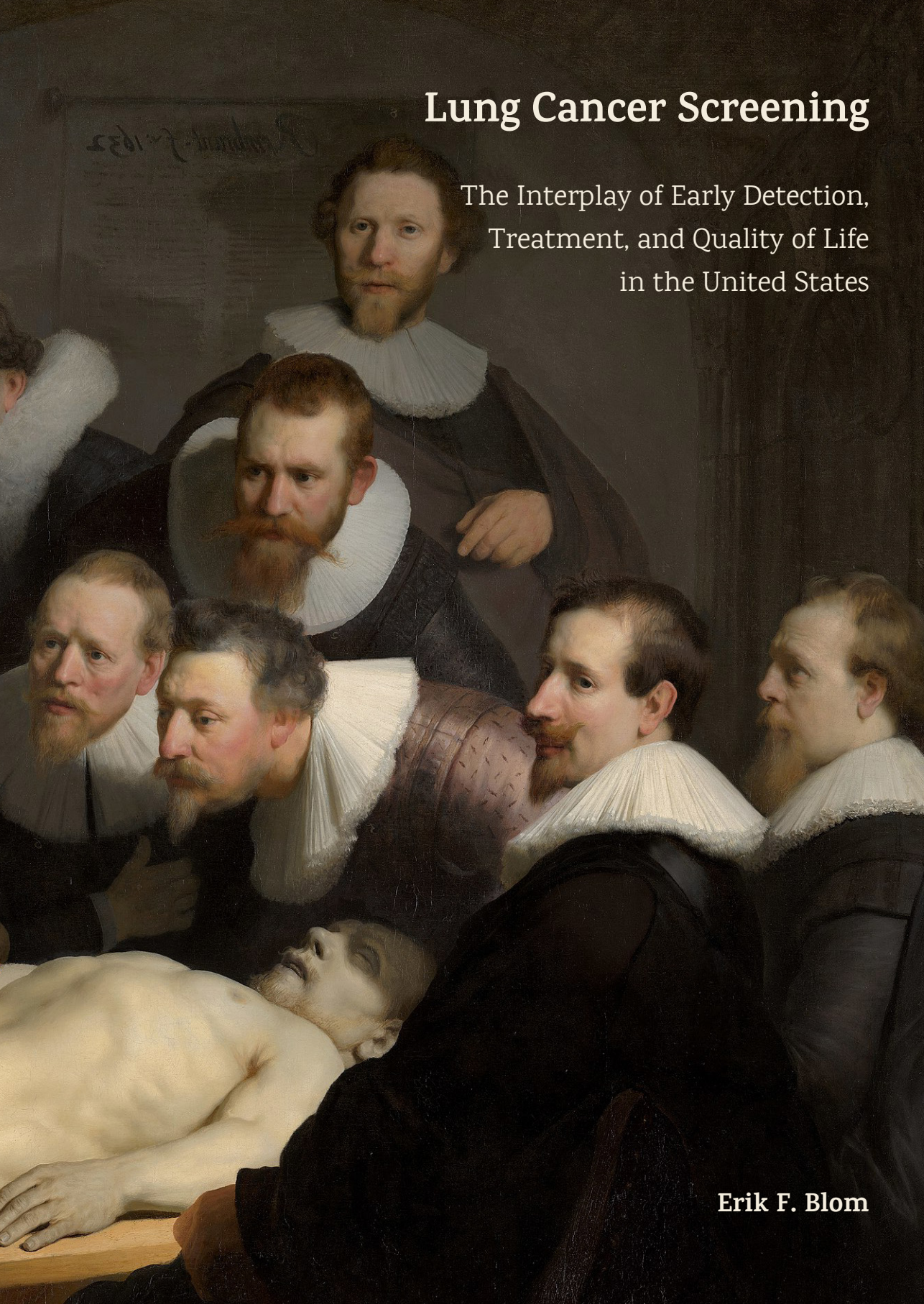

Lung Cancer Screening

The Interplay of Early Detection, Treatment, and Quality of Life in the United States

Erik F. Blom

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Longkankerscreening

Het samenspel tussen vroege opsporing, behandeling
en kwaliteit van leven in de Verenigde Staten

Thesis

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Preface

The cover of this thesis shows the famous painting "The anatomy lesson of dr. Nicolaes Tulp" by Rembrandt van Rijn. The painting, which was made in 1632, portrays dr. Nicolaes Tulp giving a public anatomy lesson to the Dutch Guild of Surgeons. According to genealogical sources recovered from my grandfather's archives, I may have a distant relation to one of the portrayed men. Unfortunately, that relation is not to dr. Tulp, but to the subject of dissection. His name was Adriaen Adriaenszn 't Kint and he was executed for theft prior to the dissection. By serving as the subject of dissection, he indirectly contributed to the scientific body of knowledge. Almost 400 years later, this thesis summarizes my own contributions to the medical sciences. Thus, this thesis marks the progression across generations, closing the circle from criminal to doctor.

Erik F. Blom
Utrecht, the Netherlands, May 2020

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General Introduction

Etiology of lung cancer

Throughout life, the genetic material inside cells is continuously damaged as a result of both endogenous and environmental factors (including exposure to certain chemical substances). Usually, such mutations are recognized, and the damaged cells are repaired or removed. Other cells reproduce to replace them. This process is regulated by complex molecular mechanisms. If mutations occur in the genetic material responsible for these regulatory mechanisms, a cell may start to behave abnormally.[1-3] In particular, such a cell may proliferate and divide abnormally, and spread or invade to other parts of the body. This is known as a malignant tumor, or cancer.[4] Usually, several mutations are necessary to develop cancer.[2,5]

For cancer originating from the lungs, tobacco smoking is by far the most important risk factor,[6,7] accounting for up to 90% of cases.[8-11] Tobacco smoke damages cells in the lungs and contains at least 15 chemicals that have been proven to cause cancer in humans.[9,12] The relative risk of lung cancer has been estimated to be up to 20 times higher in smokers compared to lifelong non-smokers.[9] The risk of lung cancer increases as a function of the intensity and duration of smoking.[9,11,13] Accumulated smoking behavior can be expressed as a function of smoking intensity and duration in terms of pack-years. A pack-year is defined as the equivalent of having smoked 20 cigarettes (i.e. one pack) per day for one year. It should be noted that the increased risk for lung cancer extends to those exposed to secondhand smoke, although to a much lesser degree. It has been estimated that non-smokers living with a smoker have a 20-30% increased risk of lung cancer.[14]

Other independent risk factors include chronic obstructive pulmonary disease,[15,16] a positive family history for lung cancer,[17] and exposure to occupational or environmental factors such as air pollution,[2,18] industrial chemicals,[2] asbestos,[2,19] and radon.[2,20] This thesis focuses on the United States, in which these factors play a relatively modest role compared to tobacco smoking. However, in other geographical areas, factors such as indoor air pollution due to cooking on coal burning stoves may play a larger role.[21,22]

Pathology

Two main types of lung cancer can be distinguished: non-small cell lung cancer and small cell lung cancer. Small cell lung cancer, which accounts for approximately 13% of cases,[23,24] is strongly associated with tobacco smoking, and is clinically the most aggressive type of lung cancer.[2] This type of lung cancer tends to develop in the central airways and grow and spread quickly.[25]

Non-small cell lung cancer is a clinically more diverse disease, but can be predominantly further classified as adenocarcinoma or squamous cell carcinoma. Adenocarcinomas, which account for approximately 50% of all lung cancer cases,[24] originate in glandular cells.[2,25] This type of lung cancer is more often located peripherally in the lungs.[2,25] Although adenocarcinomas are related to smoking, they are also the most common subtype of lung cancer among never-smokers.[25] Squamous cell carcinomas arise from the epithelial cells that line the airways.[2] This type of

non-small cell lung cancer accounts for approximately 23% of all lung cancer cases.[24] Squamous cell carcinomas are closely related to smoking exposure, and are more often located centrally in the lungs.[2,25] In this thesis, the remaining histological subtypes are grouped together in the common category other non-small cell lung cancer.

Epidemiology

Incidence and mortality in the United States

As smoking is the main risk factor for lung cancer, the number of new cases in the population (i.e. incidence) and the number of persons dying from lung cancer (i.e. disease-specific mortality) depend on patterns of smoking behavior.

Although the causal relationship between smoking and lung cancer has been established since the 1950s,[6,7] it was the 1964 Surgeon General's report that raised awareness among the general public of the dangers of tobacco smoking.[26] As a result, the percentage of the population that smokes (i.e. smoking prevalence) among men in the United States is much lower for those born in more recent years (see Figure 1).[27] This is due to lower rates of smoking initiation and higher rates of smoking cessation. Patterns in women are similar to those in men, but lag because women started smoking later. Across the entire US population, cigarette smoking prevalence has decreased by approximately two thirds since 1965, from approximately 40% in 1965[10] to 13.7% in 2018.[28]

As the risk of lung cancer builds up with age and continued exposure to smoke, there is a lag time of 20 to 30 years between changes in smoking prevalence in the population and changes in lung cancer mortality. Therefore, the peak in smoking prevalence among men in the 1960s resulted in a peak in lung cancer mortality of over 50 deaths per 100,000 men in 1990.[29] Following the drop in smoking prevalence after the 1960s, lung cancer mortality dropped to approximately 30 deaths per 100,000 men around 2010.[29] Nevertheless, lung cancer remains an important health issue to date. It is still the second most common form of cancer in the United States for both males and females, with an estimated 228,150 new cases in 2019.[30] The lifetime chance of developing lung cancer is approximately 1 in 15 for men and 1 in 17 for women.[23] In 2019, an estimated 142,670 persons died of lung cancer, which is more than of colon, breast, and prostate cancer together.[23,30] Lung cancer mainly (but not exclusively) occurs in elderly persons; the mean age at diagnosis is 70 years.[23]

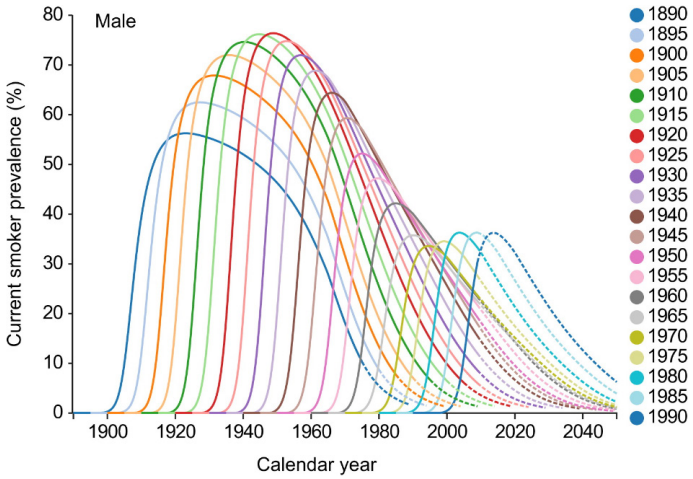

Figure 1: Smoking prevalence among males in the United States by calendar year and birth year. Reprinted from Am J Prev Med, 46(2), Holford TR et al., Patterns of birth cohort-specific smoking histories, 1965-2009, pages e31-7, Copyright (2014), with permission from Elsevier.

Stage at diagnosis

The extent to which cancer has spread at the time of diagnosis is called the stage. The American Joint Committee on Cancer developed a widely adopted staging system based on the size of the primary tumor, the presence of spread to regional lymph nodes, and the presence of spread to distant sites in the body. In this thesis, the 7th edition of this staging system is used, which was in effect from 2010-2017.[31] This system distinguishes 7 stages of malignant lung cancer: IA, IB, IIA, IIB, IIIA, IIIB, and IV. For clinical purposes, these stages are grouped into wider categories.

Non-small cell lung cancer stages IA to IIB comprise tumors that have not invaded any clinically significant anatomical structures, such as the heart or great vessels. Also, there is no spread or limited spread to regional lymph nodes, and there is no metastasis to distant sites. Therefore, these stages are generally referred to as early-stage or localized non-small cell lung cancer. This stage group comprises approximately 19% of non-small cell lung cancer cases.[24]

Stages IIIA-IIIB non-small cell lung cancer are a clinically diverse group of patients. The tumor may or may not have spread to important anatomical structures, and spread to regional lymph nodes may be either limited or more extensive. However, these stages show no metastasis to distant sites. Stages IIIA-IIIB are commonly referred to as locally advanced or regional non-small cell lung cancer. This stage group comprises approximately 24% of cases.[24]

If distant metastasis is present (e.g. in the adrenal glands, brain, or bones), non-small cell lung cancer is categorized as stage IV, regardless of the tumor size or lymph node involvement. This stage group is commonly referred to as advanced or distant non-small cell lung cancer, and comprises the majority of cases (approximately 55%).

For small cell lung cancer, metastatic disease (stage IV) is referred to as extensive disease. This stage group comprises approximately 75% of cases,[24] which reflects the aggressive nature of this type of lung cancer. All other small cell lung cancer stages are referred to as limited disease, which is relatively uncommon.

Survival

The time that a person remains alive after receiving the diagnosis of cancer is called the overall survival. As stated earlier, lung cancer is an aggressive disease. Therefore, overall survival is generally short. However, overall survival strongly depends on the stage at diagnosis (see Figure 2). For stage IA, the median overall survival time is 58 months.[32] For stage IV, median overall survival time is only 6 months.[32] The corresponding percentage of patients that are alive five years after they were diagnosed with lung cancer is 52% for stage IA and 4% for stage IV.

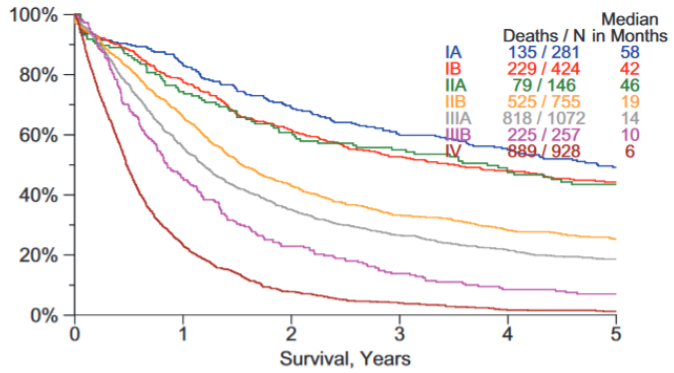

Figure 2: Overall survival by clinical stage at diagnosis. Reprinted from J Thor Oncol, 2(8), Groome PA et al., The IASLC Lung Cancer Staging Project: Validation of the Proposals for Revision of the T, N, and M Descriptors and Consequent Stage Groupings in the Forthcoming (Seventh) Edition of the TNM Classification of Malignant Tumours, pages 694-705, Copyright (2007), with permission from Elsevier.

Treatment

The overall survival statistics reflect the available treatment options, which are better when the type of lung cancer is less aggressive, and when the stage at diagnosis is limited. As such, the minimal recommended treatment for lung cancer differs by lung cancer type (i.e. non-small cell lung or versus small cell lung cancer) and stage at diagnosis.[33,34]

The most important curative treatment option for lung cancer is the surgical removal of (part of) the affected lung. This is only feasible if the disease has not spread

too far, and if the patient is fit enough to live with the reduced lung volume. Therefore, surgical treatment is recommended for early-stage non-small cell lung cancer, as well as for a small subgroup of patients with locally advanced non-small cell lung cancer or limited disease small cell lung cancer.[33,34] However, when surgical treatment for locally advanced non-small cell lung cancer or limited disease small cell lung cancer is deemed feasible, an additional treatment with chemotherapy is recommended to improve the chance of complete removal of the tumor.[33,34] Chemotherapy is administered systemically, and can therefore reach tumor cells that have potentially spread from the primary tumor.

If surgical treatment for these stage groups is technically not feasible, or when the patient is not fit enough, other treatments are recommended. For early-stage non-small cell lung cancer, the recommended alternative to surgery is stereotactic body radiation therapy.[33] This type of treatment provides a high dose of radiation to a small target.[35,36] Therefore, stereotactic body radiation therapy can cure small tumors, while limiting damage to surrounding tissue. For inoperable patients with locally advanced non-small cell lung cancer or limited disease small cell lung cancer, stereotactic body radiation therapy is not feasible because the disease is too widespread. Instead, a combination of conventional radiotherapy and chemotherapy is recommended.[33,34]

Finally, when distant metastasis is present, curative treatment is not possible. Nevertheless, guidelines recommend that chemotherapy should always be provided.[33,34] In some cases, metastases of the brain and bones may require additional treatment with radiotherapy to reduce symptoms.[33,34] Very recently, two new classes of drugs have been introduced. One class of drugs, called targeted therapy, targets specific molecular pathways in tumor cells. The second class of drugs, called immunotherapy, prompts the patient's immune system to recognize and attack tumor cells. Although non-curative, these drugs may prolong survival in select patients.[37-39] Currently, their use is limited to metastatic disease, although this may extend to earlier stages in the future. However, the recommendations for these treatments are so recent that they are not considered in this thesis. For example, in October 2016 pembrolizumab was the first immunotherapy agent approved by the US Food and Drug Administration for the first-line treatment of certain advanced lung cancer cases.

Primary prevention (smoking cessation)

As tobacco smoking is the main risk factor for lung cancer, preventing individuals from starting to smoke and encouraging current smokers to quit is potentially the most effective method to prevent lung cancer.[10]

Examples of tobacco control policies are increased taxes on tobacco products and the introduction of smoke free indoor air policies.[10] It has been estimated that nearly 800,000 lung cancer deaths have been averted in the United States between 1975-2000 due to such tobacco control policies.[40] However, this number represents only about a third of the 2.5 million lung cancer deaths that could have been avoided if tobacco control would have been immediate and complete.[40] Another study projected that, despite continuing current tobacco control policies since the 1965 Surgeon General's report, 50,000 persons will still die of lung cancer in the United States in

2065.[41] Therefore, despite the successes of tobacco control, lung cancer will remain an important public health issue in the foreseeable future.

Secondary prevention (screening)

Principles of screening

According to the World Health Organization, screening is defined as "the identification of unrecognized disease in an apparently healthy, asymptomatic population [...]".[42] In the case of cancer, a tumor may exist for a period of time before it progresses and causes symptoms (see Figure 3). During this period, which is called the preclinical phase, a screening test may provide an early diagnosis. The time with which screening may advance the diagnosis is called the lead time. If early diagnosis allows for more favorable treatment options, death may be postponed.

However, early diagnosis does not always change the time of death, for example if treatment was not successful. In that case, overall survival after the diagnosis of lung cancer is longer, while the patient does not live any longer. This is known as lead time bias. To account for lead time bias, the benefit of screening in a screened population compared to a non-screened population is generally either expressed as the number of life-years gained due to postponing death, or as the difference in the number of persons that died due to the disease within a specified period of follow-up (i.e. disease-specific mortality reduction).

Generally, the quality of life of cancer patients is poor.[43] Therefore, it is also important to account for changes in quality of life due to early diagnosis and treatment. This is done by weighing the number of life-years gained due to screening by a factor that measures quality of life, a so called health state utility value. The resulting outcome is a quality-adjusted life year.

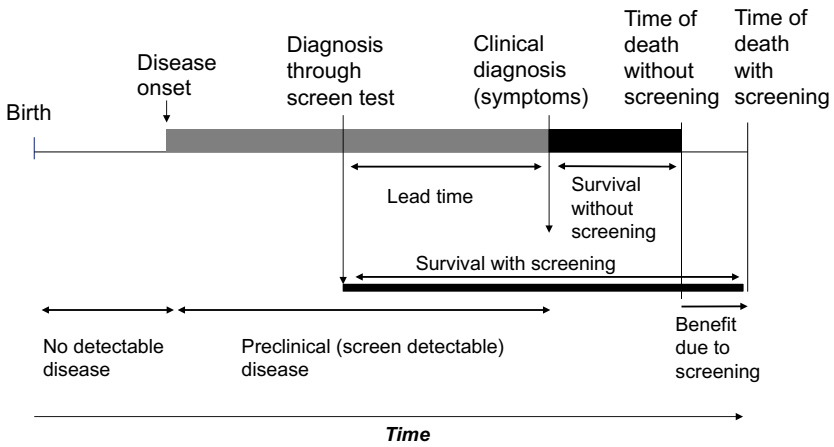

Figure 3: Principles of screening.

In some cases, a screen-detected cancer would have never caused symptoms if screening had not occurred. This is referred to as overdiagnosis, and is considered the main harm of cancer screening. Overdiagnosis can lead to unnecessary treatment and anxiety, and can happen for two reasons. First, a screen-detected cancer may progress very slowly, or not at all, and may therefore never have reached the size at which it would cause symptoms if screening had not occurred (as indicated by the green arrows in Figure 4). The tendency of screening to detect slower growing tumors is called length bias. Second, a person with a progressive screen-detected cancer may die of other causes before the cancer would have progressed to a size at which it causes symptoms (as indicated by the red arrow in Figure 4). This is especially likely when screening patients with a limited life expectancy, such as elderly persons with comorbidities. Another harm of screening is a false positive screening result, in which case unnecessary invasive diagnostic procedures such as biopsies may occur.

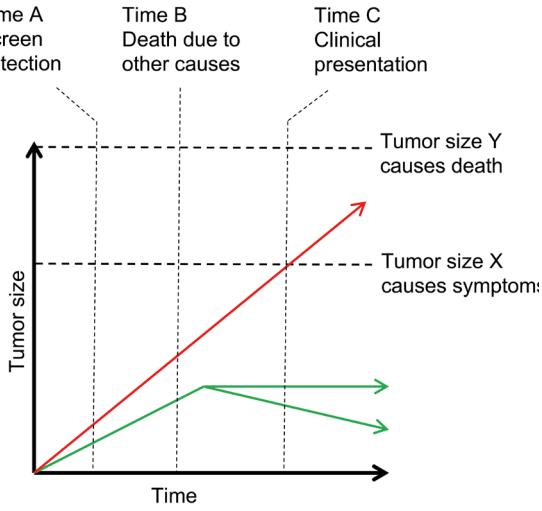

Figure 4: Principles of overdiagnosis. Adapted with permission from the U.S. National cancer Institute: https://prevention.cancer.gov/news-and-events/infographics/what-cancer-overdiagnosis.

Current evidence for lung cancer screening

Most lung cancer cases are diagnosed at an advanced stage, with limited treatment options. Therefore, lung cancer screening has been investigated since the 1960s. Several studies investigated the benefits of screening with chest radiography, but found no mortality benefit.[44-48]

After low-dose computed tomography technology was introduced, several new lung cancer screening studies were initiated. The single-arm International Early Lung Cancer Action Project (I-ELCAP) showed that up to 85% of screen-detected lung cancer

were found in stage I.[49] However, the mortality benefit due to early detection could not be assessed due to the lack of a control group.

In 2002, the US-based National Lung Screening Trial (NLST) was initiated, which randomized 53,454 participants to receive either three annual low-dose computed tomography scans or three annual chest radiography screens.[50] Those included were current or former smokers (quit less than 15 years ago) aged 55-74, with a smoking history of at least 30 pack-years. The NLST found a statistically significant 20% reduction in lung cancer mortality, as well as a statistically significant reduction in all-cause mortality of 6.7%.[51]

Whereas the control group in the NLST received three annual chest radiography screens, seven smaller European randomized controlled trials compared low-dose computed tomography screening to usual care. The inclusion criteria and screening protocol differed across studies (see Table 1).[50,52-58] The Dutch-Belgian randomized lung cancer screening trial (NELSON), which randomized 15,822 high-risk individuals,[52] showed a statistically significant 24% reduction in lung cancer mortality after a minimum of 10 years of follow-up.[59] Thus far, the other European trials did not find a statistically significant reduction in lung cancer mortality,[54,60-62] although it should be noted that these studies were not powered to find such a difference. Nevertheless, pooling of data across these trials may provide additional evidence.

Role of microsimulation modeling

Although the published and ongoing randomized trials are important sources of evidence, results are not necessarily representative for members of the general population. For example, the main risk factor for lung cancer (i.e. smoking behavior) is decreasing.[27] Also, it is impossible to compare many different screening policies in randomized controlled trials. For example, only a single set of screening eligibility criteria was assessed in each lung cancer screening trial, while other criteria may be more effective or efficient.[63,64] In addition, only several screening rounds were assessed, whereas a screening program in the general population considers continued screening. Microsimulation models use existing data sources to extrapolate the effects of screening to such situations. Therefore, such models can provide valuable information to policy makers.[63,65]

Table 1: Overview of study protocols of low-dose computed tomography screening studies.

Study	N	Ages	Smoking history	Smoking cessation	Control	Screening Interval	Number of screens
NLST[50]	53,454	55-74	≥30 pack-years	<15 years	3 annual chest radiography screens	Annual	3
NELSON[52]	15,822	50-75	≥15 cigarettes per day for ≥25 years or ≥10 cigarettes per day for ≥30 years	≤10 years	Usual care	Depending on round: 1, 2, or 2,5 years	4
DLCST[53]	4,104	50-70	≥20 pack-years	≤10 years	Usual care	Annual	5
MILD[54]	4,099	≥49	≥20 pack-years	≤10 years	Usual care	Annual or biennial	5 (annual) or 3 (biennial)
UKLS[55]	4,055	50-75	Predicted 5-year risk of lung cancer diagnosis ≥5%	-	Usual care	Single screen	1
LUSI[56]	4,052	50-69	≥15 cigarettes per day for ≥25 years or ≥10 cigarettes per day for ≥30 years	≤10 years	Usual care	Annual	4
ITA-LUNG[57]	3,206	55-69	≥20 pack-years	≤10 years	Usual care	Annual	4
DANTE[58]	2,472	60-74	≥20 pack-years	≤10 years	Usual care	Annual	5

Lung cancer screening recommendations

In 2013, the United States Preventive Task Force recommended annual screening between ages 55-80 of current smokers and former smokers that quit less than 15 years ago, and that accumulated a smoking history of at least 30 pack-years.[66] This recommendation was partly based on modeling efforts.[63] Also, the Centers for Medicare & Medicaid Services issued a decision memo approving reimbursement of lung cancer screening.[67] Nevertheless, lung cancer screening uptake in the United States has remained low.[68,69] In Europe, many countries are planning for a possible implementation of lung cancer screening.[70] In the meantime, many questions remain, some of which are answered in this thesis.

Research questions and outline of this thesis

This thesis aims to answer two main research questions:

- Research question I: How does the implementation of lung cancer screening affect the demand for different treatment modalities?
- Research question II: What are the benefits and harms of population-based lung cancer screening programs?

The first research question is discussed in chapters 1 to 3. Although the benefits of early detection of lung cancer due to screening have been established in randomized controlled trials,[51,59] successful implementation in the general population depends on optimal treatment of cases detected at an early stage. Chapters 1 and 2 investigate which treatments lung cancer patients in the United States currently receive. Chapter 1 investigates whether treatments received by lung cancer patients in the United States are in concordance with clinical practice guidelines. Also, chapter 1 identifies which groups of patients are less likely to receive the recommended treatment. Chapter 2 investigates the uptake of the new treatment modalities minimally invasive surgery and stereotactic body radiation therapy among early-stage non-small cell lung cancer patients. Finally, the implementation of a population-based lung cancer screening program will shift the stage at which lung cancer is diagnosed towards early stages. Chapter 3 investigates how current lung cancer treatment patterns will change as a result of that shift. This information is used to project the future demand for the different treatment modalities used in lung cancer care.

The second research question is dealt with in chapters 3 to 6. Population-based screening programs are different from randomized trials. First, the screened population is dynamic, with new persons becoming eligible for screening each year. Second, screening occurs far beyond the 1-5 rounds offered in the randomized trials. The benefits and harms of population-based lung cancer screening programs have been previously assessed for a single cohort of the general U.S. population.[63] However, it is unclear how the decreasing smoking prevalence across different birth cohorts[27] affects these benefits and harms. Therefore, chapter 4 projects how overdiagnosis, which is considered the main harm of lung cancer screening, will change over time in a population-based lung cancer screening program in the United States. When assessing the benefits of a population-based cancer screening, it is important to consider the generally poor quality of life of cancer patients.[71] Such an adjustment can be done by using health state utility values. Therefore, Chapter 5 provides an overview of the literature on health state utility values for lung cancer. Also, pooled values are calculated. In Chapter 6, we use the identified health state utility values to assess the benefits and harms of a population-based lung cancer screening program among screening-eligible individuals. To account for age and cohort effects, the benefits and harms of continued screening from the year 2020 are assessed for persons at different ages. The key benefits and harms are summarized in a clinical decision aid which can be used to facilitate shared decision making between clinicians and potentially screening-eligible individuals.

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Part 1

Lung Cancer Treatment

Chapter 1

Disparities in Receiving Guideline-Concordant Treatment for Lung Cancer in the United States

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Abstract

Rationale

The level of adherence to lung cancer treatment guidelines in the United States is unclear. In addition, it is unclear whether previously identified disparities by racial or ethnic group and by age persist across all clinical subgroups.

Objectives

To assess the level of adherence to the minimal lung cancer treatment recommended by the National Comprehensive Cancer Network guidelines (guideline-concordant treatment) in the United States, and to assess the persistence of disparities by racial or ethnic group and by age across all clinical subgroups.

Methods

We evaluated whether 441,812 lung cancer cases in the National Cancer Database diagnosed between 2010 and 2014 received guideline-concordant treatment. Logistic regression models were used to assess possible disparities in receiving guideline-concordant treatment by racial or ethnic group and by age across all clinical subgroups, and whether these persist after adjusting for patient, tumor, and health care provider characteristics.

Results

Overall, 62.1% of subjects received guideline-concordant treatment (range across clinical subgroups: 50.4–76.3%). However, 21.6% received no treatment (range: 10.3–31.4%) and 16.3% received less intensive treatment than recommended (range: 6.4–21.6%). Among the most common less intensive treatments for all subgroups was "conventionally fractionated radiotherapy only" (range: 2.5–16.0%), as was "chemotherapy only" for nonmetastatic subgroups (range: 1.2–13.7%), and "conventionally fractionated radiotherapy and chemotherapy" for localized non-small-cell lung cancer (5.9%). Guideline-concordant treatment was less likely with increasing age, despite adjusting for relevant covariates (age ≥80 yr compared with <50 yr: adjusted odds ratio = 0.12, 95% confidence interval = 0.12–0.13). This disparity was present in all clinical subgroups. In addition, non-Hispanic black patients were less likely to receive guideline-concordant treatment than non-Hispanic white patients (adjusted odds ratio = 0.78, 95% confidence interval = 0.76–0.80). This disparity was present in all clinical subgroups, although statistically nonsignificant for extensive disease small-cell lung cancer.

Conclusions

Between 2010 and 2014, many patients with lung cancer in the United States received no treatment or less intensive treatment than recommended. Particularly, elderly patients with lung cancer and non-Hispanic black patients are less likely to receive guideline-concordant treatment. Patterns of care among those receiving less intensive treatment than recommended suggest room for improved uptake of treatments such as stereotactic body radiation therapy for subjects with localized non-small-cell lung cancer.

Introduction

An estimated 142,670 persons will die of lung cancer in the United States in 2019, making it the leading cause of cancer-related deaths.[1] Reflecting the large burden to society, lung cancer treatment is an important topic of medical research. A recent bibliometric analysis identified a total of 32,161 studies published on lung cancer between 2004 and 2013, of which 36% focused on treatments.[2] Clinical practice guidelines, which can be considered the basis for measures of quality of care, compile the available evidence and expert consensus.[3]

However, literature indicates that the minimal treatment recommended in these guidelines (i.e., guideline-concordant treatment) may not be provided to all patients with lung cancer in the United States.[4] Furthermore, there is evidence that specific subgroups are less likely than others to receive guideline-concordant treatment. For example, the proportion of cases that receive guideline-concordant treatment is lower for more advanced stages.[4] Also, disparities by racial or ethnic group have been described. For example, black patients are less likely to receive surgical treatment for localized non-small-cell lung cancer (L-NSCLC; stages I-II) than white patients.[5-10] In addition, elderly patients with lung cancer are less likely to receive guideline-concordant treatment, despite controlling for comorbidity.[4,9,10] However, comparability and generalizability of the available literature are limited because often only one specific subset of clinical cases is examined,[5,11] relatively small sample sizes are used,[8,10] different methodologies are applied,[5,7] or the data cover different timespans.[5,7] Thus, it is unclear whether disparities in receiving guideline-concordant treatment by racial or ethnic group and by age persist, and whether these are similar across clinical subgroups of lung cancer in the United States.

Therefore, the first aim of this study was to assess the level of adherence to predefined, stage-specific guideline-concordant treatment for each clinical subgroup of patients with lung cancer in a large U.S. dataset. The second aim was to assess whether previously identified disparities in receiving guideline-concordant treatment by racial or ethnic group and by age persist across all clinical subgroups of lung cancer. Some of the results of this study have been previously reported in the form of an abstract.[12]

Methods

Data

We used the U.S. National Cancer Database (NCDB) to extract a cohort of 441,812 patients diagnosed with lung cancer between 2010 and 2014 (see Figure E1 in the online supplement). The NCDB, established in 1989, is a nationwide, facility-based, comprehensive clinical surveillance resource oncology dataset that currently captures 70% of all newly diagnosed malignancies in the United States annually, from more than 1,500 affiliated facilities. The NCDB records the first course of treatment, defined as all methods of treatment recorded in the treatment plan and administered to the patient before disease progression or recurrence. Analysis of individual-level NCDB

data was performed on site at the University of Michigan Medical School.

To assess the generalizability of the NCDB data to the general U.S. population, we compared baseline characteristics to a cohort of patients with lung cancer from the population-based Surveillance, Epidemiology, and End Results (SEER) dataset.[13] A detailed version of the methods, including the rationale for case selection, data cleaning, and the analysis of the SEER dataset, is available online (see supplemental methods and Tables E1 and E2). This study was deemed exempt by the Institutional Review Board of the University of Michigan.

Definition of guideline-concordant treatment

Two main lung cancer types can be distinguished: NSCLC and small-cell lung cancer (SCLC), with the majority presenting as NSCLC. Because SCLC is clinically more aggressive than NSCLC, clinical guidelines provide specific treatment recommendations for clinical subgroups of lung cancer type and stage at diagnosis. For each of these clinical subgroups, we assessed whether guideline-concordant treatment was received, defined as the minimal first course treatment these patients should receive according to the National Comprehensive Cancer Network guidelines.[14,15]

Although surgery is still recommended as the primary minimal treatment for L-NSCLC (stages I-II), stereotactic body radiation therapy (SBRT) is now recommended as an alternative treatment to surgery for patients with L-NSCLC.[14] SBRT delivers high-dose radiation to a specific target in only a few fractions and provides local tumor control rates of up to 90% with moderate toxicity.[16,17] Therefore, both surgery and SBRT were considered guideline-concordant treatment for L-NSCLC. The minimal recommended treatment for locally advanced NSCLC (LA-NSCLC; stage III) and limited-disease SCLC (LD-SCLC; stages I-III) depends on operability.[14,15] If operable, the minimal recommendation is surgery combined with chemotherapy. However, the majority of patients with LA-NSCLC and those with LD-SCLC are inoperable, in which case the minimal recommendation is a combination of radiotherapy and chemotherapy. Therefore, both treatment combinations were considered guideline-concordant for LA-NSCLC and LD-SCLC. For advanced NSCLC (A-NSCLC; stage IV) and extensive disease SCLC (ED-SCLC; stage IV), the minimally recommended treatment is chemotherapy.[14,15] As we assessed the minimal recommended treatment for each clinical subgroup, additional treatments were allowed beside guideline-concordant treatment (e.g., radiotherapy for bone metastases beside chemotherapy in A-NSCLC). A summary of the treatment combinations that were considered guideline-concordant for each clinical subgroup can be found in Table E3.

Because the most frequently used SBRT schemes in the United States comprise a total dose of 45 Gray or more over 1-5 fractions[18-20] and the U.S. billing code for SBRT includes a maximum of 5 fractions,[14] SBRT was defined as thoracic radiotherapy with a total radiation dose of 45 Gray or more delivered in 5 fractions or less. There were no restrictions on radiation dose or fractionation for stages other than L-NSCLC. Chemotherapy included the use of targeted therapies. We were not able to separately assess the use of immunotherapy agents in these data, because their use was not recommended in the evaluated time-period (see supplemental methods).

Statistical analysis

For each clinical subgroup, we assessed the proportion of cases that received guideline-concordant treatment, less intensive treatment than recommended (defined as treatment that was not guideline-concordant), and no treatment. We used clinical stage at diagnosis for creating clinical subgroups because pathological stage can only be known after the outcome of interest (initial treatment) has occurred. For the groups of patients who received guideline-concordant treatment and less intensive treatment than recommended, we separately assessed which mutually exclusive combinations of surgery, SBRT, conventionally fractionated radiotherapy (CRT; defined as all radiotherapy other than SBRT), chemotherapy (including targeted therapy), and other treatment (including immunotherapy and experimental treatments) were received.

To identify whether previously identified disparities in receiving guideline-concordant treatment by racial or ethnic group and by age persist, we fitted a logistic regression model with receipt of guideline-concordant treatment as binary outcome and racial or ethnic group and age as independent variables. We further adjusted this model for several covariates that could be associated with racial or ethnic group and age, and also affect receiving guideline-concordant treatment. Based on previous literature, we included sex,[9] health insurance status[21] Charlson comorbidity score,[22] facility type,[11] and stage at diagnosis.[4] We further included histology, because squamous cell carcinomas are often located centrally,[23] potentially making them more difficult to surgically resect. Finally, we included hospital volume, because it is a well-established indicator of quality of care.[24] The derivation and composition of these variables is detailed in the supplemental methods.

To identify whether disparities by racial or ethnic group and by age extend across all clinical subgroups, we also fitted a separate model for each clinical subgroup. For clinical subgroups with multiple guideline-concordant treatment combinations, we fitted a separate model for each treatment combination. For example, two separate models were fitted for L-NSCLC: one with SBRT as binary outcome and one with surgery as binary outcome. These models were adjusted for the same covariates as the overall model.

All analyses were performed using R software version 3.4.1.[25] The base-R glm function was used to fit the logistic regression models. We used multiple imputation to address missing data, using three imputations.[26] Multicollinearity was assessed by calculating generalized variance inflation factors.[27]

Results

Patient characteristics

Baseline characteristics of the 441,812 included patients are shown in Table 1. When comparing these with lung cancer cases in the population-based SEER registry, we found only very small differences in sex, age, racial or ethnic group, health insurance status, histology, and stage at diagnosis (Table E4).

Table 1: Characteristics of patients in the National Cancer Database diagnosed with non-small cell lung cancer or small cell lung cancer in the years 2010–2014.

		Overall (N = 441,812)	NSCLC (n = 375,832)	SCLC (n = 65,980)
Patient characteristics				
Sex, n (%)	Male	228,519 (51.7)	196,454 (52.3)	32,065 (48.6)
	Female	213,293 (48.3)	179,378 (47.7)	33,915 (51.4)
Age at diagnosis, n (%)	<50 yr	22,328 (5.1)	19,224 (5.1)	3,104 (4.7)
	50–54 yr	33,619 (7.6)	27,968 (7.4)	5,651 (8.6)
	55–59 yr	50,955 (11.5)	42,054 (11.2)	8,901 (13.5)
	60–64 yr	62,839 (14.2)	51,902 (13.8)	10,937 (16.6)
	65–69 yr	75,298 (17.0)	62,838 (16.7)	12,460 (18.9)
	70–74 yr	71,798 (16.3)	60,983 (16.2)	10,815 (16.4)
	75–79 yr	58,053 (13.1)	50,616 (13.5)	7,437 (11.3)
	≥80 yr	66,922 (15.1)	60,247 (16.0)	6,675 (10.1)
Racial or ethnic group, n (%)	Non-Hispanic white	349,842 (79.2)	294,833 (78.4)	55,009 (83.4)
	Non-Hispanic black	48,060 (10.9)	42,799 (11.4)	5,261 (8.0)
	Non-Hispanic Asian	9,483 (2.1)	8,741 (2.3)	742 (1.1)
	Hispanic	12,081 (2.7)	10,587 (2.8)	1,494 (2.3)
	Other	2,806 (0.6)	2,441 (0.6)	365 (0.6)
	Unknown	19,540 (4.4)	16,431 (4.4)	3,109 (4.7)
Health insurance status, n (%)	Private	117,168 (26.5)	99,666 (26.5)	17,502 (26.5)
	Medicare	256,740 (58.1)	219,916 (58.5)	36,824 (55.8)
	Medicaid	34,278 (7.8)	28,118 (7.5)	6,160 (9.3)
	Other government insurance	7,023 (1.6)	5,928 (1.6)	1,095 (1.7)
	No insurance	18,112 (4.1)	15,009 (4.0)	3,103 (4.7)
	Unknown	8,491 (1.9)	7,195 (1.9)	1,296 (2.0)
Charlson comorbidity score, n (%)	0	24,6887 (55.9)	211,483 (56.3)	35,404 (53.7)
	1	130,577 (29.6)	110,304 (29.3)	20,273 (30.7)
	≥2	64,348 (14.6)	54,045 (14.4)	10,303 (15.6)
Health care provider characteristics				
Facility type, n (%)	Academic	140,344 (31.8)	121,914 (32.4)	18,430 (27.9)
	Nonacademic	298,618 (67.6)	251,260 (66.9)	47,358 (71.8)
	Unknown	2,850 (0.6)	2,658 (0.7)	192 (0.3)
Hospital volume, median (IQR)		524 (302–861)	533 (304–871)	500 (288–837)

table continues

		Overall (N = 441,812)	NSCLC (n = 375,832)	SCLC (n = 65,980)
Tumor characteristics				
Histology*, n (%)	Adenocarcinoma	192,943 (43.7)	192,943 (51.3)	-
	Squamous cell	98,848 (22.4)	98,848 (26.3)	-
	Other non-small cell	84,041 (19.0)	84,041 (22.4)	-
	Small cell	65,980 (14.9)	-	65,980 (100.0)
Clinical stage at diagnosis, n (%)	IA	62,694 (14.2)	61,123 (16.3)	1,571 (2.4)
	IB	26,984 (6.1)	26,049 (6.9)	935 (1.4)
	IIA	17,456 (4.0)	15,898 (4.2)	1,558 (2.4)
	IIB	15,199 (3.4)	14,300 (3.8)	899 (1.4)
	IIIA	57,989 (13.1)	48,881 (13.0)	9,108 (13.8)
	IIIB	34,088 (7.7)	26,941 (7.2)	7,147 (10.8)
	IV	227,402 (51.5)	182,640 (48.6)	44,762 (67.8)

Abbreviations: NSCLC = non-small-cell lung cancer; SCLC = small-cell lung cancer; yr = year; IQR = interquartile range.
* NSCLC is subdivided into three distinct histology categories, whereas SCLC is considered a separate disease category.

