In stage III disease not suitable for concurrent chemoradiotherapy and in metastatic disease (IIIB-IV), treatment is considered palliative. However, in the rare case of oligometastatic disease (≤ 5 metastases) with solitary metastases to the brain or adrenal gland, an aggressive approach with metastasectomy may offer long term survival for selected patients [109-111]. Prognostic factors in oligometastatic disease are gender (female), adenocarcinoma histology, (y)pT-stage and absence of disease in lymph nodes [112].

Until the introduction of immune checkpoint inhibitors and targeted therapies, the standard treatment for patients with extensive metastatic spread and a WHO performance score (PS) of 0-1, has been a combination treatment with a platinum drug (cisplatin, carboplatin) and gemcitabine, pemetrexed, docetaxel, paclitaxel or vinorelbine in 4-6 cycles [46]. This was followed by maintenance treatment (only non-squamous cell carcinomas) with bevacizumab or pemetrexed which improved overall survival compared to chemotherapy alone [113, 114]. Patients with poorer PS were usually offered single agent chemotherapy.

However, in recent years there have been major changes in the treatment panorama of NSCLC, including the introduction of immune checkpoint inhibitors and targeted therapies. The treatments are tailored for each patient based on PS, histology, the presence of targetable oncogenic drivers and the degree of PD-L1-expression. Specific drugs in clinical practice are directed to genetic alterations in EGFR, ALK, BRAF V600E, MET exon 14, KRAS G12c, ROS1, RET and NTRK and drugs directed against human epidermal growth factor 2 (HER-2) mutations and neuregulin gene (NRG) fusions are on its way [115]. For an overview of treatment options in patients with a targetable oncogenic drivers see **Figure 15**.

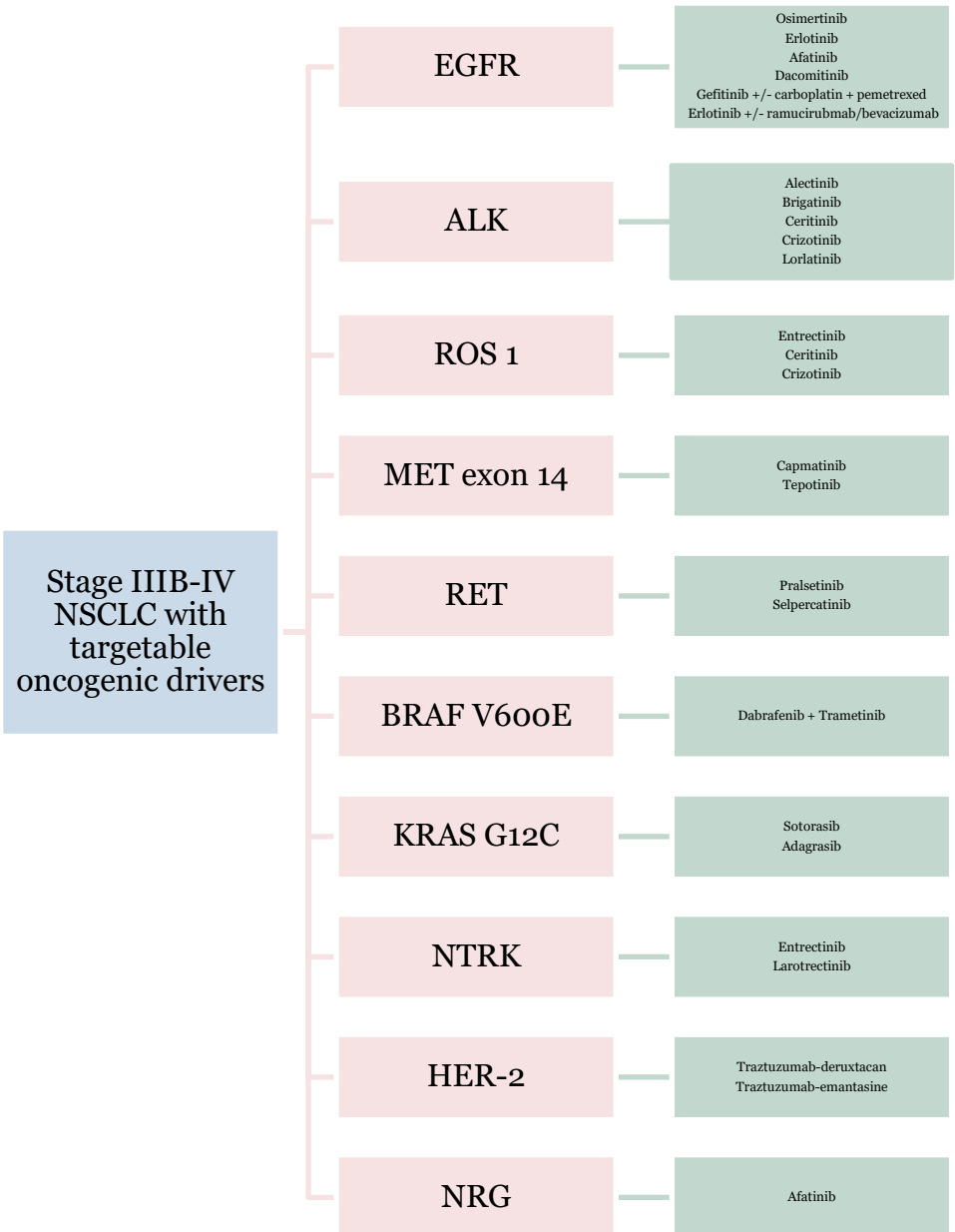


***Figure 15**. Schematic overview of targetable oncogenic drivers and the pharmaceutical drugs available adapted from ESMO guidelines and Swedish clinical guidelines [88].*

For the approximately 10-15 % of patients presenting with a mutation in the Epidermal growth factor receptor (EGFR), which is most common in adenocarcinomas, Asian patients, females and non-smokers, treatment with tyrosine kinase inhibitors (TKI) (afatinib, dakomitinib, osimertinib, erlotinib, gefitinib) are available. The third-generation TKI Osimertinib showed improved OS of 38.6 months compared to 31.8 months for first generation TKI and is now considered standard of care first line treatment, especially in patients with a T790M mutation [116]. Monoclonal antibodies as well as combination therapies with immune checkpoint inhibitors are also available [117, 118]. The TKIs can be combined with bevacizumab, ramucirumab or carboplatin and pemetrexed.

For patients presenting with rearrangements in ALK (4-5%), most common in patients who are young, non-smokers and presenting with adenocarcinomas, treatments with ALK inhibitors (alectinib, brigatinib, crizotinib, ceritinib) are available [115, 117, 119-122]. An improved PFS for the second generation ALK inhibitors alectinib (PFS 35 months vs 11 months) and brigatinib (PFS 24 months vs 11 months) was seen compared to the first generation crizotinib as well as improved response in CNS metastasis and are now standard of care first line therapies [123, 124]. The third generation ALK inhibitor lorlatinib can be used upon progression or in first line, treatment sequencing remains controversial [125].

For patients with ROS-1 rearrangements (1-2%), treatment with crizotinib, entrectinib and ceritinib are available [117, 126, 127]. The treatments have a high ORR of 62-77 % and present a median PFS of approximately 19 months [126, 128, 129].

Approximately 2 % of NSCLC present with a BRAF mutation, which is most common in smokers [115]. For patients with a BRAF V600E mutation combination therapy with the BRAF V600E inhibitor dabrafenib and the MEK inhibitor trametinib gives a 63 % ORR and a progression free survival of 10.8 months [130-132].

KRAS mutations are seen in 30-40 % of adenocarcinomas and 4 % of squamous cell NSCLC and the subtype KRAS G12C is the most common subtype representing 40 % of the KRAS mutations in adenocarcinomas [118, 133]. The KRAS G12C-inhibitor drugs sotorasib and adagrasib are available with objective response rates of 37 % and 43 % respectively and a median PFS of 6.8 vs 6.5 months in patients who had progressive disease following platinum-based chemotherapy and checkpoint inhibitors [134, 135]. The KRAS G12C inhibitors are small molecules and passes the blood-brain-barrier, they therefore have an effect also on metastasis to the central nervous system; confirmed objective response rate in brain metastasis for Adagrasib is 33.3 % (95 % CI 18.0-51.8) [135].

Mutations in MET occur in up to 3 % of patients with NSCLC, more common in older patients with a history of smoking. Treatment with MET-TKI capmatinib (ORR 67.9 %, PFS 12.6 months) and tepotinib (ORR 46 %, median PFS 11.1 months) and available [136]. The efficacy of checkpoint inhibitors in patients with a MET mutations is debated and studies on MET antibodies, newer MET-TKIs as well as combinations therapies are ongoing [136].

Rearrangements in RET are present in 1-2 % of patients with NSCLC, predominantly in adenocarcinomas, younger patients (<60 years), women and those with a low or no history of smoking [137]. Two selective RET inhibitors are available; selpercatinib and pralsetinib. Selpercatinib treatment is associated with an ORR of 84 % and median PFS of 22 months and pralsetinib with an ORR of 70% in first line treatment [138, 139]. Studies on RET-inhibitors combined with chemotherapy, checkpoint inhibitors and anti-VEGF-drugs are ongoing [115]. The multi-kinase inhibitor, i.e. a non-selective RET-inhibitor, Cabozantinib in second line gave ORR 28% and PFS 5.5 months) [140].

For NSCLC patients with the rare NTRK gene fusion, approximately 0.2 %, treatments with entrectinib (ORR 69 %, median PFS 14.9 months) and larotrectinib (ORR 73 %, median PFS 35.4 months) are available [141, 142]. Studies are ongoing on next-generation NTRK inhibitors selitrectinib, repotrectinib and taletrectinib.

Another oncogene driver for NSCLC occurs upon activation of HER-2 and is more common in females, patients with an Asian ethnicity, non-smokers and adenocarcinomas [143]. Non-selective tyrosine kinase inhibitors afatinib, dacomitinib and neratinib as well as combination therapy with chemotherapy and HER-2 directed antibodies trastuzumab and pertuzumab has been tested with limited response. Further studies are conducted with antibody-drug conjugates directed against HER-2: trastuzumab-emtansine and trastuzumab-deruxtecan [143]. Most promising results have been reported on trastuzumab-deruxtecan tested on HER-2 mutated NSCLC refractory to standard treatment, ORR 55 % and median PFS 8.2 months [144].

NRG fusions lead to an activation of the ErbB/HER 2-receptor group, but are rare in NSCLC (<1%). They are more common in non-smokers and mucinous adenocarcinomas and respond very poorly to platinum- and taxanebased chemotherapy as well as treatment combinations with checkpoint inhibitors. Second line treatment with non-selective TKI afatinib gives ORR 25% and PFS 2.8 months. Several studies are ongoing on NRG fusion-directed antibody therapies [145].

Immune checkpoint inhibitors for treatment of lung cancer were introduced in 2015 with several studies being published the following years [146-154]. The field is rapidly evolving with many new studies being presented. For patients without a targetable oncogenic driver, the histology type and the degree of expression of PD-L1 will dictate recommended treatment. For overview of treatments in stage IIIB-IV lung cancer without targetable oncogenic drivers see **Figure 16.** Other patient related factors such as PS and comorbidity will also influence the choice of optimal treatment, i.e. immune checkpoint inhibitors are contraindicated in severe autoimmune diseases.

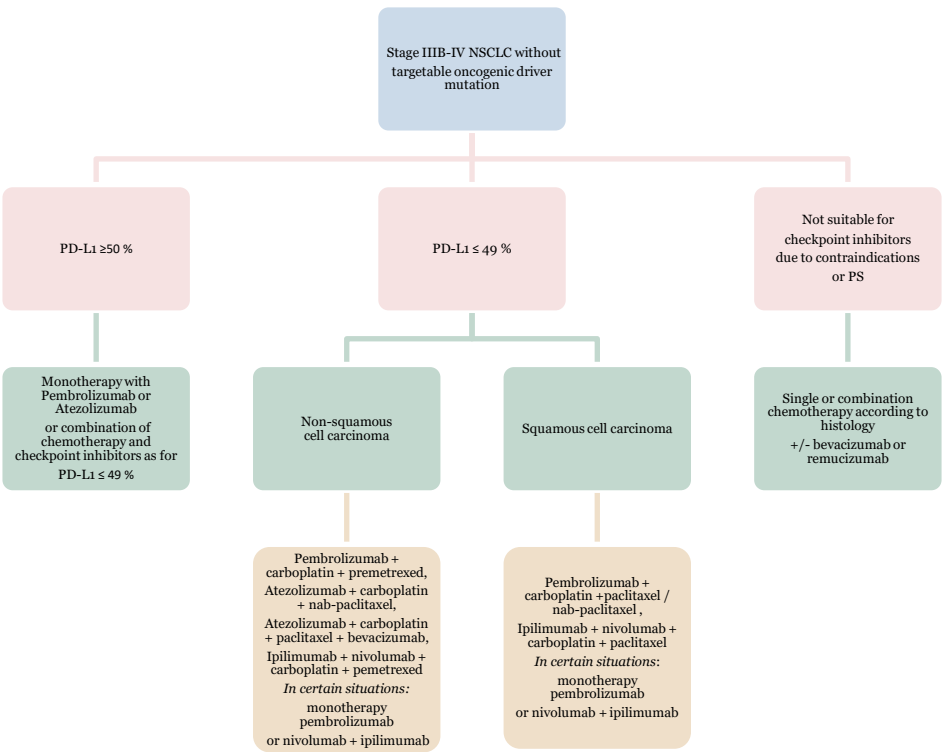


***Figure 16**. Schematic flowchart for overview of treatment of Stage IIIB-IV non-small cell lung cancer without targetable oncogene driver adapted from ESMO guidelines and Swedish clinical guidelines [88].*

First line therapy with single-agent checkpoint inhibitor (pembrolizumab, atezolizumab) can be offered to patients with both non-squamous and squamous cell carcinoma expressing a high PD-L1 expression (≥50 %). This is based on the KEYNOTE-024 study that demonstrated that single-agent pembrolizumab compared to platinum based chemotherapy increased ORR from 27.8 % to 44.8 % and median OS from 14.2 months to 30.0 months in patients with a PD-L1 expression ≥50 % [155]. For Atezolizumab, results from IMpower110 presented a median OS of 20.2 months vs 13.1 months [156]. Combination therapy with chemotherapy and checkpoint inhibitor can be considered in fit patients and in case of high symptomatology or tumor burden especially to those with liver or brain metastasis.[157]

In patients with a PD-L1 expression <50 %, combination therapy with chemotherapy and checkpoint inhibitors are recommended. For non-squamous cell carcinomas one treatment option is pembrolizumab, carboplatin and pemetrexed based on the KEYNOTE-189 study where the addition of pembrolizumab prolonged the median OS from 10.7 to 22.0 months [158]. Survival benefits were seen regardless of PD-L1 expression. Another treatment option is atezolizumab in combination with carboplatin and nab-paclitaxel or in combination with carboplatin, paclitaxel and bevacizumab based on IMpower 130 and IMpower 150 [154, 159].

For squamous cell carcinoma pembrolizumab, carboplatin and paclitaxel or nab-paclitaxel based on KEYNOTE-407 where addition of pembrolizumab prolonged median OS from 11.6 to 17.1 months [160]. Also in this study positive results were seen regardless of PD-L1-expression.

Regardless of histology, double checkpoint inhibitor therapy with ipilimumab and nivolumab in combination with histology-based chemotherapy has also been proven effective, in CheckMate 9LA OS survival improved from 10.9 months to 15.6 months [161]. The role of this combination is primarily in patients with less favorable results from other combinations, i.e. PD-L1 negative NSCLC.

For patients with contraindications to immunotherapy, chemotherapy combinations alone are usually offered. The addition of antibodies directed to the Vascular Endothelial Growth Factor Receptors (VEGF) (bevacizumab, ramucirumab) have marginally improved progression free survival [113]. The addition of bevacizumab to chemotherapy paclitaxel or carboplatin improved median survival from 10.3 to 12.3 months, but is not offered to patients with squamous cell carcinoma because of an increased risk of bleedings [113]. Ramucirumab can be offered to both squamous

and non-squamous NSCLC and improved median survival from 9.1 to 10.5 months [162].

In patients with metastatic lung cancer, symptoms of dyspnea, cough, hemoptysis and pain are common. Respiratory symptoms may be relieved with thoracentesis or treatment with cortisone, morphine, sedatives or oxygen. Many patients are offered palliative radiotherapy due to pathological fractures, a vena cava superior syndrome or metastasis to the brain. Hyponatremia due to SIADH may be treated with tolvaptan. An early introduction of palliative care is important for lung cancer patients. Temel et al found that early introduction of palliative care for patients with NSCLC compared to a control group not receiving palliative care improved quality of life (FACT-L score 98.0 vs 91.5), limited depressive symptoms (38 % vs 16 %) and prolonged survival (11.6 months vs 8.9 months) [163].

### Prognostic factors

Several factors are known to influence outcome in lung cancer; clinical stage being the most important determinant of prognosis. Other factors of importance include histology, performance status, comorbidity, age, sex and lung function [45, 76]. Despite advances in diagnostics and treatment, the overall 5-year survival in lung cancer remains poor; approximately 20 % in 2010 compared to 11 % 1973 [67]. Several factors have been found to be associated with long term survival (≥ 2 years). Long-term survivors are more likely to have EGFR mutation, a PS of 0-1, normal LDH levels at diagnosis and limited extra thoracic spread or fewer metastatic sites or single site distant metastasis. Long-term survival is also associated with a complete surgical resection or in metastatic disease a good response to chemotherapy or TKI [164-169]. Genetic aberrations with gene copy number gains and losses have been found to be associated with survival in adenocarcinomas and squamous cell carcinomas [170].

## Scoring comorbidity and performance status

In 1987, Dr. Mary Charlson published a new scoring system for longitudinal studies; the Charlson Comorbidity Index (CCI). The initial goal was to predict the risk of death within a year based on a scoring system for comorbidity[171]. The original index was based on the ICD-codes of 19 predefined comorbidities that were weighed based on severity where higher scores indicate a poorer prognosis. One point was appointed for myocardial infarction, congestive heart failure, peripheral vascular disease, dementia, cerebrovascular disease, chronic lung disease, connective tissue disease, peptic ulcer, chronic liver disease or diabetes. Two points was appointed for hemiplegia, moderate or severe chronic kidney disease, diabetes with end-organ damage, solid tumor, leukemia or lymphoma. Three points were appointed for moderate or severe liver disease and the highest score of six points was appointed for tumor metastasis or AIDS. The index has been tested for accuracy to predict mortality in a 1- and 10-year follow-up [171]. The CCI has since been developed and adapted to improve prediction of mortality and to adapt the score to the International Classification of Disease (ICD) [172, 173]. The index remains the most widely used proxy for comorbidity measurement in register-based research [174, 175]. Several different versions of the index are presently available also with adaptations to Swedish conditions [173]. Combination with other scoring systems, i.e. Elixhauser as well as scoring systems developed for geriatric patients i.e. Comprehensive Geriatric Assessment (CGA) and Cumulative Illness Rating Scale for Geriatrics (CIRS-G) can also be used [176-179].

A score to measure functional status, Performance score, was introduced by the Eastern Cooperative Oncology Group and adopted by the WHO [180]. The score ranges from 0 to 5 with zero indicating a fully active patient without performance restrictions and four being a completely disabled patient confined to bed or chair. (**Table 4**). In general, a PS of 2 is considered the lower limit for a patient considered for treatment with chemotherapy and a PS of 0-1 a limit to use double immune checkpoint inhibitors. In Sweden, most patients with NSCLC have a PS of 0-2: in stage I 98 %, in stage II 93 %, in stage III 89 % and in stage IV 72 % [47].

***Table 4.*** *ECOG WHO Performance score, adapted from Oken et al [180].*

| Performance status | Definition |
|---|---|
| **0** | Fully active; no performance restrictions. |
| **1** | Strenuous physical activity restricted; fully ambulatory and able to carry out light work. |
| **2** | Capable of all self-care but unable to carry out any work activities. Up and about >50% of waking hours. |
| **3** | Capable of only limited self-care; confined to bed or chair >50% of waking hours. |
| **4** | Completely disabled; cannot carry out any self-care; totally confined to bed or chair. |
| **5** | Dead |

# Present investigations

## Aims of the thesis

The overall aim of this thesis was to examine aspects of equality of care by studying patient and clinical characteristics potentially associated with the management and survival in non-small cell lung cancer, as well as psychological consequences of a lung cancer diagnosis.

The specific aims were:

- To examine whether there are differences in the management and survival in non-small cell lung cancer in patients with a high compared to low socioeconomic status.

- To evaluate and compare patterns of management and outcome between older and younger patients diagnosed with non-small cell lung cancer.

- To compare patterns of non-small cell lung cancer care and survival between foreign- and Swedish-born patients.

- To examine the rates of depressive and anxiety disorders, intoxication and suicide following a lung cancer diagnosis.

# Materials and Methods

## Study design and data material

This thesis includes four population-based cohort studies based on data in Lung Cancer Database Sweden (LCBaSe). LCBaSe is a research database generated by individual level record-linkage between the Swedish National Lung Cancer Register and other national demographic and health care registers: the Swedish Cancer Register, the National Patient Register, The Prescribed Drug Register, The Total Population Register, The Cause of Death register and the social database Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA) (**Figure 17**). LCBaSe is a de-identified data file including more than 95 % of all individuals with a lung cancer diagnosis between 2002 and 2016. Approximately 53,000 patients with lung cancer were identified, of which 40,000 were registered with a diagnosis of non-small cell lung cancer.

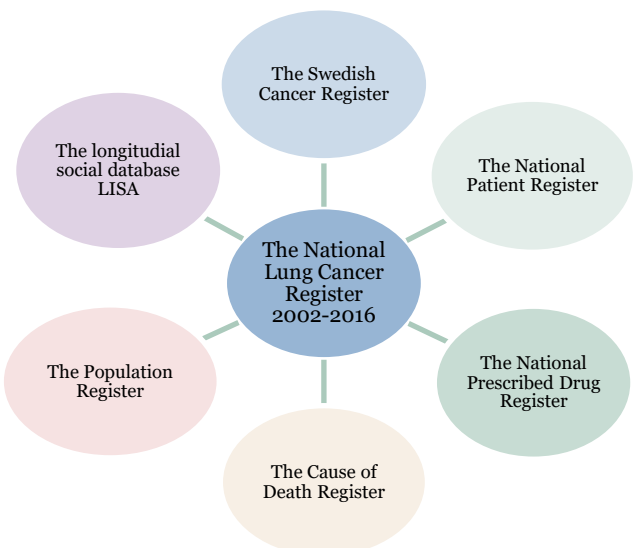


***Figure 17.*** *An overview of Lung Cancer Database Sweden (LCBaSe) with record-linkages between The National Lung Cancer Register and several other population-based registers in Sweden.*

For the purpose of the fourth study, information on lung cancer-free individuals (comparators) was used. The comparators were randomly selected and individually matched in a ratio of 1:5 according to sex, age and area of residence.