Adherence to guideline-concordant treatment

The proportion of cases that received guideline-concordant treatment within each clinical subgroup was stable between 2010 and 2014 (Figure E2). As shown in Table 2, 62.1% of all cases diagnosed between 2010 and 2014 received guideline-concordant treatment (range = 50.4% in A-NSCLC to 76.3% in L-NSCLC). However, 16.3% received less intensive treatment than recommended (range = 6.4% in ED-SCLC to 21.6% in LA-NSCLC), and 21.6% received no treatment (range = 10.3% in L-NSCLC to 31.4% in A-NSCLC).

Table 2: Receipt of guideline-concordant treatment among lung cancer patients by clinical subgroup.

Clinical Subgroup	n	Guideline-Concordant Treatment* n (%)	Less Intensive Treatment Than Recommended† n (%)	No Treatment n (%)
Overall	441,812	274,338 (62.1)	72,155 (16.3)	95,319 (21.6)
L-NSCLC	117,370	89,503 (76.3)	15,741 (13.4)	12,126 (10.3)
LA-NSCLC	75,822	45,774 (60.4)	16,412 (21.6)	13,636 (18.0)
A-NSCLC	182,640	92,119 (50.4)	33,227 (18.2)	57,294 (31.4)
LD-SCLC	21,218	14,765 (69.6)	3,927 (18.5)	2,526 (11.9)
ED-SCLC	44,762	32,177 (71.9)	2,848 (6.4)	9,737 (21.8)

Abbreviations: L-NSCLC = localized non-small-cell lung cancer (stages I-II); LA-NSCLC = locally advanced non-small-cell lung cancer (stage III); A-NSCLC = advanced non-small-cell lung cancer (stage IV); LD-SCLC = limited-disease small-cell lung cancer (stages I-III); ED-SCLC = extensive disease small-cell lung cancer (stage IV).

* Guideline-concordant treatment was defined as the minimal treatment patients should receive according to the National Comprehensive Cancer Network guidelines. Hence, additional treatment was allowed beside guideline-concordant treatment. We considered guideline-concordant treatment to be either surgery or stereotactic body radiation therapy for L-NSCLC; either radiotherapy and chemotherapy or surgery and chemotherapy for LA-NSCLC; chemotherapy for A-NSCLC; either radiotherapy and chemotherapy or surgery and chemotherapy for patients with LD-SCLC; and chemotherapy for patients with ED-SCLC.

† Less intensive treatment than recommended was defined as treatment that was not guideline-concordant.

Patterns of care among patients that received guideline-concordant treatment

Among L-NSCLC cases that received guideline-concordant treatment, "surgery only" was received most frequently (49.1%), followed by "surgery and chemotherapy" (11.4%), and "SBRT only" (10.0%) (Table 3). In every other clinical subgroup, "CRT and chemotherapy" was most common (range = 25.9% in A-NSCLC to 63.5% in LD-SCLC). Among subjects with LA-NSCLC and LD-SCLC, "surgery, CRT, and chemotherapy" was also used (7.4% and 2.6%, respectively), as was "surgery and chemotherapy" (4.4% and 2.4%, respectively). Among subjects with A-NSCLC and ED-SCLC, "chemotherapy only" was common (19.5% and 35.0%, respectively).

Table 3: Patterns of care among patients with lung cancer by clinical subgroup.

Clinical Subgroup	Treatment Received*	n (%)
L-NSCLC	Guideline-concordant treatment	
	Surgery only	57,605 (49.1)
	Surgery and chemotherapy	13,359 (11.4)
	SBRT only	11,740 (10.0)
	Surgery, CRT, and chemotherapy	4,405 (3.8)
	Surgery and CRT	1,562 (1.3)
	Less intensive treatment than recommended	
	CRT only	7,129 (6.1)
	CRT and chemotherapy	6,953 (5.9)
	Chemotherapy only	1,465 (1.2)
LA-NSCLC	Guideline-concordant treatment	
	CRT and chemotherapy	36,108 (47.6)
	Surgery, CRT, and chemotherapy	5,580 (7.4)
	Surgery and chemotherapy	3,335 (4.4)

table continues

Clinical Subgroup	Treatment Received*	n (%)
	Less intensive treatment than recommended	
	CRT only	6,577 (8.7)
	Chemotherapy only	6,008 (7.9)
	Surgery only	2,676 (3.5)
A- NSCLC	Guideline-concordant treatment	
	CRT and chemotherapy	47,370 (25.9)
	Chemotherapy only	35,620 (19.5)
	CRT, chemotherapy, and other treatment	2,970 (1.6)
	Chemotherapy and other treatment	2,715 (1.5)
	Less intensive treatment than recommended	
	CRT only	29,219 (16.0)
LD-SCLC	Guideline-concordant treatment	
	CRT and chemotherapy	13,477 (63.5)
	Surgery, CRT, and chemotherapy	545 (2.6)
	Surgery and chemotherapy	514 (2.4)
	Less intensive treatment than recommended	
	Chemotherapy only	2,917 (13.7)
	CRT only	534 (2.5)
	Surgery only	340 (1.6)
ED-SCLC	Guideline-concordant treatment	
	CRT and chemotherapy	15,671 (35.0)
	Chemotherapy only	15,658 (35.0)
	Less intensive treatment than recommended	
	CRT only	2,597 (5.8)

Abbreviations: L-NSCLC = localized non-small-cell lung cancer (stages I-II); LA-NSCLC = locally advanced non-small-cell lung cancer (stage III); A-NSCLC = advanced non-small-cell lung cancer (stage IV); LD-SCLC = limited-disease small-cell lung cancer (stage I-III); ED-SCLC = extensive disease small-cell lung cancer (stage IV); SBRT = stereotactic body radiation therapy, defined as thoracic radiotherapy with a dose of ≥45 Gray in ≤5 fractions; CRT = conventionally fractionated radiotherapy, defined as all radiotherapy other than Stereotactic Body Radiation Therapy.
* All mutually exclusive combinations of treatment modalities (i.e., all combinations of surgery, SBRT, CRT, chemotherapy, and other treatment) were assessed. However, for each clinical subgroup, only those treatment combinations that were more prevalent than 1% are reported in this table.

Patterns of care among patients that received less intensive treatment than recommended

"CRT only" was among the most commonly received less-intensive-than-recommended therapies for each clinical subgroup, as was "chemotherapy only" for subgroups other than A-NSCLC and ED-SCLC (Table 3). Most common among L-NSCLC were "CRT only" (6.1%), "CRT and chemotherapy" (5.9%), and "chemotherapy only" (1.2%). Among

subjects with LA-NSCLC and LD-SCLC, the most commonly received less-intensive-than-recommended treatments were "CRT only" (8.7% and 2.5%, respectively) and "chemotherapy only" (7.9% and 13.7%, respectively). "CRT only" was the most common among metastatic subgroups A-NSCLC (16.0%) and ED-SCLC (5.8%).

Disparities in receiving guideline-concordant treatment

As can be seen in Table 4, the odds of receiving guideline-concordant treatment decreased with advancing age (for those aged ≥80 yr compared with those aged <50 yr: odds ratio [OR] = 0.14; 95% confidence interval [CI] = 0.13-0.14). This association remained present after adjusting for covariates (for those aged ≥80 yr compared with those aged <50 yr: adjusted odds ratio [aOR] = 0.12; 95%CI = 0.12-0.13). In addition, the association between age and receiving guideline-concordant treatment was consistent across clinical subgroups, with a notable exception in L-NSCLC (Table E5). In L-NSCLC, advancing age was associated with a decreased odds of receiving surgery (for those aged ≥80 yr compared with those aged <50 yr: aOR = 0.06; 95%CI = 0.05-0.06). However, the odds of receiving SBRT for L-NSCLC increased with advancing age (for those aged ≥80 yr compared with those aged <50 yr: aOR = 18.39; 95%CI = 14.09-23.99).

Compared with non-Hispanic white patients, non-Hispanic black patients (OR = 0.82; 95%CI = 0.81-0.84) and Hispanic patients (OR=0.87, 95%CI=0.84-0.90) were less likely to receive guideline-concordant treatment. This association remained present after adjusting for covariates (non-Hispanic black patients: aOR = 0.78; 95%CI = 0.76-0.0.80; Hispanic patients: aOR = 0.94; 95%CI = 0.90-0.98). On the other hand, non-Hispanic Asian patients were more likely to receive guideline-concordant treatment after adjusting for covariates (aOR = 1.09; 95%CI = 1.04-1.15). However, results for non-Hispanic Asian patients and Hispanic patients varied within clinical subgroups (table E5). For example, within the subgroup of L-NSCLC, both non-Hispanic Asian patients and Hispanic patients were more likely to receive surgery than non-Hispanic white patients (non-Hispanic Asian patients: aOR = 1.23; 95%CI = 1.10 - 1.37; Hispanic patients: aOR = 1.24; 95%CI = 1.13-1.36), but less likely to receive SBRT (non-Hispanic Asian patients: aOR = 0.51; 95%CI = 0.43-0.62; Hispanic patients: aOR = 0.47; 95%CI = 0.40-0.56). In addition, non-Hispanic Asian patients with A-NSCLC were more likely to receive chemotherapy (aOR = 1.25; 95%CI = 1.18-1.34).

Table 4: Effect of age and racial or ethnic group on the odds of receiving guideline-concordant treatment for lung cancer.

Age	**<50 yr**	**50-54 yr**	**55-59 yr**	**60-64 yr**	**65-69 yr**	**70-74 yr**	**75-79 yr**	**≥80 yr**
No. of subjects	22,328	33,619	50,955	62,839	75,298	71,798	58,053	66,922
No. events	17,710	25,242	36,765	43,702	50,822	44,959	31,977	23,161
Event risk	0.79	0.75	0.72	0.70	0.67	0.63	0.55	0.35
Crude OR (95% CI) *	Reference	0.79 (0.75-0.82)	0.68 (0.65-0.70)	0.60 (0.57-0.62)	0.54 (0.52-0.56)	0.44 (0.42-0.45)	0.32 (0.31-0.33)	0.14 (0.13-0.14)
Adjusted OR (95%CI) *	Reference	0.76 (0.73-0.79)	0.63 (0.60-0.65)	0.53 (0.51-0.55)	0.48 (0.47-0.50)	0.39 (0.37-0.40)	0.28 (0.27-0.29)	0.12 (0.12-0.13)
Racial or ethnic group	**Non-Hispanic white**	**Non-Hispanic black**	**Non-Hispanic Asian**	**Hispanic**	**Other**			
No. of subjects†	365,922	50,256	9,958	12,682	2,995			
No. events†	229,378	29,206	6,344	7,529	1,881			
Event risk †	0.63	0.58	0.64	0.59	0.63			
Crude OR (95% CI) *	Reference	0.82 (0.81-0.84)	1.04 (1.00-1.09)	0.87 (0.84-0.90)	1.00 (0.93-1.09)			
Adjusted OR (95%CI) *	Reference	0.78 (0.76-0.80)	1.09 (1.04-1.15)	0.94 (0.90-0.98)	0.94 (0.86-1.03)			

Abbreviations: yr = years; no. = number; OR = odds ratio 95% CI = 95% confidence interval.

* The crude and adjusted ORs are from the pooled regression model based on all three imputed datasets. Adjusted ORs are adjusted for sex, insurance status, Charlson comorbidity score, treating facility type, hospital volume, histology, and clinical stage at diagnosis. Variance inflation factors were ≤2 for all covariates, indicating that multicollinearity was limited.

† The number of subjects, number of events, and event risks for racial or ethnic group are based on the mean values across the three imputed datasets.

Discussion

To our knowledge, this study is the first to investigate adherence to guideline-concordant treatment as well as disparities by racial or ethnic group and by age in a uniform manner for all clinical subgroups of lung cancer including SCLC.

Adherence to guideline-concordant treatment

We show that overall, the level of adherence to guideline-concordant treatment among patients with lung cancer in the United States is only 62.1%, and varies across clinical subgroups. The rate of guideline-concordant treatment was highest for L-NSCLC. This makes sense as treatment for L-NSCLC is potentially curative and therefore offers the most obvious benefits. The rate of guideline-concordant treatment was lowest for A-NSCLC.

A possible explanation for this finding could be a lack of referral to medical oncologists among patients with A-NSCLC. A recent study reported that only 54% of stage IIIB-IV NSCLC cases triaged at the British Columbia Cancer Agency were assessed by a medical oncologist.[28] Another study found that one of the most common reasons for not referring patients to a medical oncologist or prescribing chemotherapy was the patient's preference against treatment.[29] Some patients with incurable disease fear that chemotherapy side-effects may negatively affect their quality of life.[30] Perhaps this could influence their willingness to accept chemotherapy. However, chemotherapy for advanced disease has been shown to improve quality of life, symptom control, and survival compared with best supportive care.[31] Therefore, discussing a patient's possible fears of chemotherapy and the potential health benefits could be an important step toward increasing the uptake of chemotherapy.

Compared with our results, Wang and colleagues[4] reported even lower rates of guideline-concordant treatment among 20,511 NSCLC cases diagnosed between 2003 and 2008. In their study, the proportion that received guideline-concordant treatment was 51% among subjects with L-NSCLC, 35% among subjects with LA-NSCLC, and 27% among subjects with A-NSCLC. The difference compared with our study is likely due to patient selection, as Wang and colleagues included only veterans aged 65 years or older.

Within the group that received guideline-concordant treatment, our data show that most L-NSCLC cases received surgery, whereas SBRT and other modalities were used much less frequently. In contrast, most cases in the potentially operable clinical subgroups LA-NSCLC and LD-SCLC did not receive surgery as guideline-concordant treatment.

In our data, 16.3% of cases received less intensive treatment than recommended. The patterns of care among these cases provide important clues toward improvements in clinical care. For example, the frequent use of "CRT only", "CRT and chemotherapy", and "chemotherapy only" among L-NSCLC suggests that the uptake of SBRT among inoperable cases may still be lagging. Among subjects with LA-NSCLC and those with LD-SCLC the most common forms of less-intensive-than-recommended treatment were "CRT only" and "chemotherapy only". These findings suggest room for improvement

in the uptake of multimodality treatments such as "CRT and chemotherapy" and "surgery and chemotherapy", for these subgroups. The frequent use of "CRT only" among A-NSCLC and ED-SCLC subgroups suggests room for an increased uptake of chemotherapy among these metastatic subgroups.

Finally, 21.6% of cases in our study received no treatment. This is consistent with findings in a smaller study among 6,662 lung cancer cases in the Kaiser Permanente Southern California tumor registry diagnosed between 2008 and 2013.[22] In that study, rates of nontreatment ranged from 9% among stage 0-II (compared with 10.3% among L-NSCLC in our study) to 34% among stage IV (compared with 31.4% among A-NSCLC in our study).

Disparities in receiving guideline-concordant treatment

In our study, advancing age was strongly associated with the odds of receiving guideline-concordant treatment across all clinical subgroups. These findings are in line with the conclusions of an earlier study.[4] This association persisted after adjusting for factors that could influence fitness for surgery, such as comorbidity, histology, and stage, as well as health care provider characteristics. Other studies also reported a lower likelihood of lung cancer surgery among older patients, although these findings cannot be directly compared with ours due to the use of different age groups and methods.[9,10,32] Although we confirm the lower likelihood of receiving surgery for elderly L-NSCLC cases, we also show that the likelihood of receiving SBRT strongly increases with advancing age. These results indicate that SBRT is indeed used as an alternative guideline-concordant treatment for L-NSCLC cases that have contraindications for surgery. However, especially in other clinical subgroups, efforts should be made to ensure that elderly patients receive the minimal recommended treatment.

Racial or ethnic group was also associated with the odds of receiving guideline-concordant treatment in both the adjusted and unadjusted analyses. Earlier research among U.S. patients with lung cancer had already shown that black patients are less likely to receive surgery for L-NSCLC[5–10,33] and chemotherapy for A-NSCLC.[33,34] Our current study shows that disparities by racial or ethnic group persist and extend to every clinical subgroup of NSCLC. Furthermore, we show that Hispanic patients are also less likely to receive guideline-concordant treatment in general, but more likely to receive surgery for L-NSCLC. In an earlier study, McCann and colleagues[35] offer a possible explanation for racial disparities. They reported that, although surgery was offered to black and white patients with lung cancer at the same rate, black patients declined surgery more often. Their study showed no statistically significant difference in insurance between the groups, and results were corrected for preoperative pulmonary function, tumor stage, and comorbidity. Furthermore, Lin and colleagues[36] reported that negative surgical beliefs, fatalism, and mistrust among racial minorities can partly explain why black patients are less likely to receive guideline-concordant treatment. More research is needed to identify the underlying reasons for such beliefs and mistrust and to test strategies to overcome any barriers to delivery of guideline-concordant treatment.

Strengths and limitations

A major strength of this study is the very large sample size, combined with the extensive treatment data available in the NCDB. The linked SEER-Medicare database, which also contains detailed treatment variables, may be biased toward older individuals as it mainly includes patients aged 65 years or older. In contrast, the NCDB data used for our study included patients with lung cancer aged 18 years or older.

There are several potential limitations to our study. The first is the hospital-based nature of the data, which captures only cases diagnosed and treated in Commission on Cancer-affiliated hospitals. However, these hospitals together treat 70% of incident cancer cases in the United States. Furthermore, we compared baseline characteristics to a cohort of patients captured by the smaller, but population-based, SEER database and found only small differences. Therefore, our results are likely generalizable to the U.S. population.

Second, our data include only the first course of treatment. Nevertheless, we were able to define guideline-concordant treatment as the minimal recommended treatment. Although the focus of this article was therefore the issue of receiving less intensive treatment than recommended, we acknowledge that receiving more intensive treatment than recommended could potentially also be an issue. However, for most clinical subgroups the NCDB data does not contain sufficient clinical variables to assess whether each possible combination of surgery, radiotherapy, chemotherapy, and other treatment was more intensive than recommended. For example, radiotherapy is not recommended as a minimal treatment for A-NSCLC, but may still be prescribed as symptomatic treatment for painful bone metastases. Nevertheless, we were able to assess that 10.4% of stage I NSCLC cases received adjuvant or neoadjuvant chemotherapy, which could provide an indication of the extent to which overtreatment occurs. In addition, 2.9% of A-NSCLC cases received surgery. Future studies should focus more in depth on the severity and consequences of receiving more intensive treatment than recommended for lung cancer.

Third, the data did not include several clinical variables that may affect the choice of treatment. Smoking cessation after the diagnosis of lung cancer has been associated with reduced all-cause mortality[37] and a reduced risk of hospital death and pulmonary complications after surgery.[38] Therefore, active smokers may have been less likely to receive surgery. However, guidelines state that surgery should not be denied to patients only due to smoking.[14] Pulmonary function and performance score may have also influenced the likelihood of receiving surgery.[39] Although our correction for comorbidities may have partially accounted for these factors, the Charlson score is an aggregate measure that does not account for all possible comorbidities. Another factor that we could not fully account for using the NCDB data is socioeconomic status, although we were able to include insurance status. We addressed the absence of these clinical variables by assessing multiple guideline-concordant treatments for some clinical subgroups. For instance, both SBRT and surgery were regarded guideline-concordant treatments for L-NSCLC. However, this carries the implicit assumption that, when the nonsurgical treatment was given, the patient was indeed medically inoperable.

Fourth, we used the official cut-off of 5 fractions in our definition of SBRT, whereas some institutions use schemes with up to 10 fractions.[19] However, using a cut-off of 10 fractions would only increase the use of SBRT among L-NSCLC in our dataset from 10.4 to 10.9%.

Fifth, hospital-based data, such as those from the NCDB, could potentially be clustered by hospital. However, in an exploratory analysis using the data before multiple imputation, incorporating clustering by hospital identification had a negligible effect on the estimates of the overall regression model (data not shown). Given that the effect of clustering by hospital is therefore likely small, we did not incorporate clustering by hospital in our final models.

Finally, we were not able to take patient preferences into account. Hence, we cannot draw firm conclusions on the underlying causes of the identified disparities by racial or ethnic group and by age.

Conclusions

We show that many patients with lung cancer in the United States do not receive guideline-concordant treatment. Efforts should be made to decrease the proportion of cases that receive no treatment or less intensive treatment than recommended. Specifically, patterns of care among those receiving less intensive treatment than recommended suggest room for an improved uptake of SBRT among L-NSCLC, multimodality therapy among LA-NSCLC and LD-SCLC subgroups, and chemotherapy among those with metastatic disease (A-NSCLC and ED-SCLC). Furthermore, we show that elderly patients and non-Hispanic black patients are less likely to receive guideline-concordant treatment across most clinical subgroups of lung cancer, despite adjusting for relevant patient, tumor, and health care provider characteristics. This knowledge may be used to target interventions for improving the rate of lung cancer cases that receive guideline-concordant treatment and to reduce disparities.

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Chapter 1

Supplementary Methods

Data

We used the National Cancer Database (NCDB) to extract a cohort of patients diagnosed with lung cancer between 2010-2014. The NCDB, established in 1989, is a nationwide, facility-based, comprehensive clinical surveillance resource oncology data set that currently captures 70% of all newly diagnosed malignancies in the United States annually, from more than 1500 affiliated facilities. The NCDB records the first course of treatment, defined as all methods of treatment recorded in the treatment plan and administered to the patient before disease progression or recurrence. Analysis of individual-level NCDB data was performed on site at the University of Michigan Medical School. This study was deemed exempt by the Institutional Review Board of the University of Michigan.

Case selection

Only cases with International Classification of Diseases for Oncology 3rd edition (ICD-0-3) malignant behavior code were selected.[1] Stages 0, occult, and unknown were excluded as guidelines provide no treatment recommendations for these patients. We further removed cases without a known stage subcategory (e.g. stage I rather than IA) because these do not provide sufficient detail. We selected only those cases staged using the American Joint Committee on Cancer (AJCC) 7th edition Cancer Staging Manual, which was effective from 2010-2017.[2] In accordance with NCDB instructions, we further excluded the following: cases with a history of multiple primary tumors of which lung cancer wasn't the first; cases with a date of diagnosis before the reporting facility's reference date (i.e. the date from which the facility guarantees the accuracy of data); and cases that did not receive any treatment at the reporting facility. Also, we excluded cases with unknown treatment. Finally, we selected only cases with less than four months (122 days) between diagnosis and onset of therapy because the NCDB uses the principle that initial treatment must begin within four months of the date of initial diagnosis.

Data cleaning

Baseline characteristics

Baseline characteristics of included patients were derived and included sex, age at diagnosis, racial or ethnic group, insurance status, Charlson comorbidity score, tumor histology, clinical stage at diagnosis, treating facility type, and treating hospital volume. The derivation of these variables is detailed below.

Deriving sex

The standard coding of sex was used.

Deriving age at diagnosis

Age at diagnosis was collapsed into categories under 50, 80 or over, and 5-year intervals in between.

Deriving racial or ethnic group

Available Race codes were recoded to categories White, Black, Asian, Other (and Unknown) using definitions from the Census 2000 Technical Documentation[3] as shown in Table E1. The variable for Spanish/Hispanic origin was collapsed into categories Non-Hispanic, Hispanic and Unknown. Cases in which the only evidence of the person's Hispanic origin was surname or maiden name were explicitly assigned the category Unknown. Cases with Hispanic origin could be of any Race. Therefore, recoded variables Race and Spanish/Hispanic origin were combined into a new variable with categories non-Hispanic White, non-Hispanic Black, non-Hispanic Asian, Hispanic, Other, and unknown.

Deriving insurance status

The standard coding of insurance status was used. According to the NCDB codebook, the first recorded payer or insurer was used if multiple forms of insurance are recorded on the patient's admission page.

Deriving Charlson comorbidity score

The Charlson comorbidity score is the sum of the scores for each of the comorbid conditions as mapped from the Charlson Comorbidity Score Mapping Table in the online NCDB Data Dictionary.[4] Individual comorbidities were not available in the data. The Charlson score in the NCDB is only available aggregated into scores 0, 1 and 2 or higher. A Charlson score of 0 does not mean that no comorbidities are present, but that none of the comorbidities from the mapping table were present.

Deriving tumor histology

ICD-0-3 morphological codes were assigned to categories adenocarcinoma (including bronchioalveolar carcinoma and large cell carcinoma), squamous cell carcinoma, other non-small cell and small cell lung cancer (SCLC), as shown in Table E2. The

classification was based on an earlier publication.[5] In accordance with the ICD-0-3 coding manual, morphological codes that were not listed in that classification or that were accompanied by a lung cancer-specific site code despite not being typically associated with lung cancer were not discarded but were assigned the histological category other.[1]

Deriving stage at diagnosis

We used clinical stage at diagnosis because pathological stage is only available after the outcome of interest (initial treatment) has taken place. As is customary in clinical guidelines, clinical stage for SCLC was collapsed to limited disease SCLC (LD-SCLC; stages I-III) and extensive disease SCLC (ED-SCLC; stage IV). For the analysis of NSCLC cases, we collapsed stages IA, IB, and II into localized NSCLC (L-NSCLC), stages IIIA and IIIB into locally advanced NSCLC (LA-NSCLC), and stage IV into advanced NSCLC (A-NSCLC).

Deriving facility type

Treating facility type was derived by combining Commission on Cancer accreditation categories into academic (includes Academic Comprehensive Cancer Programs and National Cancer Institute-designated Comprehensive Cancer Centers) and non-academic (all other reported program types). Commission on Cancer programs categories are based on type of facility, program structure, services provided, and the volume of patients. Key characteristics of the category "Academic Comprehensive Cancer Program" are the annual accession of at least 500 newly diagnosed cancer cases, the availability of a full range of diagnostic and therapeutic services, the participation in research, and the participation in postgraduate medical education in at least four programs including internal medicine and surgery.[6] The category National Cancer Institute-Designated Comprehensive Cancer Center Program only requires the availability of a full range of diagnostic and treatment facilities.[6]

Deriving hospital volume

Hospital volume was calculated by determining how many lung cancer cases (both NSCLC and SCLC) were treated at the reporting (and therefore treating) facility, using the unique facility identifier. Hospital volume was aggregated in quartiles and used as a categorical variable.

Extracting a cohort from the Surveillance, Epidemiology, and End Results dataset

Applying a case selection process similar to that of the studied NCDB cohort, we

extracted a cohort from the Surveillance, Epidemiology, and End Results (SEER) 18 Registries Research Data + Hurricane Katrina Impacted Louisiana Cases November 2016 data submission using proprietary SEER*Stat software.[7] First, only cases with ICD-0-3 topography codes for lung cancer (C340 - C343, C348 and C349) and malignant behavior code were selected. We only selected cases staged using the AJCC 7th Edition Cancer Staging Manual.[2] Stages 0 and occult and cases with unspecified substage (i.e. stage I rather than IA) were excluded. For full comparability of baseline characteristics between the NCDB and the SEER database, we did not exclude cases with an unknown stage in this comparison. Only cases with "one primary only" or "1st of 2 or more primaries" were selected. Finally, only cases with known age diagnosed in years 2010 through 2014 were selected.

To assess the generalizability of NCDB data to the general US population, we compared baseline characteristics of the cohort from the SEER database to the cohort of lung cancer patients from the NCDB database. Where possible, ICD-0-3 morphological codes were assigned to histology categories using the same classification that we used for the NCDB cohort, as shown in Table E2. The following histologies were available in the NCDB cohort, but not in the SEER cohort: 8143, 8572, 8573 (classified as adenocarcinoma); 8005, 8040, 8080, 8090, 8094, 8120, 8154, 8160, 8210, 8211, 8243, 8262, 8280, 8313, 8380, 8401, 8453, 8503, 8510 (classified as other non-small cell). The following histologies were available in the SEER cohort, but not in the NCDB cohort and were classified as follows: 8201, 8571 (adenocarcinoma); 8034, 8300, 8410, 9590, 9591, 9650, 9651, 9663, 9671, 9673, 9680, 9687, 9690, 9699, 9714 (other non-small cell). We recoded and categorized racial or ethnic groups in the exact same way as for the NCDB cohort, as described elsewhere in the Supplementary Methods. As the insurance status variable in the SEER database is less granular than in the NCDB, we recoded insurance status in both datasets to categories insured (NCDB: private, Medicare, Medicaid, other government insurance; SEER: insured, insured with no specifics, any Medicaid), uninsured, and unknown. The treatment facility type variable that we used in the NCDB analysis is NCDB-specific and was therefore unavailable for the SEER database. Finally, the Charlson comorbidity score was also not available in the SEER database.

Constructing treatment variables

The NCDB records the first course of treatment, defined as all methods of treatment recorded in the treatment plan and administered to the patient before disease progression or recurrence. We were not able to distinguish whether multiple therapies were given concurrently or sequentially. Available treatment modalities in the dataset were surgery, radiotherapy, chemotherapy, hormone therapy, immunotherapy and other treatment (including experimental treatments).

The use of each of these modalities was coded in one or several variables. For each modality, crosstables were constructed between the available variables to check the internal consistency of the dataset. If possible based on these crosstables, unknown values were recoded (e.g. for n=43 cases, the variable RX_SUMM_SURG_PRIM_SITE indicated that it was unknown whether surgery was given while the variable

REASON_FOR_NO_SURGERY indicated that surgery was not given. These were recoded as not having received surgery). Based on these crosstables, we constructed a set of binary variables to indicate whether surgery, radiotherapy, chemotherapy, hormone therapy, immunotherapy and other treatment were administered.

The names of individual systemic agents are not recorded by the NCDB. The NCDB uses the SEER*Rx Interactive Antineoplastic Drugs Database[8] to determine whether systemic agents are to be coded as chemotherapy, hormone therapy, or immunotherapy. We investigated the targeted therapy agents that are most commonly used in lung cancer care (i.e. EGFR-inhibitors erlotinib, afatinib and gefitinib and ALK-inhibitors crizotinib and ceritinib) in the SEER*Rx database and found that these were all coded as chemotherapy. Therefore, we were not able to separately report on the use of targeted agents.

When investigating other novel treatment agents used in lung cancer care in the SEER*Rx database, we found that Vascular Endothelial Growth Factor (VEGF) inhibitor bevacizumab has been coded as immunotherapy for cases diagnosed after January 1st 2013 only. For cases diagnosed prior to that date, bevacizumab had been coded as chemotherapy. Protein Programmed Cell Death 1 (PD-1) inhibitors pembrolizumab, nivolumab and Protein Programmed Cell Death-Ligand 1 (PD-L1) inhibitor atezolizumab were coded as immunotherapy for all cases. The recommendation and clinical use of these agents in lung cancer therapy is very recent though, and is unlikely to be captured in the available dataset with cases diagnosed between 2010-2014. To our knowledge, there are no hormone therapy agents that have an accepted role in the treatment of lung cancer. As a result, hormone therapy and immunotherapy were aggregated with the other treatment category.

Radiotherapy was further divided into Stereotactic Body Radiotherapy (SBRT) and conventionally fractionated radiotherapy (CRT). SBRT delivers high-dose radiation to a specific target in only a few fractions and provides local tumor control rates of up to 90% with moderate toxicity.[9,10] Since the most frequently used SBRT schemes in the US comprise a total dose of 45 Gray or more over 1-5 fractions[11-13] and the US billing code for SBRT includes a maximum of 5 fractions,[14] SBRT was defined as thoracic radiotherapy with a total radiation dose of 45 Gray or more delivered in 5 fractions or less. CRT was defined as all radiotherapy that was not SBRT.

The remaining treatment variables were: surgery, SBRT, CRT, chemotherapy (including targeted therapies), and other treatment (including experimental treatments and immunotherapy). Cases that received none of these therapies were coded as having received no therapy.

Definition of guideline-concordant treatment

Two main lung cancer types can be distinguished: NSCLC and SCLC, with the majority presenting as NSCLC. Since SCLC is clinically more aggressive than NSCLC, clinical treatment guidelines provide specific recommendations for clinical subgroups of lung cancer type and stage at diagnosis. For each of these clinical subgroups, we assessed whether guideline-concordant treatment was received, defined as the minimal first course treatment these patients should receive according to the National

Comprehensive Cancer Network guidelines.[14,15]

While surgical treatment is still recommended as the primary minimal treatment for L-NSCLC, SBRT is now recommended as an alternative treatment to surgery for L-NSCLC patients.[14] Therefore, both surgery and SBRT were considered guideline-concordant treatment for L-NSCLC. The minimal recommended treatment for LA-NSCLC and LD-SCLC depends on operability.[14,15] If operable, the minimal recommendation is surgery combined with chemotherapy. However, the majority of LA-NSCLC and LD-SCLC patients are inoperable, in which case the minimal recommendation is a combination of radiotherapy and chemotherapy. Therefore, both treatment combinations were considered guideline-concordant for LA-NSCLC and LD-SCLC. For A-NSCLC and ED-SCLC, the minimal recommended treatment is chemotherapy.[14,15] As we assessed the minimal recommended treatment for each clinical subgroup, additional treatments were allowed beside guideline-concordant treatment (e.g. radiotherapy for bone metastases beside chemotherapy in A-NSCLC). There were no restrictions on radiation dose or fractionation for stages other than L-NSCLC. A summary of the treatment combinations that were considered guideline-concordant for each clinical subgroup can be found in Table E3 in the Online Supplement.

Statistical analysis

For each clinical subgroup, we assessed the proportion of cases that received guideline-concordant treatment, less treatment than recommended (defined as treatment that was not guideline-concordant), and no treatment. We used clinical stage at diagnosis for creating clinical subgroups because pathological stage can only be known after the outcome of interest (initial treatment) has occurred. For the groups of patients who received guideline-concordant treatment and less intensive treatment than recommended, we separately assessed which mutually exclusive combinations of surgery, SBRT, CRT, chemotherapy (including targeted therapy) and other treatment (including immunotherapy and experimental treatments) were received.

To identify whether previously identified disparities in receiving guideline-concordant treatment by racial or ethnic group and by age persist, we fitted a logistic regression model with receipt of guideline-concordant treatment as binary outcome and racial or ethnic group and age as independent variables. We further adjusted this model for several covariates that could be associated with racial or ethnic group and age, and also affect receiving guideline-concordant treatment. Based on previous literature, we included sex,[16] health insurance status,[17] Charlson comorbidity score,[18] facility type,[19] and stage at diagnosis.[20] We further included histology because squamous cell carcinomas are often located centrally,[21] potentially making them more difficult to surgically resect. Finally, we included hospital volume because it is a well-established indicator of quality of care.[22]

To identify whether disparities by racial or ethnic group and by age extend across all clinical subgroups, we also fitted a separate model for each clinical subgroup. For clinical subgroups with multiple guideline-concordant treatment combinations, we fitted a separate model for each treatment combination. For example, two separate

models were fitted for L-NSCLC; one with SBRT as binary outcome and one with surgery as binary outcome. These models were adjusted for the same covariates as the overall model.

All analyses were performed using R software version 3.4.1.[23] The base-R glm() function was used to fit the logistic regression models. We used multiple imputation to address missing data, using three imputations.[24] Multicollinearity was assessed by calculating generalized variance inflation factors.[25]

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Chapter 1

Supplementary Tables and Figures

Supplementary Table E1: Recoding race categories from the National Cancer Database Participant User File.

Recoded race category	Original race categories
White	White
Black	Black
Asian	Chinese; Japanese; Filipino; Hawaiian; Korean; Vietnamese; Laotian; Hmong; Kampuchean (including Khmer and Cambodian); Thai; Asian Indian or Pakistani NOS; Asian Indian; Pakistani; Other Asian (including Asian NOS and Oriental NOS)
Other	American Indian, Aleutian or Eskimo; Micronesian NOS; Chamorran; Guamanian NOS; Polynesian NOS; Tahitian; Samoan; Tongan; Melanesian NOS; Fiji Islander; New Guinean; Pacific Islander NOS; Other

Supplementary Table E2: Assigning International Classification of Diseases for Oncology 3rd Edition histological codes to histology categories.

Histology category	ICD-0-3 histological codes included
Adenocarcinoma	8140; 8141; 8143; 8200; 8230; 8260; 8310; 8323; 8480; 8481; 8490; 8550; 8570; 8572; 8573; 8574; 8575; 8576
Bronchioalveolar carcinoma*	8250; 8251; 8252; 8253; 8254; 8255
Large cell carcinoma*	8012; 8013; 8014
Squamous Cell Carcinoma	8052; 8070; 8071; 8072; 8073; 8074; 8075; 8076; 8083; 8084
Other	8000; 8001; 8003; 8004; 8005; 8010; 8011; 8020; 8021; 8022; 8030; 8031; 8032; 8033; 8035; 8040; 8046; 8050; 8051; 8080; 8082; 8090; 8094; 8120; 8123; 8144; 8154; 8160; 8210; 8211; 8240; 8241; 8243; 8244; 8245; 8246; 8247; 8249; 8262; 8280; 8290; 8313; 8320; 8333; 8341; 8380; 8401; 8430; 8441; 8453; 8470; 8500; 8503; 8507; 8510; 8551; 8560; 8562; 8940; 8980
Small cell lung cancer	8002; 8041; 8042; 8043; 8044; 8045

Abbreviations: ICD-0-3 = International Classification of Diseases for Oncology 3rd Edition.
* Bronchioalveolar carcinoma and large cell carcinoma were later grouped with adenocarcinoma.

Supplementary Table E3: Overview of therapy that was considered guideline-concordant treatment for each clinical subgroup.

Clinical subgroup	Guideline-concordant treatment*
L-NSCLC (%)	Surgery ± additional treatments AND/OR SBRT ± additional treatments
LA-NSCLC (%)	Surgery + chemotherapy ± additional treatments AND/OR Radiotherapy (any regimen) + chemotherapy ± additional treatments
A-NSCLC (%)	Chemotherapy ± additional treatments
LD-SCLC (%)	Surgery + chemotherapy ± additional treatments AND/OR Radiotherapy (any regimen) + chemotherapy ± additional treatments
ED-SCLC (%)	Chemotherapy ± additional treatments

Abbreviations: L-NSCLC = localized non-small cell lung cancer (stages I-II); LA-NSCLC = locally-advanced non-small cell lung cancer (stage III); A-NSCLC = advanced non-small cell lung cancer (stage IV); LD-SCLC = limited disease small cell lung cancer (stages I-III); ED-SCLC = extensive disease small cell lung cancer (stage IV); SBRT = Stereotactic Body Radiation Therapy, defined as thoracic radiotherapy with a dose of ≥45 Gray in ≤5 fractions.

* Guideline-concordant treatment was defined as the minimal treatment patients should receive. Hence, ± sign indicates that additional treatment was allowed beside the minimal recommended treatment. Available treatment modalities were surgery, radiotherapy (further specified as Stereotactic Body Radiotherapy or conventional radiotherapy), chemotherapy (including targeted therapies), and other treatment (including experimental treatments and immunotherapy).

Supplementary Table E4: Comparison of baseline characteristics of non-small cell lung cancer and small cell lung cancer patients diagnosed between years 2010–2014 in the National Cancer Database and the Surveillance, Epidemiology, and End Results database.

Database		**NCDB**	**SEER**	**NCDB**	**SEER**
Lung cancer type		**NSCLC (N = 399,682)***	**NSCLC (N = 163,141)**	**SCLC (N = 68,740)**	**SCLC (N = 23,285)**
Patient characteristics					
Sex (%)	Male	208,212 (52.1)	85,944 (52.7)	33,316 (48.5)	11,742 (50.4)
	Female	191,470 (47.9)	77,197 (47.3)	35,424 (51.5)	11,543 (49.6)
Age at diagnosis (%)	< 50	20,455 (5.1)	7,201 (4.4)	3,203 (4.7)	922 (4.0)
	50 - 54	29,459 (7.4)	10,187 (6.2)	5,872 (8.5)	1,771 (7.6)
	55 - 59	44,363 (11.1)	16,236 (10)	9,228 (13.4)	2,902 (12.5)
	60 - 64	54,899 (13.7)	21,446 (13.1)	11,363 (16.5)	3,806 (16.3)
	65 - 69	66,778 (16.7)	26,578 (16.3)	12,973 (18.9)	4,505 (19.3)
	70 - 74	64,950 (16.3)	25,777 (15.8)	11,276 (16.4)	3,817 (16.4)
	75 - 79	54,016 (13.5)	22,870 (14.0)	7,776 (11.3)	2,892 (12.4)
	≥ 80	64,762 (16.2)	32,846 (20.1)	7,049 (10.3)	2,670 (11.5)
Racial or ethnic group (%)	Non-Hispanic White	31,3067 (78.3)	120,577 (73.9)	57,227 (83.3)	19,038 (81.8)
	Non-Hispanic Black	45,403 (11.4)	19,357 (11.9)	5,500 (8.0)	2,124 (9.1)
	Non-Hispanic Asian	9,330 (2.3)	11,072 (6.8)	771 (1.1)	804 (3.5)
	Hispanic	11,523 (2.9)	8,731 (5.4)	1,582 (2.3)	896 (3.8)
	Other	2,645 (0.7)	1,348 (0.8)	376 (0.5)	177 (0.8)
	Unknown	17,714 (4.4)	2,056 (1.3)	3,284 (4.8)	246 (1.1)
Health insurance status (%)	Insured	375,267 (93.9)	146,763 (90.0)	64,075 (93.2)	21,771 (93.5)
	Uninsured	15,778 (3.9)	5,108 (3.1)	3,222 (4.7)	927 (4.0)
	Unknown	8,637 (2.2)	11,270 (6.9)	1,443 (2.1)	587 (2.5)

table continues

Database		NCDB	SEER	NCDB	SEER
Lung cancer type		**NSCLC (N = 399,682)***	**NSCLC (N = 163,141)**	**SCLC (N = 68,740)**	**SCLC (N = 23,285)**
Tumor characteristics					
Histology (%)†	Adenocarcinoma	204,865 (51.3)	79,549 (48.8)	-	-
	Squamous cell carcinoma	104,537 (26.2)	37,549 (23.0)	-	-
	Other non-small cell	90,280 (22.6)	46,043 (28.2)	-	-
Stage at diagnosis (%)‡	IA	61,123 (15.3)	19,091 (11.7)	1,571 (2.3)	420 (1.8)
	IB	26,049 (6.5)	10,967 (6.7)	935 (1.4)	310 (1.3)
	IIA	15,898 (4.0)	6,171 (3.8)	1,558 (2.3)	396 (1.7)
	IIB	14,300 (3.6)	6,437 (3.9)	899 (1.3)	256 (1.1)
	IIIA	48,881 (12.2)	19,212 (11.8)	9,108 (13.2)	2,724 (11.7)
	IIIB	26,941 (6.7)	8,846 (5.4)	7,147 (10.4)	2,239 (9.6)
	IV	18,2640 (45.7)	79,230 (48.6)	44,762 (65.1)	16,304 (70)
	Unknown	23,850 (6.0)	13,187 (8.1)	2,760 (4.0)	636 (2.7)

Abbreviations: NSCLC = non-small cell lung cancer; SCLC = small cell lung cancer; NCDB = National Cancer Database; SEER = Surveillance, Epidemiology, and End Results.

* Other analyses in this study exclude cases with unknown stage. For full comparability of baseline characteristics between the National Cancer Database and the Surveillance, Epidemiology, and End Results database, this table does include unknown stages. Therefore, the total number of cases in this table is different from other tables in the manuscript.

† NSCLC is subdivided into three distinct histology categories, while SCLC is considered a separate disease category.

‡ In our main analysis for the NCDB data, we used clinical stage because pathological stage can only be known after the outcome of interest has taken place (i.e. treatment). Clinical stage is not available in the SEER database. Instead, the SEER database uses an algorithm based on Collaborative Stage variables to derive AJCC 7th edition stages. This algorithm occasionally uses pathological data if available.

Supplementary Table E5: Effect of patient, health care provider, and tumor characteristics on the odds of receiving guideline-concordant treatment for lung cancer by clinical subgroup.

	Overall	L-NSCLC		LA-NSCLC		A-NSCLC	LD-SCLC		ED-SCLC
	Guideline-Concordant Treatment*	Surgery	SBRT	Radio-therapy & Chemo-therapy	Surgery & Chemo-therapy	Chemother-apy	Radio-therapy & Chemo-therapy	Surgery & Chemo-therapy	Chemo-therapy
Patient characteristics									
Sex									
Male	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Female	1.01 (0.99-1.02)	0.97 (0.95-1.00)	1.07 (1.02-1.11)	0.94 (0.91-0.97)	1.05 (1-1.1)	1.04 (1.02-1.06)	1.05 (0.99-1.12)	0.78 (0.68-0.89)	0.98 (0.94-1.02)
Age									
<50	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
50-54	0.76 (0.73-0.79)	0.49 (0.43-0.55)	2.78 (2.07-3.73)	0.99 (0.9-1.08)	0.78 (0.7-0.87)	0.76 (0.72-0.8)	0.78 (0.64-0.96)	0.65 (0.43-0.98)	0.74 (0.64-0.87)
55-59	0.63 (0.6-0.65)	0.35 (0.32-0.39)	4.57 (3.48-6.01)	0.87 (0.8-0.95)	0.68 (0.62-0.76)	0.63 (0.59-0.66)	0.65 (0.54-0.79)	0.75 (0.52-1.08)	0.61 (0.53-0.7)
60-64	0.53 (0.51-0.55)	0.28 (0.26-0.32)	5.82 (4.46-7.61)	0.75 (0.69-0.82)	0.62 (0.56-0.68)	0.53 (0.5-0.56)	0.53 (0.44-0.64)	0.8 (0.56-1.14)	0.52 (0.45-0.6)
65-69	0.48 (0.47-0.5)	0.27 (0.24-0.30)	6.66 (5.10-8.70)	0.64 (0.59-0.7)	0.58 (0.52-0.65)	0.5 (0.47-0.52)	0.49 (0.4-0.59)	0.86 (0.6-1.24)	0.46 (0.4-0.53)
70-74	0.39 (0.37-0.4)	0.21 (0.19-0.24)	8.55 (6.55-11.16)	0.53 (0.48-0.58)	0.43 (0.38-0.48)	0.39 (0.37-0.42)	0.39 (0.32-0.47)	0.65 (0.45-0.95)	0.35 (0.3-0.41)
75-79	0.28 (0.27-0.29)	0.15 (0.14-0.17)	11.44 (8.76-14.94)	0.37 (0.34-0.4)	0.27 (0.24-0.31)	0.28 (0.27-0.3)	0.25 (0.21-0.31)	0.54 (0.36-0.8)	0.26 (0.23-0.3)
≥80	0.12 (0.12-0.13)	0.06 (0.05-0.06)	18.39 (14.09-23.99)	0.15 (0.14-0.17)	0.09 (0.08-0.11)	0.12 (0.11-0.13)	0.12 (0.1-0.15)	0.22 (0.14-0.34)	0.12 (0.1-0.14)
Racial or ethnic group									
Non-Hispanic White	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Non-Hispanic Black	0.78 (0.76-0.8)	0.62 (0.59-0.64)	1.03 (0.95-1.1)	0.87 (0.83-0.91)	0.62 (0.58-0.68)	0.85 (0.82-0.87)	0.97 (0.87-1.08)	0.6 (0.45-0.79)	0.93 (0.86-1.01)

table continues

	Overall	L-NSCLC		LA-NSCLC		A-NSCLC	LD-SCLC		ED-SCLC
	Guideline-Concordant Treatment*	Surgery	SBRT	Radio-therapy & Chemo-therapy	Surgery & Chemo-therapy	Chemother-apy	Radio-therapy & Chemo-therapy	Surgery & Chemo-therapy	Chemo-therapy
Non-Hispanic Asian	1.09 (1.04-1.15)	1.23 (1.1-1.37)	0.51 (0.43-0.62)	0.84 (0.75-0.94)	1.12 (0.95-1.32)	1.25 (1.18-1.34)	0.98 (0.75-1.28)	0.75 (0.34-1.67)	1.02 (0.83-1.25)
Hispanic	0.94 (0.9-0.98)	1.24 (1.13-1.36)	0.47 (0.4-0.56)	0.81 (0.73-0.89)	0.99 (0.85-1.14)	1.02 (0.96-1.08)	0.67 (0.55-0.83)	0.75 (0.44-1.29)	0.92 (0.8-1.07)
Other	0.94 (0.86-1.03)	0.96 (0.81-1.15)	1.03 (0.79-1.33)	0.72 (0.6-0.87)	0.79 (0.59-1.06)	1.04 (0.91-1.18)	0.79 (0.53-1.17)	0.8 (0.32-2.05)	1.18 (0.88-1.58)
Health Insurance status									
Private insurance	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Medicare	0.72 (0.7-0.73)	0.63 (0.6-0.65)	1.55 (1.45-1.65)	0.83 (0.8-0.87)	0.67 (0.63-0.72)	0.71 (0.69-0.73)	0.76 (0.7-0.84)	0.79 (0.65-0.95)	0.74 (0.69-0.79)
Medicaid	0.58 (0.56-0.59)	0.42 (0.39-0.45)	1.92 (1.7-2.16)	0.78 (0.73-0.83)	0.55 (0.5-0.6)	0.56 (0.54-0.58)	0.64 (0.57-0.73)	0.54 (0.39-0.74)	0.65 (0.59-0.71)
Other government insurance	0.6 (0.57-0.64)	0.25 (0.23-0.28)	4.46 (3.91-5.08)	1.04 (0.93-1.17)	0.51 (0.42-0.61)	0.51 (0.47-0.56)	0.94 (0.73-1.2)	0.63 (0.36-1.1)	0.71 (0.6-0.86)
No insurance	0.48 (0.46-0.49)	0.43 (0.39-0.47)	1.13 (0.9-1.41)	0.66 (0.61-0.72)	0.42 (0.37-0.48)	0.46 (0.44-0.48)	0.58 (0.49-0.68)	0.53 (0.33-0.85)	0.49 (0.44-0.54)
Charlson comorbidity score									
0	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
1	0.83 (0.82-0.84)	1.29 (1.25-1.33)	0.77 (0.73-0.8)	0.74 (0.72-0.77)	1.14 (1.09-1.2)	0.73 (0.71-0.74)	0.75 (0.7-0.81)	1.47 (1.27-1.71)	0.85 (0.81-0.89)
≥2	0.59 (0.58-0.6)	0.88 (0.85-0.92)	0.97 (0.92-1.02)	0.55 (0.53-0.58)	0.82 (0.76-0.89)	0.5 (0.49-0.52)	0.61 (0.56-0.66)	1.09 (0.89-1.33))	0.61 (0.58-0.65)
Health care provider characteristics									
Facility type									
Academic	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Non-academic	0.91 (0.89-0.92)	0.89 (0.86-0.92)	0.76 (0.72-0.79)	1.1 (1.06-1.14)	0.75 (0.71-0.79)	0.94 (0.92-0.96)	1.11 (1.03-1.2)	0.73 (0.62-0.85)	0.97 (0.92-1.03)
Hospital volume†									
861-3596 (Q4)	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
524-861 (Q3)	0.96 (0.94-0.98)	0.94 (0.9-0.97)	0.98 (0.93-1.03)	1.1 (1.05-1.15)	0.84 (0.79-0.9)	0.93 (0.91-0.96)	1.11 (1.02-1.22)	0.69 (0.57-0.84)	0.96 (0.9-1.02)
302-524 (Q2)	0.86 (0.85-0.88)	0.93 (0.9-0.97)	0.77 (0.73-0.81)	1.04 (0.99-1.08)	0.84 (0.79-0.9)	0.86 (0.84-0.89)	1.01 (0.92-1.1)	0.66 (0.55-0.8)	0.85 (0.79-0.9)
1-302 (Q1)	0.77 (0.76-0.79)	0.89 (0.86-0.93)	0.44 (0.41-0.48)	0.96 (0.92-1.01)	0.76 (0.7-0.81)	0.81 (0.79-0.83)	0.93 (0.85-1.02)	0.62 (0.5-0.76)	0.73 (0.68-0.77)

table continues

	Overall	L-NSCLC		LA-NSCLC		A-NSCLC	LD-SCLC		ED-SCLC
	Guideline-Concordant Treatment*	Surgery	SBRT	Radio-therapy & Chemo-therapy	Surgery & Chemo-therapy	Chemother-apy	Radio-therapy & Chemo-therapy	Surgery & Chemo-therapy	Chemo-therapy
Tumor characteristics									
Histology†									
Adenocarci-noma	Reference	Reference	Reference	Reference	Reference	Reference	-	-	-
Squamous cell	0.83 (0.81-0.84)	0.51 (0.5-0.53)	1.52 (1.45-1.59)	1.22 (1.17-1.26)	0.58 (0.55-0.61)	0.85 (0.83-0.87)			
Other non-small cell	0.44 (0.43-0.45)	0.26 (0.25-0.27)	1.92 (1.83-2.02)	0.66 (0.63-0.69)	0.39 (0.37-0.43)	0.48 (0.47-0.5)	-	-	-
Small cell	1.61 (1.58-1.65)	-	-	-	-	-	-	-	-
Clinical stage at diagnosis§									
IA	Reference	Reference	Reference	-	-	-	Reference	Reference	-
IB	0.51 (0.49-0.53)	0.78 (0.75-0.81)	0.64 (0.61-0.68)	-	-	-	1.42 (1.19-1.68)	0.41 (0.33-0.51)	-
IIA	0.25 (0.24-0.26)	0.57 (0.55-0.6)	0.16 (0.14-0.17)	-	-	-	2.7 (2.32-3.15)	0.2 (0.16-0.25)	-
IIB	0.15 (0.15-0.16)	0.35 (0.34-0.37)	0.17 (0.16-0.19)	-	-	-	1.98 (1.66-2.36)	0.17 (0.12-0.22)	-
IIIA	0.22 (0.21-0.23)	-	-	Reference	Reference	-	2.71 (2.42-3.04)	0.04 (0.04-0.05)	-
IIIB	0.19 (0.19-0.2)	-	-	1.13 (1.09-1.16)	0.19 (0.17-0.20)	-	2.33 (2.07-2.62)	0.01 (0.01-0.02)	-
IV	0.15 (0.14-0.15)	-	-	-	-	-	-	-	-

Abbreviations: L-NSCLC = localized non-small cell lung cancer (stages I-II); LA-NSCLC = locally-advanced non-small cell lung cancer (stage III); A-NSCLC = advanced non-small cell lung cancer (stage IV); LD-SCLC = limited disease small cell lung cancer (stages I-III); ED-SCLC = extensive disease small cell lung cancer (stage IV); SBRT = Stereotactic Body Radiotherapy, defined as thoracic radiotherapy with a dose of ≥45 Gray in ≤5 fractions.

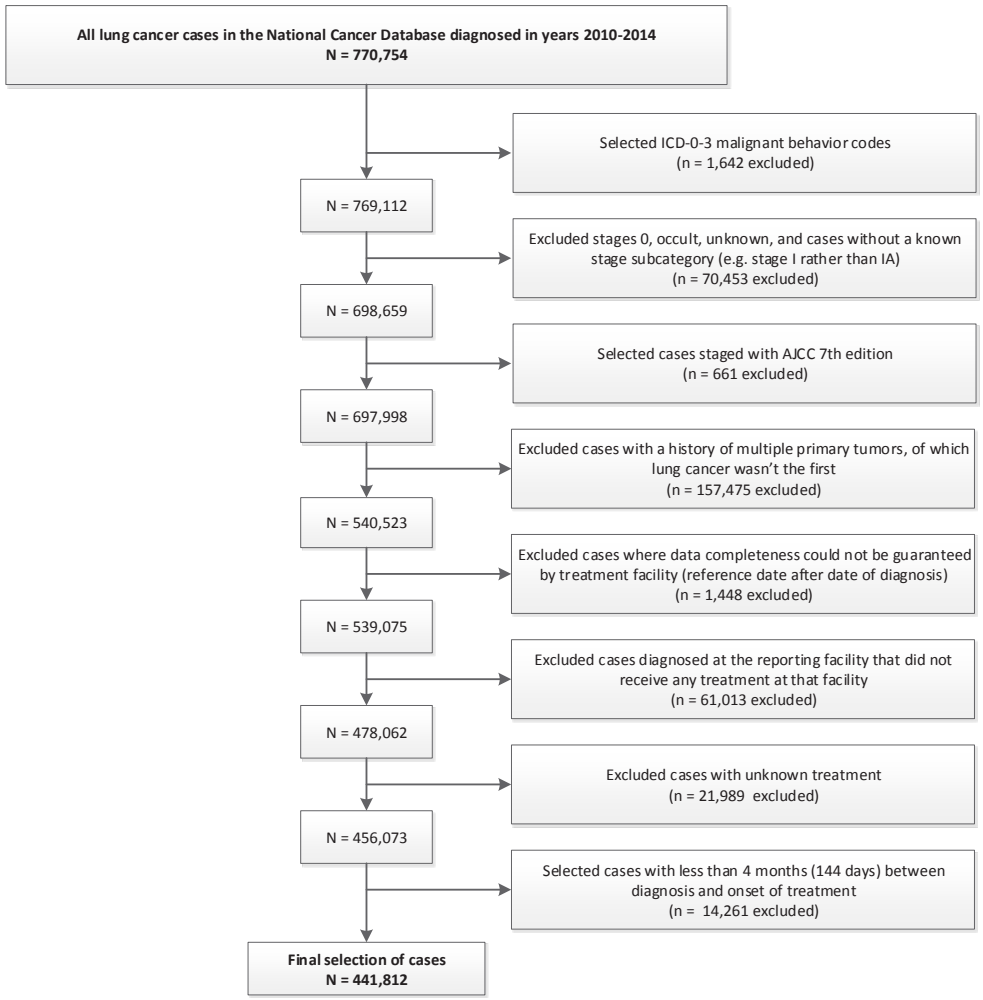
* A separate logistic regression model was fitted to a subset of patients for each clinical subgroup. The binary dependent variable in each model was receipt of guideline-concordant treatment for that clinical subgroup, defined as the minimal treatment those patients should receive according to the National Comprehensive Cancer Network guidelines. Hence, additional treatment was allowed beside guideline-concordant treatment. Guideline-concordant treatment was either surgery or SBRT for L-NSCLC; either radiotherapy and chemotherapy or surgery and chemotherapy for LA-NSCLC; chemotherapy for A-NSCLC; either surgery and chemotherapy or radiotherapy and chemotherapy for patients with LD-SCLC; and chemotherapy for patients with ED-SCLC. In clinical subgroups with multiple guideline-concordant treatment combinations, each

of these treatment combinations was assessed in a separate model. Results are presented as adjusted odds ratio (95% confidence interval).

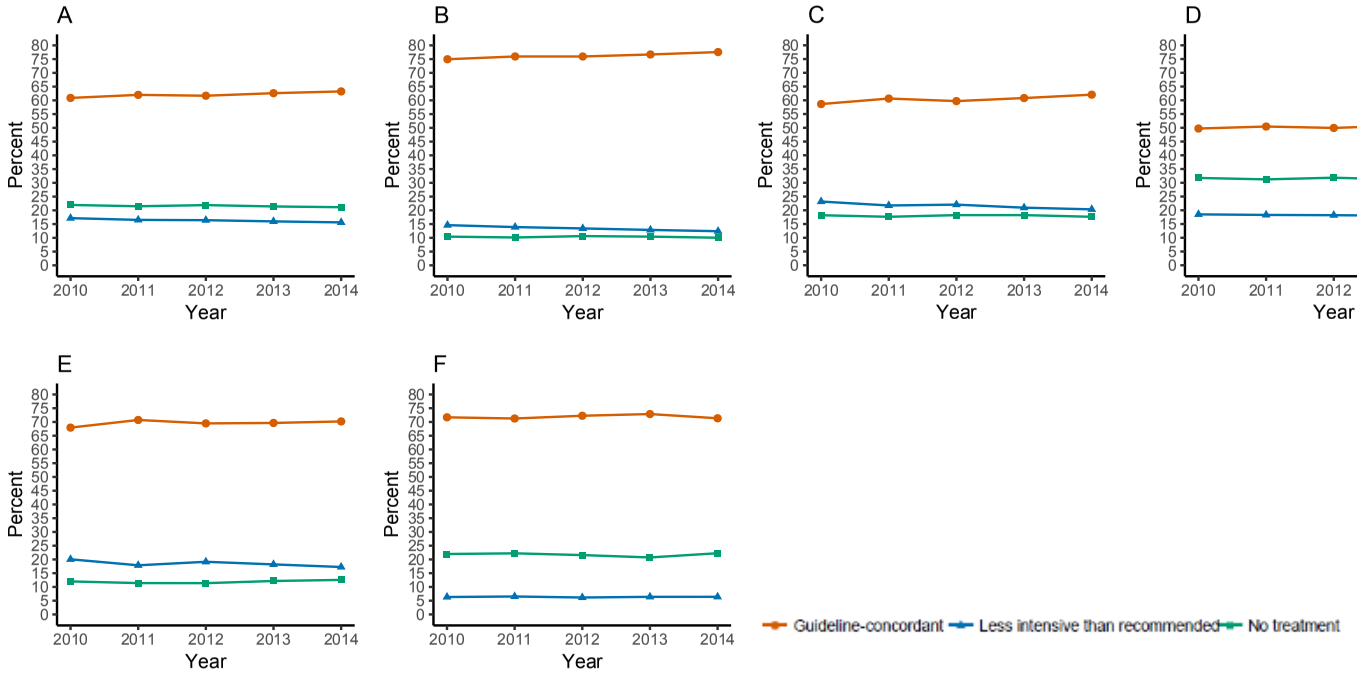
† Hospital volume (i.e. the number of unique cases treated at the treating facility) was categorized in quartiles (Q1-Q4).

‡ NSCLC is subdivided into three distinct histology categories, while SCLC is considered a separate disease category.

§ As clinical subgroups are defined by stage and lung cancer type, different stages are used as the reference category across the different models.



Supplementary Figure E1: Selection of lung cancer cases from the National Cancer Database. Abbreviations: ICD-0-3 = International Classification of Diseases for Oncology 3rd Edition; AJCC = American Joint Committee on Cancer.



Supplementary Figure E2: Time trends for therapy received by lung cancer patients in the National Cancer Database. Time trend for therapy received among [A] All cases; [B] localized non-small cell lung cancer cases (stages I-II); [C] locally-advanced non-small cell lung cancer cases (stage III); [D] advanced non-small cell lung cancer cases (stage IV); [E] limited disease small cell lung cancer cases (stages I-III); and [F] extensive disease small cell lung cancer cases (stage IV). We considered guideline-concordant treatment to be either surgery or stereotactic body radiotherapy for localized non-small cell lung cancer; either a combination of radiotherapy and chemotherapy or a combination of surgery and chemotherapy for locally advanced non-small cell lung cancer; chemotherapy for advanced non-small cell lung cancer; a combination of radiotherapy and chemotherapy or surgery and chemotherapy for patients with limited disease small cell lung cancer; and chemotherapy for patients with extensive disease small cell lung cancer. For each year, the proportion of cases that received guideline-concordant treatment, less intensive treatment than recommended, and no treatment add up to 100%.

Chapter 2

Uptake of Minimally Invasive Surgery and Stereotactic Body Radiation Therapy for Early Stage Non-Small Cell Lung Cancer in the USA: an Ecological Study of Secular Trends Using the National Cancer Database

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Abstract

Background

We aimed to assess the uptake of minimally invasive surgery (MIS) and stereotactic body radiation therapy (SBRT) among early-stage (stage IA-IIB) non-small cell lung cancer (NSCLC) cases in the USA, and the rate of conversions from MIS to open surgery.

Materials and Methods

Data were obtained from the US National Cancer Database, a nationwide facility-based cancer registry capturing up to 70% of incident cancer cases in the USA. We included cases diagnosed with early-stage (clinical stages IA-IIB) NSCLC between 2010 and 2014. In an ecological analysis, we assessed changes in treatment by year of diagnosis. Among surgically treated cases, we assessed the uptake of MIS and whether conversion to open surgery took place. For cases that received thoracic radiotherapy, we assessed the uptake of SBRT.

Results

Among 117,370 selected cases, radiotherapy use increased 3.4 percentage-points between 2010 and 2014 ($p<0.0001$). Surgical treatments decreased 3.5 percentage-points ($p<0.0001$). Rates of non-treatment remained stable (range: 10.0-10.6% [$p=0.4066$]). Among surgically treated stage IA cases, uptake of MIS increased from 28.7% (95%CI: 27.8-29.7) in 2010 to 48.6% (95%CI:47.6-49.6) in 2014 ($p<0.0001$), while conversions decreased from 17.0% (95%CI: 15.6-18.6) in 2010 to 9.1% (95%CI: 8.3-10.0) in 2014 ($p<0.0001$). MIS uptake among stages IB-IIB was lower and conversion rates were higher, but time trends were similar. Uptake of SBRT among stage IA receiving thoracic radiotherapy increased from 53.4% (95%CI:51.2-55.6) in 2010 to 73.0% (95%CI:71.4-74.6) in 2014 ($p<0.0001$). SBRT uptake among stage IB increased from 32.5% (95%CI:29.9-35.2) in 2010 to 48.2% (95%CI:45.6-50.8) in 2014 ($p<0.0001$).

Conclusion

Between 2010 and 2014, uptake of MIS and SBRT among early-stage NSCLC significantly increased, while the rate of conversions to open surgery significantly decreased. Continuing these trends may contribute to improving patient care, in particular with the expected increase in early-stages due to the implementation of lung cancer screening.

Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide.[1,2] The majority of lung cancer cases are non-small cell lung cancer (NSCLC).[3] Currently, most NSCLC cases are diagnosed with metastatic disease,[4] in which case curative treatment is usually not possible.[5] However, the number of cases diagnosed with potentially curative early-stage disease is expected to increase in upcoming years[6] due to the ongoing (USA) and considered (EU and UK) implementation of lung cancer screening.[7-9]

While surgical resection is still standard of care for early-stage NSCLC, the preferred surgical approach has shifted from thoracotomy to minimally invasive surgery (MIS). MIS includes video-assisted thoracoscopic surgery (VATS) and, more recently, robotic-assisted thoracic surgery (RATS).[5] MIS is associated with less postoperative pain, shorter hospital stay, less pulmonary complications, and improved quality of life compared with thoracotomy, without compromising perioperative mortality or short-term survival.[10-13] Although a recent analysis suggests that the uptake of VATS among patients with lung cancer in the US Veterans Affairs is increasing,[14] the generalizability of these findings to early-stage NSCLC cases in the general US population remains unknown. In addition, the Veterans Affairs analysis did not include cases treated with RATS. Also, the current rate of conversions from MIS to open surgery and whether this rate has changed with the increased uptake of MIS is unclear.

Some patients with early-stage NSCLC are unfit for surgery due to comorbidity or may prefer not to undergo surgery for non-medical reasons. For those patients, stereotactic body radiation therapy (SBRT) is now recommended as an alternative standard of care.[5] SBRT concentrates a high dose of radiotherapy on a small target volume using only a few fractions. In medically inoperable patients with early-stage NSCLC, SBRT provides local tumor control rates of up to 90% with moderate toxicity.[15,16] A previous analysis suggested that the uptake of SBRT in the USA could still be lagging.[17]

The degree of uptake of these therapies is topical because the effectiveness of the recent recommendations and plans for lung cancer screening will depend on optimal treatment of early-stage lung cancer. Therefore, we aimed to assess the uptake of MIS and SBRT among early-stage NSCLC cases in the USA, as well as the rate of conversions from MIS to open surgery. We hypothesized that the uptake of MIS and SBRT in the USA increases over time. This hypothesis was tested in an ecological analysis of secular trends in the facility-based US National Cancer Database (NCDB).

Methods

Data

We extracted all individual-level records from the NCDB of persons diagnosed with early-stage (i.e. clinical stages IA, IB, IIA, and IIB) NSCLC between 2010 and 2014. The NCDB, established in 1989, is a nationwide, facility-based, comprehensive clinical surveillance resource oncology data set that currently captures 70% of all newly diagnosed malignancies in the USA annually, from more than 1,500 affiliated facilities.

To ensure the accuracy of treatment data we excluded the following groups: non-malignant cases; cases not staged using the American Joint Commission on Cancer (AJCC) seventh edition system;[18] cases with a history of multiple primary tumors of which lung cancer was not the first; cases diagnosed before the date from which the reporting facility guarantees accuracy of the data; cases that were diagnosed at the reporting facility but received therapy elsewhere; cases with more than 4 months (i.e. 122 days) between diagnosis and onset of treatment, and cases for which it was unknown whether any treatment was received. These exclusion criteria are in concordance with NCDB guidelines and with a previous investigation of NCDB data conducted by our group.[17]

Statistical analysis

We assessed the proportion of cases that received surgery, radiotherapy, and no therapy as first course treatment by clinical stage and by year of diagnosis. Among surgically treated cases, we assessed whether the planned approach was MIS (which includes VATS and RATS), and whether conversion to open surgery took place. If a patient received multiple surgeries, the NCDB records the surgical approach of the most invasive and definitive surgical treatment. In addition, we assessed the extent of resection (sublobar, lobectomy or bilobectomy, pneumonectomy, or other; see Supplementary Methods for coding). Because the extent of disease may affect the technical difficulty of performing MIS, time trends in the uptake of MIS and the rate of conversions were assessed by clinical stage and by extent of resection.

For cases that received radiotherapy, we assessed the radiation target (thoracic vs non-thoracic). For cases with a thoracic radiation target, we further assessed whether SBRT or another radiation modality was used. In accordance with a previous report we defined SBRT as thoracic radiotherapy with a total radiation dose of at least 45 Gray over five fractions or less.[17] Because the extent of disease may affect the feasibility of SBRT, time trends in the uptake of SBRT were assessed by clinical stage.

Trends were formally tested using χ^2 trend tests. Exact binomial 95% CIs were calculated for proportions. All analyses were performed using R software V.3.6.1.[19] This analysis of NCDB data was deemed exempt by the Institutional Review Board at the University of Michigan.

Sensitivity analyses

If the surgical approach was unknown we assumed that MIS had not taken place. Similarly, we assumed that SBRT was not used if the radiation modality was unknown. In a sensitivity analysis, we excluded those cases with missing data on either of these variables.

A second sensitivity analysis assessed whether time trends in the uptake of MIS and SBRT differed by sex and by age.

Patient and public involvement statement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Results

Patient characteristics

We identified records for 209,627 cases diagnosed with early-stage (i.e. clinical stages IA, IB, IIA, and IIB) NSCLC between 2010 and 2014. After exclusions, 117,370 cases were selected for analysis (see Figure 1). Among the selected cases, 55,248 (47.1%) were male. Median age at diagnosis was 70 years (IQR: 62-77 years). Clinical stage at diagnosis was IA for 61,123 cases (52.1%), IB for 26,049 cases (22.2%), IIA for 15,898 cases (13.5%), and IIB for 14,300 cases (12.2%).

General treatment patterns

Table 1 presents general treatment patterns by clinical stage at diagnosis and by year of diagnosis. Overall, the percentage of early-stage NSCLC cases receiving surgery decreased with advancing stage at diagnosis, from 72.2% (95%CI: 71.9-72.6) among stage IA to 48.3% (95%CI: 47.5-49.1) among stage IIB (-23.9 percentage-points; p< 0.0001). Conversely, the percentage receiving radiotherapy increased with advancing stage (from 22.4% [95%CI: 22.1-22.7] among stage IA to 44.6% [95%CI: 43.8-45.4] among stage IIB [+22.2 percentage-points; p< 0.0001]). Also, the percentage of cases receiving no treatment increased from 7.6% (95%CI: 7.4-7.9) among stage IA to 15.5% (95%CI: 15.0-16.1) among stage IIB (+7.9 percentage-points; p< 0.0001).

Between 2010 and 2014, the number of early-stage NSCLC cases that received surgery decreased by 3.5 percentage-points (p< 0.0001), from 67.9% (95%CI: 67.3-68.5) in 2010 to 64.4% (95%CI: 63.8-65) in 2014. The number of cases that received radiotherapy increased by 3.4 percentage-points (p<0.0001), from 25.6% (95%CI: 25.0-26.2) in 2010 to 29.0 (95%CI: 28.4-29.5) in 2014. The percentage of cases that did not receive any treatment varied between 10.0% (95%CI: 9.7-10.4) and 10.6% (95%CI: 10.2-11.0) across years 2010-2014, with no particular time trend (p=0.4066).

Supporting Table 1 shows the extent of resection among surgically treated cases by clinical stage and year of diagnosis. Overall, 18.1% (95%CI: 17.8-18.4) received a sublobar resection, 77.0% (95%CI: 76.7-77.3) received a lobectomy or a bilobectomy, and 3.7% (95%CI: 3.6-3.8) received a pneumonectomy. Only minor changes in the distribution of surgical extent occurred over time. However, the percentage receiving sublobar resection decreased from 24.3% (95%CI: 23.9-24.7) among stage IA to 9.4% (95%CI: 8.8-10.2) among stage IB (-14.9 percentage-points; p<0.0001). Conversely, the percentage receiving pneumonectomy increased with advancing stage, from 0.8% (95%CI: 0.7-0.9) among stage IA to 13.2% (95%CI: 12.4-14.0) among stage IIB (+12.4%; p<0.0001).

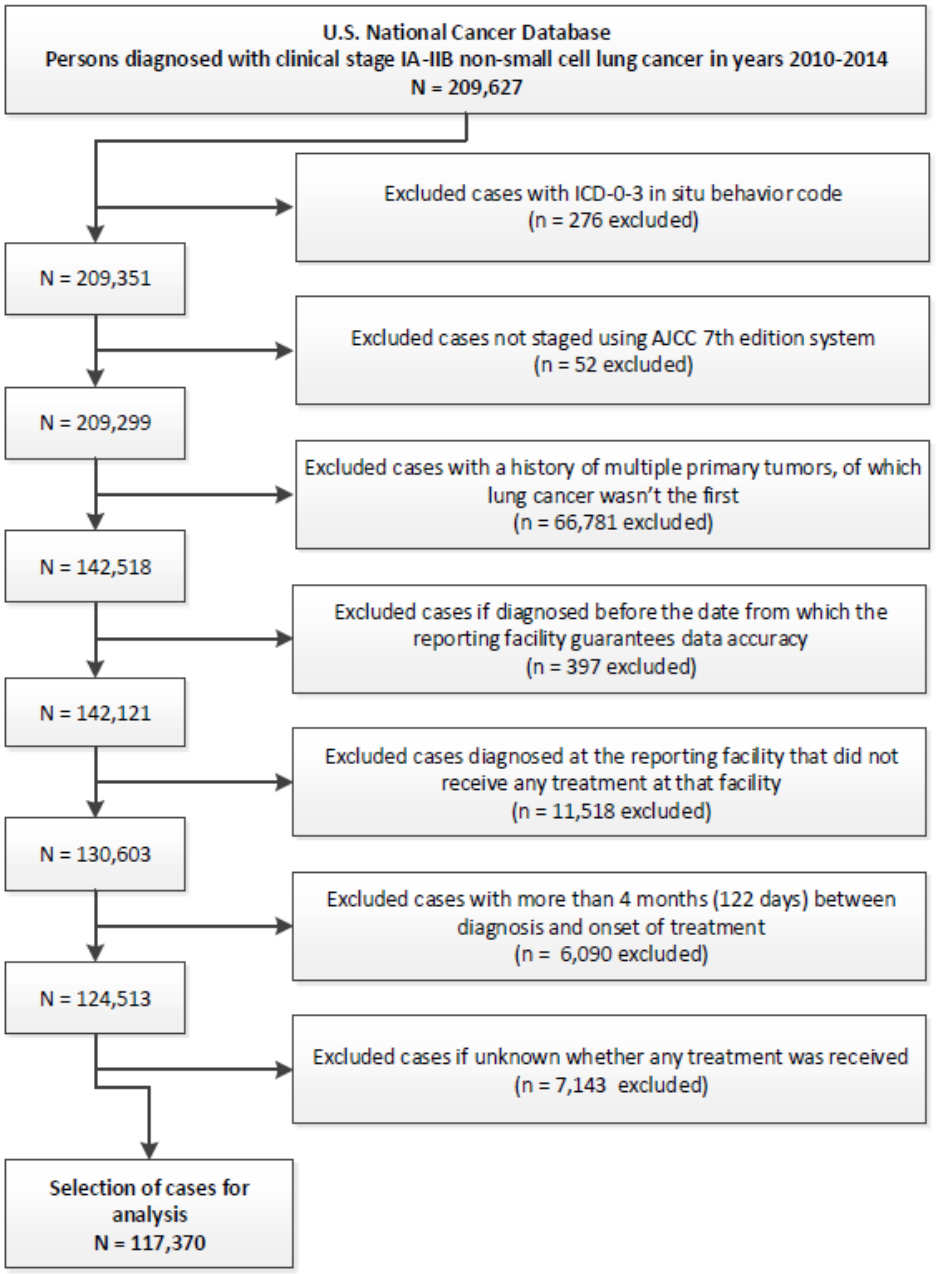

Figure 1: Flow chart of case selection. Abbreviations: ICD-0-3 = International Classification of Diseases for Oncology, third edition; AJCC = American Joint Committee on Cancer.

Table 1: Treatment patterns among early-stage non-small cell lung cancer cases by clinical stage at diagnosis and by year of diagnosis.

	Surgery n (% [95% CI]) [a]	**Radiotherapy n (% [95% CI])**	**No therapy n (% [95% CI])**
Stage			
IA	44,160 (72.2 [71.9-72.6]) [b]	13,690 (22.4 [22.1-22.7]) [b]	4,673 (7.6 [7.4-7.9]) [b]
IB	16,902 (64.9 [64.3-65.5])	7,043 (27.0 [26.5-27.6])	3,029 (11.6 [11.2-12.0])
IIA	9,388 (59.1 [58.3-59.8])	5,288 (33.3 [32.5-34.0])	2,201 (13.8 [13.3-14.4])
IIB	6,907 (48.3 [47.5-49.1])	6,376 (44.6 [43.8-45.4])	2,223 (15.5 [15.0-16.1])
Year			
2010	15,016 (67.9 [67.3-68.5]) [b]	5,659 (25.6 [25.0-26.2]) [b]	2,308 (10.4 [10.0-10.8]) [c]
2011	15,194 (67.3 [66.7-67.9])	6,044 (26.8 [26.2-27.4])	2,287 (10.1 [9.7-10.5])
2012	15,385 (65.8 [65.1-66.4])	6,465 (27.6 [27.1-28.2])	2,487 (10.6 [10.2-11.0])
2013	15,827 (64.5 [63.9-65.1])	7,062 (28.8 [28.2-29.3])	2,562 (10.4 [10.1-10.8])
2014	15,935 (64.4 [63.8-65.0])	7,167 (29.0 [28.4-29.5])	2,482 (10.0 [9.7-10.4])

[a] Patients could receive multiple treatments. Hence, the percentages receiving surgery, radiotherapy and no therapy do not add up to 100%.

[b] Statistically significant trend ($p<0.0001$).

[c] Statistically non-significant trend ($p=0.4066$).

Uptake of MIS and rate of conversions

Figure 2A shows the trend in uptake of MIS by clinical stage among those treated surgically between 2010 and 2014. Among surgically treated stage IA cases (n=44,160), the uptake of MIS increased by 19.9 percentage-points, from 28.7% (95%CI: 27.8-29.7) in 2010 to 48.6% (95%CI: 47.6-49.6) in 2014. Although the percentage receiving MIS in 2010 was lower for stages IB-IIB than for stage IA (22.9% [95%CI: 21.5-24.3] among stage IB, 20.0% [95%CI: 18.2-21.8] among stage IIA, 15.7% [95%CI: 13.8-17.8] among stage IIB), the increase over time was similar (+18.5, +15.1, and +16.8 percentage-points, respectively). Whereas the uptake of MIS increased over time, the rate of conversions to open surgery among these cases decreased. For stage IA, the rate of conversions decreased by 7.9 percentage-points, from 17.0% (95%CI: 15.6-18.6) in 2010 to 9.1% (95%CI: 8.3-10.0) in 2014 (Figure 2B). The rate of conversions was higher for stages IB-IIB compared with stage IA in 2010, but the decreases over time were similar (range across stages: -7.0 to

-10.6 percentage-points). All stage-specific trends in the uptake of MIS and the rate of conversions to open surgery were statistically significant (p<0.0001).