## Data sources

### *The National Lung Cancer Register*

Administered by the Regional Cancer Centre Central Sweden, the National Lung Cancer Register is a national quality register established in 2002 and includes approximately 74, 000 patients diagnosed with lung cancer between 2002 and 2021. The register has national coverage with a completeness exceeding 95 % compared to the mandated reporting to the Swedish Cancer register. It includes malignant lung cancers, while in situ cancers, tracheal and pleural cancers are not included. Approximately 4,200 lung cancer patients are registered yearly with data on patient characteristics (age, gender, smoking habits, and performance status), date and mode of detection, diagnostic procedures, histology, stage, planned first line treatment and outcome. No information on treatment beyond first line or relapse are available [87].

### *The Swedish Cancer Register*

The reporting of newly detected malignancies as well as certain benign tumors to the Swedish Cancer Register is mandatory. At present, more than 60 000 incident cancers are reported each year. The register is population-based, was founded in 1958 and contains information on patient characteristics (the national registration number, sex, age and region of residence), selected tumor characteristics (date of diagnosis, stage, histology, site) and outcome (date of death or migration, cause of death) [181]. Reporting is based on mandated separate notifications from both Departments of Pathology and the treating physician. The register has a high level of completeness with an estimated overall underreporting of 3.7 %. Underreporting is more common in older patients and in advanced stage disease where a histopathological diagnosis cannot be obtained, and therefore there is a small selection bias in the register [182, 183]. As opposed to most other national cancer registries, information from the Cause of Death register is not used to identify cases that have not been reported to the Cancer Register.

*The National Patient Register*

The National Patient Register is administered by the Swedish National Board of Health and Welfare. It was established in the 1960's, and reached national coverage in 1987 based on mandated reporting by all 21 County Councils in Sweden. The register includes data on in- and outpatient hospital care provided in public or private care settings. No information on primary care is included. The completeness of reported data is higher for inpatient compared to outpatient data. The register holds patient data (the national registration number, gender, age, region of residence), geographical data (hospital, clinic, county council), administrative data (i.e. dates of admissions and discharge, place of admission and discharge, if the admission was unplanned or planned) and clinical data (main and secondary diagnosis, procedures and if applicable external cause of injury or poisoning). The submitted data is validated by regular quality controls [181].

*The Cause of Death Register*

The origin of the Swedish Cause of Death register dates back to the 18th century when the government agency Tabellverket, the predecessor of Statistics Sweden, was founded in 1749 [5]. Data on deaths were also recorded in parish books by the Church of Sweden. Since 1961, information on cause of death is collated in the Cause of Death Register managed by the Swedish Board of Health and Welfare, containing data from 1952 an onwards [184]. The register includes information on all deaths in Sweden and on Swedish citizens dying abroad. Approximately 98,000 deaths are reported each year. The register is updated yearly and contains data on age, gender, date of death, place of birth, residence and death, underlying and contributing causes of death [185]. In 2020 circulatory disease was the leading cause of death followed by malignancies and COVID-19 [186]. The completeness of the register is high with an overall estimated missingness of 2.6 %, primarily of deaths occurring at high age [184, 186].

*The Longitudinal Integrated Database for Health Insurance and Labour Market Studies (LISA)*

Statistics Sweden manages the database Longitudinal Integrated Database for Health Insurance and Labour Market Studies (LISA), a database initiated 2003 containing information from 1990 and onward on

the Swedish population age 16 and older with data on demographics, education, employment, income, receipt of welfare benefits and family relations [187]. Reporting is mandatory. Data are pooled from several other registers and updated annually [187, 188].

*The Total Population Register*

Since 1968, Statistics Sweden keeps The Total Population Register containing demographic data on the population of Sweden. It contains data on sex, gender, birth country, citizenship, marital status and family relationships. It also includes data on births, deaths, place of residence, changes in residence and in- and outmigration [32]. One source of uncertainty is an over-coverage due to underreporting of migration, The over-coverage is more common in some Swedish regions and for immigrants and is estimated to 0.25 %-0.5 % of the Swedish population corresponding to approximately 68 100 individuals in 2018 [32, 189]. The under-coverage is low, and was estimated to 12 500 individuals in 2018, mainly because of unreported births or immigration [32].

*The National Prescribed Drug Register*

The Swedish National Prescribed Drug Register contains detailed information on dispensed prescribed pharmaceutical drugs in Swedish Pharmacies. Since July 2005, data is collected by the Swedish eHealth Agency and transferred monthly to the register kept by the Swedish Board of Health and Welfare. Medications administered in nursing homes or hospitals are not included nor vaccines or over-the-counter medications. About 67 % of the Swedish population was prescribed at least one pharmaceutical drug in 2019 and approximately 100 million posts are recorded yearly [190]. The drugs are classified according the Anatomical Therapeutic Chemical classification system (ATC) and the register includes information on the patient (age, gender, place of residence), the drug (ATC-code, drug name, dosage, pack size), the drug prescription (amount, date prescribed and date dispensed), data on the prescriber (work title, work place, education or specialist code), and costs (total cost, patient cost etc.).

## Patient related data

*Performance Status*

Performance status was scored by the treating physician at time of diagnosis according to the Eastern Cooperative Oncology Group and WHO performance score and recorded in the National Lung Cancer Register [180]. While the score ranges from 0 to 5, only scores between 0 and 4 were used for the purpose of the present studies (a score of 5 indicates a deceased individual).

*Smoking status*

Information on smoking status at time of lung cancer diagnosis was obtained from the National Lung Cancer Register as recorded by the treating physician. Data were based on patient self-report and categorized into three groups: smoker (current smoker), former smoker (no smoking during the last year) and non-smoker (never smoked on a regular basis).

*Comorbidity*

Data on comorbidity was estimated by use of the Charlson Comorbidity Index and based on records of diagnoses available in the National Patient Register 15 years prior to the lung cancer diagnosis. The scores were categorized into three groups; no, mild and severe comorbidity corresponding to a Charlson Comorbidity Index of 0, 1-2 and 3+.

*Tumor Stage*

Staging was obtained from the National Lung Cancer Register and classified according to the Union for International Cancer Control (UICC) tumor, node, metastasis (TNM) system, mainly the 6$^{th}$-7$^{th}$ editions. However, during the period 2002-2016 the 5$^{th}$-8$^{th}$ editions were in use; the 5$^{th}$ edition published in 1997 was still valid for the earliest data in 2002, scoring according to the 6$^{th}$ edition was used in late 2002 to 2009, the 7$^{th}$ edition from January 1, 2010 and the 8$^{th}$ edition from November 1 2016 until end of follow-up December 31, 2016.

*ICD-codes*

Diseases included to assess comorbidity, depression, anxiety, intoxication and suicide were classified according to International Classification of Diseases (ICD)-codes. ICD-9 was valid 1987-2010 and hence used for the

first period under study 2002-2010. From January 1, 2011 and until end of follow-up December 31, 2016 diseases were classified according to ICD-10. Data was obtained from the National Patient Register.

*Covariates*

Paper I-III included covariates on demographic and socioeconomic factors, comorbidity and tumor characteristics. Analyses were adjusted for sex, educational level, smoking history, stage at diagnosis, CCI, PS, histology, region and year of diagnosis.

## Statistics

Descriptive demographic and clinical characteristics were presented for the full cohorts and by different subgroups of interest. Independent samples t-test was used for normally distributed data and the Pearson $\chi^2$ or Fisher exact test for categorical data and the Mann-Whitney U and Kruskal Wallis for non-normal continuous data.

In Paper I-III, univariable and multivariable logistic regression models were performed to examine differences in management with adjustments for potential cofounding factors (age, sex, educational level, smoking history, stage at diagnosis, CCI, PS, histopathology, health care region in Sweden and year of diagnosis). These analyses were restricted to patients with PS 0-2, i.e. those eligible for treatment. Odds ratios were calculated with 95 % confidence intervals using logistic regression models to assess association between educational level, age and country of origin in relation to pattern of care. Cause-specific and overall mortality was examined using the time-to-event approach with the log-rank test and estimated with the Kaplan-Meier method for univariate and the Cox regression models with hazard ratios and 95 % confidence intervals for multivariable analyses. Survival time was calculated between the date of lung cancer diagnosis and date of death (death due to lung cancer, or death due to all causes), emigration or end of follow-up December 31, 2016.

In Paper IV, the absolute numbers of events of depression, anxiety, intoxication and suicide were presented before and after index date for the NSCLC patients and the individuals free of lung cancer. In order to handle multiple events of interest, a multistage model was used to estimate the cumulative incidence for each outcome, and the rate ratio between the NSCLC patients and the comparators, respectively.

All tests were two-sided and $p < 0.05$ was considered statistically significant. Statistical analysis was performed in R version 3.5.0.

# Ethical considerations

This project was approved by the Research Ethics Board in Stockholm (Dnr 2012-1162-31-4; 2016-1137-32; 2017-2026-32; 2017-445-32). The studies were performed in accordance with regulations for register-based research in Sweden. The patients were included based on assumed consent. Due to the large number of participants and that the risk of invasion of privacy was deemed small, individual patient informed consent was not necessary according to regulations and the assessment of the Research Ethics Board. The data was de-identified by the Swedish Board of Health and Welfare and Statistics Sweden and the code-key was not accessible by the research team. The delivered de-identified data file was kept in a secure data environment with access restricted to designated members of the research team. All results were presented on an aggregated level.

# Funding

The project was supported by grants from the Swedish Cancer Society (15-0804, 17-678 and 18-0689), the Regional Research Council Uppsala-Örebro (RFR-654111) and the Gävle Cancer Society.

# Study populations

Data in LCBaSe contains information on more than 52,000 individuals diagnosed with lung cancer (SCLC, NSCLC and carcinoids) between 2002 and 2016. All studies included in the thesis were based on data on men and women diagnosed with NSCLC during that time period, approximately 40,000 individuals. Follow-up ended at time of death, emigration or end of follow-up (December 31 2016).

*Paper I: Educational level and management and outcomes in non-small cell lung cancer.*

In Paper I we selected patients with information available on educational level from LISA, n= 39,671. Data on education were categorized into three groups according to highest achieved educational level. A level of ≤9 years of schooling was classified as low, 10-12 years as middle and ≥13 years as high level of education.

*Paper II: Are older patients with non-small cell lung cancer receiving optimal care? A population-based study.*

In Paper II on older patients, data on 40,026 patients were available. The patients were divided into age groups: ≤69 years, 70-74 years, 75-79 years, 80-84 years and ≥85 years.