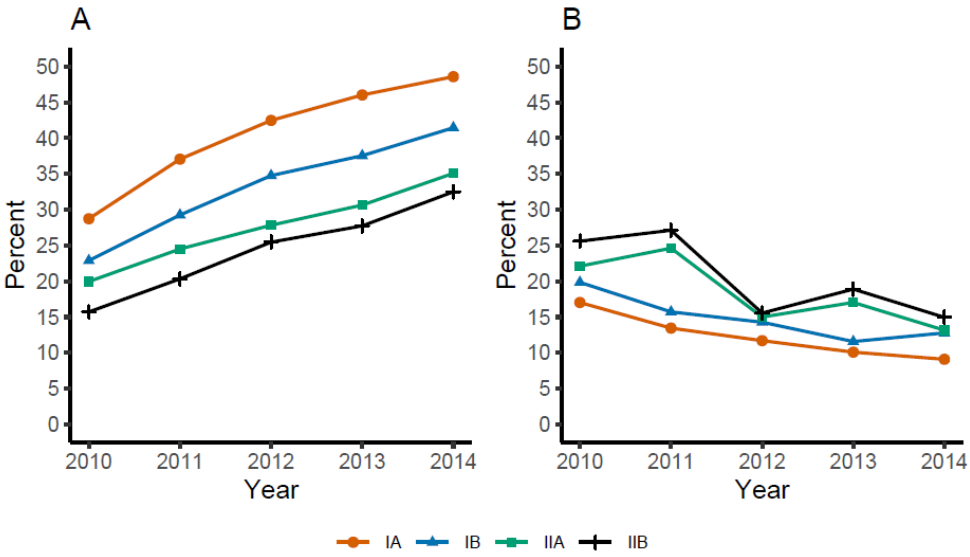

Figure 2: Uptake of minimally invasive surgery among early-stage non-small cell lung cancer cases between 2010 and 2014 by clinical stage at diagnosis. (A) The percentage of lung cancer surgeries that were started as minimally invasive surgery between 2010 and 2014 by clinical stage at diagnosis. (B) The percentage of lung cancer surgeries which started as minimally invasive surgery that were converted to open surgery between 2010 and 2014, by clinical stage at diagnosis.

Time trends in the uptake of MIS and the rate of conversions to open surgery by extent of resection are shown in Figure 3. In 2010, the uptake of MIS was highest among those receiving a sublobar resection (33.6% [95%CI: 31.8-35.4], followed by lobectomy or bilobectomy (23.6% [95%CI: 22.8-24.4]) and pneumonectomy (11.2% [95%CI: 8.8-14.0]). Between 2010 and 2014, uptake of MIS increased for all extents of resection (for sublobar resection: +20.8 percentage-points [p<0.0001]; lobectomy or bilobectomy: +19.0 percentage-points [p<0.0001]; for pneumonectomy: +8.9 percentage-points [p=0.0002]). In 2010, rates of conversions were highest for those receiving pneumonectomy (36.8% [95%CI: 25.4-49.3]), followed by those receiving lobectomy or bilobectomy (20.9% [95%CI: 19.4-22.5]), and finally those who received a sublobar resection (11.8% [95%CI: 9.7-14.1]). The rate of conversions decreased over time for sublobar resections (-5.4 percentage-points; p<0.0001) and for lobectomy or bilobectomy (-9.4 percentage-points; p<0.0001), but not for pneumonectomy (p=0.5813).

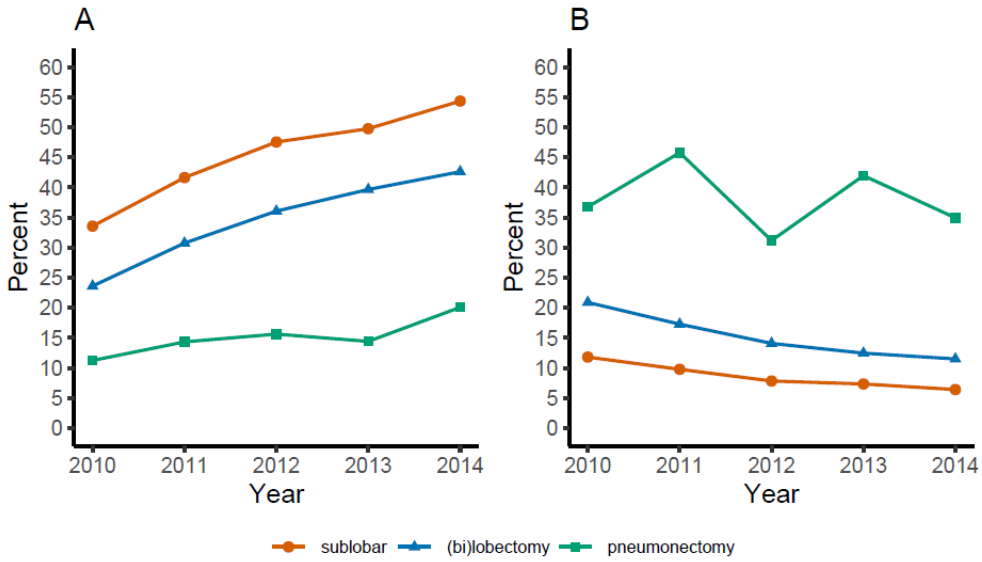

Figure 3: Uptake of minimally invasive surgery among early-stage non-small cell lung cancer cases between 2010 and 2014 by extent of resection. (A) The percentage of lung cancer surgeries that were started as minimally invasive surgery between 2010 and 2014 by extent of resection. (B) The percentage of lung cancer surgeries which started as minimally invasive surgery that were converted to open surgery between 2010 and 2014, by extent of resection. Overall, only 1.3% of surgically treated cases received surgery of "other" extent. Therefore, time trends were not assessed for this category.

Uptake of SBRT

Among early-stage NSCLC cases treated with radiotherapy, 95.5% (95%CI: 95.3-95.7) received thoracic radiotherapy. Figure 4 shows the uptake of SBRT among these cases by clinical stage. Among the 13,252 stage IA NSCLC cases that received thoracic radiotherapy, the use of SBRT increased from 53.4% (95%CI: 51.2-55.6) in 2010 to 73.0% (95%CI: 71.4-74.6) in 2014 (+19.6 percentage-points). The uptake of SBRT among the 6,729 stage IB NSCLC cases that received thoracic radiotherapy increased by 15.7 percentage-points, from 32.5% (95%CI: 29.9-35.2) in 2010 to 48.2% (95%CI: 45.6-50.8) in 2014. However, during the same period the percentage receiving SBRT remained low among the 4,962 stage IIA cases and the 6,005 stage IIB cases that received thoracic radiotherapy. The uptake of SBRT among stage IIA was 5.5% (95%CI: 4.2-7.2) in 2010 and 10.5% (95%CI: 8.7-12.6) in 2014 (+5.0 percentage-points). Among stage IIB, the uptake of SBRT was 4.8% (95%CI: 3.7-6.2) in 2010 and 9.6% (95%CI: 8.0-11.4) in 2014 (+4.8 percentage-points). All stage-specific time trends in the uptake of SBRT were statistically significant ($p<0.0001$).

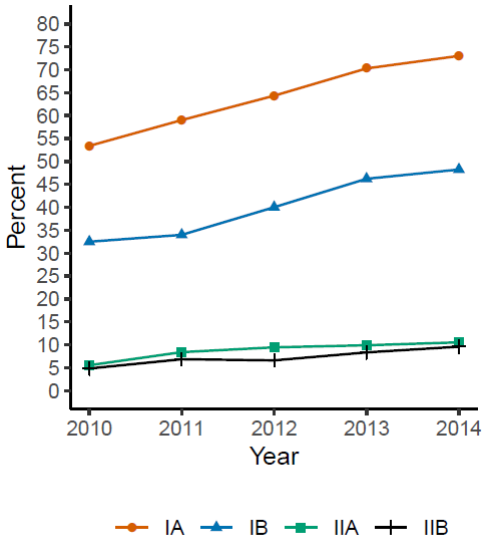

Figure 4: Uptake of stereotactic body radiation therapy among early-stage non-small cell lung cancer cases treated with thoracic radiotherapy between 2010 and 2014 by clinical stage at diagnosis.

Sensitivity analyses

Data on the surgical approach or radiation modality were missing for 5,089 cases. After excluding those cases, the uptake of MIS and SBRT were higher, although stage-specific time trends remained similar (see Supporting Figures 1 and 2). For example, among 42,773 surgically treated stage IA cases, the uptake of MIS increased by 20.6 percentage-points, from 29.2% (95%CI: 28.2-30.2) in 2010 to 49.8% (95%CI: 48.8-50.8) in 2014 (p<0.0001). The rate of conversions to open surgery among these stage IA cases decreased from 17.1 (95%CI: 15.6-18.6) in 2010 to 9.1% (95%CI: 8.3-10.0) in 2014 (-8.0 percentage-points; p<0.0001). Among 12,241 stage IA cases that received thoracic radiotherapy, the uptake of SBRT increased from 59.0% (95%CI: 56.7-61.2) in 2010 to 77.8% (95%CI: 76.3-79.3) in 2014 (+18.8 percentage-points; p<0.0001).

The uptake of MIS and SBRT increased over time for both sexes and all age groups (see Supporting Figures 3-6). In addition, the rate of conversions to open surgery decreased over time for both sexes and all age groups. The uptake of VATS and SBRT were slightly higher among women than among men, whereas the rate of conversions was slightly lower. For example, the uptake of VATS among men in 2010 was 23.5% (95%CI: 22.5-24.5, compared with 26.6% among women (95%CI: 25.7-27.6). The uptake of SBRT was notably higher for more advanced ages (see Supporting Figure 6). For example, the uptake of SBRT in 2010 was 5.3% (95%CI: 2.1-10.5) among those younger than 50 years, compared with 38.8% (95%CI: 36.2-41.5) among those older than 80 years.

Discussion

General treatment patterns

Patterns of care indicate that most early-stage NSCLC cases receive surgery and/or radiotherapy. However, whereas the percentage receiving radiotherapy increased with advancing stage, the percentage receiving surgery decreased with advancing stage. This likely reflects the increasing difficulty of performing more extensive surgical resections, even among those with stage IA-IIB disease.

Uptake of MIS and rate of conversions

The use of MIS among surgically treated cases increased over time, up to 48.6% among stage IA cases in 2014. This increasing uptake of MIS was robust across the different conducted sensitivity analyses. Our findings are similar to those in a recent study, in which 44.5% of wedge resections and lobectomies among patients with non-metastatic lung cancer in Veterans Affairs hospitals between 2012 and 2015 were conducted using VATS.[14] The European Thoracic Surgery Database, which collects data from 170 hospitals across 22 European countries, reported that the uptake of VATS lobectomies increased from 5.4% in 2007–2011 to 29.3% in 2012–2015.[20] Thus, it appears that the uptake of MIS in Europe is also increasing, although its uptake may lag compared with the USA.[20] In the UK, the uptake of MIS is similar to the USA; increasing from 53.4% in 2016 to 55.8% in 2017.[21] Rates of conversions were similar in the UK (10.6% of lobectomy and bilobectomy procedures in 2017), compared with our US-based study (11.5% of lobectomy and bilobectomy procedures in 2014).[21] The increasing use of MIS may particularly benefit patients with a reduced lung function or cardiopulmonary reserve, in whom this approach has been shown to reduce rates of pulmonary morbidity compared with open surgery.[22]

While we confirm that the uptake of MIS is increasing, we add that the rate of conversions to open surgery decreased during the same period. This may reflect increasing experience of thoracic surgeons.[23] Whereas the uptake of MIS decreased with advancing stage, the rate of conversions increased with advancing stage. This finding may be partly explained by the decreasing use of sublobar resections and the increasing use of pneumonectomy with advancing stage. Indeed, the uptake of MIS was lower for more extensive resections (e.g. pneumonectomy < (bi)lobectomy < sublobar resection). These observations may reflect the technical difficulty of performing more extensive resections by MIS.

In the USA, annual lung cancer screening has been recommended for high-risk individuals.[7] It has been estimated that the full-scale implementation of lung cancer screening in the USA will shift the percentage of stage I diagnoses in the general population (which includes individuals that are not eligible for screening) from 22.2% to 30.6%.[6] This will increase demand for lung cancer surgery in the USA by up to 37.0%.[6] If screening is to be effective, these cases should receive optimal treatment by MIS resection in a high-volume hospital.[24,25] Therefore, we expect that the uptake of MIS in the USA will continue to increase in coming years. In Europe, lung cancer

screening has not yet been implemented. Nevertheless, several European countries have expressed the intention to start planning for the implementation of lung cancer screening.[8] Therefore, we expect that the uptake of MIS lung resections will continue to increase in Europe as well.

Uptake of SBRT

Among patients with stage IA-IB NSCLC, the uptake of SBRT increased substantially between 2010 and 2014. This finding was robust to the different sensitivity analyses. The increasing uptake of SBRT may particularly benefit patients with lung cancer with comorbidities, which can increase the risks related to surgery. In the Netherlands, Palma and colleagues demonstrated that an increased use of SBRT among patients with stage I NSCLC led to fewer untreated elderly patients.[26] In our US-based study, the overall percentage of early-stage patients that received radiotherapy (both SBRT and conventional radiotherapy) also increased (by 3.4 percentage-points). However, we did not find a corresponding reduction in the rate of non-treatment. Instead, we found that the percentage of early-stage cases that received surgery decreased by 3.5 percentage-points. This suggests a possible shift from operable patients towards medically inoperable patients (e.g. due to comorbidities), which should be further investigated in future studies. The constant non-treatment rate of approximately 10% suggests possibilities for a further increase in the use of radiotherapy, and in particular SBRT, among early-stage cases that would otherwise not receive any treatment.

Currently, SBRT is only recommended for medically inoperable early-stage NSCLC cases. However, some studies have suggested that SBRT may be feasible in medically operable patients,[27] which could increase the future uptake of SBRT. Because lung cancer screening is only recommended for patients fit to undergo curative lung surgery,[7] it's continued implementation may not directly increase the future use of SBRT. However, in practice it may be difficult to assess fitness for surgery prior to screening. Therefore, the increase in early-stage cases due to screening may still lead to a further increase in the use of SBRT. Consequently, it is likely that the uptake of SBRT will continue to increase.

The uptake of SBRT was modest but present among stages IIA and IIB. This is most likely due to concerns about either lymph node involvement, tumor size, or size of the irradiated field. SBRT is indeed most appropriate for tumors smaller than 5 cm (which encompasses stage I-IIA). Nevertheless, SBRT may also be used for larger isolated tumors (T1-3,N0,M0).[5,28]

Strengths and limitations

The most important strength of this current analysis is the use of the NCDB data set, which captures treatment data on 70% of incident cancer cases in the USA. Although this database is facility-based, an earlier report found no major differences in the distributions of sex, age, race or ethnicity, health insurance status, histology, and

stage between lung cancer cases in the NCDB and the population-based Surveillance, Epidemiology, and End Results data set.[17] Therefore, in contrast to previous reports, the findings of our study are likely representative for the general US population.[14]

A possible limitation of our study is the lack of clinical information in the NCDB, such as performance status. Therefore, we could not determine whether cases were medically operable or not. Future research is necessary to determine whether cases that do not receive any treatment may have been medically eligible for surgery or SBRT.

A second possible limitation of using cancer registry data is that coding practices may change over time. However, the AJCC seventh edition staging manual was almost exclusively used during the study time period, which limits changes in study eligibility over time. In addition, no changes occurred in the coding of any of the outcome variables (e.g. surgical approach, surgical extent, or radiation modality).

A third limitation is that we did not assess whether the increasing use of MIS and SBRT affected patient outcomes. The NCDB does not include patient-reported outcomes, such as quality of life. In addition, we feel that a prospective randomized trial is the best method to provide an unbiased comparison of oncological outcomes across treatment modalities. Recently, the prospective VIdeo-assisted thoracoscopic lobectomy versus conventional Open LobEcTomy for lung cancer trial confirmed that that VATS lobectomy is associated with significantly lower in-hospital complications and a shorter length of stay than open lobectomy, without compromising oncological outcomes.[29] Another recent prospective randomized controlled trial, which included inoperable stage I NSCLC cases, showed that SBRT provides superior tumor control compared with standard radiotherapy, without increasing toxicity.[30] These studies indicate that the increasing uptake of MIS and SBRT in the USA will likely provide clinical benefit to patients with early-stage NSCLC.

Conclusions

In conclusion, patterns of care show that surgeons in the USA have been increasingly using MIS to treat early-stage NSCLC while the rate of conversions decreased. SBRT is also increasingly used. The increasing uptake of MIS and SBRT may particularly benefit patients with lung cancer at higher operative risk. Nevertheless, the increasing use of radiotherapy does not seem to coincide with a reduction in the percentage of cases that do not receive any treatment. Therefore, there may be room for an additional increase in the use of radiotherapy, and in particular SBRT, among cases that would otherwise receive no treatment. Continuing the increasing trends in uptake of MIS and SBRT may contribute to improving overall patient care, in particular with the expected increase in early-stage lung cancer due to the implementation of lung cancer screening.

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Chapter 2

Supplementary Methods

Deriving surgical extent variable

Original code RX_SUMM_ SURG_PRIM_SITE	Meaning	Recode
0	None; no surgery of primary site; autopsy ONLY	No surgery
20	Excision or resection of less than one lobe, NOS	Sublobar resection
21	Wedge resection	Sublobar resection
22	Segmental resection, including lingulectomy	Sublobar resection
23	Excision, NOS	Sublobar resection
24	Laser excision	Sublobar resection
25	Bronchial sleeve resection ONLY	Sublobar resection
30	Resection of lobe or bilobectomy, but less than the whole lung (partial pneumonectomy, NOS)	Lobectomy or bilobectomy
33	Lobectomy WITH mediastinal lymph node dissection	Lobectomy or bilobectomy
45	Lobe or bilobectomy extended, NOS	Lobectomy or bilobectomy
46	WITH chest wall	Lobectomy or bilobectomy
47	WITH pericardium	Lobectomy or bilobectomy
48	WITH diaphragm	Lobectomy or bilobectomy
55	Pneumonectomy, NOS	Pneumonectomy
56	WITH mediastinal lymph node dissection (radical pneumonectomy)	Pneumonectomy
65	Extended pneumonectomy	Pneumonectomy
66	Extended pneumonectomy plus pleura or diaphragm	Pneumonectomy
70	Extended radical pneumonectomy	Pneumonectomy
12	Laser ablation or cryosurgery	Other
13	Electrocautery; fulguration (includes use of hot forceps for tumor destruction)	Other
15	Local tumor destruction, NOS	Other
19	Local tumor destruction or excision, NOS	Other
80	Resection of lung, NOS	Other
90	Surgery, NOS	Other

Chapter 2

Supplementary Tables and Figures

Supporting Table 1: Extent of resection among early-stage non-small cell lung cancer cases by clinical stage at diagnosis and by year of diagnosis.

	Sublobar n (% [95% CI])	**Lobectomy or bilobectomy n (% [95% CI])**	**Pneumonectomy n (% [95% CI])**	**Other n (% [95% CI]) [a]**
Stage				
IA	10727 (24.3 [23.9-24.7]) [b]	32569 (73.8 [73.3-74.2]) [b]	367 (0.8 [0.7-0.9]) [b]	497 (1.1 [1-1.2]) [b]
IB	1903 (11.3 [10.8-11.7])	14110 (83.5 [82.9-84])	683 (4 [3.7-4.3])	206 (1.2 [1.1-1.4])
IIA	714 (7.6 [7.1-8.2])	7679 (81.8 [81-82.6])	894 (9.5 [8.9-10.1])	101 (1.1 [0.9-1.3])
IIB	652 (9.4 [8.8-10.2])	5180 (75 [74-76])	910 (13.2 [12.4-14])	165 (2.4 [2-2.8])
Year				
2010	2624 (17.5 [16.9-18.1]) [c]	11550 (76.9 [76.2-77.6]) [e]	605 (4 [3.7-4.4]) [d]	237 (1.6 [1.4-1.8]) [b]
2011	2776 (18.3 [17.7-18.9])	11611 (76.4 [75.7-77.1])	579 (3.8 [3.5-4.1])	228 (1.5 [1.3-1.7])
2012	2765 (18 [17.4-18.6])	11851 (77 [76.4-77.7])	595 (3.9 [3.6-4.2])	174 (1.1 [1-1.3])
2013	2875 (18.2 [17.6-18.8])	12219 (77.2 [76.5-77.9])	562 (3.6 [3.3-3.9])	171 (1.1 [0.9-1.3])
2014	2956 (18.6 [17.9-19.2])	12307 (77.2 [76.6-77.9])	513 (3.2 [3-3.5])	159 (1 [0.8-1.2])
Overall	13996 (18.1 [17.8-18.4])	59538 (77 [76.7-77.3])	2854 (3.7 [3.6-3.8])	969 (1.3 [1.2-1.3])

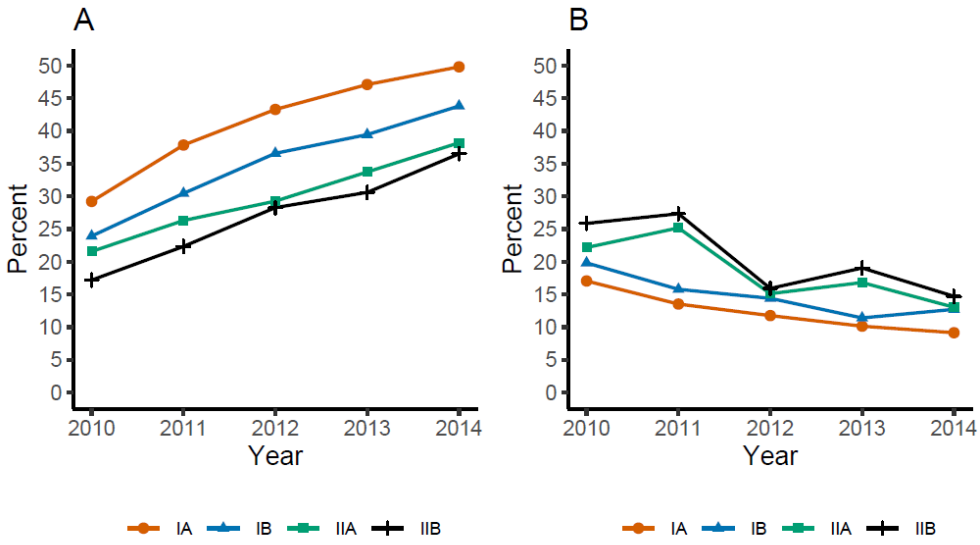
[a] As the percentage of surgically treated cases that received an "other" type of resection was low, time trends in the uptake of MIS and the rate of conversions were not further analyzed for this subgroup.

[b] Statistically significant trend (p<0.0001).

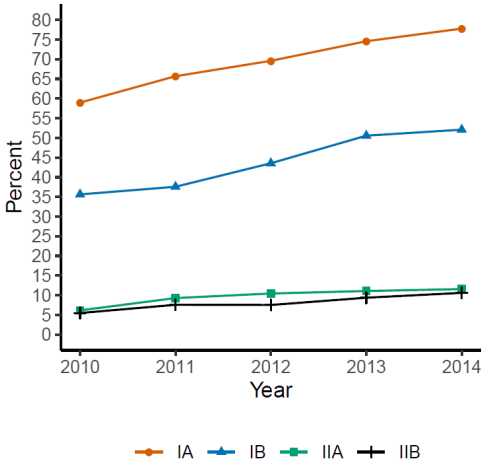
[c] Statistically significant trend (p=0.0370).

[d] Statistically significant trend (p=0.0001).

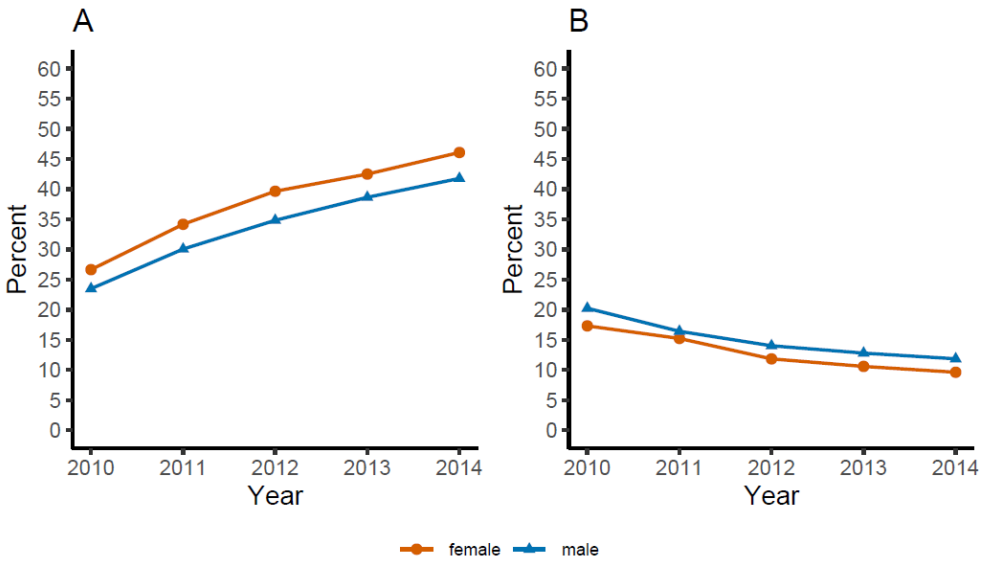
[e] Statistically non-significant trend (p=0.1837).



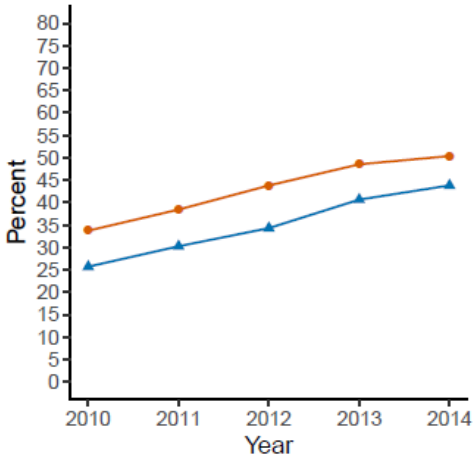
Supporting Figure 1: Uptake of minimally invasive surgery among early-stage non-small cell lung cancer cases treated surgically between 2010-2014 by clinical stage at diagnosis. In this sensitivity analysis, cases with missing data on surgical approach or missing data on radiation modality were excluded. Panel A shows the percentage of lung cancer surgeries which started as minimally invasive surgery between 2010-2014 by clinical stage at diagnosis. Panel B shows the percentage of lung cancer surgeries which started as minimally invasive surgery that were converted to open surgery between 2010-2014, by clinical stage at diagnosis.



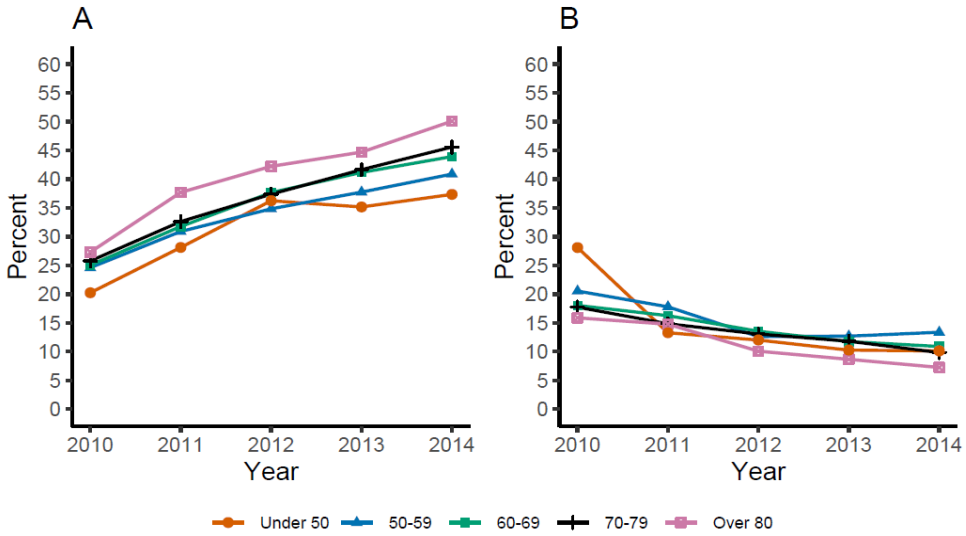
Supporting Figure 2: Uptake of stereotactic body radiation therapy among early-stage non-small cell lung cancer cases treated with thoracic radiotherapy between 2010-2014 by clinical stage at diagnosis. Sensitivity analysis where cases with missing data on surgical approach or missing data on radiation modality were excluded.



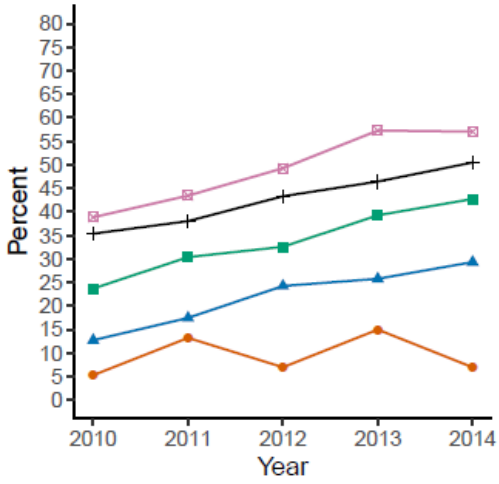
Supporting Figure 3: Uptake of minimally invasive surgery among early-stage non-small cell lung cancer cases treated surgically between 2010-2014 by sex. Panel A shows the percentage of lung cancer surgeries that were started as minimally invasive surgery between 2010-2014 by sex. Panel B shows the percentage of lung cancer surgeries which started as minimally invasive surgery that were converted to open surgery between 2010-2014, by sex.



Supporting Figure 4: Uptake of stereotactic body radiation therapy among early-stage non-small cell lung cancer cases treated with thoracic radiotherapy between 2010-2014 by sex.



Supporting Figure 5: Uptake of minimally invasive surgery among early-stage non-small cell lung cancer cases treated surgically between 2010-2014 by age.Panel A shows the percentage of lung cancer surgeries that were started as minimally invasive surgery between 2010-2014 by age. Panel B shows the percentage of lung cancer surgeries which started as minimally invasive surgery that were converted to open surgery between 2010-2014, by age.



Supporting Figure 6: Uptake of stereotactic body radiation therapy among early-stage non-small cell lung cancer cases treated with thoracic radiotherapy between 2010-2014 by age.

Chapter 3

Treatment Capacity Required for Full-Scale Implementation of Lung Cancer Screening in the United States

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Abstract

Background

Full-scale implementation of lung cancer screening in the United States will increase detection of early stages. This study was aimed at assessing the capacity required for treating those cancers.

Methods

A well-established microsimulation model was extended with treatment data from the National Cancer Database. We assessed how treatment demand would change when implementing lung cancer screening in 2018. Three policies were assessed: 1) annual screening of current smokers and former smokers who quit fewer than 15 years ago, aged 55 to 80 years, with a smoking history of at least 30 pack-years (US Preventive Services Task Force [USPSTF] recommendations); 2) annual screening of current smokers and former smokers who quit fewer than 15 years ago, aged 55 to 77 years, with a smoking history of at least 30 pack-years (Centers for Medicare and Medicaid Services [CMS] recommendations); and 3) annual screening of current smokers and former smokers who quit fewer than 10 years ago, aged 55 to 75 years, with a smoking history of at least 40 pack-years (the most cost-effective policy in Ontario [Ontario]). The base-case screening adherence was a constant 50%. Sensitivity analyses assessed other adherence levels, including a linear buildup to 50% between 2018 and 2027.

Results

The USPSTF policy would require 37.0% more lung cancer surgeries in 2015–2040 than no screening, 2.2% less radiotherapy, and 5.4% less chemotherapy; 5.7% more patients would require any therapy. The increase in surgical demand would be 96.1% in 2018, 46.0% in 2023, 38.3% in 2028, and 24.9% in 2040. Adherence strongly influenced results. By 2018, surgical demand would range from 52,619 (20% adherence) to 96,121 (80%). With a gradual buildup of adherence, the increase in surgical demand would be 9.6% in 2018, 38.3% in 2023, 42.0% in 2028, and 24.4% in 2040. Results for the CMS and Ontario policies were similar, although the changes in comparison with no screening were smaller.

Conclusions

Full-scale implementation of lung cancer screening causes a major increase in surgical demand, with a peak within the first 5 years. A gradual buildup of adherence can spread this peak over time. Careful surgical capacity planning is essential for successfully implementing screening.

Introduction

Despite decreasing incidence rates, lung cancer is still the leading cause of cancer-related mortality in the United States.[1] The National Lung Screening Trial (NLST) has shown that 3 annual low-dose computed tomography (LDCT) screenings for lung cancer can reduce lung cancer mortality by 20% in comparison with 3 annual chest radiography screenings.[2] Since then, both the US Preventive Task Force (USPSTF)[3] and the Centers for Medicare and Medicaid Services (CMS)[4] have issued recommendations for LDCT screening for lung cancer. The USPSTF recommendations have been partly based on modeling efforts.[5]

The standard of care is surgery for early-stage non-small cell lung cancer (NSCLC), a combination of chemotherapy and radiotherapy for locally advanced NSCLC, and chemotherapy for advanced NSCLC.[6] Consequently, early detection by lung cancer screening is expected to increase the demand for surgery and decrease the demand for radiotherapy and chemotherapy. The magnitude of this shift in treatment will depend on the number of screened individuals, which will decrease over time[7] because younger birth cohorts smoke less.[8]

The benefits of early detection depend on the availability of adequate treatment. Hence, assessing the demand for treatment and planning for sufficient manpower are essential to successfully implementing screening. In screening programs where capacity (e.g., for follow-up) has been limited, program implementation has been done gradually to take this into account.[9] Therefore, the aim of the current study was to project the treatment capacity required for the full-scale implementation of LDCT screening for lung cancer in the United States.

Materials and methods

Simulation of lung cancer incidence rates

In this study we used the MIcrosimulation SCreening ANalysis Lung (MISCAN-Lung) model, which simulates individual life histories in the presence and absence of screening to project benefits and harms of different screening policies on a population level. This study was deemed exempt by the Institutional Review Board at the University of Michigan. MISCAN-Lung has been calibrated to individual-level incidence and mortality data from the NLST and the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial.[10,11] It accounts for differences in smoking behavior across birth cohorts by incorporating the National Cancer Institute's Smoking History Generator.[8] The model has been previously used to inform the USPSTF on the LDCT screening scenario with the most favorable ratio of benefits and harms for a 1950 US birth cohort.[5] Also, it has been used to identify the most cost-effective scenario for Cancer Care Ontario.[12]

In the current analysis, we first simulated a scenario without lung cancer screening. Then, we simulated 3 scenarios with screening: 1) using the USPSTF recommendations (i.e., annual screening of current smokers and former smokers who quit fewer than 15 years ago, aged 55–80 years, with a smoking history of at least

30 pack-years),[3] 2) using the CMS recommendations (i.e., stopping screening 3 years earlier than the USPSTF scenario at the age of 77 years),[4] and 3) using the most cost-effective policy from a recent cost-effectiveness analysis for Cancer Care Ontario (i.e., annual screening of current smokers and former smokers who quit fewer than 10 years ago, aged 55-75 years, with a smoking history of at least 40 pack-years).[12]

The timeframe for this study was 2015-2040. We assumed that screening started in 2018 because the current uptake of lung cancer screening in the United States is low.[13] We simulated the full range of birth-year cohorts from 1916 (i.e., patients aged 99 years in 2015) through 2005 (i.e., patients aged 35 years in 2040). We assumed that no lung cancer occurred under the age of 35 years. We further assumed that the maximum age in the population was 99 years.

Treatment capacity requirements

For each screening scenario, we adjusted the year-, sex-, age-, stage- and histology-specific lung cancer incidence rates estimated by MISCAN-Lung to the projected US population by using the US Census National Population Projections.[14] Therefore, we accounted for growth and aging of the population. Next, we obtained lung cancer treatment patterns from the National Cancer Database (NCDB) participant user file for 440,566 lung cancer cases diagnosed between years 2010 and 2014. The NCDB, established in 1989, is a nationwide, facility-based, comprehensive clinical surveillance resource oncology data set that currently captures 70% of all newly diagnosed malignancies in the United States annually from more than 1500 affiliated facilities. The NCDB is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. An analysis of individual-level NCDB data was performed on site at the University of Michigan Medical School. Details of the analysis of the NCDB data, including case selection and data cleaning are provided as Supplementary Methods in the Supporting Information. In short, we obtained the sex-, age-, stage-, and histology-specific proportions of patients with lung cancer who received surgery, radiotherapy, chemotherapy, and any therapy as first-course treatment. Because treatment patterns among patients with lung cancer in the NCDB remained stable over time (see Supporting Fig. 1), the mean treatment proportions across years 2010-2014 were used in this study (see Supporting Table 1). For each scenario that we simulated, we then calculated the required lung cancer treatment capacity by multiplying the year-, sex-, age-, stage- and histology-specific Census-adjusted incidence from MISCAN-Lung with the mean sex-, age-, stage- and histology-specific treatment proportions from the NCDB. In the base-case analysis, the same treatment proportions were applied to screen-detected cases and clinically detected cases. Because screen-detected cases may have less comorbidity than clinically detected cases, a sensitivity analysis was also performed that used stage-specific treatment proportions from the LDCT arm of the NLST for screen-detected cases (see Supporting Table 2).[2]

Effect of adherence

On the basis of the results of an implementation study of lung cancer screening in the US Veterans Affairs Administration, we assumed a constant screening adherence of 50% for the base-case analysis.[15] Another study in the Stanford Health Care system reported an adherence level of 60%.[16] That study also reported national adherence rates of 69% for colorectal cancer screening, 79% for breast cancer screening, and 75% for cervical cancer screening in the United States. We assume that it is unlikely that adherence to lung cancer screening will surpass that of existing screening programs in the near future. Therefore, we assessed the effect of constant adherence levels of 20%, 35%, 65%, and 80% in a sensitivity analysis. In a second sensitivity analysis, we assessed the effect of a linear buildup of screening adherence from 5% in 2018 to a plateau of 50% from 2027 onward.

Statistical analysis

All analyses were performed with the MISCAN-Lung model and R software (version 3.4.1).[17]

Results

Simulation of lung cancer incidence rates

In 2018, the projected number of screening eligible persons in the US population would be 11,816,790 for the USPSTF scenario, 11,258,937 for the CMS scenario, and 6,505,609 for the Ontario scenario (Supporting Fig. 2). By 2023, screening eligibility would decrease to 10,192,541 (USPSTF), 9,574,244 (CMS), and 5,548,430 (Ontario). By 2040, 4,710,017 persons would be eligible in the USPSTF scenario, 4,145,176 would be eligible in the CMS scenario, and 2,322,388 would be eligible according to the Ontario criteria.

In the absence of screening, annual Census-adjusted lung cancer incidence would increase to 215,392 cases by 2033 and would then gradually decrease (see Supporting Fig. 3). The implementation in 2018 of a screening program with a constant 50% adherence would lead to an immediate peak in incidence in comparison with no screening. This peak would be highest for the USPSTF scenario (n=253,938), which would be followed by the CMS scenario (n=247,556) and the Ontario scenario (n=233,841). With a gradual buildup of adherence, this peak would be lower but last longer (Supporting Fig. 4).

Over the entire study period, the cumulative number of lung cancer cases would be 5,525,593 for the USPSTF scenario, 5,495,049 for the CMS scenario, 5,462,657 for the Ontario scenario, and 5,402,854 for the no screening scenario (Supporting Table 3).The proportions of screen-detected cases would be 16.8% (USPSTF), 14.3% (CMS), and 10.1% (Ontario). In the absence of screening, 22.2% of clinically detected cases would be diagnosed at stage I, 5.9% would be diagnosed at stage II, 25.5% would be diagnosed at stage III, and 46.3% would be diagnosed at stage IV (see Fig. 1A). Among screen-detected cases in the USPSTF scenario, 65.6% would be diagnosed at stage I, 6.8% would

be diagnosed at stage II, 16.5% would be diagnosed at stage III, and 11.1% would be diagnosed at stage IV (see Fig. 1B). For both clinically detected and screen-detected cases, differences in stage distributions across scenarios were minimal. Overall, the proportion of cases diagnosed at stage I would be 30.6% in the USPSTF scenario, 29.4% in the CMS scenario, 27.3% in the Ontario scenario, and 22.2% without screening (see Fig. 1C). Conversely, the proportion of cases diagnosed at stage IV would decrease because of screening: from 46.3% without screening to 38.9% (USPSTF), 40.0% (CMS), and 41.8% (Ontario).