*Paper III: Patterns of care and outcomes in immigrants with non-small cell lung cancer. A population-based study (Sweden)*

In Paper III we used data on region of birth obtained from the Total Population Register. Data were complete for 40,075 men and women with NSCLC. Since 83.6 % were born in Sweden, 7.4 % in the other Nordic Countries (Norway, Finland, Denmark and Iceland) and only 9.0 % in the rest of the world, the data set did not allow for a detailed analysis based on individual country of origin. Instead, patients were divided into three groups according to region of origin: Sweden, Nordic (excluding Sweden) and non-Nordic immigrants.

*Paper IV: Depression, anxiety, intoxication and suicide following a diagnosis of non-small cell lung cancer*

In Paper IV data on depression, anxiety, intoxication and suicide was obtained from the National Patient Register and the Cause of Death Register. The number of individuals available for analysis was 38,454. Each patient had five randomly selected comparators from the

background population, matched on gender, age and area of residence at the date of the index date i.e. the date of the corresponding patient's lung cancer diagnosis, n=184,090. During the time period under study two versions of the International Classification of Diseases (ICD) - codes was in use, ICD-9 from 2002-2010 and ICD 10 from 2011-2016. For codes used see **Table 5**.

***Table 5.*** *ICD-codes for depressive disorders, anxiety disorders, intoxications and suicide from ICD-9 and ICD-10 used in Paper IV.*

| **ICD-codes used in Paper IV** | | |
|---|---|---|
| **Disorder** | **ICD-codes in ICD-9** | **ICD-codes in ICD 10** |
| Depressive disorders | 296.2, 296.3, 311 | F32, F33 |
| Anxiety disorders | 300.4 | F34.1 |
| Acute intoxication with alcohol | 2914, 2922, 3050 | F10.0 |
| Acute intoxication with opioids | 2922, 3055 | F11.0 |
| Acute intoxication with sedatives and hypnotics | 2922, 3054 | F13.0 |
| Suicide and suicide attempt | E950-E959, E980-E989 | X60-X84, Y87 |

# Results

*Paper I: Educational level and management and outcomes in non-small cell lung cancer.*

Paper I investigated associations between educational level and management and outcome in NSCLC. The study included more than 39 000 individuals of which 15.6 % had a high and 43.7% a low level of education.

There were no differences in the distribution of stage at diagnosis or waiting times between educational groups. A low level of education was more common in men compared to women (54.5 % vs 45.5 %). Compared to patients with a high level of education, those with a low education were more often smokers (45.3 % vs 34.2 %), had a higher comorbidity burden (CCI 1-3: 48.8 % vs 39.8) and a lower PS (PS 0 17.9 % vs 32.3 %). Adenocarcinomas were more common in patients with a high educational level (67.1 % vs 55.1 %) while patients with a low education to a higher extent were diagnosed with squamous cell carcinoma (29.1 % vs 19.7 %).

Patients with a high level of education were more likely to undergo PET-CT (48.6% vs 39.8 %; aOR 1.14; 95 % CI 1.05-1.23) and to be discussed in a multidisciplinary team setting (69.7 % vs 60.5 %; aOR 1.22; CI 1.14-1.32). Treatment with SBRT in patients with PS 0-2 and stage IA-IIB disease was, following adjustments, more likely in patients with a high educational level (aOR 1.40; 95 % CI 1.03-1.91).

In more advanced stage disease, there were no significant discrepancies in patterns of offered care between educational groups.

Following adjustments for demographic and clinical characteristics, patients with a high educational level had a better survival in early-, but not in late-stage disease; Stage IA-IIB all-cause mortality (aHR 0.86; CI 0.77-0.92) and cause-specific mortality (aHR 0.83; CI 0.74-0.92).

In more advanced stage of disease, survival was similar across educational groups.

*Paper II: Are older patients with non-small cell lung cancer receiving optimal care? A population-based study.*

Paper II examined and compared patterns of management and outcome in NSCLC across age at diagnosis with a special focus on the oldest age groups. The study included 40,000 individuals with NSCLC divided into age groups: 48.6 % were ≤ 69 years, 19.7 % 70-74 years, 16.6 % 75-79 years, 10.8 % 80-84 years and 4.3 % ≥85 years.

Educational level differed between age groups: in age group ≤69 years 34.8 % had a low level of education compared to 55.1 % in patient ages 80-84 years. Also, squamous cell carcinomas were more common in elderly patients. Compared to patients 85 years and older, current smokers were more common in the youngest age group ≤69 years (53.8 % vs 14.5 %). As expected, a poor PS and a high comorbidity burden was more common in the oldest age-groups. Up to age 84 years, there were no differences in stage at presentation across age groups.

A higher proportion of elderly compared to younger patients underwent thoracocentesis. Other diagnostic modalities methods were performed evenly in patients aged <80 years. A lower diagnostic intensity was found in the oldest age groups.

Analyses on treatment were restricted to patients with PS 0-2. In early-stage disease (IA-IIB) surgery was more common in the youngest age groups and SBRT in the oldest. In stage IIIA disease, concurrent chemoradiotherapy was more common in younger patients and surgery mainly restricted to patients aged ≤74 years. In advanced stage disease (IIIB-IB), treatment was readily offered to patients aged 79 years or younger. However, systemic medical treatment was also offered to more than 50 % of patients aged 80-84 years and 30 % of those aged ≥85 years with a PS of 0-2.

In early-, but not late-stage, NSCLC, both overall and cause-specific mortality was higher in older patients. (**Figure 18)**.

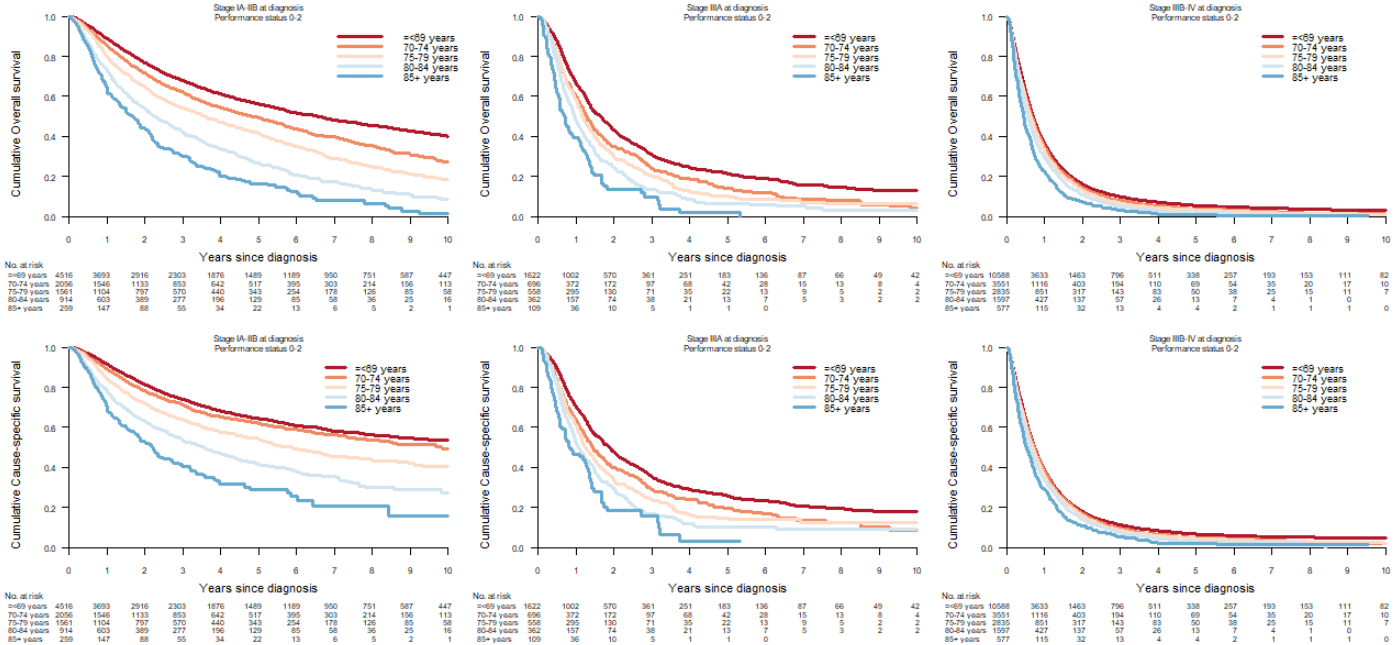


***Figure 18:*** *Cumulative overall and cause-specific survival in patients with non-small cell lung cancer and performance status 0-2 diagnosed in Sweden 2002-2016, by age group and stage at diagnosis.*

*Paper III: Patterns of care and outcomes in immigrants with non-small cell lung cancer. A population-based study (Sweden)*

Paper III examined patterns of care and outcome in immigrants with non-small cell lung cancer. The cohort of 40,000 patients was divided into three groups based on region of birth: Swedish-born, Nordic-born and non-Nordic born individuals. The large majority of patients (83.6 %) were Swedish-born, 9 % were born outside the Nordic countries and 7.4 % had a Nordic background.

Compared to Swedish-born patients, non-Nordic patients were to a higher extent male (66.3 % vs 50.2 %), younger at diagnosis (age 0-59 years 29.3 % vs 13.8 %), had a higher educational level (high educational level 22.2 % vs 15.6 %), had a good PS (PS 0: 26.8 % vs 21.9 %) but were also to a higher extent current smokers (48.5 % vs 42.4 %). Squamous cell carcinoma was more frequent in patients with a Nordic origin compared to Swedish-born patients (30.1 % vs 25.3 %). No differences in comorbidity or stage at diagnosis was observed.

A higher use of PET-CT and discussions in a multidisciplinary team setting was seen in non-Nordic immigrants, findings that remained following adjustments for age and other potentially modifying factors. PET-CT was performed in 50.5 % of non-Nordic immigrants and 42.9 % of Swedish-born patients; aOR 1.22 (95 % CI 1.13-1.33) following adjustment for age and aOR 1.32 (95 % CI 1.19-1.45) after full adjustments. Multidisciplinary team discussions took place in 70.1 % of non-Nordic immigrants and 63.4 % of Swedish-born patients; aOR 1.29 (95 %CI 1.18-1.42) after adjustment for age and 1.30 (95 % CI 1.17-1.44) following full adjustments.

A higher use of some treatments was seen in non-Nordic immigrants (surgery in stage IA-IIB, surgery and concurrent chemoradiotherapy in stage IIIA) and in Nordic immigrants (SBRT in stage IA-IIB), but these findings did not remain following adjustments for age alone or full adjustments.

There were no differences in survival between groups in advanced stage disease (IIIB-IV) (**Figure 19**). In early-stage diseases (IA-IIB) a better survival was seen in non-Nordic immigrants with a cause-specific mortality HR 0.80 (95 % CI 0.70-0.91). A finding that remained following full adjustments (aHR 0.86; 95% CI 0.75-0.98), but was not significant following adjustments for age only (aHR 0.90; 95% CI 0.79-1.02). Also, in stage IIIA a survival advantage could be noted for non-Nordic immigrants; cause-specific HR 0.75 (95 % CI 0.64-0.86) that remained following adjustment for age HR 0.83; 95 % CI 0.72-0.97), but due to low numbers full adjustments were not possible.

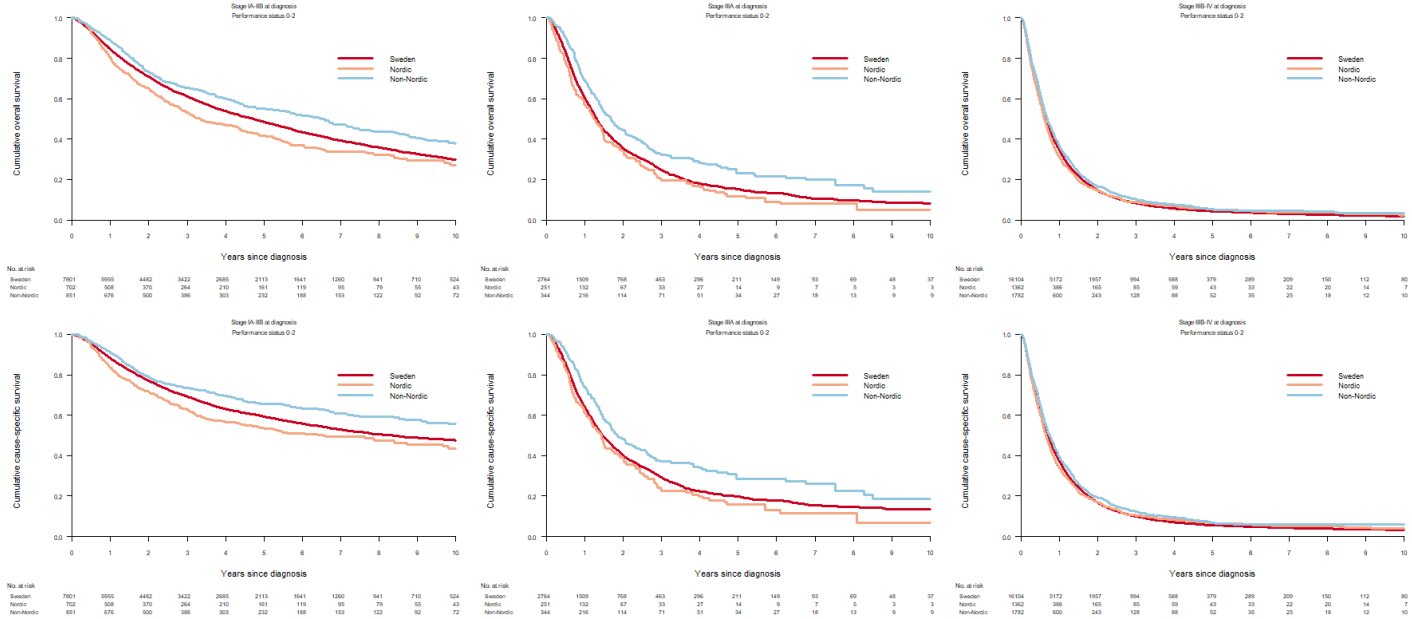


***Figure 19.*** *Cumulative overall and cause-specific survival in patients with non-small cell lung cancer and performance status 0-2 diagnosed in Sweden 2002-2016 by geographic region of origin (Sweden, Nordic, non-Nordic).*

In contrast, Nordic immigrants had poorer survival than Swedish-born patients in stage IA-IIB disease; cause-specific mortality HR 1.21 (95 % CI 1.07-1.37) and aHR 1.24 (95 % CI 1.10-1.41) following adjustment for age and aHR 1.31 (95 % CI 1.15-1.48) after full adjustments.

*Paper IV: Depression, anxiety, intoxication and suicide following a diagnosis of non-small cell lung cancer*

Paper IV investigated indicators of quality of life following a lung cancer diagnosis compared to lung cancer free individuals (comparators) representing the background population. The main indicators of interest included depression, anxiety, intoxication (alcohol, opioids, sedatives or hypnotics) and suicide. We identified >38,000 NSCLC patients and >184,000 lung cancer free controls.

Patients with NSCLC had a poorer health status compared to lung cancer free individuals (CCI ≥2: 28.3 % vs 16.4 %), more often had a low educational level (42.9 % vs 36.7 %) and were more likely to have an immigrant background (14.9 % vs 12.6 %).

As expected, NSCLC patients had dramatically higher risk of death compared to lung cancer free individuals. (**Figure 20**)

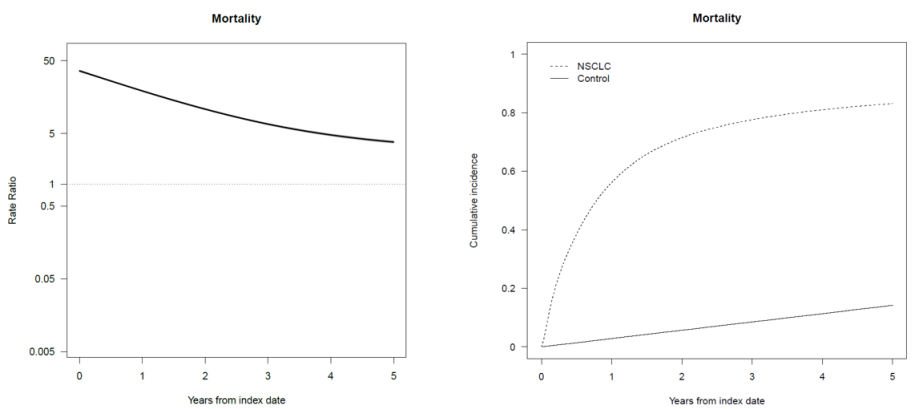


***Figure 20**. Rate ratio and the cumulative incidence of death in patients with non-small cell lung cancer. Reference group: lung cancer free individuals.*

Compared to the lung cancer free individuals, the risk of depression, anxiety, intoxication and suicide were higher in NSCLC patients post diagnosis. (**Figure 21-22).** Relatively few recorded events of depression and anxiety both before and after a diagnosis of NSCLC indicate a likely underreporting to the National Patient Register.

Over time, the elevated risk of anxiety, depression and suicide decreased, however the risk of intoxication requiring hospital care was higher in NSCLC patients throughout the period under study.

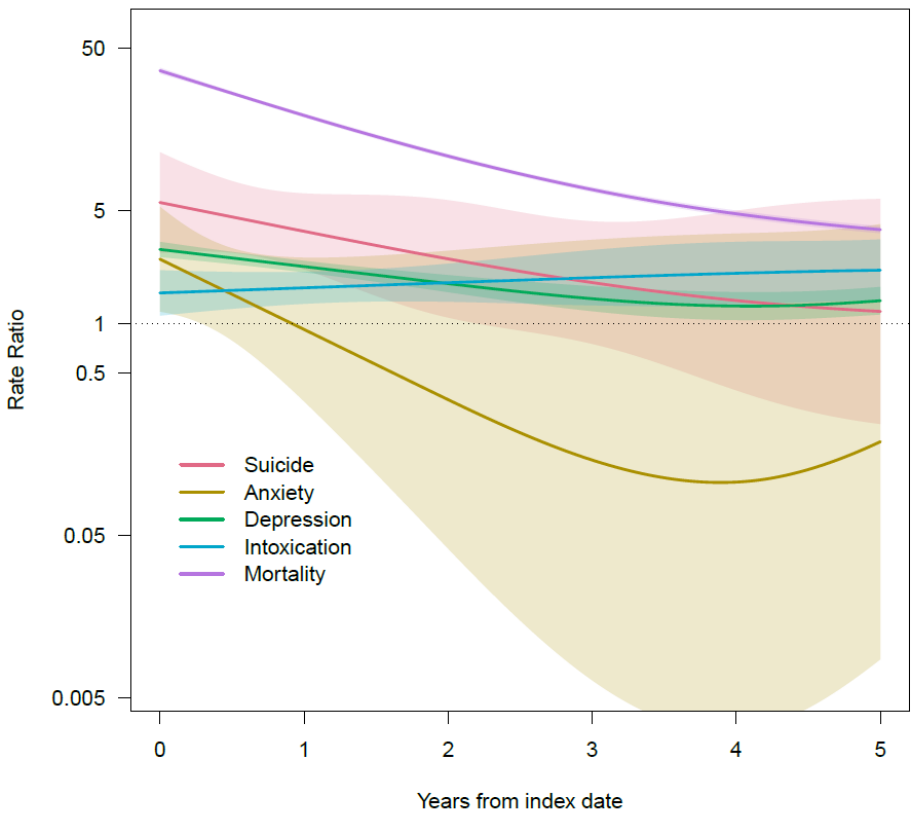


***Figure 21.*** *Rate ratios for suicide, anxiety, depression, intoxication and death in patients with non-small cell lung cancer compared to lung cancer free individuals (comparators).*

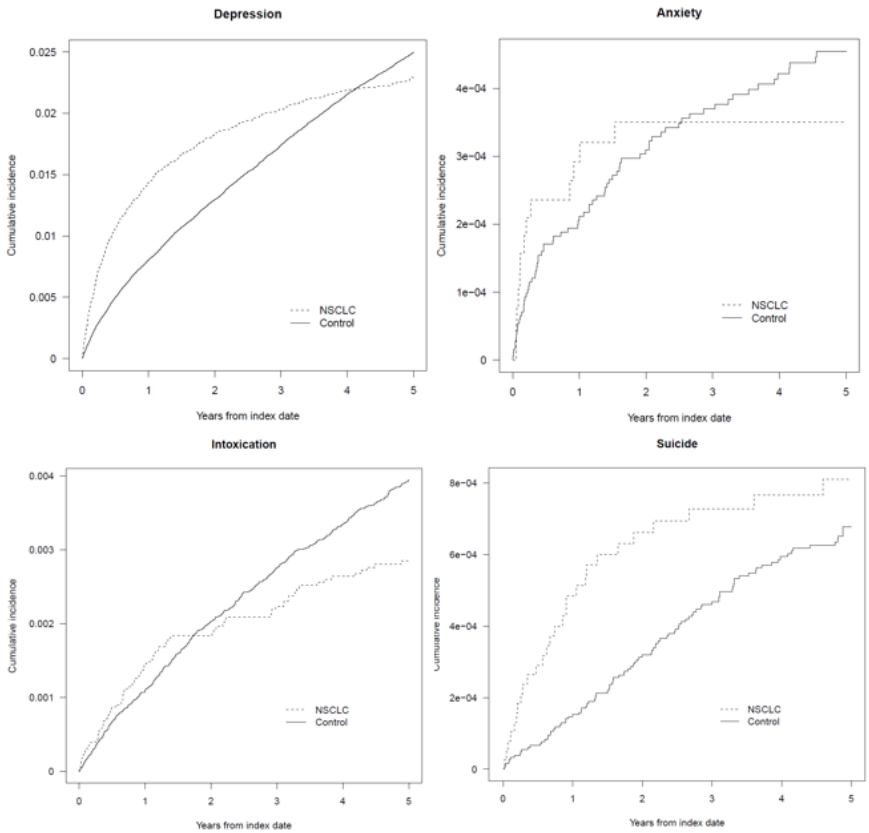


***Figure 22**. Cumulative incidence of depression, anxiety, intoxication and suicide in patients with non-small cell lung cancer in comparison to matched lung cancer free individuals.*

# Discussion

## Summary of results and clinical significance

In these four retrospective, population-based, studies on NSCLC, we found no differences in clinical stage at diagnosis in relation to educational level, age ≤84 years or region of origin indicating no inequalities in access to health care. However, there was evidence of a higher use of novel diagnostic and treatment modalities in patients with a high socioeconomic status as measured by educational level. In elderly with early-stage disease and a good PS, we found differences in cause-specific survival. Only small differences in management and outcome were observed between patients born in Sweden and immigrants, if anything in favor of the non-Nordic immigrant population, indicating that lung cancer care is offered on equal terms, regardless of region of origin. A diagnosis of lung cancer has a major impact on quality of life and an excess rate of depression, anxiety, intoxication and suicide could be observed, especially following the first years of diagnosis, which warrants specific care to identify patients at risk and support them.