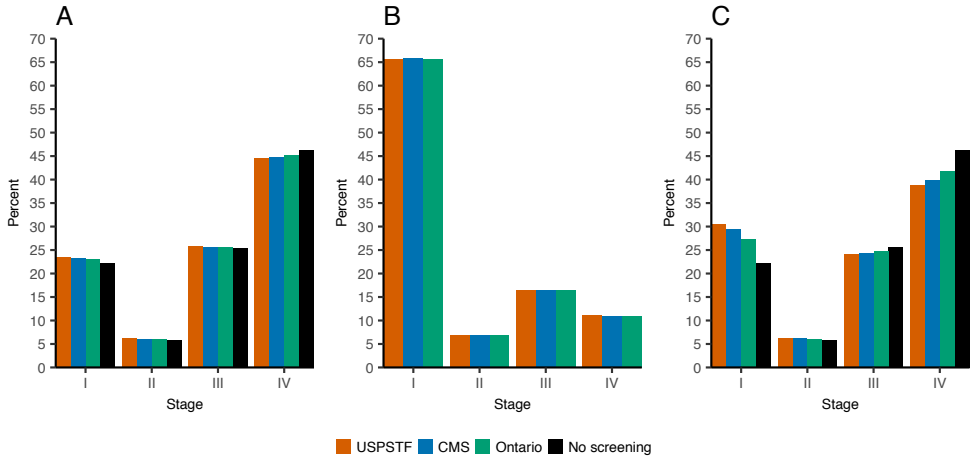

Figure 1. Distribution of stages at diagnosis for (A) clinically detected lung cancer cases, (B) screen-detected cases, and (C) all cases in the United States between 2015 and 2040 in the absence of low-dose computed tomography screening and for the 3 screening policies implemented in 2018. All policies assumed a constant 50% adherence to screening. CMS indicates Centers for Medicare and Medicaid Services recommendations (annual screening of current smokers and former smokers who quit fewer than 15 years ago, aged 55-77 years, with a smoking history of at least 30 pack-years); Ontario, most cost-effective policy from a study for Cancer Care Ontario (annual screening of current smokers and former smokers who quit fewer than 10 years ago, aged 55-75 years, with a smoking history of at least 40 pack-years); USPSTF, US Preventive Services Task Force recommendations (annual screening of current smokers and former smokers who quit fewer than 15 years ago, aged 55-80 years, with a smoking history of at least 30 pack-years).

Treatment capacity requirements

Figure 2 shows the changes in lung cancer therapy due to the implementation of LDCT screening in 2018. The main change would be a large cumulative increase in the demand for lung cancer surgery. At the base-case adherence of 50%, the demand for lung cancer surgery would increase in comparison with no screening by 37.0% (USPSTF), 32.1% (CMS), and 22.8% (Ontario). However, the demand for radiotherapy would decrease by 2.2% (USPSTF), 2.6% (CMS), and 2.1% (Ontario). The demand for

chemotherapy would decrease by 5.4% (USPSTF), 5.1% (CMS), and 3.8% (Ontario). Finally, the number of patients who would receive any therapy would increase by 5.7% (USPSTF), 4.5% (CMS), and 3.0% (Ontario). If we assume that screen-detected cases would receive stage-specific treatment as reported in the NLST, the increase in surgery in comparison with no screening would be 55.3% (USPSTF), 46.3% (CMS), and 32.3% (Ontario; Supporting Fig. 5). The demand for radiotherapy would decrease by 7.4% (USPSTF), 6.8% (CMS), and 5.1% (Ontario). Chemotherapy demand would decrease by 4.3% (USPSTF), 4.7% (CMS), and 3.7% (Ontario). Finally, the demand for any therapy would increase by 7.6% (USPSTF), 5.9% (CMS), and 3.9% (Ontario).

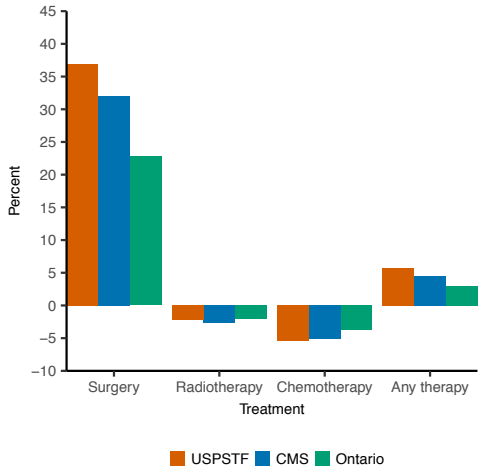

Figure 2. Cumulative changes in demand for lung cancer therapy in the United States between 2015 and 2040 with the implementation of low-dose computed tomography screening for lung cancer in 2018. The data are expressed as cumulative percentage changes in comparison with no screening. All policies assumed a constant 50% adherence to screening. CMS indicates Centers for Medicare and Medicaid Services recommendations (annual screening of current smokers and former smokers who quit fewer than 15 years ago, aged 55-77 years, with a smoking history of at least 30 pack-years); Ontario, most cost-effective policy from a study for Cancer Care Ontario (annual screening of current smokers and former smokers who quit fewer than 10 years ago, aged 55-75 years, with a smoking history of at least 40 pack-years); USPSTF, US Preventive Services Task Force recommendations (annual screening of current smokers and former smokers who quit fewer than 15 years ago, aged 55-80 years, with a smoking history of at least 30 pack-years).

Figure 3 shows the absolute annual number of lung cancer treatments required between 2015 and 2040 for the base-case scenario. Supporting Table 4 additionally shows the percentage change in comparison with no screening in 2018, 2023, 2028, and 2040. In the absence of screening, the annual required number of lung cancer surgeries would remain relatively constant: 37,964 in 2018, 38,903 in 2023, 38,876 in

2028, and 34,021 in 2040. Implementing the USPSTF recommendations would increase demand for lung cancer surgery in comparison with no screening by 96.1% in 2018, 46.0% in 2023, 38.3% in 2028, and 24.9% in 2040. In the CMS scenario, the increases in comparison with no screening would be 87.5% (2018), 41.2% (2023), 33.0% (2028), and 19.7% (2040). Finally, implementing the Ontario recommendations would increase demand in comparison with no screening by 64.5% in 2018, 30.1% in 2023, 23.7% in 2028, and 13.1% in 2040.

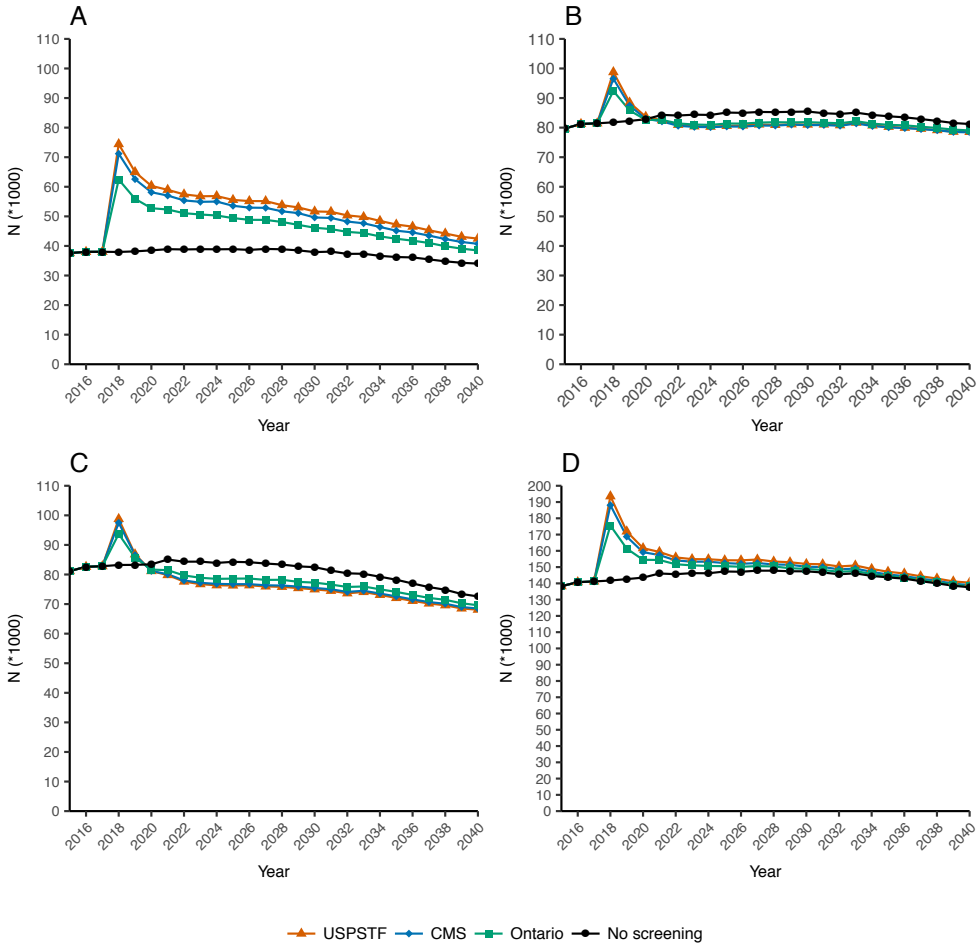

Figure 3. Absolute annual number of patients with lung cancer in the United States requiring (A) surgery, (B) radiotherapy, (C) chemotherapy, and (D) any therapy with the implementation of low-dose computed tomography screening for lung cancer in 2018. All policies assumed a constant 50% adherence to screening. CMS indicates Centers for Medicare and Medicaid Services recommendations (annual screening of current smokers and former smokers who quit fewer than 15 years ago, aged 55-77 years, with a smoking history of at least 30 pack-years); Ontario, most cost-effective policy from a study for Cancer Care Ontario (annual screening of current

smokers and former smokers who quit fewer than 10 years ago, aged 55-75 years, with a smoking history of at least 40 pack-years); USPSTF, US Preventive Services Task Force recommendations (annual screening of current smokers and former smokers who quit fewer than 15 years ago, aged 55-80 years, with a smoking history of at least 30 pack-years).

In the absence of screening, the annual number of patients with lung cancer requiring radiotherapy would increase from 81,802 in 2018 to 84,378 in 2023 and 85,242 in 2028, after which it would gradually decrease to 81,219 in 2040. Implementing the USPSTF recommendations would first increase demand for radiotherapy by 20.7% in 2018. However, demand would decrease in comparison with no screening shortly after that by 4.7% in 2023, 5.1% in 2028, and 3.3% in 2040. Results for the CMS and Ontario scenarios were similar, although differences in comparison with no screening were less pronounced.

We found a similar pattern for the number of cases that required chemotherapy. In the absence of screening, the demand for chemotherapy would be 83,221 in 2018, 84,351 in 2023, 83,366 in 2028, and 72,586 in 2040. In the USPSTF scenario, demand would first increase by 18.7% in 2018, and this would be followed by relative decreases in comparison with to no screening of 9.0% in 2023 and 2028 and 6.2% in 2040.

Finally, the number of lung cancer cases that would receive any therapy in the no screening scenario would increase from 141,751 in 2018 to 146,288 in 2023, and 147,815 in 2028. Then, it would decrease to 137,607 in 2040. For each screening scenario, the number of cases receiving any therapy peaked in 2018: +36.5% (USPSTF), +32.7% (CMS), and +23.8% (Ontario) in comparison with no screening. The difference in comparison with no screening would then become smaller within the 5 years after implementation. For the USPSTF scenario, the increase in comparison with no screening would be 5.9% in 2023, 3.8% in 2028, and 2.1% in 2040.

Effect of adherence

Figure 4 shows the effect of different levels of constant screening adherence on the number of patients requiring lung cancer surgery for the USPSTF scenario. In 2018, the required surgical capacity would be 52,619 (20% adherence), 63,623 (35%), 74,437 (50%), 85,312 (65%), and 96,121 (80%). If we consider 20% adherence as the lower limit and 80% adherence as the upper limit, the number of surgeries would range from 47,790 to 62,849 in 2023, from 46,213 to 58,752 in 2028, and from 38,259 to 45,172 in 2040. Results for the CMS and Ontario scenarios are shown in Supporting Figures 6 and 7, respectively.

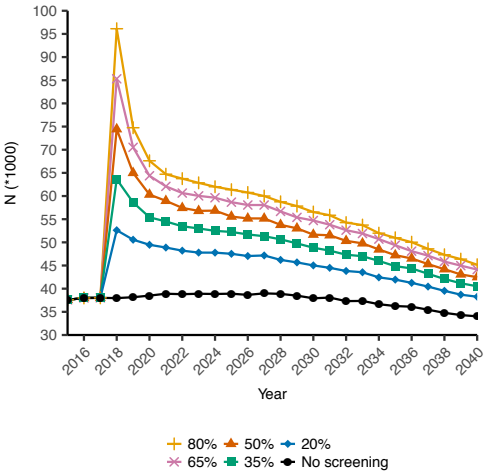

Figure 4. Absolute annual number of patients with lung cancer in the United States requiring surgery with the implementation of low-dose computed tomography screening for lung cancer in 2018 using the US Preventive Services Task Force criteria at different constant screening adherence levels. USPSTF indicates US Preventive Services Task Force recommendations (annual screening of current smokers and former smokers who quit fewer than 15 years ago, aged 55-80 years, with a smoking history of at least 30 pack-years).

Figure 5 and Supporting Table 5 show the effect of a linear buildup of screening adherence from 5% in 2018 to a constant 50% from 2027 onward. In 2018, the increases in surgical demand in comparison with no screening would be 9.6% (USPSTF), 8.7% (CMS), and 7.9% (Ontario). In 2023, the increases would be 38.3% (USPSTF), 34.2% (CMS), and 30.4% (Ontario). In 2028, the increases would be 42.0% (USPSTF), 36.1% (CMS), and 31.6% (Ontario). Finally, in 2040, the increases would be 24.4% (USPSTF), 19.4% (CMS), and 16.1% (Ontario). For the USPSTF scenario, the demand for radiotherapy would change in comparison with no screening by +2.1% (in year 2018), +1.7% (2023), -2.9% (2028), and -3.4% (2024). Demand for chemotherapy would change by +1.9% (2018), -0.6% (2023), -6.8% (2028), and -6.2% (2040). Finally, demand for any therapy would change by +3.7% (2018), +9.3% (2023), +6.3% (2028), and +1.9% (2040). Changes in the demand for radiotherapy, chemotherapy, and any therapy for the CMS and Ontario scenarios were similar to the USPSTF scenario but less pronounced.

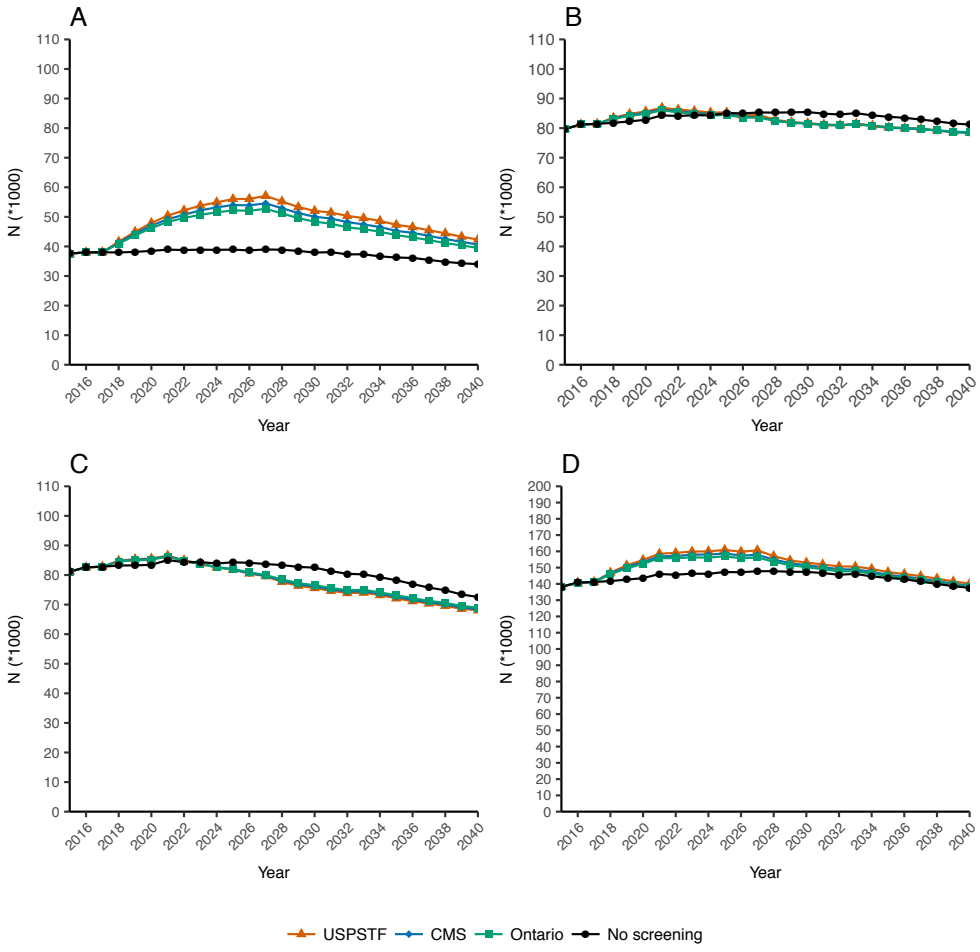

Figure 5. Absolute annual number of patients with lung cancer in the United States requiring (A) surgery, (B) radiotherapy, (C) chemotherapy, and (D) any therapy with the implementation of low-dose computed tomography screening for lung cancer in 2018. All policies assume an adherence level of 5% in 2018 with an annual increase of 5 percentage points until a constant adherence of 50% is reached in 2027. CMS indicates Centers for Medicare and Medicaid Services recommendations (annual screening of current smokers and former smokers who quit fewer than 15 years ago, aged 55-77 years, with a smoking history of at least 30 pack-years); Ontario, most cost-effective policy from a study for Cancer Care Ontario (annual screening of current smokers and former smokers who quit fewer than 10 years ago, aged 55-75 years, with a smoking history of at least 40 pack-years); USPSTF, US Preventive Services Task Force recommendations (annual screening of current smokers and former smokers who quit fewer than 15 years ago, aged 55-80 years, with a smoking history of at least 30 pack-years).

Discussion

The aim of this study was to quantify the expected treatment capacity required for the full-scale implementation of LDCT screening for lung cancer in the United States.

Simulation of lung cancer incidence rates

The introduction of screening caused an immediate peak in lung cancer incidence. This initial peak can be explained by the lead time of screen-detected preclinical cases, which would have otherwise been clinically detected later in time.

We found that screening caused a shift in the stage at diagnosis from stage IV to stage I. This stage shift was more pronounced for scenarios with less stringent eligibility criteria (i.e. stage shift for USPSTF > stage shift for CMS > stage shift for Ontario). This may be explained by the higher number (and proportion) of screen-detected cases in those scenarios (see Supporting Table 3). In the NLST, which followed participants from 2002 to 2009, the proportion of stage I lung cancers in the LDCT arm was 50.0%.[2] This is much higher than the 30.6% that we found in the USPSTF scenario. This difference may be explained by 3 factors. Most importantly, our simulation of the general population included all lung cancer cases, not just those detected in the screen-eligible population. Second, we conducted our model under assumptions of much lower (and perhaps more realistic) screening adherence (50%) than was achieved in the NLST (>90%).[2] Third, our results were projected from 2015 to 2040 and, therefore, included younger cohorts than the NLST. A previous MISCAN-Lung simulation of the 1950 cohort found that 48% of lung cancer cases were diagnosed at stage I or II when the USPSTF recommendations were implemented.[5] In our current analysis, this proportion was only 36.9%. This may be explained by declining smoking trends for younger birth cohorts,[8] which cause fewer individuals to be eligible for screening.[7] These findings underline the necessity of modeling multiple birth cohorts when one is assessing lung cancer interventions over a time period.

Treatment capacity requirements

We found that the implementation of lung cancer screening would lead to a substantial increase in the demand for lung cancer surgery. A previous study that investigated the radiological capacity requirements for implementing lung cancer screening in the United States defined capacity constraints as "a greater than 5% and (alternatively) greater than 25% projected increase in scans".[18] If we apply the 5% increase criterion to our base-case estimates, surgical capacity would be restrained in every year, for each scenario, and at each adherence level. If we apply the 25% increase criterion to our base-case estimates, capacity would be restrained for each scenario and adherence level in 2018. By 2023, capacity would be restrained for the USPSTF and CMS scenarios with ³35% adherence and for the Ontario scenarios with ³50% adherence. Finally, by 2040, capacity would be restrained only for the USPSTF scenarios with ³65% adherence and for the CMS scenario with 80% adherence. With

the treatment proportions from the NLST for screen-detected cases, surgical capacity constraints would be even more pronounced. However, because the NLST was conducted under selective and controlled circumstances, these estimates should be considered an upper bound. Finally, if we applied the 5% criterion to the results of the sensitivity analysis with a gradual buildup of adherence, surgical capacity would still be restrained in each year for each scenario. If we applied the 25% increase criterion to the same analysis, capacity would be not be restrained in 2018. However, capacity would still be restrained in 2023 and 2028 for each scenario.

Thoracic surgeons have lower operative and postoperative mortality rates for lung cancer surgery than general surgeons.[19,20] Consequently, guidelines state that thoracic surgeons should be involved in treating screen-detected lung cancer.[21,22] However, earlier research projected that the future demand for thoracic surgeons would increase while the supply would decline.[23] Without taking into account lung cancer screening, Moffatt-Bruce et al.[24] reported that by 2035 the caseload per thoracic surgeon may increase by 121%. In addition, Edwards et al.[25] reported that implementing LDCT lung cancer screening in Canada in 2014 could increase the number of operable (i.e., stage I and II) lung cancer cases per thoracic surgeon by 19.8% in 2030. However, our analysis of NCDB data indicates that many stage I and II NSCLC cases in fact do not receive surgery. Nevertheless, these studies provide indications that the current workforce of thoracic surgeons may not be able to cope with the additional demand caused by lung cancer screening.

Residency training of additional thoracic surgeons takes on average 8.7 years.[26] However, the projected surgical demand peaked in the first 5 years after the implementation of screening. This peak would be more spread out over time with a gradual buildup of adherence. However, delaying the full-scale implementation of lung cancer screening may reduce the potential health benefits because smoking trends have been declining.[7] Therefore, our data suggest that training of additional thoracic surgeons should start as soon as possible. In the meantime, a careful assessment and allocation of available capacity should be undertaken to ensure the maximum benefits of lung cancer screening.

We found that the overall reduction in the demand for radiotherapy (-2.2%) and chemotherapy (-5.4%) was smaller than the overall increase in the demand for surgery (+37.0%). This is due to 3 factors. First, patients could receive multiple treatments. Second, radiotherapy and chemotherapy demand first increased because of the large incidence peak and then decreased. Third, the demand for surgery in the absence of screening was much lower than the demand for radiotherapy and chemotherapy. The initial peak in the demand for radiotherapy would exceed a 25% increase in comparison with no screening only by 2018 and only for the base-case USPSTF scenarios with 65% adherence and for the CMS scenario with 80% adherence. Similarly, the initial increase in the demand for chemotherapy in comparison with no screening would surpass the 25% mark only in 2018 for the base-case USPSTF and CMS scenarios with 80% adherence. Therefore, it is unlikely that the implementation of lung cancer screening will cause a major shortage of radiation oncology or chemotherapy services.

Limitations

There are several potential limitations to the current study. First, earlier research has identified treatment disparities among US patients with lung cancer by race[27] and insurance status.[28] Although we implicitly account for these disparities by using the NCDB data, which cover 70% of incident cancer cases in the United States, MISCAN-Lung currently does not explicitly model the effects of these variables.

Second, our model is currently unable to estimate lung cancer incidence on a state level, whereas lung cancer incidence rates have been shown to vary by state.[29] This should be the subject of future research so that policy makers can plan treatment capacity on a local level. Policy makers should also note that simply increasing the number of trained thoracic surgeons may not be sufficient if patients at the highest risk for lung cancer are also encumbered by geographical (distance) or financial barriers (health insurance) to access.

Third, we have not modeled recurrent tumors. Also, the NCDB records only the first course of therapy, which is defined as all methods of treatment recorded in the treatment plan and administered to the patient before disease progression or recurrence. This might lead to an underestimation of the total number of treatments required for the implementation of lung cancer screening.

Finally, because we projected demand in the future, there may be some future developments that could alter our estimates. For instance, we could not project the demand for targeted or immunotherapy agents because these are very recent developments. Furthermore, although current guidelines recommend stereotactic body radiotherapy only for patients with medically inoperable early-stage NSCLC,[6] there is an ongoing debate on its appropriateness in operable patients.[30,31] Therefore, the proportion of early-stage cases that require radiotherapy could increase in the future. Two other developments that may possibly alter our estimates are the introduction of risk models to select individuals for screening and the use of nodule management strategies such as Lung-RADS. Finally, if future developments allow clinicians to distinguish indolent screen-detected cancers that would never cause symptoms from more aggressive cancers, overdiagnosis could decrease. In turn, this could decrease treatment demand.

In conclusion, we show that full-scale implementation of lung cancer screening in the United States will cause a major increase in the demand for lung cancer surgery, with a peak within the first 5 years. The current workforce of thoracic surgeons may not be able to cope with this increased demand. The question is whether this could jeopardize the benefits of screening. Although a gradual buildup of adherence could spread the peak in surgical demand over time, a delayed implementation of screening may reduce the potential health benefits. Therefore, implementation of lung cancer screening can be done only with a careful assessment and allocation of surgical capacity.

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Chapter 3

Supplementary Methods

Analysis of National Cancer Database data

Data

Lung cancer treatment patterns were derived from the National Cancer Database (NCDB) Participant User File for lung cancer cases diagnosed in the United States between years 2010-2014.

Case selection

We selected cases with International Classification of Diseases for Oncology 3rd edition lung cancer topography codes (C340 - C343, C348 and C349) and malignant behavior code.[1] We included cases that were staged using the American Joint Committee on Cancer 7th edition Cancer Staging Manual, which was effective from 2010 through 2017.[2] Reasons for exclusion were: (1) stage 0, occult stage, unknown stage, or unknown stage subcategory (e.g. stage I rather than stage IA); (2) more than 4 months (122 days) between date of diagnosis and onset of therapy; (3) patient did not receive any treatment at the reporting facility; (4) date of diagnosis before facility's reference date (i.e. the date from which the facility guarantees the accuracy of data); (5) cases with a history of multiple primary tumors of which lung cancer wasn't the first; (6) cases with unknown treatment; and (7) patients aged younger than 35 at diagnosis. This resulted in a final selection of 440,566 cases.

Derivation of variables

In order to match NCDB data with the MISCAN-lung model, we obtained gender, age, stage and histology specific proportions of patients receiving surgery, radiotherapy, chemotherapy, or no therapy as first course treatment. The derivation of these variables is detailed below.

Derivation of age

Age at diagnosis was used as a continuous variable for ages 35-89. However, the NCDB aggregates data for ages 90 and over.

Derivation of stage

We used clinical stage at diagnosis, as defined by the American Joint Committee on Cancer 7th edition Cancer Staging manual.[2] We did not include stage 0, occult, and unknown cancers because these do not have a clear standard treatment. Also, the MISCAN-lung model does not include these stages. We collapsed stage at diagnosis into the following categories to match MISCAN-lung output: IA, IB, II, IIIA, IIIB, IV.

Derivation of histology

We classified International Classification of Diseases for Oncology 3rd Edition morphological codes into MISCAN-lung histology categories *adenocarcinoma* (including *bronchioalveolar carcinoma* and *large cell carcinoma*), *squamous cell carcinoma, other non-small cell lung cancer* and *small cell lung cancer*. This classification was based on an earlier publication.[3]

Derivation of treatment variables

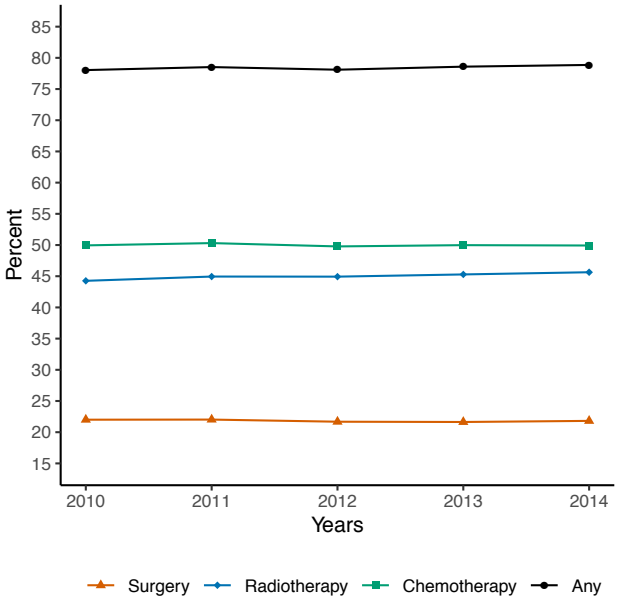
The NCDB records the first course of treatment, defined as all methods of treatment recorded in the treatment plan and administered to the patient before disease progression or recurrence. The NCDB includes treatment modalities *surgery, radiotherapy, chemotherapy, immunotherapy, hormone therapy,* and *other therapy*. If a patient received any of these therapies, they were coded as having received *any therapy.* For this current study, we were not able to separately report on the use of *hormone therapy immunotherapy,* and *other therapy* because these were recorded very infrequently. Patients could receive multiple treatments. Hence, treatment proportions for *surgery, radiotherapy,* and *chemotherapy* do not add up to those for *any therapy*. We were not able to distinguish whether multiple therapies were given concurrently or sequentially.

References

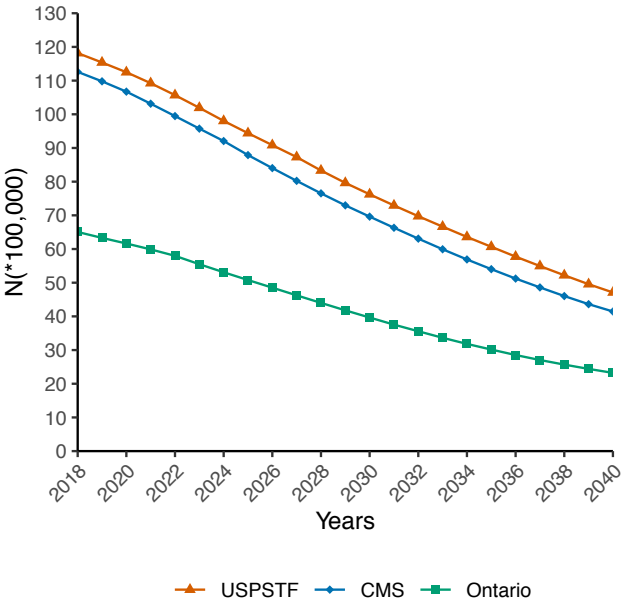
1. Fritz A, Percy C, Jack A, et al. International Classification of Diseases for Oncology. 3rd ed. Geneva, Switzerland: World Health Organization; 2013.
2. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 2010;17(6):1471-1474.
3. ten Haaf K, van Rosmalen J, de Koning HJ. Lung cancer detectability by test, histology, stage, and gender: estimates from the NLST and the PLCO trials. Cancer Epidemiol Biomarkers Prev 2015;24(1):154-161.

Chapter 3

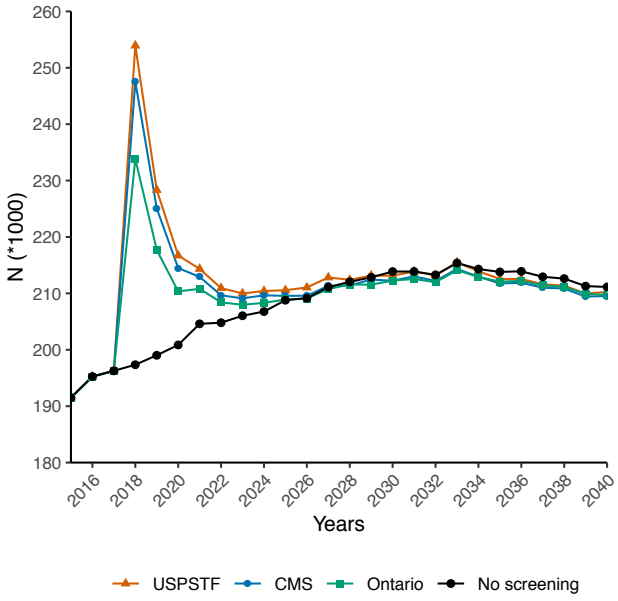
Supplementary Tables and Figures



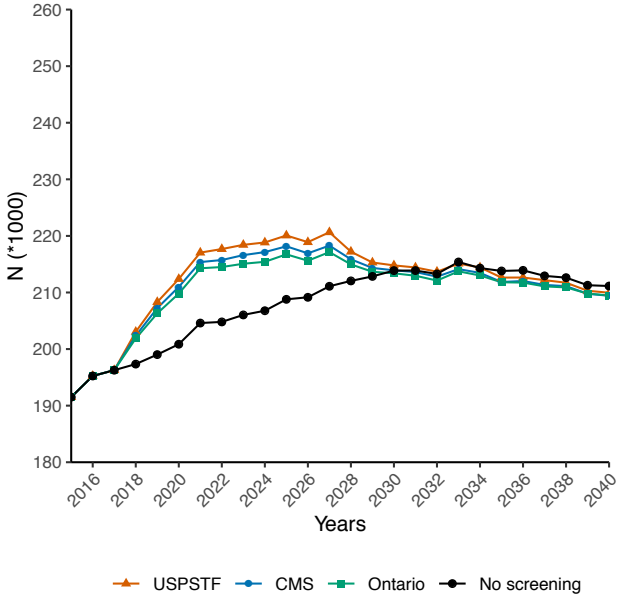
Supporting Figure 1: Time trends for therapy received by lung cancer patients in the United States. Figure based on analysis of 440,566 cases from the National Cancer Database diagnosed with lung cancer between 2010-2014.



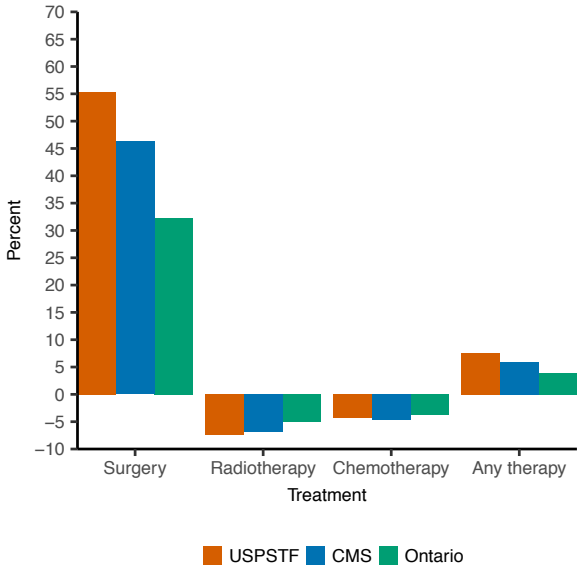
Supporting Figure 2: Number of persons in the United States that are eligible for Low-Dose Computed Tomography lung cancer screening in the United States between 2018-2040 for three screening policies.



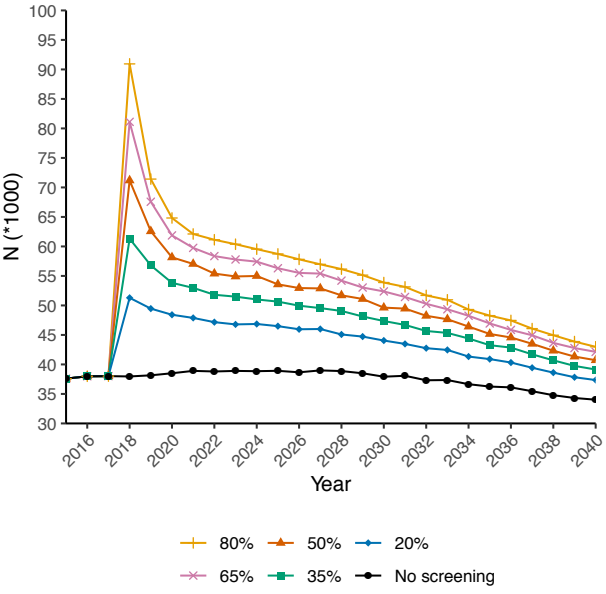
Supporting Figure 3: Census-adjusted lung cancer incidence in the United States between 2015-2040 in the absence of Low-Dose Computed Tomography screening and for three screening policies implemented in 2018. All policies assumed 50% adherence to screening.



Supporting Figure 4: Census-adjusted lung cancer incidence in the United States between 2015-2040 in the absence of Low-Dose Computed Tomography screening and for three screening policies implemented in 2018. All policies assume an adherence level of 5% in 2018, with an annual 5 percentage point increase until a constant adherence of 50% is reached in 2027.

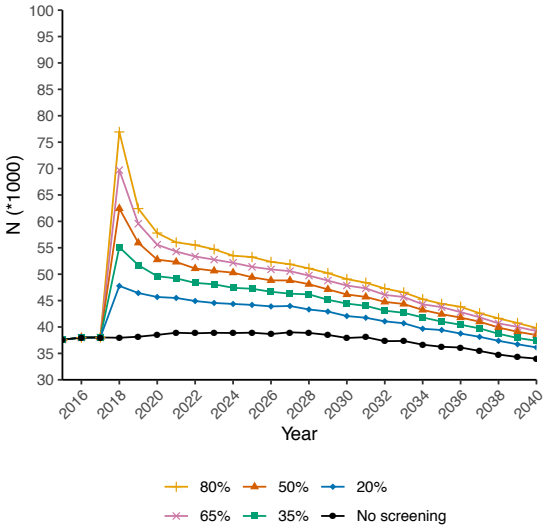


Supporting Figure 5: Cumulative change in demand for lung cancer therapy in the United States between 2015-2040 when implementing Low-Dose Computed Tomography screening for lung cancer in 2018, assuming that screen detected cases received stage-specific treatment as reported in the National Lung Screening Trial. Expressed as cumulative percentage change compared to no screening. All policies assumed constant 50% adherence to screening.



Supporting Figure 6: Absolute annual number of lung cancer patients in the United States requiring surgery when implementing Low-Dose Computed Tomography screening for lung

cancer in 2018 using the Centers for Medicare & Medicaid Services criteria at different constant screening adherence levels.



Supporting Figure 7: Absolute annual number of lung cancer patients in the United States requiring surgery when implementing Low-Dose Computed Tomography screening for lung cancer in 2018 using the Ontario criteria at different constant screening adherence levels.

Supporting Table 1: Lung cancer therapy observed in the National Cancer Database by lung cancer type and clinical stage at diagnosis.[a]

Clinical stage	n	Surgery (%)	Radiotherapy (%)	Chemotherapy (%)	Any therapy (%)
Non-small cell lung cancer					
IA	60,876	43,920 (72.1)	13,689 (22.5)	5,476 (9.0)	56,210 (92.3)
IB	25,924	16,783 (64.7)	7,035 (27.1)	6,199 (23.9)	22,899 (88.3)
II	30,101	16,203 (53.8)	11,658 (38.7)	15,129 (50.3)	25,680 (85.3)
IIIA	48,808	10,538 (21.6)	31,196 (63.9)	32,757 (67.1)	39,803 (81.6)
IIIB	26,878	1,489 (5.5)	18,499 (68.8)	19,117 (71.1)	22,253 (82.8)
IV	182,056	5,224 (2.9)	82,756 (45.5)	91,641 (50.3)	124,814 (68.6)
Subtotal	374,643	94,157 (25.1)	164,833 (44.0)	170,319 (45.5)	291,659 (77.8)
Small cell lung cancer					
IA	1,571	689 (43.9)	825 (52.5)	1,108 (70.5)	1,413 (89.9)
IB	934	199 (21.3)	565 (60.5)	683 (73.1)	795 (85.1)
II	2,456	250 (10.2)	1,747 (71.1)	2,002 (81.5)	2,141 (87.2)
IIIA	9,103	227 (2.5)	6,636 (72.9)	7,742 (85.0)	7,988 (87.8)
IIIB	7,139	59 (0.8)	5,084 (71.2)	6,168 (86.4)	6,340 (88.8)
IV	44,720	304 (0.7)	18,771 (42.0)	32,138 (71.9)	34,986 (78.2)
Subtotal	65,923	1,728 (2.6)	33,628 (51.0)	49,841 (75.6)	53,663 (81.4)
Total	440,566	95885 (21.8)	198,461 (45.0)	220,160 (50.0)	345,322 (78.4)

[a] Based on analysis of 440,566 cases from the National cancer Database diagnosed with lung cancer between 2010-2014. For the actual analysis in the main paper, treatment proportions were further stratified by gender, age, stage, and histology. Patients could receive multiple treatments. Hence, treatment categories do not add up to 100%.

Supporting Table 2: Lung cancer therapy observed in the Low-Dose-Computed Tomography arm of the National Lung Screening Trial by stage at diagnosis.[a]

Stage	n	Surgery (%)	Radiotherapy (%)	Chemotherapy (%)	Any therapy (%)
IA	415	388 (93.5)	26 (6.3)	28 (6.7)	407 (98.1)
IB	104	93 (89.4)	7 (6.7)	34 (32.7)	101 (97.1)
II	72	59 (81.9)	23 (31.9)	46 (63.9)	71 (98.6)
IIIA	98	37 (37.8)	71 (72.4)	77 (78.6)	95 (96.9)
IIIB	121	36 (29.8)	63 (52.1)	91 (75.2)	111 (91.7)
IV	220	23 (10.5)	72 (32.7)	149 (67.7)	180 (81.8)

[a] Proportions were calculated based on treatment frequencies reported in Table 3 in the Supplementary Appendix of Aberle DR, Adams AM, Berg CD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N. Engl. J. Med.* 2011;365(5):395-409.
Patients could receive multiple treatments. Hence, treatment categories do not add up to 100%.