## Methodological considerations

There are several advantages of register-based research. The pre-collected data are readily available and often at low cost, containing detailed individual information allowing for follow-up over time and across the country. This keeps selection bias to a minimum. Epidemiological studies can generate data and hypotheses that can be used as a basis for clinical studies. The National Government Registers generally include non-selected high-quality data with high completeness since reporting is mandatory by law. Reporting to the National Quality Registers is not mandatory and the quality of data may vary depending on quality of reporting from each individual treatment center. No validation of the National Lung Cancer Register has been published. When linking data from several databases one must consider both the ethics of combining large datasets, but also understand that there are limitations on conclusions on causality. It is important to consider whether statistically significant findings also have clinical implications.

Data on smoking is based on patient reported information and may be less reliable. Due to changes in the educational system over time as well as developments in the level of education in society with fewer blue collar and farming/forestry/fishing jobs available, level of education may over

time become a poorer measure of socioeconomic status. Age, even if the present studies combined data on age with PS and CCI, remains a coarse measurement of physical and mental stamina. For detailed studies on elderly further individual estimates should be performed, these data are however not yet available in register-based research. In immigrant cohorts, loss of follow-up of patients returning to their country of origin is likely somewhat underreported.

Data on depression and anxiety is based on diagnosis in the National Patient Register which does not include the primary care setting which in turn handles the majority of depressive and dysthymic disorders. Therefore, these disorders are underreported in our data. In a cancer patient with disseminated disease, signs of depression and anxiety may not be reported at all due to depressive symptoms and anxiety being considered part of a cancer associated crisis. Reported rates of intoxication and suicide are possibly underreported due the event being masked by progression of disease or maybe even due to the stigma relatives or health care staff may experience.

## Socioeconomic status in relation to health and cancer

Socioeconomic status, measured by financial, environmental, social and psychosocial factors, is a well-known factor to influence health. For example, a strong association between socioeconomic status and cardiovascular disease has been found. Individuals with a high educational level have been found to have better cardiovascular health, in contrast to individuals with low socioeconomic status who have been found to have a higher incidence of acute coronary syndrome, heart failure, a lower access to coronary procedures and secondary prevention as well as higher mortality [191-194]. Many of the socioeconomic inequalities in health may be due to socioeconomic differences in smoking and alcohol consumption, obesity or instead a poor nutritional status. Also, differences in financial ability to seek health care or pay for offered treatments, differences in compliance and adherence to treatments as well as communication factors may impact. Paper I corroborates these findings with higher rates of current smokers, poorer performance status and a higher comorbidity burden seen in individuals with a low educational level. However, the access of health care was not affected. In Paper I there were no differences in stage at diagnosis nor in waiting times which may reflect that the access to health care for socioeconomically frail

individuals is higher in countries such as Sweden with a universal health care system [192].

Similar to cardiovascular disease, socioeconomic inequalities of incidence, screening, treatment and mortality are seen in studies on cancer. A large systematic review on socioeconomic inequalities in Europe, studying site specific cancer incidence, found several cancer sites to be more common in patients with a low socioeconomic status (head and neck, esophagogastric, liver and gallbladder, pancreatic, lung, kidney, bladder, penile, cervical) but also some cancers linked to a high socioeconomic status (thyroid, breast, prostate, skin cancers). No socioeconomic gradient was seen for hematological cancers or cancers in the central nervous system [195]. A study from the Nordic countries found increasing risks of lung cancer correlating to a decrease in socioeconomic status as measured by occupation regardless of subtype of histology and sex [196]. In Paper IV, where the cohort of NSCLC was compared to a lung cancer free matched cohort, these findings were confirmed as a low socioeconomic position was more common in the cohort of NSCLC patients.

In Paper I, no differences in stage of lung cancer was noted between educational groups. These findings contrast a systematic review on studies of cancers in the Nordic countries reporting socioeconomic inequalities in stage at diagnosis, treatment and mortality [197]. These results may change following the introduction of lung cancer screening in Sweden. Screening aims to detect early-stage cancer accessible for curative treatment, however the adherence to screening programs for other malignancies (breast, colorectal, cervical cancers) have been found to be poorer in socioeconomically challenged groups [198-200]. Therefore, specific measures are needed to recruit this group to screening.

Differences in the likelihood to be offered and to accept surgery have been seen in individuals with a low educational level diagnosed with pancreatic cancer [201]. Socioeconomic differences in receipt of treatment for lung cancer has been seen in countries with both universal and non-universal health care systems [202]. In Paper I, PET-CT and SBRT were more common in individuals with a high educational level but no differences were seen for other diagnostic and treatment modalities including surgery. Both PET-CT and SBRT were new modalities in the studied time period and to a higher extent available in the larger hospital regions where highly educated individuals more often reside. This may explain parts of our findings.

A low socioeconomic status is associated with poorer survival of cervical, breast and prostate cancer [199, 203, 204]. In Paper I, differences in mortality was seen in early- but not late-stage disease. This may be due NSCLC having an overall poor prognosis in late-stage disease where socioeconomic differences does not have enough time to present. Many of the socioeconomic inequalities in health may be due to differences in smoking and alcohol consumption, obesity or poor nutritional status, weak financial ability to seek health care or pay for offered treatments, differences in compliance and adherence to treatments as well as communication factors. A systematic review on observational studies on cancer survival found cancer stage, other tumor factors, health-related lifestyle factors, comorbidity and receipt of treatment to be the major explanatory factors of poorer survival [205]. For lung cancer, especially receipt of treatment as well as comorbidity are important factors whereas for breast cancer and prostate cancer differences in stage at diagnosis is the main factor influencing mortality [205]. In Paper I, the findings of an increased use of PET-CT in patients with a high educational level is likely to give a more correct staging for this group and therefore a more accurate treatment. Also, the findings of increased use of SBRT may in part explain survival differences in in early- stage disease. It is obvious that socioeconomic inequalities in health and smoking prevalence are major factors influencing risk of lung cancer and also outcome. To reduce socioeconomic inequalities in smoking, a study found the most effective tobacco control intervention to be an increase of the price of tobacco compared to many other interventions such as advertising bans, warning labels and smoking cessation support [206].

A strength of Paper I is the assessment of each patient's individual data on socioeconomic status as measured by educational level. Future studies could also be based on the patient's occupation and income whereas researchers in other countries may have to depend on deprivation indexes calculated based on area of residence or other indirect measurements of socioeconomic status. Also, many studies have solely data on incidence and mortality but lack information on diagnostics and treatment and cannot adjust for explanatory factors. This is the main strength of the studies included in this thesis; the high quality of data and the adjustment for factors reflecting what health care staff consider when they decide upon optimal treatment and care for each individual patient.

# Cancer in older individuals

A well-known risk factor for cancer is high age. Older individuals may have impaired physical and mental capacity, a higher comorbidity and polypharmacy, all factors that may affect the options of cancer treatment and consequently the cancer prognosis. Despite an aging population, older patients are typically not included in randomized controlled cancer treatment research, and when they are, they are underrepresented [207]. A systematic review on randomized controlled cancer studies including 649 studies found patients with an age ≥70 to be included in only 11 % of the studies [208]. Also, the distribution of age in study participants is only rarely reported in clinical trials [209]. The optimal treatment of cancer in older individuals is therefore not fully explored and they are hence at risk of both overtreatment and undertreatment which is particularly true for lung cancer patients with a median age at diagnosis of 69 years. The definition of old varies between studies, many use an age of ≥65 years or ≥70 years but some even ≥60 years. In Paper II, a major strength is the defined age groups dividing older individuals into several age groups. We found no evidence of inequality in access to care in patients 84 years or younger.

In Paper II, as expected, older patients had a poorer performance status and the comorbidity burden was significantly lower in the youngest cohort of patients 69 years or younger. Lung cancer is a disease with a high median age at diagnosis and the prevalence of frailty in lung cancer patients as well as patients with other cancer types has been estimated to approximately 45 % [210, 211]. Frailty in older cancer patients has been associated with choice of treatment, toxicity of chemotherapy, postoperative complications as well as mortality [211, 212]. In Paper II, we found that younger individuals with early-stage disease more often were offered curative treatment with surgery older individuals more often offered SBRT. This corroborates findings of lower rates of cancer surgery seen in individuals aged ≥75 years diagnosed with breast, colorectal and lung cancer, following adjustments for performance status, comorbidity, stage and other factors [213]. This may reflect the knowledge of increased occurrence of postoperative complications with increasing age seen i.e. in studies on cancer in the bladder and esophagus [214, 215]. Also, there are known cognitive complications of the anesthesia itself in older patients undergoing cancer surgery, propofol more so than sevoflurane [216]. Therefore, due to comorbidity and frailty, SBRT is often the preferred choice for older patients which was confirmed in Paper II. However, limited surgery may be an option for the elderly. A systematic review

comparing surgical techniques in elderly patients with NSCLC found no significant differences in overall survival or local recurrence between lobectomy and segmentectomy but inferior results for wedge resections [217]. The alternative to surgery, SBRT, was a new treatment introduced during the period under study and could initially not be offered throughout all treatment centers which may explain diverging survival curves according to age groups in early-stage disease. Now that more modern treatment options have been made readily available, these survival differences may diminish over time.

In Paper II, treatment in locally advanced disease followed the same trends as in early-stage disease where younger patients to a higher extent were offered potentially curative treatment with surgery or chemoradiotherapy. A correct assessment of the individual patient is important, a previous study on lung cancer stage IIIA found treatment with chemoradiotherapy compared to radiotherapy alone in selected individuals aged ≥70 years to be associated with more hematological toxicity but improved overall survival (HR 0.66; 95% CI 0.53-0.82) [218].

Medical treatment with systemic anticancer drugs are less common in older individuals, confirmed i.e. in studies on pancreatic cancer, breast cancer [219, 220]. In Paper II, 86.4 % of individuals with advanced stage disease and performance status 0-2, aged 69 years or younger were offered chemotherapy in contrast to 58.1 % of patients aged 80-84 years and 30.3 % of patients >85 years. A common belief is that older patients to a higher extent decline treatment. However, a systematic review based mainly on qualitative studies, found that older patients to a high extent follow the recommendation of the treating physician. Common reasons for older patients to decline treatment include fear of discomfort of treatment, fear of toxicity as well as difficulties in transportation to care and therefore these factors are important to communicate on [221]. Other factors identified to be associated with refusal of treatment is gender (female), marital status (unmarried), cancer stage (III-IV) and comorbidity (CCI ≥2) [222]. A previous study identified patient factors associated with chemotherapy intolerance in older patients to be: more than one fall in the last six months, mobility problems, poor performance status and severe comorbidity [223]. However, if possible, treatment with doublet chemotherapy should be offered to older NSCLC patients with advanced stage disease as it has been found to improve overall and response rate compared to single agent chemotherapy [224].

The patients included in Paper II were mainly diagnosed before the introduction of immune checkpoint inhibitors for NSCLC and therefore

future studies may find a higher fraction of elderly eligible for treatment and also improvements in survival. Check-point inhibitors have been found to have similar toxicity and outcome in older compared to younger patients despite older patients having an impaired immune system [225, 226]. Also, monotherapy with checkpoint inhibitors may be a treatment option for patients unfit for platinum regimens. For example, the IPSOS study, a phase III-study on atezolizumab vs singe-agent chemotherapy, included patients with NSCLC without driver mutations not fit for platinum regimens with a median age of 75 years and 80 % with a PS ≥2. Early results presented improved OS for atezolizumab (HR 0.78; 95 % CI 0.63-0.97) regardless of PD-L1-expression, PS and histology and twice as many patients were alive in the atezolizumab-arm after 2 years [227].

# Cancer in immigrant populations

In Paper III, non-Nordic immigrants presented with a lower age at diagnosis, better performance status and a higher educational level. We found only minor differences in patterns of care in non-Nordic immigrants and those findings were attenuated following adjustments for age and other confounding factors. Non-Nordic immigrants also had improved survival in stage IA-IIIA disease, following adjustments this was found to be mainly attributed to a younger age. The "healthy migrant effect" or the "healthy migrant paradox" i.e. that immigrants have improved outcome compared to the native population in both overall mortality, cardiovascular disease, malignancies and mental health has been noted in previous studies [228-232]. The improved outcomes have been suggested to be due to a health selection of immigrants; to be able to leave your home country you need to be young and healthy. In a previous study on Swedish immigrants, health benefits have been attributed age, socioeconomic status as measured by educational level as well as occupation and the benefits were higher in Western compared to non-Western immigrants [233]. One hypothesis on the findings of improved survival in immigrants has been the "salmon bias effect" or the "remigration bias"; that immigrants return to their country of origin upon a diagnosis of severe disease without notifying authorities and therefore is lost to follow-up and thus underestimating mortality. This could be expected to be more common in our Nordic immigrants due to the close proximity of the home country. However, the Nordic countries cross check their population registers every 6 months and therefore this should not be a major factor. Also, a population-based study from Denmark examining refugees and family reunification immigrants noted that immigrants with

severe comorbidity emigrated to a lower extent compared to healthy immigrants [234]. Another study corroborates these findings in a Swedish cohort, especially in individuals with the highest comorbidity score according to CCI [235].

Paper III could not confirm a "healthy migrant effect" in Nordic immigrants. The Nordic immigrants are to a high extent originating from Finland, many of which immigrated to Sweden in the 1960s due to labor immigration. They worked in the heavy manufacturing industries and are thus likely to have a low educational level and a higher risk of exposure to occupational chemicals increasing the risk of cancer and other illnesses. This group has been found to be particularly frail due to increased risk of alcohol-related disorders, myocardial infarctions and esophageal cancer [236, 237]. Finnish immigrants in Sweden also have higher mortality rates; 3.16/1,000 person-years compared to <2.6/1,000 person years in the native born Swedes [238]. A higher overall mortality has been seen in previous studies on Finish immigrants but also specifically for suicide, some malignancies (breast and gynecological) and circulatory diseases (general circulatory disease, ischemic or coronary heart disease, stroke, heart failure and cerebrovascular disease) [239].

There were no differences in stage at diagnosis between Swedish-born, Nordic or non-Nordic immigrants. However, as for individuals with low socioeconomic status, this may change upon introduction of lung cancer screening. In Sweden, non-Nordic immigrants have an OR of 2.4 (95 % CI 2.0-2.8) to not attend breast cancer screening and international data found significant differences in breast cancer stage where immigrants were 12 % less likely to have early-stage disease [240, 241]. Similarly, immigrants have a lower attendance to cervical screening [242].

In Paper III, current smokers were more common in both Nordic and non-Nordic immigrants. In Paper IV, an immigrant background was more common in the NSCLC cohort compared to controls. This corroborates findings in a previous Swedish study with lower cancer incidence in immigrants for most cancer sites, but higher incidence for lung cancer in male immigrants [243].

# Depression and death by suicide

In Paper IV, the risk of depression, anxiety, intoxication and suicide was elevated following a diagnosis of NSCLC compared to the general population corroborating results from previous studies [15, 25, 244, 245]. Individual capabilities and previous experiences from life will guide cancer patients to coping strategies, alongside with support from relatives as well as support from supportive systems from government and health care professionals. A systematic review investigating optimal treatment of depression in patients with non-small cell lung cancer found evidence of an effect on depressive symptoms with enhanced care but very limited evidence for optimal choice of medical treatment [246].

In Paper IV, death due to suicide were rare events but increased risks compared to the general population were seen within the first two years following diagnosis. In a British cohort of cancer patients, the overall standardized mortality rate for suicide was estimated to 1.20 (95% CI 1.16-1.25) and the highest risk was seen within 6 months of diagnosis [247]. The relative risk of suicide within a week of a cancer diagnosis has in a large historical cohort of more than 6 million Swedes been estimated to 12.6 (95% CI 8.6-17.8) and within a year to 3.1 (95% CI 2.7-3.5) but following the first year the risk rapidly decreased. Another study on the timing of suicide in patients undergoing cancer surgery found a suicide rate of 0.08 %; 3 % of the suicides occurred within one month, 21 % within one year and 50 % within three years of surgery [248]. The delay in death of suicide following cancer surgery may be associated with stage of disease; advanced stage of cancer is associated with early suicide within a year of diagnosis [249]. Studies on the general population report that individuals dying from suicide to a high extent (>80%) received health care within a year prior of death but only half had a diagnosis of a psychiatric disease [250]. This stresses the need for health care staff to provide increased psychiatric support in the first months following a diagnosis of lung cancer as approximately 50 % has advanced stage cancer with a poor prognosis. An improved knowledge of the patient related factors that have been identified to increase the risk of self-harm and suicide is needed: a low socioeconomic status, especially in men, high age, to be widowed and to be diagnosed with a cancer associated with a poor prognosis [251-255]. These factors are common in individuals diagnosed with NSCLC and several studies confirm that lung cancer is one of the most common cause of cancer-associated suicide [245, 247, 249, 255]. Feelings of hopelessness, anger to be hit by such a severe disease, shame for causing cancer by i.e. by smoking, fears of an agonizing death, guilt of

being a burden to relatives as well as a lack of quality of life both physically and mentally are all factors likely to induce suicide ideation or wishes of a hastened death. Cancer patients may also have access to lethal means with the strong medications often prescribed due to severe symptoms of the cancer. An early introduction of palliative care may impact not only survival but also quality of life and reduce depression and the risk of suicide.

Suicide prevention is important not only for the individual patient but also for relatives and health care staff. Studies have found an increased suicide risk in relatives to individuals dying by suicide. Upon losing a spouse to suicide the partner has an increased risk of suicide, in men the risk is three times higher than in women [256]. Also children of parents who died of suicide have an increased risk of suicide; incidence rate ratio of suicide has been estimated to 1.9 (95% CI 2.1-4.6) [257, 258]. The greatest risk was seen in children aged 13-17 years at the time of the parent's passing and the suicide risk was highest within 1-2 years of the parent's death and then declined [259]. For health care staff, a patient dying of suicide may cause distress, feelings of inadequacy and guilt.

# Conclusions

- There were no differences in stage at diagnosis of NSCLC in relation to socioeconomic status, age ≤84 years or geographic region of origin indicating equal access of health care in Sweden.

- Socioeconomic gradients were found in the use of PET-CT, discussions in a multidisciplinary team setting and use of SBRT in early-stage disease but not for other diagnostic and treatment modalities. Patients with a high educational level had better survival in early-, but not in late-stage disease.

- No age-related differences in diagnostics of NSCLC were seen in patients below 80 years of age. Treatments were adapted according to age. In advanced-stage disease, systemic treatment were readily offered to patients 79 years or younger. Two thirds of patients in age-group 80-84 and one third of patients in age-group ≥85 years with a PS of 0-2 received treatment. In early-, but not late-stage disease survival was poorer in the elderly.

- There was evidence of a "healthy migrant effect" in non-Nordic immigrants. We found only minor differences in management between immigrant and Swedish-born patients following adjustments. In early-stage disease non-Nordic immigrants had better and Nordic immigrants had poorer survival compared to Swedish-born patients.

- After a diagnosis of NSCLC, rates of depressive and anxiety disorders, intoxication and suicide were elevated compared to the background population. The risk of depression, anxiety, and suicide decreased over time in contrast to the risk of intoxication that remained high throughout the period of follow-up.

# Future research perspectives

Continued assessments of equality of cancer care and outcomes will remain relevant in the foreseeable future. The treatment panorama of lung cancer has changed dramatically in recent years, enabling treatment to a larger number of patients with NSCLC. Also, the conclusions of the present studies may need to be re-evaluated because of ongoing demographic changes including an increasing number of elderly patients and changes in the composition of the immigrant population. The following research questions could be addressed in future studies:

- Has the introduction of novel treatment modalities in NSCLC enabled more treatments for frail patients? Will novel therapies affect outcomes also in socioeconomically deprived and elderly patients?

- How do we best estimate life expectancy, physical and mental capacity in older lung cancer patients? Can geriatric assessments or geriatric screening tools improve the choice of treatment and improve outcomes in the elderly?

- Can older patients with early-stage NSCLC to a larger extent receive curative treatments and will this translate into improved survival?

- Will changing trends in the composition of the immigrant population with an increase of refugees and family reunifications immigrants change our present conclusions?

- How will an introduction of lung cancer screening influence the distribution of stage at diagnosis? Will attendance to lung cancer screening be lower in individuals with a low socioeconomic status, high age or an immigrant background?

- What are the rates of prescribed antidepressants, anxiolytics and sedatives in lung cancer patients compared to the general population?

- What is the optimal strategy for screening and choice of treatment for depression and anxiety in cancer patients at large, and in older cancer patients in particular?

- Can use of psychiatric screening scales for depression and anxiety reduce the risk of self-harm in lung cancer patients?

# Final remarks

Equality of care remains important for the government, health care staff and patients. Ongoing measures are needed to include also frail groups in society. There are several factors that can improve lung cancer survival including early detection by implementation of population-based screening, adherence to national management guidelines and rapid and equal access of novel drugs. Also, lifestyle changes that improves general health status is likely to contribute to a better prognosis by allowing a broader range of treatment options to a larger number of patients.

Data available in Swedish population-based registers remains an underused resource in clinical research. There is clear need to increase future use where clinicians play an important role by identifying clinically relevant research questions to be addressed in collaboration with epidemiologists and biostatisticians.