Supporting Table 3: Cumulative number of lung cancer cases in the United States between 2015-2040 and the proportion of screen detected and clinically detected cases in the absence of Low-Dose Computed Tomography screening and for three screening policies implemented in 2018.[a]

Policy	n	Clinically detected (%)	Screen detected (%)
USPSTF	5,525,593	4,597,593 (83.3)	927,999 (16.8)
CMS	5,495,049	4,709,017 (85.7)	786,032 (14.3)
Ontario	5,462,657	4,908,971 (89.9)	553,686 (10.1)
No screening	5,402,854	5,402,854 (100)	-

[a] All policies assumed constant 50% adherence to screening.

Supporting Table 4: Absolute annual number of lung cancer patients in the United States requiring surgery, radiotherapy, chemotherapy, and any therapy when implementing Low-Dose Computed Tomography screening for lung cancer in 2018 (percentage change compared to no screening).[a]

Surgery

Scenario/ Year	2018	2023	2028	2040
No screening	37,964	38,903	38,876	34,021
USPSTF	74,437 (+96.1)	56,794 (+46.0)	53,781 (+38.3)	42,482 (+24.9)
CMS	71,188 (+87.5)	54,912 (+41.2)	51,710 (+33.0)	40,719 (+19.7)
Ontario	62,442 (+64.5)	50,632 (+30.1)	48,105 (+23.7)	38,463 (+13.1)

Radiotherapy

Scenario / Year	2018	2023	2028	2040
No screening	81,802	84,378	85,242	81,219
USPSTF	98,766 (+20.7)	80,426 (-4.7)	80,920 (-5.1)	78,554 (-3.3)
CMS	96,539 (+18.0)	80,246 (-4.9)	80,677 (-5.4)	78,409 (-3.5)
Ontario	92,377 (+12.9)	81,048 (-3.9)	81,830 (-4.0)	79,053 (-2.7)

Chemotherapy

Scenario / Year	2018	2023	2028	2040
No screening	83,221	84,351	83,366	72,586
USPSTF	98,776 (+18.7)	76,729 (-9.0)	75,831 (-9.0)	68,098 (-6.2)
CMS	97,483 (+17.1)	77,192 (-8.5)	76,263 (-8.5)	68,507 (-5.6)
Ontario	93,698 (+12.6)	78,889 (-6.5)	78,217 (-6.2)	69,603 (-4.1)

Any therapy

Scenario / Year	2018	2023	2028	2040
No screening	141,751	146,288	147,815	137,607
USPSTF	193,546 (+36.5)	154,914 (+5.9)	153,441 (+3.8)	140,452 (+2.1)
CMS	188,069 (+32.7)	153,346 (+4.8)	151,635 (+2.6)	138,978 (+1.0)
Ontario	175,527 (+23.8)	151,076 (+3.3)	150,401 (+1.7)	138,121 (+0.4)

[a] All policies assumed constant 50% adherence to screening.

Supporting Table 5: Absolute annual number of lung cancer patients in the United States requiring surgery, radiotherapy, chemotherapy, and any therapy when implementing Low-Dose Computed Tomography screening for lung cancer in 2018 (percentage change compared to no screening).[a]

Surgery

Scenario/ Year	2018	2023	2028	2040
No screening	37,964	38,903	38,876	34,021
USPSTF	41,599 (+9.6)	53,811 (+38.3)	55,220 (+42.0)	42,334 (+24.4)
CMS	41,248 (+8.7)	52,213 (+34.2)	52,926 (+36.1)	40,612 (+19.4)
Ontario	40,966 (+7.9)	50,732 (+30.4)	51,160 (+31.6)	39,497 (+16.1)

Radiotherapy

Scenario / Year	2018	2023	2028	2040
No screening	81,802	84,378	85,242	81,219
USPSTF	83,538 (+2.1)	85,821 (+1.7)	82,811 (-2.9)	78,473 (-3.4)
CMS	83,293 (+1.8)	85,244 (+1.0)	82,499 (-3.2)	78,391 (-3.5)
Ontario	83,134 (+1.6)	84,862 (+0.6)	82,416 (-3.3)	78,590 (-3.2)

Chemotherapy

Scenario / Year	2018	2023	2028	2040
No screening	83,221	84,351	83,366	72,586
USPSTF	84,819 (+1.9)	83,872 (-0.6)	77,684 (-6.8)	68,058 (-6.2)
CMS	84,675 (+1.7)	83,797 (-0.7)	78,153 (-6.3)	68,503 (-5.6)
Ontario	84,560 (+1.6)	83,741 (-0.7)	78,506 (-5.8)	68,974 (-5.0)

Any therapy

Scenario / Year	2018	2023	2028	2040
No screening	141,751	146,288	147,815	137,607
USPSTF	146960 (+3.7)	159881 (+9.3)	157104 (+6.3)	140200 (+1.9)
CMS	146366 (+3.3)	157940 (+8.0)	155035 (+4.9)	138840 (+0.9)
Ontario	145931 (+2.9)	156304 (+6.8)	153622 (+3.9)	138295 (+0.5)

[a] All policies assume an adherence level of 5% in 2018, with an annual 5 percentage point increase until a constant adherence of 50% is reached in 2027.

Part 2

Benefits and Harms of Population-Based Screening Programs

Chapter 4

Trends in Lung Cancer Risk and Screening Eligibility Affect Overdiagnosis Estimates

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Kevin ten Haaf
Douglas A. Arenberg
Harry J. de Koning

Lung Cancer 2020; 139:200-206

Abstract

Objectives

The degree of overdiagnosis due to lung cancer screening in the general US population remains unknown. Estimates may be influenced by the method used and by decreasing smoking trends, which reduce lung cancer risk and screening eligibility over time. Therefore, we aimed to estimate the degree of overdiagnosis due to lung cancer screening in the general US population, using three distinct methods.

Material and methods

The MISCAN-Lung model was used to project lung cancer incidence and overdiagnosis in the general US population between 2018-2040, assuming perfect adherence to the United States Preventive Task Force recommendations. MISCAN-Lung was calibrated to the NLST and PLCO trials and incorporates birth-cohort-specific smoking trends and life expectancies. We estimated overdiagnosis using the cumulative excess-incidence approach, the annual excess-incidence approach, and the microsimulation approach.

Results

Using the cumulative excess-incidence approach, 10.5% of screen-detected cases were overdiagnosed in the 1950 birth-cohort compared to 5.9% in the 1990 birth-cohort. Incidence peaks and drops due to screening were larger for older birth-cohorts than younger birth-cohorts. In the general US population, these differing incidence peaks and drops across birth-cohorts overlap. Therefore, annual excess-incidence would be absent between 2029-2040, suggesting no overdiagnosis occurs. Using the microsimulation approach, overdiagnosis among screen-detected cases increased from 7.1%-9.5% between 2018-2040, while overdiagnosis among all lung cancer cases decreased from 3.7%-1.4%.

Conclusion

Overdiagnosis studies should use appropriate methods to account for trends in background risk and screening eligibility in the general population. Estimates from randomized trials, based on the cumulative excess-incidence approach, are not generalizable to the general population. The annual excess-incidence approach does not account for trends in background risk and screening eligibility, and falsely suggests no overdiagnosis occurs in the general population. Using the microsimulation approach, overdiagnosis was limited but not nil. Overdiagnosis increased among screen-detected cases, while overdiagnosis among all cases decreased.

Introduction

Overdiagnosis is considered to be one of the main harms of cancer screening, and is typically defined as a screen-detected cancer that would not have become symptomatic during an individual's lifetime.[1] There are two ways overdiagnosis can happen. First, a patient with a progressive screen-detected cancer may die of other causes before their cancer would have progressed to a point at which it would cause symptoms (i.e. before clinical presentation). This becomes more likely when the chances of dying from competing causes are higher, for example when screening elderly persons[2] or those with many comorbidities. Second, some screen-detected cancers may not be progressive (i.e. indolent or regressing), and would thereby never reach a point at which they would cause symptoms. In both cases, it is impossible to determine whether an individual screen-detected case has been overdiagnosed.

There are several methods for estimating overdiagnosis.[3] A commonly used method is the cumulative excess-incidence approach, in which the difference in cumulative incidence between a screened group and a matched control group is attributed to overdiagnosis. Several studies used this approach to estimate the degree of overdiagnosis in low-dose computed tomography screening for lung cancer. Using data from the National Lung Screening Trial, Patz et al. reported that 18.5% of screen-detected lung cancers in the low-dose computed tomography arm were overdiagnosed at 7 years of follow-up.[4] The Danish Lung Screening Trial reported that 67.2% of screen-detected cancers were overdiagnosed at 11 years of follow-up.[5] Finally, researchers from the ITALUNG trial reported no overdiagnosis at 9 years of follow-up.[6]

The variation in overdiagnosis estimates between these randomized trials has been suggested to be due to several factors, including a different number of screening rounds and differences in baseline lung cancer risk.[7] The number of screening rounds per participant would be much higher in a continuous population screening program. On the other hand, the background lung cancer risk (and screening eligibility) in the population has been shown to decrease over time, as younger birth-cohorts smoke less.[8] Finally, while all randomized trial estimates used the cumulative excess-incidence approach, this approach should not be used in a continuous screening program in the general population.[9] Using other methods may also lead to different estimates.[10] Consequently, it remains uncertain whether the published estimates of lung cancer overdiagnosis are generalizable to a continuous screening program in the general population. Therefore, we used three distinct methods to estimate the degree of lung cancer overdiagnosis in the general US population when fully implementing a continuous lung cancer screening program in 2018.

Materials and methods

MISCAN-Lung model

Although the United States Preventive Task Force (USPSTF) has recommended lung cancer screening in the United States since 2013,[11] current uptake is limited.[12] Consequently, comprehensive data on lung cancer incidence and overdiagnosis in

a continuous screening program are currently not available. Therefore, we used the MIcrosimulation SCreening ANalysis Lung (MISCAN-Lung) model to project future lung cancer incidence and overdiagnosis in the presence and absence of screening.

MISCAN-Lung uses the National Cancer Institute's Smoking History Generator[8] to generate sex and birth-cohort specific life histories, including smoking histories and non-lung cancer specific causes of death (corrected for smoking behavior). The generated smoking histories determine the chance of developing preclinical lung cancer. When preclinical lung cancer develops, it can progress to more advanced preclinical stages. At each of these stages, the preclinical cancer can be either clinically detected or screen-detected. For each individual, full life histories are generated in the presence and absence of screening. Key model parameters, such as the mean histology and sex-specific duration in each stage (i.e. the natural history), and the stage and histology-specific screening test sensitivity, have been calibrated to data from the National Lung Screening Trial and the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. Details of model calibration have been described in previous publications.[13,14] The model was previously used to inform the USPSTF on the lung cancer screening policy with the optimal ratio of benefits and harms.[11,15]

Projecting incidence

We used MISCAN-Lung to project lung cancer incidence in the US population in the absence and presence of screening. First, we simulated histology, stage, age, and sex-specific lung cancer incidence rates for each individual birth-cohort from 1916 to 2005 (i.e. persons aged 35-99 in years 2015-2040). Thereby, we account for different smoking trends and life-expectancies in the evaluated population. Next, we used the age and sex-specific Census population projections[16] to convert the annual incidence rates for each birth-cohort to cohort-specific Census-adjusted annual incidence counts. Finally, we aggregated these Census-adjusted annual incidence counts across all cohorts, forming the Census-adjusted annual incidence count for the general US population. In the screening scenario, we assumed perfect adherence to the USPSTF recommendations between 2018-2040 (i.e. annual screening of those aged 55-80 with a smoking history of at least 30 pack-years, that currently smoke or quit less than 15 years ago).

Estimating overdiagnosis

We used three distinct methods to estimate overdiagnosis: the cumulative excess-incidence approach, the annual excess-incidence approach, and the microsimulation approach. The cumulative excess-incidence approach subtracts the cumulative incidence in the absence of screening after a certain period of follow-up from the cumulative incidence in the presence of screening, and attributes this difference to overdiagnosis. This approach provides an unbiased estimate of overdiagnosis in a closed cohort with a limited number of screens and sufficient follow-up.[3,9] We assume that the effect of radiation exposure due to LDCT screening on lung cancer incidence

was negligible.[15,17] Therefore, we used this approach to estimate overdiagnosis in several separate US birth-cohorts with a lifetime follow-up. As the number of individuals differs per birth-cohort, overdiagnosis using the cumulative excess-incidence approach was expressed as the rate of overdiagnosed cases per 100,000 persons in the cohort alive in 2015. Also, we expressed overdiagnosis as the lifetime percentage of screen-detected cases that would be overdiagnosed, calculated by dividing the rate of overdiagnosed cases by the rate of screen-detected cases. Finally, we expressed overdiagnosis as the lifetime percentage of all lung cancer cases that would be overdiagnosed, calculated by dividing the rate of overdiagnosed cases by the cumulative incidence rate in the presence of screening.

In a continuous screening program in the general population, the annual excess-incidence should be used instead of the cumulative excess-incidence.[9] The underlying principle is that in a continuous screening program in the general population, new persons will receive their first screening at the end of a chosen follow-up period, which would bias the cumulative excess-incidence approach. In each calendar year, an increased incidence due to early detection is partly compensated by a drop in incidence among individuals that are no longer eligible. In the annual excess-incidence approach, incidence in the absence of screening is therefore subtracted from incidence in the presence of screening for each calendar year, and this difference is attributed to overdiagnosis. This approach should provide an unbiased overdiagnosis estimate after waiting until screening uptake stabilizes plus the longest preclinical duration.[9,18] A recent analysis suggests that the lead time of screen-detected lung cancers in the National Lung Screening Trial can be as long as 9 years.[19] Therefore, we used the annual excess-incidence approach to estimate the Census-adjusted annual number of overdiagnosed cases between 2027 (i.e. 2018 plus 9 years of lead time) and 2040 in the general US population. Overdiagnosis was also expressed as the annual percentage of screen-detected cases that would be overdiagnosed, calculated by dividing the Census-adjusted excess-incidence count by the Census-adjusted number of screen-detected cases in each year. Finally, we expressed overdiagnosis as the annual percentage of all lung cancer cases that would be overdiagnosed, calculated by dividing the Census-adjusted excess-incidence count by the Census-adjusted overall incidence count in the presence of screening in each year.

In the microsimulation approach, we used the identical individually simulated life histories in the presence and absence of screening to determine the Census-adjusted annual number of overdiagnosed cases in the general US population between 2018-2040. The percentage of overdiagnosis among screen-detected cases was calculated by dividing the Census-adjusted number of overdiagnosed cases by the Census-adjusted number of screen-detected cases in each year. The percentage of overdiagnosis among all cases was calculated by dividing the Census-adjusted number of overdiagnosed cases by the Census-adjusted overall incidence count in the presence of screening in each year.

Sensitivity analyses

A previous study found that the degree of lung cancer overdiagnosis varies across histologies.[4] As the MISCAN-lung model incorporates sex and histology-specific natural history parameters, our estimates account for these differences. To provide insight into these differences, we stratified our lifetime cumulative excess-incidence estimates of the percentage of screen-detected cancers that are overdiagnosed for several separate birth-cohorts by histology and sex.

Furthermore, smoking trends in the general population are different for men and women.[8] Therefore, we also stratified our estimates of overdiagnosis in the general US population using the annual excess-incidence approach and the microsimulation approaches by sex.

Results

Projecting incidence

For each separate birth-cohort, the Census-adjusted annual lung cancer incidence count would increase when individuals first become eligible for screening (see Fig. 1). As individuals reach the upper age limit for screening eligibility, there would be a compensatory drop in incidence. Both these peaks and drops in the Census-adjusted annual incidence count would be higher for older birth-cohorts than for younger birth-cohorts. For example, the peak difference in the Census-adjusted annual incidence count between screening and no screening would be +5,389 cases for the 1950 cohort compared to +374 cases for the 1990 cohort.

In the aggregated general US population, the full-scale (i.e. 100% adherence) introduction of lung cancer screening in 2018 would increase the Census-adjusted annual incidence count in that year from 197,348 to 309,327 (+ 56.7%). Subsequently, incidence in the presence of screening would gradually decrease (Fig. 2A). By 2028, the Census-adjusted annual incidence count in the presence of screening (212,810 cases in 2028) would approach incidence in the absence of screening (212,050 cases in 2028). Figure 2B shows that the projected Census-adjusted annual incidence count in the presence of screening would even be lower than in the absence of screening from 2029 onwards (up to -1.0% in 2036).

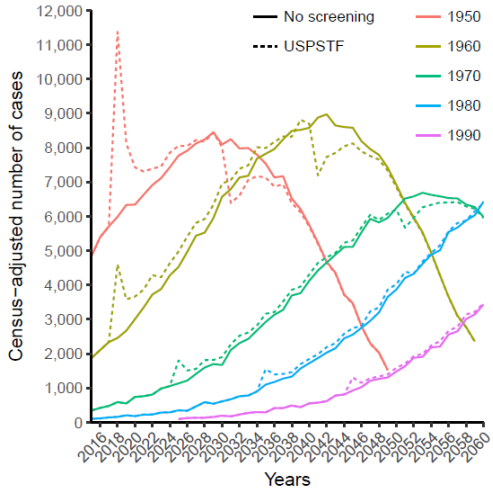

Figure 1: Census-adjusted annual lung cancer incidence count between 2015–2060 for several US birth-cohorts when implementing lung cancer screening using the United States Preventive Task Force eligibility criteria in 2018. Results are presented through 2060 to show the lifetime effect of screening on incidence for several birth-cohorts.

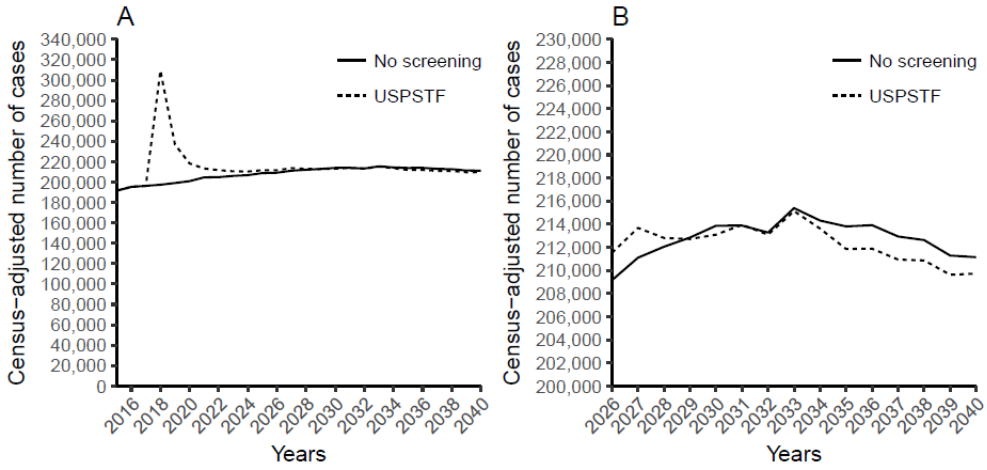

Figure 2: A) Census-adjusted annual lung cancer incidence count in the general United States population between 2015–2040 when fully implementing lung cancer screening using the United States Preventive Task Force eligibility criteria in 2018. B) Detail of panel A for years 2026–2040.

Overdiagnosis estimate using the cumulative excess-incidence approach

As shown in Table 1, the cumulative background incidence rate in the absence of screening would be higher in older birth-cohorts than in younger birth-cohorts (1950 cohort: 6,206 per 100,000; 1990 cohort: 4,157 per 100,000). Also, the percentage of persons ever screened would be higher in older birth-cohorts (1950 cohort: 15.5%; 1990 cohort: 2.9%). Consequently, the rate of screen-detected cases and the rate of overdiagnosed cases would also be lower in younger birth-cohorts (1950 cohort: 1,414 screen-detected cases and 148 overdiagnosed cases per 100,000; 1990 cohort: 287 screen-detected cases and 17 overdiagnosed cases per 100,000). With lifetime follow-up, 10.5% of screen-detected cases would be overdiagnosed in the 1950 birth-cohort compared to 5.9% in the 1990 birth-cohort. Finally, 2.3% of all lung cancer cases would be overdiagnosed in the 1950 birth-cohort compared to 0.4% of the 1990 birth-cohort.

Table 1: Lung cancer incidence rates, screening eligibility, and overdiagnosis for several separate US birth-cohorts when fully implementing lung cancer screening in 2018 using the United States Preventive Task Force recommendations.

Birth-cohort	Cumulative incidence in the absence of screening [a]	Percentage of the cohort ever screened [b]	Number of screen-detected cases [a]	Cumulative incidence in the presence of screening [a]	Number of over-diagnosed cases [a,c]	Percentage of screen-detected cases that would be over-diagnosed [d]	Percentage of all cases that would be over-diagnosed [e]
1950	6,206	15.5%	1,414	6,354	148	10.5%	2.3%
1960	5,791	13.8%	1,307	5,899	108	8.2%	1.8%
1970	4,665	7.1%	660	4,712	47	7.1%	1.0%
1980	4,635	5.1%	492	4,666	31	6.2%	0.7%
1990	4,157	2.9%	287	4,174	17	5.9%	0.4%

[a] Because the absolute size of each birth-cohort is different, numbers are expressed as rates per 100,000 persons of the cohort that were alive in 2015.
[b] For cohorts 1950 and 1960, it is assumed that individuals who would have been eligible before the implementation of screening in 2018 did not receive screening before 2018.
[c] Calculated by subtracting the cumulative incidence in the absence of screening from the cumulative incidence in the presence of screening.
[d] Calculated by dividing the rate of overdiagnosed cases by the rate of screen-detected cases.
[e] Calculated by dividing the rate of overdiagnosed cases by the cumulative incidence rate in the presence of screening.

Overdiagnosis estimate using the annual excess-incidence approach

In the general US population, the Census-adjusted annual excess-incidence count would be 2,579 cases in 2027 (4.3% of screen-detected cases and 1.2% of all lung cancer

cases). By 2028, the Census-adjusted annual excess-incidence count would have decreased to 760 cases (1.4% of screen-detected cases and 0.4% of all lung cancer cases). From 2029 onwards, incidence in the presence of screening would be lower than incidence in the absence of screening (see Fig. 2B). Therefore, there would be no annual excess-incidence from 2029 onwards, suggesting that no overdiagnosis would occur between 2029-2040.

Overdiagnosis using the microsimulation approach

Using the individually simulated life histories in the presence and absence of screening, the Census-adjusted annual number of overdiagnosed cases in the general US population in 2018 would be 11,429 (see Fig. 3A). After that, overdiagnosis would gradually decrease to 2,851 cases in 2040. Figure 3B shows the components necessary to express overdiagnosis as a percentage of screen-detected cases and as a percentage of all cases. Similar to the Census-adjusted annual number of overdiagnosed cases, the Census-adjusted annual number of screen-detected cases would also decrease, although at a faster rate (see Fig. 3B). Consequently, the proportion of screen-detected cases that are overdiagnosed would initially increase from 7.1% in 2018 to 9.5% in 2035 (see Fig. 4).

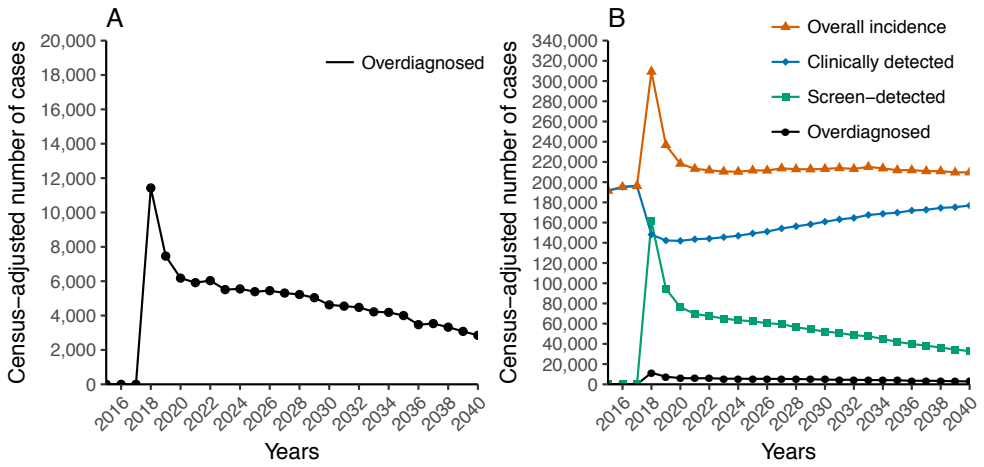

Figure 3: A) Census-adjusted annual number of overdiagnosed lung cancer cases in the general US population between 2015–2040 when fully implementing screening using the United States Preventive Task Force recommendations in 2018. B) Census-adjusted annual lung cancer incidence count in the general US population between 2015–2040 when fully implementing screening using the United States Preventive Task Force recommendations in 2018, stratified by mode of detection, and the Census-adjusted annual number of overdiagnosed cases.

In contrast to the decreasing Census-adjusted annual number of screen-detected cases, the Census-adjusted overall annual incidence count in the general population would remain relatively stable after the initial incidence peak. Combined with the declining Census-adjusted number of overdiagnosed cases, the percentage of all lung cancer cases that are overdiagnosed would decrease from 3.7% of all lung cancer cases in 2018 to 1.4% in 2040 (see Fig. 4).

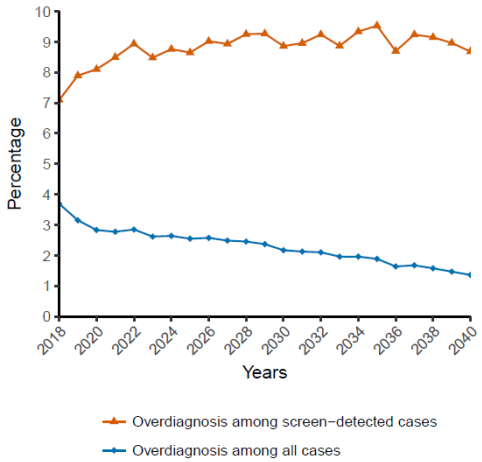

Figure 4: Annual percentage of overdiagnosed lung cancer cases in the United States between 2018–2040 when fully implementing lung cancer screening using the United States Preventive Task Force eligibility criteria in 2018. The percentage of overdiagnosis among screen-detected cases was calculated by dividing the Census-adjusted number of overdiagnosed cases by the Census-adjusted number of screen-detected cases in each year. The percentage of overdiagnosis among all cases was calculated by dividing the Census-adjusted number of overdiagnosed cases by the Census-adjusted overall incidence count in the presence of screening in each year.

Sensitivity analyses

Using the cumulative excess-incidence approach, the percentage of screen-detected cancers that were overdiagnosed was higher for women (range: 5.7% in the 1990 cohort to 11.2% in the 1950 cohort) than for men (range: 6.1% in the 1990 cohort to 9.8% in the 1950 cohort) in each evaluated birth-cohort except the 1990 cohort (see Supplementary Fig. 1). This was also the case for the percentage of screen-detected adenocarcinomas that were overdiagnosed (range across women: 6.3% in the 1990 cohort to 12.7% in the 1950 cohort; range across men: 6.8% in the 1990 cohort to 10.9% in the 1950 cohort). Across histologies, screen-detected adenocarcinomas were most likely to be overdiagnosed (range: 6.6% in the 1990 cohort to 11.9% in the 1950 cohort).

The proportion of screen-detected squamous cell carcinomas that were overdiagnosed was higher for men (range: 7.1% in the 1990 cohort to 10.4% in the 1950 cohort) than for women (range: 6.4% in the 1990 cohort to 9.9% in the 1950 cohort). The

percentage of overdiagnosed screen-detected small cell lung cancers was low for both sexes (range: 1.7% in the 1990 cohort to 2.8% in the 1950 cohort).

Using the annual excess-incidence approach, the Census-adjusted number of overdiagnosed cases would still approach zero in 2029 in both men and women (see Supplementary Fig. 2). Using the microsimulation approach, overdiagnosis among screen-detected cases and all cases was more common among women than men (see Supplementary Fig. 3). However, time trends were similar to the base-case analysis.

Discussion

Modeling incidence

To our knowledge, we are the first to project the impact of continuous lung cancer screening on incidence and overdiagnosis for a multitude of US birth-cohorts as well as for the general US population, using three different methods. Stratified by birth-cohort, incidence would increase once individuals reach the lower age threshold for screening (55 years). This increase is due to the early detection of prevalent and incident preclinical cases. As individuals within each cohort pass the upper age threshold for screening (80 years), there would be a compensatory drop in incidence. To fully account for this compensatory drop in incidence, the follow-up after screening stops should be at least as long as the longest lead-time.[3] As we used lifetime follow-up, we fulfill this criterion. We found that the effect of screening on lung cancer incidence (i.e. both the peak and drop) would be much larger for older cohorts than for younger cohorts. This can be explained by reductions in smoking trends,[8] due to which younger birth-cohorts 1) have a lower background risk of getting lung cancer, and 2) are less often eligible for screening.[20,21]

In the aggregated general US population, we projected a large incidence peak upon the implementation of screening in 2018, which occurs because several cohorts would become eligible for screening in that year (i.e. cohorts 1938-1963). In most other cancer screening programs, incidence with screening remains higher than incidence without screening.[22] However, we found that as lung cancer screening in the general population stabilizes, annual incidence with screening would become lower than without screening. This happens because annual incidence in the general population consists of overlapping incidence peaks and drops from different birth-cohorts. Eventually, the larger incidence drops from older cohorts start to overlap with the smaller incidence peaks from younger birth-cohorts.

Estimating overdiagnosis

Using the cumulative excess-incidence approach, we found that overdiagnosis was much more common in older birth-cohorts than in younger birth-cohorts. These differences are also driven by declining background lung cancer risk and screening eligibility. Due to these trends, cumulative excess-incidence estimates from closed cohorts are not generalizable to a broader population. Therefore, existing lung cancer

overdiagnosis estimates from randomized controlled trials are not representative for a continuous lung cancer screening program in the general US population. In the general US population, the lack of annual excess-incidence as a result of these declining smoking trends would suggest that no overdiagnosis occurs after 2029. However, we used the microsimulation modeling approach to show that overdiagnosis would be present in the general US population in each year since the implementation of screening.

Using the microsimulation approach, the percentage of screen-detected lung cancers in the general US population that would be overdiagnosed increased between 2018-2040, while the percentage of all lung cancer cases that would be overdiagnosed decreased in the same period. The increasing percentage of overdiagnosis among screen-detected cases can be explained by the average age of the pool of screening-eligible individuals. Over time, this pool will increasingly consist of elderly individuals because fewer individuals from younger birth-cohorts become eligible for screening. As overdiagnosis is more common among elderly individuals (due to limited life expectancy), the Census-adjusted annual number of overdiagnosed cases decreases at a slower rate than the Census-adjusted annual number of screen-detected cases. Therefore, the percentage of screen-detected cases that is overdiagnosed will increase over time. In contrast, the total Census-adjusted annual incidence count will remain relatively constant over time due to growth and aging of the population. Therefore, the percentage of all lung cancer cases that is overdiagnosed will decrease. These findings confirm previous work stating that overdiagnosis estimates across different studies can only be compared when the same denominator is used (i.e. among screen-detected cases or among all cases).[23] We add that using different denominators can lead to different conclusions regarding possible time trends in overdiagnosis.

Our sensitivity analyses show that overdiagnosis estimates differ by sex and histology. Overdiagnosis was generally most common among adenocarcinomas and among women. These findings may be explained by the preclinical duration of disease, which has been estimated to be longer for women and for adenocarcinomas.[14] With a longer preclinical duration, the likelihood of overdiagnosis increases. Conversely, small cell carcinomas are known to progress quickly, which explains the lower likelihood of overdiagnosis. Among cases with squamous cell histology, overdiagnosis was more common in men than in women. This can be explained by the fact that while the preclinical duration is similar between men and women, the overall life expectancy for men is lower.[14] The small differences between men and women in the 1990 cohort can be explained by the small numbers due to the low background risk of lung cancer. Differences in population smoking trends between men and women did not affect our conclusions regarding the appropriateness of the annual excess-incidence approach and regarding time trends in overdiagnosis using the microsimulation approach.

Considerations for other screening programs

Compared to other cancer screening programs, lung cancer screening is unique because the main risk factor for lung cancer (i.e. smoking) reduces over time, which affects not only the background risk, but also screening eligibility. In most other cancer screening programs, screening eligibility is only determined by age.

Nevertheless, screening participation rates can still vary over time. Also, background risk may change over time due to changes in behavioral, lifestyle, and medical factors. For example, the risk of breast cancer has been related to body mass index, reproductive behavior, and the use of hormone replacement therapy,[24] all of which may change over time. An earlier theoretical study found that, if breast cancer risk and breast screening participation rates increase over time, the excess-incidence approach would overestimate overdiagnosis.[25] Indeed, the background risk of breast cancer seems to increase over time.[23] Therefore, previous studies that have applied the excess-incidence approach to a population setting may have overestimated breast cancer overdiagnosis.[26]

Strengths and limitations

A major strength of our study is the use of the MISCAN-Lung model, which allows for a comparison of identical full life histories in the absence and presence of screening. Also, our model can take smoking trends across birth-cohorts into account. Finally, microsimulation modeling can assess the effects of many different screening strategies. For example, Han et al. showed that lung cancer overdiagnosis estimates (within a fixed cohort) are sensitive to the eligibility criteria used, such as screening starting and stopping age, and different pack-years criteria.[27] Nevertheless, using microsimulation modeling to estimate overdiagnosis can have limitations. Most importantly, constructing a model implies making underlying assumptions. Also, some parameters of microsimulation models, such as the natural history, must be calibrated. This should be done with great care, as different combinations of parameters can fit the same data.[28] For MISCAN-Lung, details on calibration and validation have been published previously.[13,14]

Conclusion

We conclude that it is crucial to use appropriate methods to account for trends in background cancer risk and screening eligibility when estimating overdiagnosis in the general population. Lung cancer overdiagnosis estimates from randomized trials, which are based on the cumulative excess-incidence approach in a closed cohort with a limited number of screens, are not generalizable to a screening program in the general population. Using the annual excess-incidence approach in the general US population suggests that no overdiagnosis will occur between 2029-2040. However, this estimate is biased as differences in background risk and screening eligibility across cohorts are not taken into account. Using the microsimulation method, we show that lung cancer overdiagnosis in the general US population between 2018-2040 will be limited but not nil. Due to trends in background risk and screening eligibility, overdiagnosis among screen-detected cases will increase between 2018-2040, while overdiagnosis among all cancer cases will decrease.

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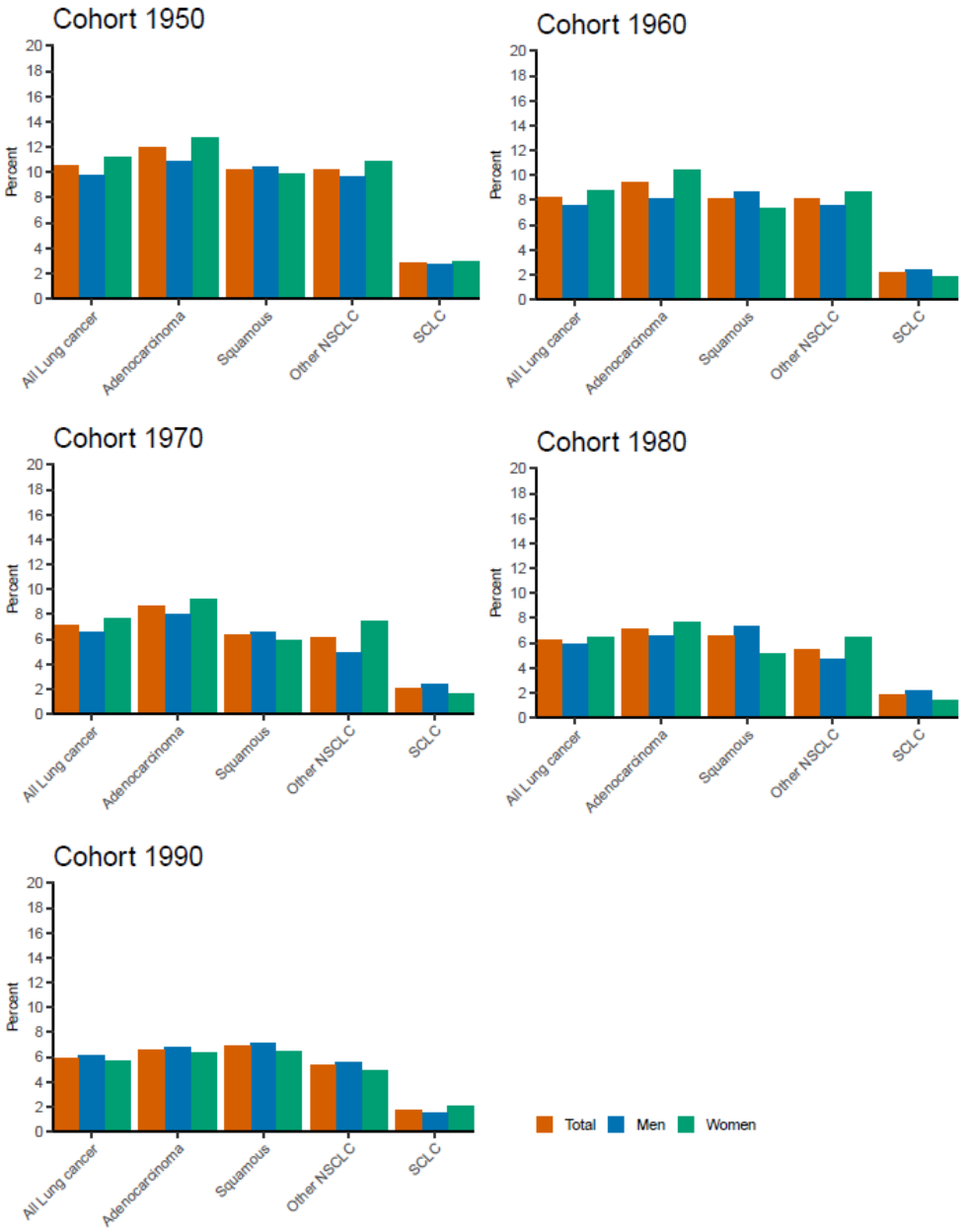
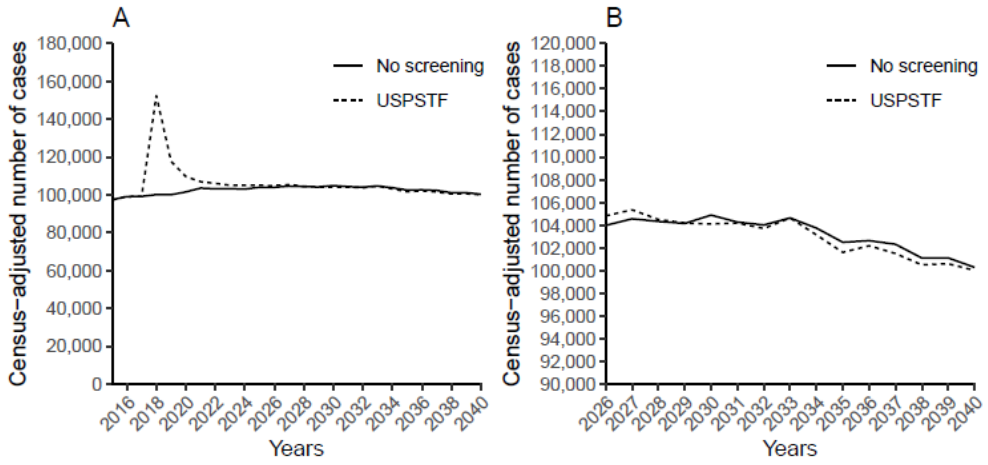
Chapter 4

Supplementary Figures

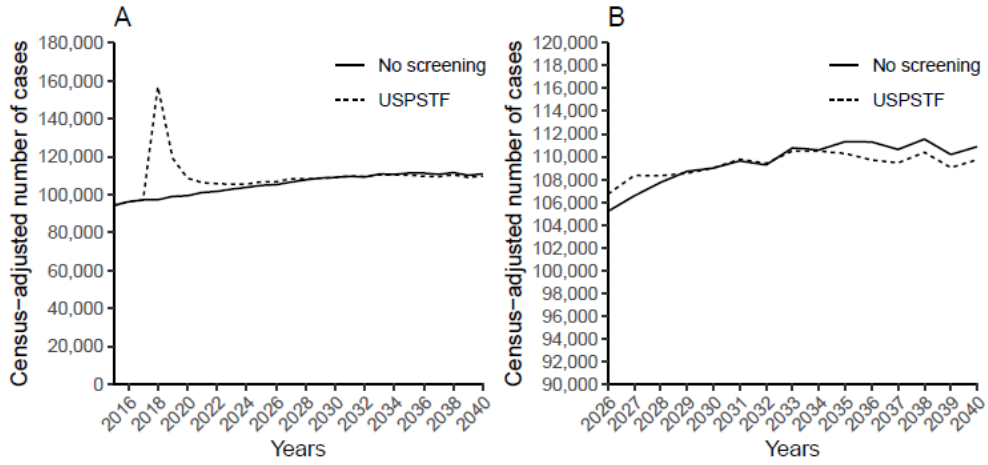


Supplementary Figure 1: Lifetime percentage of screen-detected cases that were overdiagnosed using the cumulative excess-incidence approach by histology, sex, and birth-cohort
Abbreviations: NSCLC = non-small cell lung cancer; SCLC = small cell lung cancer.

For men:

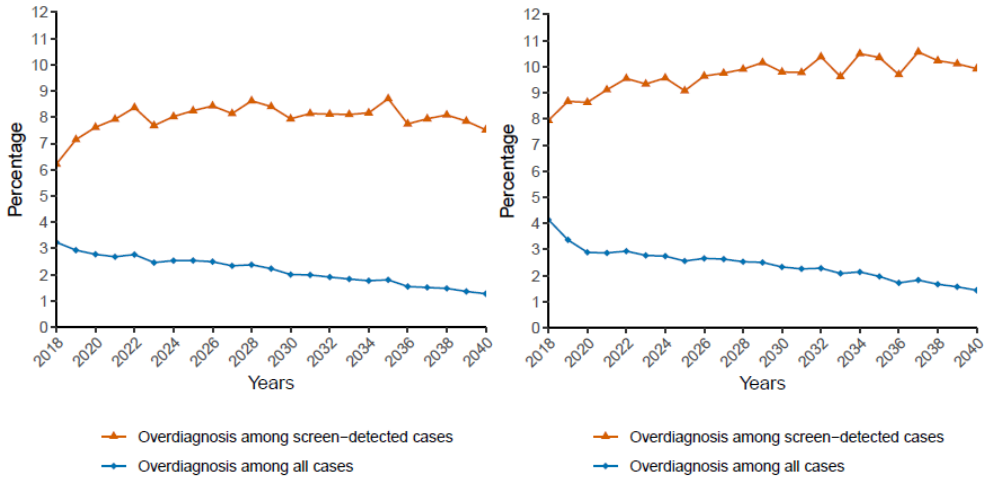


For women:



Supplementary Figure 2: A) Census-adjusted annual lung cancer incidence count in the general United States population between 2015-2040 when fully implementing lung cancer screening using the United States Preventive Task Force eligibility criteria in 2018, by sex. B) Detail of panel A for years 2026-2040.

For men: **For women:**



Supplementary Figure 3. Annual percentage of overdiagnosed lung cancer cases in the United States between 2018-2040 when fully implementing lung cancer screening using the United States Preventive Task Force eligibility criteria in 2018. The percentage of overdiagnosis among screen-detected cases was calculated by dividing the Census-adjusted number of overdiagnosed cases by the Census-adjusted number of screen-detected cases in each year. The percentage of overdiagnosis among all cases was calculated by dividing the Census-adjusted number of overdiagnosed cases by the Census-adjusted overall incidence count in the presence of screening in each year.

Chapter 5

Systematic Review and Meta-Analysis of Community- and Choice-Based Health State Utility Values for Lung Cancer

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Kevin ten Haaf
Harry J. de Koning

PharmacoEconomics 2020

Abstract

Background

Using appropriate health state utility values (HSUVs) is critical for economic evaluation of new lung cancer interventions, such as low-dose computed tomography screening and immunotherapy. Therefore, we provide a systematic review and meta-analysis of community and choice-based HSUVs for lung cancer.

Methods

On March 6, 2017, we conducted a systematic search in Embase, Ovid Medline, Web of Science, Cochrane CENTRAL, Google Scholar, and the School of Health and Related Research Health Utility database. The search was updated on April 17, 2019. Studies reporting mean or median lung cancer specific HSUVs including a measure of variance were included, and assessed for relevance and validity. Studies with high relevance (i.e. community and choice-based) were further analyzed. Mean HSUVs were pooled using random effects models for all stages, stages I-II, and stages III-IV. For studies with a control group, we calculated the disutility due to lung cancer. A sensitivity analysis included only the methodologically most comparable studies (i.e. using the EQ-5D instrument and matching tariff). Subgroup analyses were conducted by time-to-death, histology, sex, age, treatment modality, treatment line, and progression status.

Results

Twenty-seven high-relevance studies were identified and analyzed. The pooled HSUV was 0.68 (95%CI=0.61-0.75) for all stages, 0.78 (95%CI=0.70-0.86) for stages I-II, and 0.69 (95%CI=0.65-0.73) for stages III-IV (p=.02 compared to stage I-II). Heterogeneity was present in each pooled analysis ($p<.01; I^2=92\%-99\%$). Disutility due to lung cancer ranged from 0.11 (95%CI=0.05-0.17) to 0.27 (95%CI=0.18-0.36). In the sensitivity analysis with the methodologically most comparable studies, stage-specific HSUVs varied by country. Such studies were only identified for Canada, China, Spain, the United Kingdom, the United States, Denmark, Germany, and Thailand. In the subgroup analysis by time-to-death, HSUVs for metastatic non-small cell lung cancer ranged from 0.83 (95%CI=0.82-0.85) at ≥360 days from death to 0.56 (95%CI=0.46-0.66) at <30 days from death. Among patients with metastatic non-small cell lung cancer, HSUVs were lower for those receiving third or fourth line treatment and for those with progressed disease. Results of subgroup analyses by histology, sex, age, and treatment modality were ambiguous.

Conclusions

The presented evidence supports the use of stage and country-specific HSUVs. However, such HSUVs are unavailable for most countries. Therefore, our pooled HSUVs may provide the best available stage-specific HSUVs for most countries. For metastatic non-small cell lung cancer, adjusting for the decreased HSUVs in the last year of life may be considered, as well as further stratification of HSUVs by treatment line or progression status. If required, HSUVs for other health states may be identified using our comprehensive breakdown of study characteristics.

Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide.[1] New interventions, such as low-dose computed tomography screening[2] and immunotherapy,[3] may reduce this burden.

For policy makers, it is important to weigh the balance between benefits and costs of such new interventions in an economic evaluation. Economic evaluations often express health benefits in terms of quality-adjusted life years. This measure adjusts the life-years gained by a new intervention (compared to current practice) for health-related quality of life (HRQoL) by using health state utility values (HSUVs). HSUVs are weights ranging from 0 to 1, with 0 representing death and 1 representing full health. In some cases, values below 0 are used to represent health states worse than death.

HSUVs can be elicited by a variety of methods. First, patients can be asked to directly value their own HRQoL. Valuation can be done using the choice-based time trade-off (TTO) or standard gamble (SG) methods, or the non-choice-based visual analogue scale (VAS). In simple terms, choice-based methods determine what respondents would be willing to give up or risk to avoid living in that health state. There are also indirect elicitation methods, such as asking patients to complete a generic (i.e. applicable across different diseases) multi-attribute instrument. Examples of such generic instruments are the EQ-5D, Short-Form Six Dimensions (SF-6D), and Assessment of Quality of Life (AQoL). Based on their answers, each patient is assigned a health state, which has been valued by members of the general public. These predetermined valuation sets are called the tariff. Another indirect elicitation method is drafting vignettes which describe a patient's HRQoL, and then asking persons to value these vignettes. Finally, some studies have attempted to convert other HRQoL measures (such as the condition-specific European Organization for Research and Treatment of Cancer Quality of Life Questionnaire) to an existing generic multi-attribute instrument without using a valuation method. This practice is called mapping.

Most international guidelines, including those from National Institute for Health and Care Excellence, prefer that the HRQoL of actual patients is valued by members of the general public (i.e. community-based), using choice-based methods.[4-6] For reasons of comparability (e.g. across studies or diseases), the preferred instrument in most guidelines is the EQ-5D.[5,6]

Because of the broad variation in elicitation methods, HSUVs for lung cancer have been reported to vary drastically across the literature.[7] Using different HSUVs can lead to different policies being ranked as cost-effective.[8] Therefore, it is important to systematically identify appropriate and high-quality HSUVs for economic evaluations.[9]

Although earlier studies attempted to provide an overview of HSUVs for lung cancer, these only included metastatic non-small cell lung cancer cases,[10] were not systematic reviews,[7] did not include an overview of study characteristics nor a critical appraisal,[7,10] and did not provide a pooled set of methodologically high-quality HSUVs.[7,10] Therefore, we aimed to provide a current systematic review of HSUVs for all types of lung cancer, including an overview of study characteristics and a critical

appraisal, and a pooled set of community and choice-based HSUVs for use in economic evaluations.

Materials and methods

Study protocol

The protocol for this study was prospectively registered in the PROSPERO database under reference number CRD42018081495.[11] This study was undertaken in concordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement,[12] the Cochrane Handbook for Systematic Reviews,[13] the good practices report by the International Society for Pharmacoeconomics and Outcomes Research entitled "Identification, Review, and Use of Health State Utilities in Cost-Effectiveness Models",[9] a similar Technical Support Document developed for the National Institute for Health and Care Excellence,[14] and recent guidance published in PharmacoEconomics.[15]

Search strategy

A broad and systematic search was conducted in the Embase, Ovid Medline, Web of Science, Cochrane CENTRAL, Google Scholar, and the School of Health and Related Research Health Utility Database (ScHARRHUD) databases on March 6, 2017, and updated on April 17, 2019. In short, synonyms for "lung cancer" were combined with synonyms for the following: "health state utility values", "quality of life", different analyses, methods and instruments suitable for eliciting HSUVs, and different valuation techniques. Conference abstracts, letters, notes, commentaries and editorials were excluded. The complete syntax is provided in the Supplementary Methods.

Study selection

We used Endnote X9 software to remove duplicates.[16] The first and second authors screened titles and abstracts of all initial references according to a pre-specified algorithm, which was designed to broadly identify studies which may report lung cancer-specific HSUVs elicited using any technique (see the Supplementary Methods). In short, references were selected when the title or abstract indicated that (1) study results were likely lung cancer-specific; and (2) HSUVs were measured, or HRQoL was measured using an instrument suitable to elicit HSUVs, or HRQoL scores from another instrument were mapped onto a utility scale, or HRQoL was measured and the use of a valuation method was mentioned, or the study was a cost-utility analysis, or the study was a quality-adjusted survival study. Those references included by only one of both reviewers were discussed until reaching consensus. References added after the search update were only screened by the first author.

The full text of selected articles was subsequently screened by the first author according to a second pre-specified algorithm (see the Supplementary Methods) and

discussed with the second author. In short, studies were included for critical appraisal if the full text reported at least one original (i.e. not previously published) lung cancer specific mean or median HSUV including a measure of variance. Only studies written in English or Dutch language were considered. Conference abstracts were not considered because often only preliminary, incomplete, or non-peer-reviewed data are presented. Secondary literature (e.g. literature reviews and cost-utility analyses that sourced HSUVs from the literature) was excluded, but checked for cross-references. Articles selected for full text screening were also checked for cross-references.

Data extraction and critical appraisal

A digital data extraction form was developed in Microsoft Excel 2016, piloted on six studies, and subsequently refined. First, study characteristics were extracted for use in a critical appraisal. We developed a custom critical appraisal tool for assessing the relevance and validity of the selected studies, based on HSUV-relevant items from several established tools and good practices reports.[9,14,17-19] In concordance with most international guidelines, study relevance was deemed high if HRQoL was measured in actual patients, while a choice-based method was used by members of the general public to value to HSUVs (i.e. elicitation was community and choice-based).[6] Studies that scored insufficiently on any of these relevance items were excluded from subsequent analyses. This approach prioritizes consistency of the methodology across studies.[9]

For the remaining studies, all study characteristics that may affect HSUVs were extracted and summarized. If a single study (or multiple studies using the same data) applied different tariffs to the same HRQoL data, only the analysis that applied the matching tariff was extracted (i.e. the tariff matching the country of participants from whom HRQoL was measured). Similarly, if a single study applied multiple instruments to the same patients, only the most commonly preferred instrument was extracted. In accordance with several international guidelines, including those of the National Institute for Health and Care Excellence, the EQ-5D was preferred, followed by other generic preference-based instruments, and finally any remaining methods.[5,6] Again, this approach prioritizes consistency of methodology across studies. Data extraction was done by the first author and subsequently discussed with the second author.

Meta-analysis and statistical methods

All studies remaining after critical appraisal were included in subsequent analyses, if appropriate. Mean or median HSUVs and standard errors were extracted. If standard errors were not available these were calculated using available information.[13] In case median HSUVs were reported, standard deviations were estimated by dividing the interquartile range by 1.35.[13] Then, the estimated standard deviation was used to calculate the standard error. For studies that reported HSUVs for a control group of the general population, we formally tested the disutility due to lung cancer using a

t-test, assuming unequal variances. For mapping studies, we extracted the observed HSUV data, if available.

If necessary, we first pooled mean HSUVs across strata within studies using a fixed effects model.[20,21] For studies measuring HSUVs at multiple time-points in the same individuals, we only extracted and pooled the HSUV at the time point closest to baseline to avoid violating the assumption of independence of observations.[22,23]

As clinical and study characteristics were expected to vary across studies,[7] HSUVs across the different studies were then pooled using a random effects model.[20,24] To account for possible differences in HSUVs by stage,[7,25] results were separately pooled for studies reporting HSUVs for all stages, for stages I-II, and for stage III-IV. Differences between the pooled HSUVs for stage I-II and stage III-IV were formally tested using a t-test, assuming unequal variances.

The study selection based on our critical appraisal accounts for several potential sources of heterogeneity, including the respondent type (i.e. only patients),[7] the elicitation method (i.e. only indirect), the valuation method (i.e. only community and choice-based),[7,25,26] and the upper bound of the utility scale (i.e. only perfect health).[7] To account for further sources of heterogeneity, a sensitivity analysis pooled HSUVs only across those studies that explicitly used the EQ-5D-3L instrument. A second sensitivity analysis included only studies that used the EQ-5D instrument (regardless of the version), while also applying the tariff matching the country of HRQoL respondents.[9,27,28] This second sensitivity analysis aimed to provide the methodologically most comparable HSUVs for each available country. We further conducted exploratory subgroup analyses by histology (non-small cell vs. small cell),[7] sex,[27] age,[27] treatment modality, treatment line, and progression status. Results of the second sensitivity analysis and the different subgroup analyses were not pooled because of the anticipated low numbers of studies within each group.

Meta-analysis was performed in R software version 3.6.1[29] using the meta[30] and metafor[31] packages. We did not assess the risk of publication bias in a funnel plot, which is recommended in the PRISMA checklist for systematic reviews,[12] because this is not meaningful for continuous outcomes in a single group.

Results

Search strategy and study selection

After removing duplicates, our search included 5,828 studies. We further identified 13 studies by cross-referencing. After screening the titles and abstracts of all identified studies, we assessed the full text of 458 studies. Of those, 407 studies were excluded for reasons outlined in Figure 1. Hence, 51 studies were included in the critical appraisal.

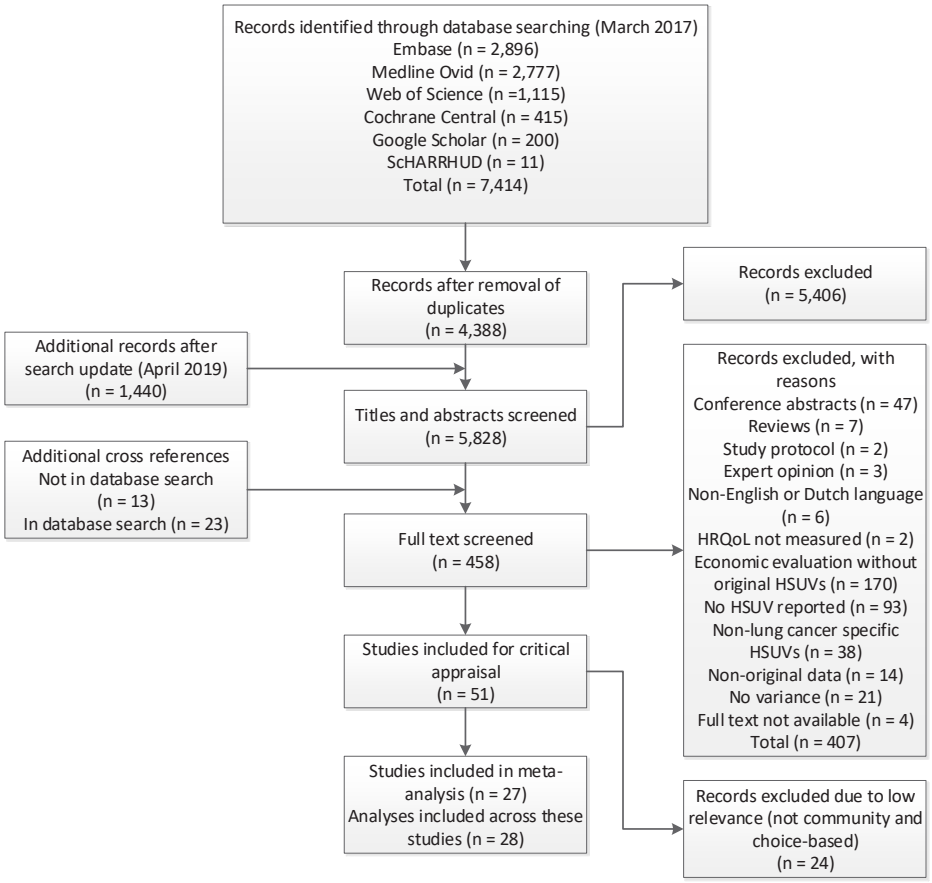

Figure 1: Flowchart of selection of studies reporting community and choice-based health state utility values for lung cancer. Abbreviations: HRQoL = health-related quality of life; HSUV = health state utility value; ScHARRHUD = School of Health and Related Research Health Utility Database.

Critical appraisal

The relevance of 27 out of 51 studies was high (see Supplementary Table 1).[32–58] Of these, one study separately analyzed two datasets,[36] which were treated as separate studies. The remaining 24 studies were excluded from subsequent analyses.[59–82] Among the excluded studies, 4 did not measure HRQoL in patients,[72,77,81,82] 9 did not use valuation by members of the general public,[59,60,63,69,71,72,74,81,82] 11 did not use a choice-based method for valuation,[59,63,65,67–71,74,76,81] and 9 had missing data on one or more of these items.[61,62,64,66,73,75,78–80]

Among included studies, the number of patients included for HSUV analysis ranged from 43 to 2396. Only 2 out of 27 studies clearly stated that missing HRQoL

data were imputed, or that HRQoL response was complete.[37,47] Six studies performed multiple HRQoL measurements in the same participants. In 2 of those studies, which used time-to-death categories, loss-to-follow-up was not reported.[57,58] These 2 studies were analyzed separately because the time since diagnosis could not be derived. The other 4 studies with repeated measures all reported loss to follow-up at each evaluated time-point.[40,46,50,52]

Study characteristics

Characteristics of the included studies are provided in Supplementary Tables 2a-2c. One study included only stage I and/or II cases,[47] while 13 studies included only stage III and/or IV cases.[35-39,44,45,48,49,51,52,57,58] However, 2 of these stage III-IV studies stratified HSUVs by time-to-death.[57,58] These studies were analyzed in a separate subgroup analysis. Among 13 studies that included all stages, 5 stratified HSUVs by stage.[33,34,40,42,46] Thus, the main analysis included 13 studies with HSUVs for all stages,[32-34,40-43,46,50,53-56] 6 studies with HSUVs for stages I-II,[33,34,40,42,46,47] and 17 analyses across 16 studies with HSUVs for stage III-IV.[33-40,42,44-46,48,49,51,52]

Mean time since diagnosis was reported in 8 of the included studies,[32,33,36,37,42,43,50,53] and ranged from 27 days to 2.59 years. All included studies used the EQ-5D instrument, except 1 study which used the AQoL instrument[40] and 2 studies which used the SF-6D instrument.[43,54] Among EQ-5D studies, 6 did not specify which version was used,[32,37,45,48,49,56] 1 used the new EQ-5D-5L version,[55] and 14 used the EQ-5D-3L version.[33-36,38,39,41,42,44,46,47,50,51,53] The 14 studies that explicitly used the EQ-5D-3L version were separately pooled in a sensitivity analysis. All EQ-5D studies and the AQoL study used the TTO method for valuation, whereas the SF-6D studies used the SG method. Only 3 studies collected data through a personal interview.[32,46,55] All studies reported mean HSUVs, except 1 study which reported median HSUVs.[40]

Thirteen out of 27 studies applied the tariff that matched the country of origin of the HRQoL respondents.[36,39-42,44-47,49,50,53,55] Out of these 13 studies, one did not use the EQ-5D instrument.[40] The remaining 12 studies, which comprised 13 analyses, were included in a second sensitivity analysis of the methodologically most comparable HSUVs for each country.[36,39,41,42,44-47,49,50,53,55]

Twelve studies included only non-small cell lung cancer cases.[33-38,41,47,49-52] The remaining studies included all lung cancer cases regardless of histology. Of these studies, 3 provided histology-specific HSUVs.[46,48,53] However, 1 of these studies included only cases with stage IIIb-IV lung cancer.[48] For reasons of comparability across studies, only the remaining 2 studies were included in a subgroup analysis by histology.[46,53]

The percentage of male patients ranged between 37 and 93. Five studies provided HSUVs stratified by sex.[33,40,46,48,53] However, 1 of these studies only included stage IIIb-IV lung cancer cases.[48] Thus, the remaining 4 studies were included in a subgroup analysis of HSUVs by sex.[33,40,46,53]

Mean or median age of patients ranged between 51 and 70. Five studies stratified HSUVs by age.[33,40,46,48,53] Two of those studies did not provide the number of patients in the different age groups.[48,53] Of the remaining three studies, which included all stages of lung cancer, two used similar age categories. These two studies were included in a

subgroup analysis of HSUVs by age.[40,46]

Thirteen studies allowed the derivation of treatment-specific HSUVs, either by inclusion criteria or by HSUV stratification.[33-39,44-47,49,53] However, only 7 of these studies allowed the derivation of HSUVs according to treatment modality (surgery, radiotherapy, chemotherapy, or a combination of those).[33,37,39,44,46,47,49] Of these 7 studies, 2 included all stages of lung cancer. Because the recommended treatment modality for lung cancer is mainly based on stage, a subgroup analysis of HSUVs by treatment modality was conducted using these 2 studies.[33,46] Only 1 study was identified that reported HSUVs by treatment line.[38] This study was included in a further subgroup analysis by treatment line.

We identified 2 studies reporting HSUVs by progression status.[38,49] Both studies included only metastatic non-small cell lung cancer patients. These studies were included in a subgroup analysis by progression status.

Health state utility values

Figure 2 provides an overview of HSUVs across all included studies. The pooled HSUV for all stages was 0.68 (95%CI=0.61-0.75) across 5,100 persons. HSUVs for all stages ranged from 0.51 (95%CI=0.49-0.53)[50] to 0.81 (95%CI=0.78-0.84),[43] indicating the presence of significant heterogeneity (p<.01). Most heterogeneity could not be attributed to sampling error (I^2=99%). For stages I-II, the pooled HSUV was 0.78 (95%CI=0.70-0.86) across 1,510 persons. There was significant heterogeneity across stage I-II studies (p<.01; I^2=92%), as results ranged from 0.62 (95%CI=0.51-0.72)[40] to 0.88 (95%CI=0.86-0.90).[47] The pooled HSUV for stage III-IV was 0.69 (95%CI=0.65-0.73) across 4,703 persons. The analysis of stage III-IV studies showed significant heterogeneity (p<.01; I^2=98%), with study results ranging from 0.51 (95%CI=0.48-0.54)[51] to 0.85 (95%CI=0.83-0.87).[39] The difference between the pooled HSUV for stage I-II and stage III-IV was statistically significant (p=.02). In a sensitivity analysis, only studies that explicitly used the EQ-5D-3L instrument were pooled (see Supplementary Figure 1). In this sensitivity analysis, the pooled HSUVs were similar to those in the main analysis.

Figures 3-5 show the results of the sensitivity analysis of the 12 methodologically most comparable studies, which excluded non-EQ-5D studies and studies which did not apply the matching tariff matching the country of HRQoL respondents. All of these studies used TTO for valuation. For all stages, mean HSUVs ranged from 0.51 (95%CI=0.49-0.53) in Spain[50] to 0.78 in the United States (95%CI=0.77-0.79)[46] and Canada (95%CI=0.74-0.82)[42] (see Figure 3). For stages I-II, results ranged from 0.78 (95%CI=0.74-0.82) for Canada[42] to 0.88 (95%CI=0.86-0.90) for Denmark[47] (see Figure 4). For stage III-IV, the range was 0.61 (95%CI=0.59-0.63) for a study in the United Kingdom[36] to 0.85 (95%CI=0.83-0.87) in Germany[39] (see Figure 5).

Among the 2 studies reporting HSUVs for patients with metastatic non-small cell lung cancer by time-to-death,[57,58] HSUVs decreased consistently throughout the last year of life (see Figure 6). HSUVs ranged from 0.83 (95%CI=0.82-0.85) at ≥ 360 days from death to 0.56 (95%CI=0.46-0.66) at <30 days from death. Both studies were U.S.-based and used the EQ-5D instrument with TTO valuation.

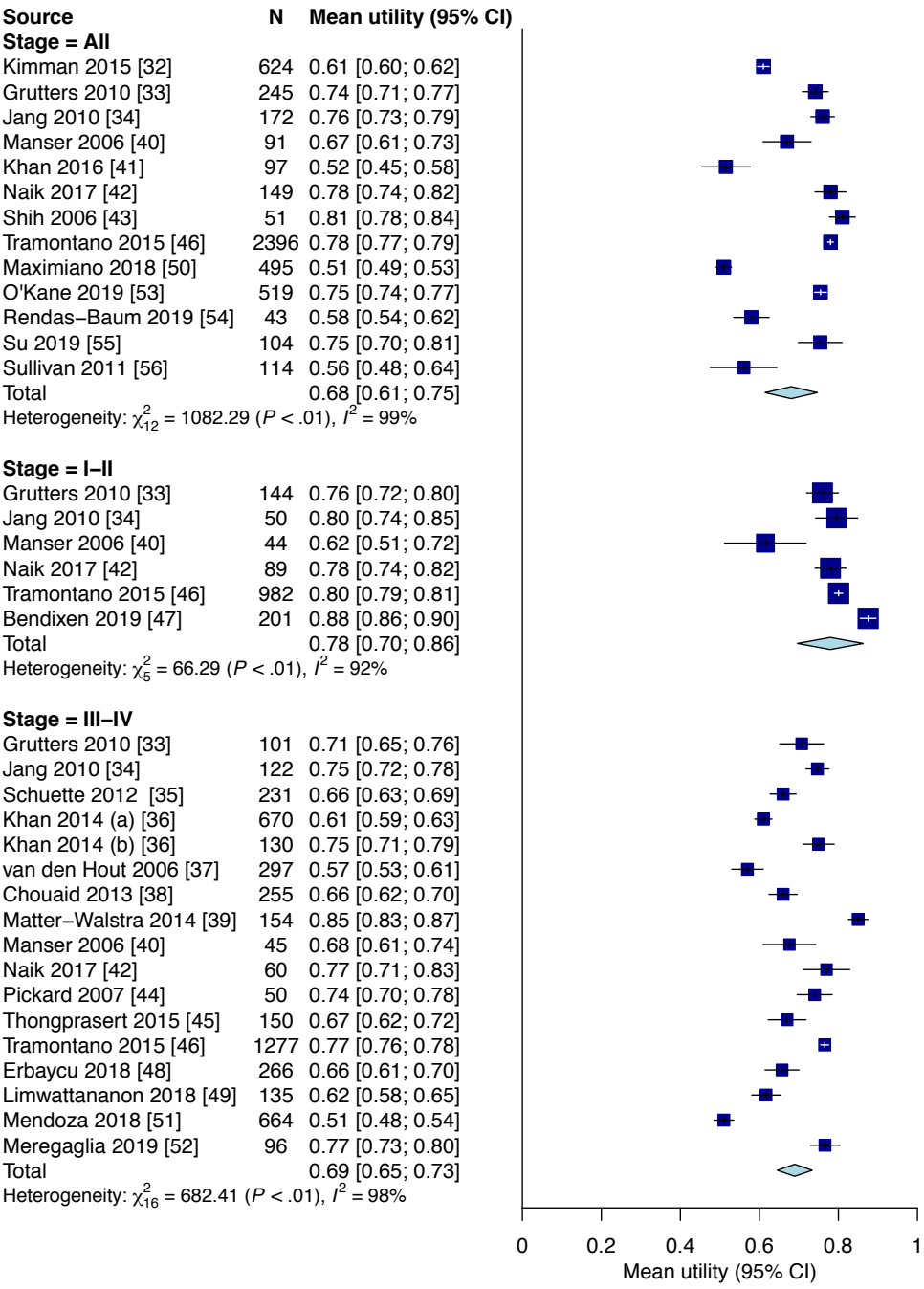

Figure 2: Pooled results of studies reporting community and choice-based health state utility values for lung cancer by stage. The size of the symbol representing the effect size in each study is relative to the weight it had in random effects meta-analysis. Not all studies included both

stage I-II and stage III-IV cases. Not all studies that did include all stages stratified by stage. The total number of persons contributing to the pooled value for all stages was 5100; for stages I-II, the total number was 1510; and for stages III-IV, the total number was 4703. The difference between the pooled values for stages I-II and III-IV was statistically significant (p=.02). Arabic numerals between square brackets next to author names refer to the reference list.

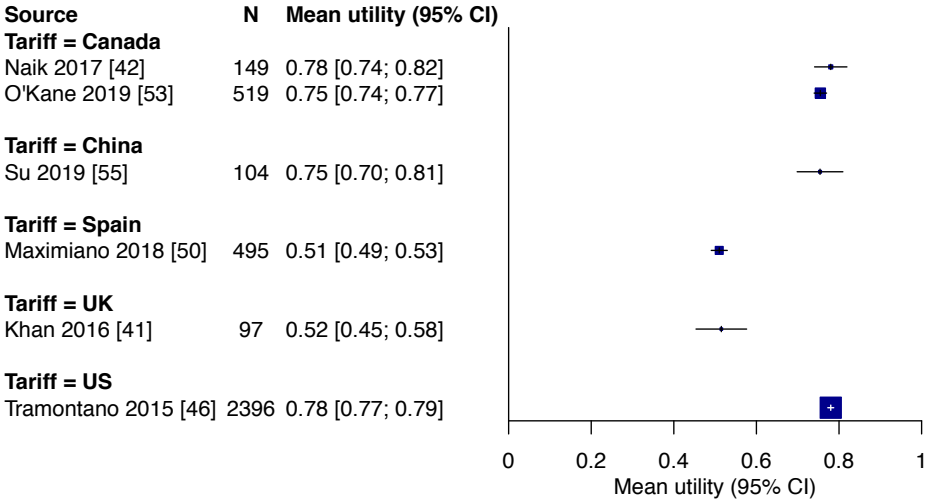

Figure 3: Results of sensitivity analysis including only the methodologically most comparable studies reporting community and choice-based health state utility values for all stages of lung cancer**.** Studies included in this sensitivity analysis used the EQ-5D instrument and applied the tariff matching the country of responding patients. Pooling results for this sensitivity analysis using a random effects model was not possible due to the small number of studies within subgroups. The size of the symbol representing the effect size in each study is relative to the weight it would have in fixed effects meta-analysis (i.e. relative to the inverse of its variance). Arabic numerals between square brackets next to author names refer to the reference list. Abbreviations: UK = United Kingdom; US = United States.

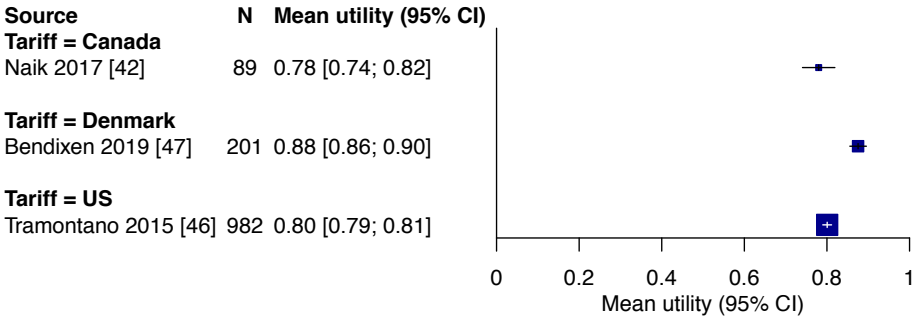

Figure 4: Results of sensitivity analysis including only the methodologically most comparable studies reporting community and choice-based health state utility values for stage I-II lung cancer. Studies included in this sensitivity analysis used the EQ-5D instrument and applied the tariff matching the country of responding patients. Pooling results for this sensitivity analysis using a random effects model was not possible due to the small number of studies within subgroups. The size of the symbol representing the effect size in each study is relative to the weight it would have in fixed effects meta-analysis (i.e. relative to the inverse of its variance). Arabic numerals between square brackets next to author names refer to the reference list. Abbreviations: US = United States.

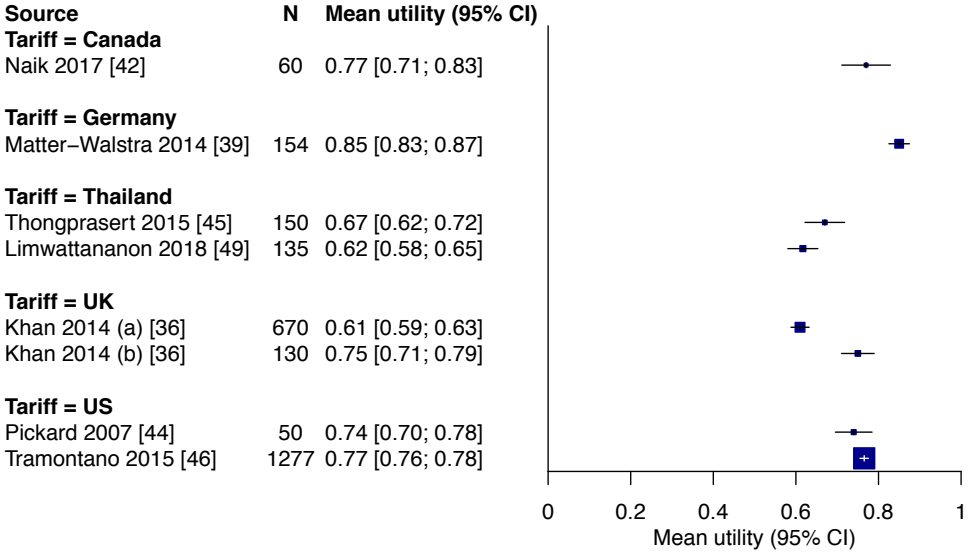

Figure 5: Results of sensitivity analysis including only the methodologically most comparable studies reporting societal choice-based health state utility values for stage III-IV lung cancer. Studies included in this sensitivity analysis used the EQ-5D instrument and applied the tariff matching the country of responding patients. Pooling results for this sensitivity analysis using a random effects model was not possible due to the small number of studies within subgroups. The size of the symbol representing the effect size in each study is relative to the weight it would

have in fixed effects meta-analysis (i.e. relative to the inverse of its variance). Arabic numerals between square brackets next to author names refer to the reference list. Abbreviations: UK = United Kingdom; US = United States.

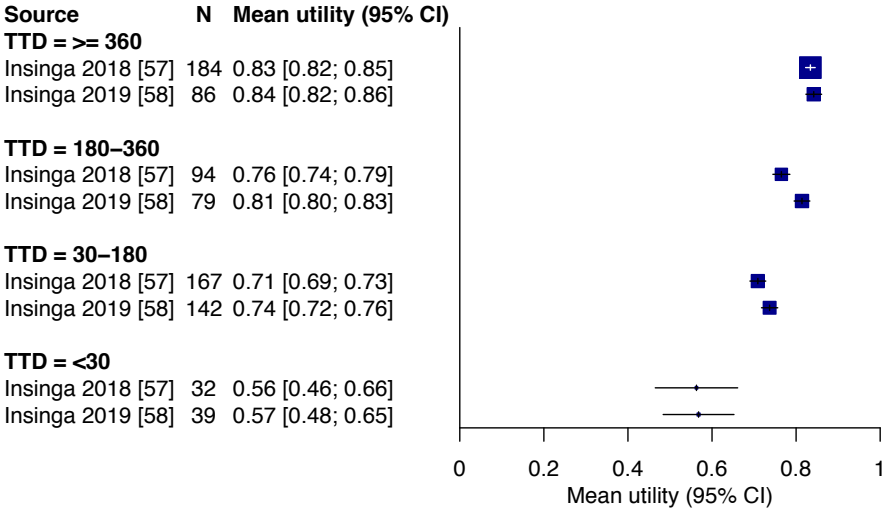

Figure 6: Results of studies reporting community and choice-based health state utility values for lung cancer by time-to-death. Patients could contribute to multiple time-to-death categories. Therefore, an overall pooled result could not be provided. The size of the symbol representing the effect size in each study is relative to the weight it would have in fixed effects meta-analysis (i.e. relative to the inverse of its variance). Arabic numerals between square brackets next to author names refer to the reference list. Abbreviations: TTD= time-to-death, expressed in days.

Results for the subgroup analysis by histology are shown in Supplementary Figure 2. The included studies both used the EQ-5D instrument with TTO valuation.[46,53] The HSUV for non-small cell lung cancer was similar in the U.S.-based study by Tramontano and colleagues and the Canadian study by O'Kane and colleagues. In the U.S.-based study, the HSUV for non-small cell lung cancer (0.78 (95%CI=0.77-0.79)) was marginally higher than the HSUV for small cell lung cancer (0.76 (95%CI=0.74-0.78)). In the smaller Canadian study, there was a more substantial difference in HSUV between non-small cell lung cancer (0.77 (95%CI=0.76-0.79)) and the HSUV for small cell lung cancer (0.63 (95%CI=0.56-0.70)).

As shown in Supplementary Figure 3, HSUVs for men did not differ substantially across the four studies included in the subgroup analysis by sex.[33,40,46,53] HSUVs for men ranged from 0.72 (95%CI=0.66-0.78) in the Australian study by Manser and colleagues, which applied the AQoL instrument with TTO valuation,[40] to 0.78 (95%CI=0.77-0.79) in the U.S.-based study by Tramontano and colleagues, which applied the EQ-5D instrument with TTO valuation.[46] In three of these studies, the HSUV for men was

similar to the HSUV for women, which ranged from 0.73 (95%CI=0.69-0.77) in the study by Grutters and colleagues, which applied the EQ-5D instrument to Dutch patients using the U.K. TTO valuation set,[33] to 0.77 (95%CI=0.76-0.78) in the U.S.-based study by Tramontano and colleagues.[46] However, the Australian study by Manser and colleagues[40] reported substantially lower HSUV for women (0.52 (95%CI=0.44-0.60)).

Results for the subgroup analysis by age are shown in Supplementary Figure 4. In both age groups, HSUVs were higher in the U.S.-based study by Tramontano and colleagues, which applied the EQ-5D instrument with TTO valuation,[46] compared with the Australian study by Manser and colleagues, which applied the AQoL instrument with TTO valuation.[40] In both of the included studies, the HSUV for patients younger than 65 years was marginally lower than the HSUV for patients older than 65 years. For example, in the U.S. based study, the HSUV for those younger than 65 years was 0.76 (95%CI=0.75-0.77), compared with 0.80 (95%CI=0.79-0.81) for those older than 65 years.[46]

Supplementary Figure 5 shows the results for the subgroup analysis by treatment modality. In the Dutch study by Grutters and colleagues,[33] which used the EQ-5D instrument with the U.K. TTO valuation set, HSUVs ranged from 0.62 (95%CI=0.51-0.73) among those receiving radiotherapy only to 0.86 (95%CI=0.76-0.96) among those receiving surgery with radiotherapy. In the U.S.-based study by Tramontano and colleagues, which also applied the EQ-5D instrument with TTO valuation, HSUVs ranged from 0.72 (95%CI=0.67-0.77) among those receiving surgery and radiotherapy to 0.81 (95%CI=0.80-0.82) among those receiving surgery only.[46]

HSUVs by treatment line are shown in Supplementary Figure 6. Only 1 study was included in this subgroup analysis.[38] This study applied the EQ-5D instrument to a multinational selection of patients with metastatic non-small cell lung cancer and applied the U.K. TTO tariff. The HSUV was 0.70 (95%CI=0.66-0.74) for the first treatment line, 0.73 (95%CI=0.67-0.78) for the second treatment line, and 0.57 (95%CI=0.47-0.66) for the third and fourth treatment lines.