# Populärvetenskaplig sammanfattning på svenska (Summary in Swedish)

**Faktorer som påverkar omhändertagande och överlevnad vid icke-småcellig lungcancer. Inverkan av socioekonomi, ålder och ursprung samt aspekter av livskvalitet.**

Lungcancer är den vanligaste orsaken till cancerrelaterad död i världen. I Sverige får årligen 4 200 svenskar en lungcancerdiagnos vilket gör det till den fjärde vanligaste cancerformen hos kvinnor och den sjunde vanligaste hos män. Denna cancersjukdom är vanligare hos äldre individer, vid insjuknande är medelåldern 69 år och endast 10 % är under 60 år vid insjuknandet. Det är nuförtiden något fler kvinnor än män som insjuknar, ca 52 % är kvinnor. Tobaksrökning är en välkänd riskfaktor för lungcancer men även exponering för radon, tungmetaller och strålning inverkar. I Sverige är det bara ca 17 % av kvinnorna och 12 % av männen som är aldrig-rökare vid diagnos av lungcancer. Drygt 85 % av de som insjuknar i lungcancer drabbas av undergruppen icke-småcellig lungcancer som i sin tur delas upp i adenocarcinom, skivepitelcancer och icke-specificerad icke-småcellig lungcancer innefattande alla andra mer ovanliga lungcancertyper. Vid diagnos klassificerar man lungcancer utifrån stadier från I till IV som är ett mått på hur spridd sjukdomen är. Lungcancer ger ofta vaga eller inga symtom i början av sjukdomen och kan vara ett accidentellt fynd på röntgen när man röntgas av annan orsak. I senare skeden kan hosta, blodtillblandade upphostningar, andfåddhet och smärta vara symtom på sjukdomen. På grund av att lungcancer ofta ger få, diffusa och ospecifika symtom har 51 % en spridd icke-botbar sjukdom vid diagnos. Årligen dör 3 600 svenskar i lungcancer. Det pågår förberedelser i Sverige för att införa screening av individer som rökt en längre tid.

Utredning av lungcancer består vanligen, utöver genomgång av sjukhistoria och en fysisk undersökning, av en s.k. PET-DT; en specialröntgen där man administrerar en radioaktiv isotop och därefter gör en datortomografiundersökning där man också detekterar var isotopen söker sig. Vidare genomförs vanligen bronkoskopi, en kameraundersökning av luftstrupe och luftvägar, samt vävnadsprovtagning. Tumörvävnaden testas för en rad olika markörer för att kunna välja optimal behandling av sjukdomen. Behandling i tidiga stadier av sjukdomen består i huvudsak av kirurgi eller s.k. stereotaktisk

strålbehandling, en teknik för punktstrålbehandling. Vid mer avancerad sjukdom erbjuds patienter vanligen en kombination av både cytostatikabehandling och strålbehandling. Vid spridd sjukdom är det i huvudsak medicinsk behandling som erbjuds med cytostatika, immunterapier eller målinriktad behandling. För de som är för sjuka eller svaga för att tåla medicinsk behandling är palliativ vård för god livskvalitet i livet slut en viktig hörnsten i behandlingen. Psykologiska följder med depression och ångest är vanligt efter en lungcancerdiagnos.

I Sverige har vi ett skattefinansierat sjukvårdssystem som strävar efter att erbjuda en jämlik vård till alla invånare oavsett kön, ålder och bostadsort. Trots detta så har jämlikheten i sjukvårdssystemet ifrågasatts. I Sverige har vi unika möjligheter att studera hela den svenska befolkningen tack vare befintliga populationsbaserade register som i hög utsträckning är kompletta och av god kvalitet. Det övergripande målet med denna avhandling var att undersöka olika aspekter av jämlikhet av vård samt psykologiska följder av en cancerdiagnos hos patienter med icke-småcellig lungcancer.

Alla studier utgick från forskningsdatabasen Lung Cancer Database Sweden (LCBaSe), en databas där information från svenska Lungcancerregistret är sammanfogat med information från flera andra svenska myndighetsregister över den svenska befolkningen. Databasen sträcker sig över tidsperioden 2002 till 2016 och identifierade ca 40 000 patienter som fått diagnosen icke-småcellig lungcancer, detta motsvarade mer än 95 % av alla patienter som fick en diagnos under den tidsperioden i Sverige. För att studera vårdens jämlikhet undersöktes omhändertagande och överlevnad av patienter med icke-småcellig lungcancer; i delarbete I utifrån socioekonomi, i delarbete II utifrån ålder och i delarbete III utifrån geografisk födelseregion. I delarbete IV undersöktes förekomsten av depression, ångest, överdos av alkohol, morfin eller lugnande läkemedel samt självmord hos patienter med icke-småcellig lungcancer jämfört med svenska lungcancerfria individer.

I delarbete I valdes utbildningsnivå som mått på socioekonomi. Individerna delades upp i tre grupper: lågutbildade (utbildning max 9 år, motsvarande högstadienivå), medelutbildade (utbildning max 12 år, motsvarande gymnasienivå) och högutbildade (utbildning mer 12 års, motsvarande högskole- eller universitetsnivå). Vi fann att lågutbildade i högre utsträckning var män, rökare, hade ett sämre allmäntillstånd och högre grad av samsjuklighet. Patienter med hög utbildningsnivå fick i högre utsträckning genomgå röntgenundersökning med s.k. PET-DT, bedömdes i högre utsträckning vid gemensam multidisciplinär rond och

behandlades i högre utsträckning med SBRT. I övrigt var det inga skillnader i utredning och behandling för högutbildade jämfört lågutbildade patienter. Överlevnaden var bättre för högutbildade i tidigt skede av icke-småcellig lungcancer, för mer framskridna skeden av sjukdomen fanns inga skillnader i överlevnad mellan hög- och lågutbildade patienter. Dessa skillnader i utredning, behandling och överlevnad kan spegla att såväl PET-DT som SBRT var nya metoder under tidsperioden och därför i högre utsträckning fanns tillgängliga i storstadsregionerna där högutbildade i högre utsträckning bor.

I delarbete II undersöktes vård och överlevnad hos äldre patienter med icke-småcellig lungcancer. Patienterna delades in i åldersgrupper med femårsintervall mellan 69-85 år d.v.s. om patienterna var under 69 år, mellan 70-74 år, mellan 75-79 år, mellan 80-84 år eller 85 år eller äldre. I de äldsta åldersgrupperna var det vanligare med sämre allmäntillstånd, högre grad av samsjuklighet, lägre utbildningsnivå och cancer av typen skivepitelcancer. Hur avancerad sjukdomen var vid diagnos, d.v.s. ett indirekt mått på om det är fördröjningar hos vården att diagnosticera lungcancer hos äldre, skilde sig inte åt för patienter under 85 år. Utredningar av cancern gjordes i samma utsträckning hos patienter upp till 79 år. Anpassningar i val av behandling gjordes mellan yngre och äldre patienter; vid tidigare stadier av sjukdomen erbjöds yngre patienter i högre utsträckning kirurgi och äldre patienter i högre utsträckning punktstrålbehandling (SBRT). Vid mer avancerad sjukdom erbjöds de äldsta patienterna bara undantagsvis kombinerad behandling med strålbehandling och samtidig cytostatikabehandling vilket är en tung behandling. Vid spridd sjukdom där cancern metastaserat till andra platser och bot inte längre är möjligt, erbjöds 58 % av patienterna 80-84 år och 30 % av patienterna 85 år eller äldre bromsande behandling. I tidigare stadier av lungcancer sjönk överlevnaden med ökande ålder hos patienten vilket inte sågs i samma utsträckning vid spridd sjukdom. Våra resultat betonar vikten av att sjukvårdspersonal gör en noggrann bedömning av äldre patienters allmäntillstånd och förväntad överlevnad för att kunna göra optimala behandlingsval. Äldre patienter utesluts ofta från forskningsstudier och det krävs ytterligare framtida studier av äldre för att på bästa sätt kunna göra rätt behandlingsval för varje individuell patient.

I delarbete III studerades vård och behandling av invandrare i Sverige. Invandrarna delades in utifrån ursprungsland men pga. få patienter med utländsk bakgrund tilläts inte djupare indelning än till de tre grupperna svenskfödda, födda i de övriga länderna i Norden eller födda utanför Norden. Vi konstaterade att 84 % av alla patienter med icke-småcellig

lungcancer är födda i Sverige, 7 % i våra nordiska grannländer och 9 % i icke-nordiska länder. Hos icke-nordiska invandrare kunde vi bekräfta en s.k. frisk-invandrar-effekt; de var yngre än svenskar vid diagnos, i högre utsträckning män, hade bättre allmäntillstånd och högre utbildningsnivå men var också till en högre grad rökare. Nordiska invandrare var istället äldre än svenskar vid diagnos, hade ett sämre allmäntillstånd och mer samsjuklighet. Det fanns, efter justering för ålder och andra faktorer bara små skillnader i omhändertagande och överlevnad. Om något, så hade icke-nordiska invandrare bättre överlevnad i tidiga stadier av sjukdomen.

I delarbete IV studerade vi psykiska besvär hos patienter som får diagnosen icke-småcellig lungcancer och jämförde det med förekomsten hos lungcancerfria individer. Gruppen av patienter med icke-småcellig lungcancer hade jämfört med jämförelsegruppen en lägre utbildningsnivå och högre grad av samsjuklighet, något fler hade också en invandrarbakgrund. Som förväntat hade patienterna med icke-småcellig lungcancer betydligt högre dödlighet. Det var låg förekomst av depression och ångest i Patientregistret och sannolikt är dessa diagnoser underrapporterade där. Förekomsten av depression, ångest, förgiftningar och självmord var högre efter en diagnos av icke-småcellig lungcancer jämfört med de lungcancerfria individerna. Den förhöjda risken för ångest, depression och självmord avtog över tid men den ökade risken för förgiftningar bestod under hela den studerade tidsperioden.

Sammanfattningsvis visar denna avhandling att Sverige i hög utsträckning erbjuder jämlik vård när man kompenserar för patienternas allmäntillstånd, samsjuklighet och andra faktorer som är viktiga för val av utredning och behandling. Vi bedömer att det är viktigt att nya metoder för diagnostik och behandling implementeras snabbt i behandlingsriktlinjer och vårdprogram för att göra dem tillgängliga till alla oavsett socioekonomi eller bostadsplats i Sverige. En noggrann bedömning av äldre patienters allmäntillstånd och förväntade överlevnad är viktigt för att undvika att beslut kring utredning och behandling baseras enbart på kronologisk ålder. Fler studier krävs för att klargöra optimal behandling av äldre lungcancerpatienter. Endast små skillnader i omhändertagande och utfall kunde konstateras mellan utlandsfödda och svenska patienter. Om något så var överlevnaden något bättre för icke-nordiska invandrare med tidiga stadier av sjukdomen. Bekräftande tidigare forskning fanns hållpunkter för att en lungcancerdiagnos försämrar livskvaliteten, att patienterna får ett sämre psykiskt mående. Det är viktigt att sjukvårdspersonal aktivt försöker identifiera symtom på ångest och oro framför allt första tiden efter diagnos samt att de arbetar

aktivt för att försöka identifiera patienter som riskerar att skada sig själva med förgiftningar eller genomgå suicid.

Det finns flera faktorer som kan förbättra överlevnaden hos lungcancerpatienter så som tidig cancerupptäckt genom införandet av nationell lungcancerscreening, god följsamhet till behandlingsriktlinjer och snabb och jämlikt införande av cancerläkemedel. Även livsstilsförändringar som förbättrar den allmänna hälsan kan sannolikt bidra till en bättre prognos genom att fler behandlingar kan erbjudas till en större andel patienter.

Data som finns i våra svenska register är underanvända för klinisk forskning. Det finns skäl att öka den framtida användningen där kliniker har en viktig roll i att identifiera relevanta forskningsfrågeställningar som kan utforskas i samarbete med epidemiologer och biostatistiker.

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