Supplementary Figure 7 shows the results for the subgroup analysis of HSUVs by progression status.[38,49] Both studies included patients with metastatic non-small cell lung cancer and used the EQ-5D instrument. The multinational study by Chouaid and colleagues applied the U.K. TTO tariff to all patients,[38] whereas the Thai study by Limwattanon and colleagues applied the matching Thai TTO tariff.[49] In both studies, the HSUV for the "progression free" health state was similar; 0.70 (95%CI=0.66-0.74) in the study by Chouaid and colleagues[38] compared with 0.68 (95%CI=0.62-0.74) in the study by Limwattanon and colleagues.[49]. In the study by Chouaid and colleagues,[38] the HSUV for the "progressive" health state (0.58 (95%CI=0.50-0.66)) was substantially lower than the HSUV for the "progression free" health state (0.70 (95%CI=0.66-0.74). This was also the case for the study by Limwattanon and colleagues,[49] although the 95%CI for the "progressive disease" health state was wide.

Finally, Supplementary Table 3 shows the results for the 2 studies that included a control group of members of the general population.[45,56] Both studies applied the EQ-5D instrument with TTO valuation. The difference in HSUV between lung cancer cases and controls (i.e. disutility) was 0.11 (95%CI=0.05-0.17) in Thailand,[45] and 0.27 (95%CI=0.18-0.36) in the study applying the U.K. tariff to HRQoL data from U.S. patients.[56] In both studies, the disutility due to lung cancer was statistically significant ($p<0.01$).

Discussion

To our knowledge, we are the first to provide a systematic review and meta-analysis of community and choice-based HSUVs across all stages of lung cancer. Our pooled results show that the mean HSUV across the literature for stage I-II lung cancer (0.78; 95%CI=0.70-0.86) is statistically significantly higher than the mean HSUV for stage III-IV lung cancer (0.69; 95%CI=0.65-0.73). This makes sense, as stage I-II lung cancer can often be treated with curative intent, whereas metastatic disease (stage III-IV) often requires an ongoing palliative treatment with chemotherapy and/or radiotherapy.[83] The pooled HSUV for all stages (0.68; 95%CI=0.61-0.75) was close to that of stage III-IV, which can be explained by the fact that lung cancer is most often diagnosed at stage IV.[84]

While these pooled stage-specific HSUVs provide an overall mean HSUV across the literature, significant heterogeneity was present in all three stage groups, which could not be explained by sampling error. In our sensitivity analysis that included only the methodologically most comparable studies, the most important study characteristics were the same (i.e. respondent type, stage of disease, elicitation method, instrument, valuation method, valuation population, and upper bound of the utility scale). Furthermore, these studies applied the tariff that matches the country of responding patients, which further reduces potential heterogeneity. Among these studies, stage-specific HSUVs strongly differed by country (and thus by tariff). Such studies were only identified for 8 countries: Canada, China, Spain, the United Kingdom, the United States, Denmark, Germany, and Thailand. If stage-specific HSUVs provide sufficient granularity, authors of future economic evaluations of lung cancer interventions conducted in one of these 8 countries may consider using HSUVs from the corresponding study identified in this sensitivity analysis. For example, a study seeking to investigate the cost-effectiveness of lung cancer screening in the United States could use the stage-specific HSUVs from the study by Tramontano and colleagues.[46] However, for most countries no such studies were identified. In addition, some authors may prioritize maximizing the use of available data over selecting one methodologically optimal study. In both cases, our pooled analysis may provide the best available stage-specific HSUVs.

For some economic evaluations, stage-specific HSUVs may not provide sufficient granularity. For example, further stratification of HSUVs for metastatic lung cancer may be sought by treatment line or progression status. Subgroup analyses indicated that HSUVs for patients with metastatic non-small cell lung cancer may indeed be lower among those with progressed disease and among those undergoing third or fourth line of treatment. Further exploratory subgroup analyses by histology, sex, age, and treatment modality did not provide unambiguous evidence for differences in HSUVs by these variables. For example, there were differences in HSUVs across treatment modalities within studies. However, the recommended and provided treatment modalities for lung cancer are mainly based on stage,[85] which may partly explain these differences. In addition, results were inconsistent across studies. For example, receiving surgery with radiotherapy was associated with the lowest HSUV in one study, but with the highest HSUV in another study. In general, few studies were available with the required level of granularity for each of the conducted subgroup

analyses, reflecting the need for more high quality research. The lack of clear evidence regarding the effect of histology, sex, age, and treatment modality on HSUVs provides additional support for our suggestion to use stage-specific (and if available, country-specific) HSUVs, if possible. Still, if authors of economic evaluations require HSUVs for other health states, Supplementary Tables 2a-2c provide a comprehensive breakdown of patient characteristics, methodological characteristics, and the stratification variables used in each of the included studies. These tables may be used to identify specific studies meeting the needs of such analyses.

We only identified two relevant studies that included a matched control group. In these studies, the disutility due to lung cancer was 0.11 (95%CI=0.05-0.17), and 0.27 (95%CI=0.18-0.36), respectively. For comparison, the minimally important difference in EQ-5D HSUVs (defined as the smallest change that is perceived by patients as beneficial or that would result in a change in treatment) has been estimated to be 0.06 for the U.S. and 0.08 for the U.K.[44,86] It is important that more future HSUV studies include an adequately matched control group of members of the general population. Otherwise, the disutility due to lung cancer could be overestimated, as members of the general public do not have perfect health.[27,56]

Strengths and limitations

A major strength of our study is the inclusion of both non-small cell lung cancer and small cell lung cancer, regardless of stage, whereas a previous review included only advanced non-small cell lung cancer cases.[10] Our search strategy, which was constructed in collaboration with an information specialist, was also a major strength. We screened almost 6000 abstracts and over 450 full text articles, identifying 51 peer-reviewed studies reporting original HSUVs. Through this search strategy, we identified a broader range of relevant studies compared with two earlier reviews. The first, which was not a systematic review, screened 147 abstracts, yielding 22 studies [7]. The second screened 1832 abstracts, yielding 34 inclusions, of which 16 appeared to be non-peer-reviewed conference abstracts (for some of these abstracts, we identified and included the full study). In addition, we included a thorough assessment of study characteristics, relevance, and validity, which allowed us to focus on comparable studies presenting the preferred community and choice-based HSUVs. In contrast, the two previous reviews included studies regardless of quality and methodology, including expert opinions.[7,10]

Due to the large number of identified studies and the assessment of study characteristics, we were able to select the methodologically most comparable community and choice-based HSUV studies. Therefore, we could control for the most important factors that may affect HSUVs without relying on meta-regression, which can be prone to false positive associations.[87] Nevertheless, heterogeneity remained present across the identified studies. These differences may be due to additional factors that we were not able to fully control for.

First, the time of measurement relative to diagnosis or treatment may influence HSUVs.[25,28] Unfortunately, we could not account for this possible effect in our main analysis. Many of the included studies in our meta-analysis did not report the mean

time between diagnosis and HSUV measurement. Also, while 4 out of 27 studies measured HSUVs at multiple time-points in the same patients, we could only include a single time-point in our main analysis to avoid violating the assumption of independent observations. For those studies, we included the observation closest to baseline to limit the variability of time-points across studies. Despite these limitations, the subgroup analysis by time-to-death showed that HSUVs for metastatic non-small cell lung cancer tend to decrease during the last year of life. In particular, HSUVs had decreased by approximately a third by the last month of life. A possible way to adjust for this effect in economic evaluations is to proportionally adjust the chosen HSUV for metastatic disease during the last phase of life.

Second, it can be difficult to disentangle the effects of some variables, even when comparing methodologically similar studies. For example, one of the studies in our meta-analysis reported HSUVs for two U.K.-based trials.[36] Both trials measured HRQoL in stage III-IV non-small cell lung cancer patients using the EQ-5D instrument, and valued using the U.K. TTO tariff. However, the mean HSUV was 0.61 (95%CI:0.59-0.63) in the first trial and 0.75 (95%CI:0.71-0.79) in the second trial. The mean age of participants was 77 years in the first trial and 62 years in the second trial. Also, participants in the first trial received erlotinib or placebo, whereas patients in the second trial received radiotherapy and chemotherapy. Therefore, both age and treatment may have driven these markedly different HSUVs. Unfortunately, reporting and stratification of HSUVs was inconsistent across studies in our meta-analysis, which limited the ability to disentangle such effects.

Conclusions

The presented evidence supports the use of stage-specific HSUVs for lung cancer. In addition, it supports the use of country-specific HSUVs. However, stage-specific HSUVs were not available for many countries. Therefore, our pooled HSUVs may provide the best available stage-specific HSUVs for most countries. For metastatic non-small cell lung cancer, adjusting for the decreasing HSUVs in the last year of life may be considered. Based on a limited number of studies, further stratification of HSUVs for metastatic non-small cell lung cancer by treatment line or progression status may also be considered. There is currently little evidence supporting the use of histology, sex, age, or treatment modality-specific HSUVs. Still, if HSUVs for other health states are required, our comprehensive breakdown of study characteristics can help identify suitable studies.

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Chapter 5

Supplementary Methods

Search Query

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('lung cancer'/de OR 'lung carcinoma'/de OR (((lung OR pulmonar*) NEAR/6 (cancer* OR carcino* OR neoplas*))):ab,ti) AND ('quality of life'/exp/mj OR 'quality of life assessment'/de/mj OR 'cost utility analysis'/de OR 'cost benefit analysis'/de OR 'quality adjusted life year'/exp OR 'vignette'/de OR 'visual analog scale'/de OR ((qualit* NEAR/3 life NEAR/6 (assess* OR measure*)) OR (utilit* NEAR/3 (cost OR Health OR value* OR scale*)) OR utilities OR qaly OR (cost NEAR/3 benefit*) OR eq-5d OR eq5d OR euroqol OR euro-qol OR hui OR ((sf or short-form) NEXT/1 (6 OR 12 OR 20 OR 36 OR thirtysix OR thirty-six OR twenty OR twelve OR six)) OR sf6* OR sf12* OR sf36* OR sf36* OR ((qualit*) NEAR/3 adjusted NEAR/3 (life-year* OR life-duration* OR life-expect* OR lifeyear*)) OR qaly* OR qald* OR qale* OR qtime* OR (qualit* NEAR/3 (well-being OR wellbeing)) OR qwb OR aqol OR 15d OR vignette* OR direct-elicitation* OR time-trade-off* OR time-tradeoff* OR tto OR standard-gamble* OR best-worst-scale* OR 'visual analog* scale' OR vas OR eortc-qlq-c30 OR fact-l OR hye OR hyes OR (health* NEAR/3 year* NEAR/3 equivalent*) OR (preference* NEAR/3 (state* OR score* OR value* OR valuat* OR weight)) OR hsuv OR hsuvs):ab,ti) NOT ([Conference Abstract]/lim OR [Letter]/lim OR [Note]/lim OR [Editorial]/lim)

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(exp "Lung Neoplasms"/ OR (((lung OR pulmonar*) ADJ6 (cancer* OR carcino* OR neoplas*))).ab,ti,kf.) AND (*"Quality of Life"/ OR "Cost-Benefit Analysis"/ OR "Quality-Adjusted Life Years"/ OR "Visual Analog Scale"/ OR ((qualit* ADJ3 life ADJ6 (assess* OR measure*)) OR (utilit* ADJ3 (cost OR Health OR value* OR scale*)) OR utilities OR qaly OR (cost ADJ3 benefit*) OR eq-5d OR eq5d OR euroqol OR euro-qol OR hui OR ((sf or short-form) ADJ (6 OR 12 OR 20 OR 36 OR thirtysix OR thirty-six OR twenty OR twelve OR six)) OR sf6* OR sf12* OR sf36* OR sf36* OR ((qualit*) ADJ3 adjusted ADJ3 (life-year* OR life-duration* OR life-expect* OR lifeyear*)) OR qaly* OR qald* OR qale* OR qtime* OR (qualit* ADJ3 (well-being OR wellbeing)) OR qwb OR aqol OR 15d OR vignette* OR direct-elicitation* OR time-trade-off* OR time-tradeoff* OR tto OR standard-gamble* OR best-worst-scale* OR "visual analog* scale" OR vas OR eortc-qlq-c30 OR fact-l OR hye OR hyes OR (health* ADJ3 year* ADJ3 equivalent*) OR (preference* ADJ3 (state* OR score* OR value* OR valuat* OR weight)) OR hsuv OR hsuvs).ab,ti,kf.) NOT (letter OR news OR comment OR editorial OR congresses OR abstracts).pt.

Cochrane CENTRAL

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Google scholar

"lung|pulmonary cancer|carcinoma|neoplasms" "quality* life assessment|measurement"|"cost|Health utility"|utilities|"quality adjusted life|lifeyear|lifeyears"

The School of Health and Related Research Health Utility Database (ScHARRHUD)

Lung cancer

Inclusion criteria for title/abstract screening

1a. Title/abstract reports the study includes specifically lung cancer patients
OR
1b. Title/abstract reports that results were stratified by cancer type **AND** (these cancer types include lung cancer **OR** keywords include "lung cancer")

AND one of the following

2a. Title/abstract reports health state utility values (HSUVs) (on a 0-1 scale) were measured or reported as an outcome
OR
2b. Title/abstract reports health-related quality of life (HRQoL) was measured **AND** the instrument used was reported **AND** the instrument used is suitable for the elicitation of HSUVs:

- EQ-5D (EuroQol five dimensions)
- SF-6D (Short-Form-6D) **OR** SF-12 **OR** SF-36
- HUI (Health utility Index; version 1,2 or 3)
- QWB (Quality of Well-Being)
- AQoL (Assessment of Quality of Life)
- 15D
- Vignettes
- Direct elicitation

OR
2c. Title/abstract reports HRQoL was measured (not including pain, nausea, or other symptoms) **AND** the use of a "valuation method" suitable for the elicitation of HSUVs was mentioned:

- Time trade-off (TTO)
- Standard gamble (SG)
- Best Worst Scale (BWS)
- Visual analogue scale (VAS)

OR
2d. Title/abstract reports the study type is a cost-utility analysis (thus using quality-adjusted life years (QALYs) and not only life years (LYs))
OR
2e. Title/abstract reports the study type is a quality adjusted-survival study (sometimes referred to as Q-TWiST)
OR
2f. Title/abstract reports HSUVs were mapped from an instrument not mentioned under item 2b (for example from a disease-specific measure, such as the EORTC-QLQ-C30), onto a utility scale (0-1)

Exclusion criteria for title/abstract screening:

- Animal studies
- Conference abstracts
- Editorials/commentaries/letters
- Reviews (systematic reviews/meta-analyses/overview articles)
- Study protocol
- Expert opinion (expert opinion was used without any instrument and/or valuation method)
- Guidelines
- Non-English or Dutch language
- Mesothelioma studies
- HRQoL not measured
- Studies with HRQoL measured as endpoint, but used instrument or valuation not mentioned in title/abstract **OR** used instrument or valuation mentioned, but other than listed under 2b and 2c.
- HRQoL values were mapped from one instrument to another **AND** HSUVs are not mentioned in title or abstract
- Economic evaluation without original HSUVs (for example, cost-effectiveness analysis not using quality adjusted life years (QALYs) but only life years (LYs), **OR** cost-utility analysis with non-original HSUVs)
- Non lung cancer specific HSUVs (non-lung cancer specific study **AND** no stratification by cancer type)
- Non-original data (previously published HSUVs reported)

Inclusion criteria for full text screening

Reports original, lung cancer specific mean or median HSUVs, including a measure of variance (e.g., sample size + variance, standard deviation, standard error, interquartile range), elicited using one of the following methods:

- EQ-5D (EuroQol Five Dimensions Questionnaire)
- SF-6D (Short-Form-6D)
- HUI (Health Utility Index; 1,2 or 3)
- QWB (Quality of Well-Being)
- AQoL (Assessment of Quality of Life)
- 15D
- Vignettes
- Direct elicitation
- Mapping of HRQOL measures from another instrument (e.g. FACT-L); HSUVs are reported in the manuscript. If utilities were mapped from an instrument listed above, include only the original HSUVs.

Exclusion criteria for full text screening:

- Animal studies
- Conference abstracts
- Editorials/commentaries/letters
- Reviews (systematic reviews/meta-analyses/overview articles)
- Study protocol
- Expert opinion (expert opinion was used without any instrument and/or valuation method)
- Guidelines
- Non-English or Dutch language
- Mesothelioma studies
- HRQoL not measured
- Economic evaluation without original HSUVs (for example, cost-effectiveness analysis not using quality adjusted life years (QALYs) but only life years (LYs), **OR** cost-utility analysis with non-original HSUVs)
- No HSUV (no numerical mean or median HSUVs reported).
- Non lung cancer specific HSUVs (non-lung cancer specific study **AND** no stratification by cancer type)
- Non-original data (previously published HSUVs reported **OR** another study used the same underlying data to derive HSUVs with higher-quality methodology, e.g. matching tariff)
- No measure of variance reported with HUVs (and no data to estimate variance)
- Full text not available

Chapter 5

Supplementary Tables and Figures

Supplementary Table 1: Critical appraisal of studies reporting mean or median health state utility values for lung cancer.

	Relevance			Validity			
Source	**Respondents** [a]	**Valuation population** [b]	**Valuation method** [c]	**Sample size** [d]	**HRQoL response** [e]	**Handling missing data** [f]	**Loss to follow-up** [g]
Kimman 2015 [1]	+	+	+	624	624	NR	NAP
Yabroff 2007 [2]	+	-	-	439	NR	NR	NAP
Lee 2011 [3]	+	-	+	241	220	-	NAP
Grutters 2010 [4]	+	+	+	374	245	-	NAP
Trippoli 2001 [5]	+	NR	NR	95	92	-	NAP
Iyer 2013 [6]	+	NR	NR	837	832	-	NAP
Jang 2010 [7]	+	+	+	172	172	NR	NAP
Chouaid 1998 [8]	+	-	-	10	10	NR	NAP
Blackhall 2014 [9]	+	NR	NR	347	313	-	NAP
Rauma 2015 [10]	+	+	-	276	230	-	NAP
Geerse 2017 [11]	+	NR	NR	223	191	-	NAP
Schuette 2012 [12]	+	+	+	542	231	-	NAP
Khan 2014 (a) [13]	+	+	+	670	670	NR	NAP
Khan 2014 (b) [13]	+	+	+	130	130	NR	NAP
Lamers 2007 [14]	+	+	-	210	131	-	NR
van den Hout 2006 [15]	+	+	+	297	297	+	NAP
Verduyn 2012 [16]	+	+	-	261	251	-	NAP
Burfeind 2010 [17]	+	-	-	113	113	-	+
Huang 2017 (1) [18]	+	+	±	NR	NR	-	NR
Chouaid 2013 [19]	+	+	+	319	255	-	NAP
Matter-Walstra 2014 [20]	+	+	+	154	154	-	NAP
Manser 2006 [21]	+	+	+	116	91	-	+
Papatheofanis 2000 [22]	+	-	-	134	23	-	NAP
Khan 2016 [23]	+	+	+	100	97	NR	NAP
Naik 2017 [24]	+	+	+	NR	149	-	NAP
Shih 2006 [25]	+	+	+	NR	51	-	NAP
Kennedy 1995 [26]	-	-	+	9	9	NR	NAP
Ilonen 2007 [27]	+	+	NR	98	31	-	NAP
Pickard 2007 [28]	+	+	+	50	50	NR	NAP
Ko 2003 [29]	+	-	-	54	54	NR	NAP
Thongprasert 2015 [30]	+	+	+	150	150	NR	NAP
Galetta 2015 [31]	+	NR	NR	118	118	+	NAP
Tramontano 2015 [32]	+	+	+	5015	2396	-	+
Bendixen 2019 [33]	+	+	+	201	201	+	NAP
Erbaycu 2018 [34]	+	+	+	266	266	-	NAP
Huang 2017 (2) [35]	+	+	±	NR	NR	-	NR

table continues

	Relevance			Validity			
Source	**Respondents** [a]	**Valuation population** [b]	**Valuation method** [c]	**Sample size** [d]	**HRQoL response** [e]	**Handling missing data** [f]	**Loss to follow-up** [g]
Insinga 2018 [36]	+	+	+	NR	NR	-	NR
Insinga 2019 [37]	+	+	+	NR	NR	-	NR
Kim 2018 [38]	-	+	+	515	515	-	NAP
Limwattananon 2018 [39]	+	+	+	135	135	NR	NAP
Maximiano 2018 [40]	+	+	+	760	495	-	+
Mendoza 2018 [41]	+	+	+	664	664	-	NAP
Meregaglia 2019 [42]	+	+	+	96	96	-	+
O'Kane 2019 [43]	+	+	+	519	519	NR	NAP
Reck 2018 (1) [44]	+	NR	NR	582	419	-	NAP
Reck 2018 (2) [45]	+	NR	NR	272	186	-	NAP
Rendas-Baum 2019 [46]	+	+	+	43	43	NR	NAP
Su 2019 [47]	+	+	+	104	104	-	NAP
Wood 2019 [48]	+	NR	NR	1030	1030	NR	NAP
Goodwin 1988 [49]	-	-	-	21	21	NR	NAP
Cykert 2000 [50]	-	-	+	64	64	NR	NAP
Sullivan 2011 [51]	+	+	+	114	114	-	NAP

Abbreviations: NR = not reported; NAP = not applicable; HRQoL = health-related quality of life; HSUV = health state utility value.

Studies with low relevance (i.e., that score a "-" sign or "NR" for any of the relevance criteria) were not included for subsequent analyses because they are not community- and choice-based.

Superscript Arabic numerals refer to the list of references at the end of this appendix.

[a] What was the respondent type?

Plus sign indicates patients

Minus sign indicates all others

[b] What population was used to valuate HRQoL (scores or vignettes) to HSUVs?

Plus sign indicates the general population.

Minus sign indicates all others (e.g., patients, caregivers, experts).

For mapping studies, consider the valuation method of the instrument to which HRQoL scores were mapped (observed data).

[c] What method was used to valuate HRQOL scores to HSUVs?

Plus sign indicates a choice-based method (i.e. time trade-off or standard gamble).

Plus/minus sign indicates that multiple methods were used according to the country of origin of respondents; at least one of these methods was choice-based.

Minus sign indicates visual analogue scale or other non-choice based methods.

For mapping studies, consider the valuation method of the instrument to which HRQoL scores were mapped (observed data).

[d] How many persons met the inclusion criteria, and, if applicable, signed informed consent and/or were randomized?

In case of multiple disease sites: only for the lung cancer stratum

In case of multiple analyses, only for the HRQoL analysis

In the case of a time series, only the baseline N for this item

[e] How many participants were included in the HRQoL analysis?

In case of multiple disease sites: only for the lung cancer stratum

In case of multiple disease sites: only for the lung cancer stratum

In the case of a time series, only consider the baseline N

[f] What was the method of handling missing HRQoL data?

Plus sign indicates that missing HRQoL data were mentioned and quantified in the study, and missing data were imputed; or it was explicitly stated that there were no missing data (and completeness of data was not an eligibility criterion).

Minus sign indicates that missing HRQoL data were mentioned in the study, and cases with missing data were dismissed (complete case analysis).

[g] Was loss to follow-up reported?

Plus sign indicates that loss to follow-up was reported for each time-point.

Plus/minus sign indicates that loss to follow-up was reported, but not for each time-point.

Minus sign indicates that cases that were lost to follow-up were excluded.

Not applicable to non-longitudinal studies (In case of multiple HRQoL measurements in the same individuals only; if results for multiple time points were based on cross-sectional samples of different patients, do not consider loss to follow-up; also, if study design was longitudinal but numerical HSUVs are only reported for a single time-point, consider the study non-longitudinal).

Supplementary Table 2a: Scope of studies reporting community and choice-based health state utility values for lung cancer.

Source	QoL response [a]	Inclusion years [b]	Lung cancer type [c]	Stage [d]	Treatment [e]	Percent male [f]	Age, mean years (range) [g]	Time of measurement, mean (range) [h]
Kimman 2015 [1]	624	2012-2013	All	All	NR	37 *	51.8 (18-100) *	27 d (<12 w) *
Grutters 2010 [4]	245	2004-2007	NSCLC	All	Any	67	68 (40-90)	2.59 y (0.82-4.76 y)
Jang 2010 [7]	172	NR-NR	NSCLC	All	Any	46.5	66 (32-65) §	NR
Schuette 2012 [12]	231	2007-2009	NSCLC	III-IV	Post-first line	69.7	66.3 (39-86)	NR
Khan 2014 (a) [13]	670	NR-NR	NSCLC	IIIB-IV	Erlotinib or placebo	NR	77 §	(<12m)
Khan 2014 (b) [13]	130	NR-NR	NSCLC	IIIA-IIIB	Radio-therapy or chemo-radi-otherapy	NR	62 §	NR
van den Hout 2006 [15]	297	1999-2002	NSCLC	III-IV	Radiothe-rapy	80 §	69 (48-85) §**	1m (0-88 m) §**
Chouaid 2013 [19]	255	2010-2011	NSCLC	IIIB-IV	Any	61.2	64.8 (32.9-99.6)	NR
Matter-Walstra 2014 [20]	154	2011-2012	All	Advan-ced	Post-first line chemo-therapy	59 *	62.1 (40-77)	NR
Manser 2006 [21]	91	NR-NR	All	All	Any	68.5	67	NR
Khan 2016 [23]	97	2014-2015	NSCLC	All	Any	44	69 (39-86) §	NR
Naik 2017 [24]	149	2012-2014	All	All	Any	47 *	59 (18-100) §*	22 m §*
Shih 2006 [25]	51	NR-NR	All	All	Any	47 §	51 §*	101 d
Pickard 2007 [28]	50	NR-NR	All	Advan-ced	Chemo-therapy	41	62	NR
Thongpra-sert 2015 [30]	150	NR-NR	All	III-IV	Chemo-therapy or radio-therapy	52	60.9	NR
Tramontano 2015 [32]	2396	2003-2005	All	All	Any	52	NR	NR
Bendixen 2019 [33]	201	2008-2014	NSCLC	I	Surgery	50 **	66 § **	NR

table continues

Source	QoL response [a]	Inclusion years [b]	Lung cancer type [c]	Stage [d]	Treatment [e]	Percent male [f]	Age, mean years (range) [g]	Time of measurement, mean (range) [h]
Erbaycu 2018 [34]	266	2010-2013	All	IIIB-IV	Chemotherapy and/or radiotherapy	93.2	61.35 (35-86)	NR
Insinga 2018 [36]	NR	NR-NR	NSCLC	IV	Pembrolizumab and/or chemotherapy	NR	63	NR
Insinga 2019 [37]	NR	NR-NR	NSCLC	IV	Pembrolizumab and/or chemotherapy	NR	65	NR
Limwattananon 2018 [39]	135	2017-2017	NSCLC	Advanced	Chemotherapy or erlotinib	NR	NR	NR
Maximiano 2018 [40]	495	2011-2012	NSCLC	All	Any	79	63.3 (33-86)	8.1 m (0-84 m)
Mendoza 2018 [41]	664	NR-NR	NSCLC	Advanced	NR	70	60.8	NR
Meregaglia 2019 [42]	96	2011-2014	NSCLC	III-IV	Any	68.7	61.1 (36-85)	NR
O'Kane 2019 [43]	519	2014-2016	All	All	Any	45	64 (29-96)	11 m (0-200 m)
Rendas-Baum 2019 [46]	43	2008-2012	All	All	NR	46.5	67.4	NR
Su 2019 [47]	104	2017-2017	All	All	Any	56 *	63.67 *	2 y *
Sullivan 2011 [51]	114	2000-2003	All	All	NR	48 *	69.6	NR

Abbreviations: d = days; w = weeks; m = months; y = years; NR = not reported; NSCLC = non-small cell lung cancer; SCLC = small cell lung cancer.

Superscript Arabic numerals refer to the list of references at the end of this appendix.

§ Median was reported instead of mean

* Baseline characteristics included also non-lung cancer patients

** Baseline characteristics were stratified by study arm, data from the (first) intervention group is reported here

[a] How many participants were included in the health-related quality of life (HRQoL) analysis?
In case of multiple disease sites: only for the lung cancer stratum
In case of multiple disease sites: only for the lung cancer stratum
In the case of a time series, only consider the baseline N

[b] Between which years were participants recruited, or from which years were data sampled?

[c] What lung cancer type was included?

[d] What is the stage of diagnosis of included patients?

[e] Did patients receive treatment at the time of measurement of health state utility values (HSUVs)? If so, which treatments?
[f] What percentage of included participants was male at baseline?
[g] What is the mean age of included participants at baseline?
[h] What was the mean time since diagnosis?

Supplementary Table 2b: Methodological characteristics of studies reporting community and choice-based health state utility values for lung cancer.

Source	Instrument [a]	Valuation [b]	Country [c]	Tariff [d]	Matching tariff [e]	Mode of administration [f]	Longitudinal [g]	Mean or median [h]
Kimman 2015 [1]	EQ-5D	TTO	Cambodia; Indonesia; Laos; Malaysia; Myanmar; Philippines; Thailand; Vietnam	Thailand	±	Personal interview	No	Mean
Grutters 2010 [4]	EQ-5D (3L)	TTO	Netherlands	United Kingdom	-	Self-administered	No	Both
Jang 2010 [7]	EQ-5D (3L)	TTO	Canada	United States	-	NR	No	Mean
Schuette 2012 [12]	EQ-5D (3L)	TTO	Germany; Austria	United Kingdom	-	Self-administered	No	Mean
Khan 2014 (a) [13]	EQ-5D (3L)	TTO	United Kingdom	United Kingdom	+	NR	No	Mean
Khan 2014 (b) [13]	EQ-5D (3L)	TTO	United Kingdom	United Kingdom	+	NR	No	Mean
van den Hout 2006 [15]	EQ-5D	TTO	the Netherlands	United Kingdom	-	Self-administered	No	Mean
Chouaid 2013 [19]	EQ-5D (3L)	TTO	Australia; Belgium; Canada; France; Italy; Turkey; the Netherlands; Sweden; United Kingdom	United Kingdom	±	Self-administered	No	Mean
Matter-Walstra 2014 [20]	EQ-5D (3L)	TTO	Germany	Germany [i]	+	NR	No	Mean
Manser 2006 [21]	AQoL	TTO	Australia	Australia	+	Self-administered	Yes, individual	Median
Khan 2016 [23]	EQ-5D (3L) [j]	TTO	United Kingdom	United Kingdom	+	Self-administered	No	Mean
Naik 2017 [24]	EQ-5D (3L)	TTO	Canada	Canada [k]	+	Self-administered	No	Mean
Shih 2006 [25]	SF-6D	SG	China	United Kingdom	-	Self-administered	No	Mean

table continues

Source	Instrument [a]	Valuation [b]	Country [c]	Tariff [d]	Matching tariff [e]	Mode of administration [f]	Longitudinal [g]	Mean or median [h]
Pickard 2007 [28]	EQ-5D (3L)	TTO	United States	United States [l]	+	NR	No	Mean
Thongprasert 2015 [30]	EQ-5D	TTO	Thailand	Thailand	+	NR	No	Mean
Tramontano 2015 [32]	EQ-5D (3L) [m]	TTO	United States	United States	+	Personal interview	Yes, individual	Both
Bendixen 2019 [33]	EQ-5D (3L)	TTO	Denmark	Denmark	+	Self-administered	Yes, cross-sectional	Mean
Erbaycu 2018 [34]	EQ-5D	TTO	Turkey	United Kingdom	-	Self-administered	No	Mean
Insinga 2018 [36]	EQ-5D (3L)	TTO	NR	United States	NR	NR	Yes, individual	Mean
Insinga 2019 [37]	EQ-5D- (3L)	TTO	NR	United States	NR	NR	Yes, individual	Mean
Limwattananon 2018 [39]	EQ-5D	TTO	Thailand	Thailand	+	NR	No	Mean
Maximiano 2018 [40]	EQ-5D (3L)	TTO	Spain	Spain	+	NR	Yes, individual	Mean
Mendoza 2018 [41]	EQ-5D (3L)	TTO	NR	United Kingdom	NR	NR	No	Mean
Meregaglia 2019 [42]	EQ-5D (5L)	TTO	Poland and Hungary	United Kindom [n]	-	NR	Yes, individual	Mean
O'Kane 2019 [43]	EQ-5D (3L)	TTO	Canada	Canada	+	Self-administered	No	Mean
Rendas-Baum 2019 [46]	SF-6D	SG	United States	United Kingdom	-	NR	No	Mean
Su 2019 [47]	EQ-5D (5L)	TTO	China	China	+	Personal interview	No	Mean
Sullivan 2011 [51]	EQ-5D	TTO	Unted States	United Kingdom	-	NR	No	Mean

Abbreviations: NR = Not reported; TTO = time trade-off; SG = standard gamble; VAS = visual analogue scale.

Superscript Arabic numerals refer to the list of references at the end of this appendix.

[a] What instrument was used to elicit health state utility values (HSUVs)?

[b] What method was used to valuate health-related quality of life (HRQOL) scores to HSUVs?
[c] From what country were HRQoL respondents recruited?
[d] What tariff was applied for valuation of HRQoL?
[e] Was a matching tariff applied?

Plus sign indicates that the tariff was used of the same country or region as the participants were recruited from. In case participants were from multiple countries, the correct tariff was applied to each patient.

Plus/minus sign indicates the use of a single value set while participants were recruited from more than one country.

Minus sign indicates that a different tariff was used than the county of origin of respon dents.

Not applicable to vignette studies, mapping, or direct elicitation of patient's own health.

[f] What was the mode of administration? (Self-administered; personal interview; or telephone interview)
[g] Are HSUVs reported for multiple time points?
If yes, code as either "individual" (multiple time points measured in individual patients) or "cross-sectional" (multiple time-points assessed based on stratification of cross-sectional sample of different patients).
If measured at multiple time points but numerical values only reported at a single time-point, code as no.
[h] Were HSUVs reported as mean or median?
[i] This study also applied direct rating to patients (VAS), and general population tariffs from France, the United Kingdom, and the European union to HRQoL data from the same sample of German patients. We included only the matching German tariff in the meta-analysis.
[j] This study also performed crosswalking of EQ-5D-3L HSUVs to the EQ-5D-5L instrument. We included the original EQ-5D-3L values for analysis.
[k] This study also applied the United Kingdom and United States general population tariffs to HRQoL data from the same sample of Canadian patients. We included only the matching Canadian tariff in the meta-analysis.
[l] This study also applied the United Kingdom tariff to HRQoL data from the same group of US-based patients. We included only the US-based tariff in the meta-analysis.
[m] This study also used the SF-6D instrument. We only include the EQ-5D HSUVs because that instrument is preferred by the National Institute for Clinical Excellence.
[n] This study applied tariffs from the United Kingdom and the Netherlands to HRQoL data from a combined sample of Polish and Hungarian patients. We included only the United Kingdom tariff in the meta-analysis because that tariff was applied more frequently across other studies, hence improving comparability of results.

Supplementary Table 2c: Stratification variables used in studies reporting community and choice-based health state utility values for lung cancer.

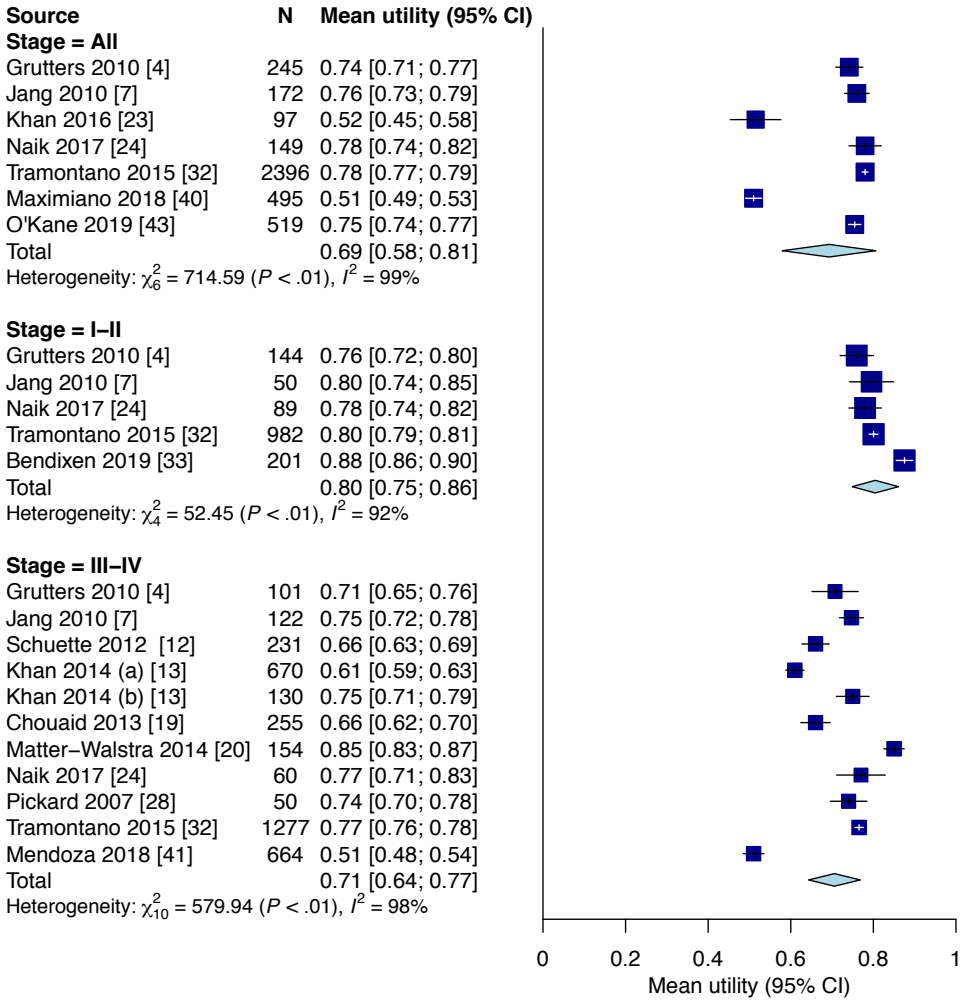
Source	Stratification variables [a]
Kimman 2015 [1]	Overall
Grutters 2010 [4]	Age; gender; initial treatment; stage; survival time; recurrence; adverse events
Jang 2010 [7]	Overall; stage; recurrence status + treatment status
Schuette 2012 [12]	Overall
Khan 2014 (a) [13]	Overall
Khan 2014 (b) [13]	Overall
van den Hout 2006 [15]	Treatment (radiotherapy regimen)
Chouaid 2013 [19]	Overall; progression status; progression status + treatment (line)
Matter-Walstra 2014 [20]	Overall
Manser 2006 [21]	Time since diagnosis + the following: overall; age; gender; employment; language; education; marital status; resectability; stage; histology; ECOG grade; comorbidities
Khan 2016 [23]	Overall
Naik 2017 [24]	Overall; stage
Shih 2006 [25]	Overall
Pickard 2007 [28]	Overall; ECOG grade
Thongprasert 2015 [30]	Overall
Tramontano 2015 [32]	Time since diagnosis + the following: overall; gender; race/ethnicity; age; stage; histology; treatment (surgery; chemo; radiotherapy combinations); comorbidity
Bendixen 2019 [33]	Time since surgery + treatment (type of surgery)
Erbaycu 2018 [34]	Gender; marital status; occupation; smoking status; graduation; comorbidity; age; histology; stage
Insinga 2018 [36]	Time to death
Insinga 2019 [37]	Time to death
Limwattananon 2018 [39]	Treatment (systemic regimen); progression status
Maximiano 2018 [40]	Time since baseline
Mendoza 2018 [41]	Overall
Meregaglia 2019 [42]	Time since baseline
O'Kane 2019 [43]	Age; gender; histology; brain metastasis status; smoking status; treatment (number of previous lines of chemotherapy treatment; radiotherapy; surgery); brain metastasis status
Rendas-Baum 2019 [46]	Overall
Su 2019 [47]	Overall
Sullivan 2011 [51]	Overall

Superscript Arabic numerals refer to the list of references at the end of this appendix.
[a] By what variables are utilities stratified?

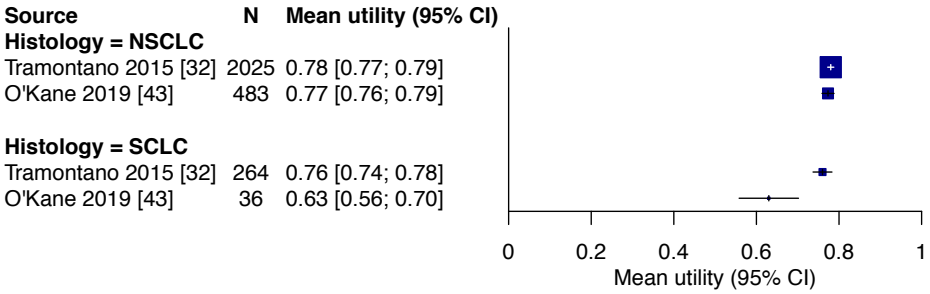
Supplementary Table 3: Results of studies reporting community and choice-based health state utility values for lung cancer as well as for a control group of members of the general population.

Source [a]	Stage III-IV		All stages		Controls		Disutility
	n	mean (SD)	n	mean (SD)	n	mean (SD)	Difference cases-controls (95% CI)
Thongprasert 2015 [30] [b]	150	0.67 (0.30)	-	-	150	0.78 (0.17)	0.11 (0.05-0.17) *
Sullivan 2011 [51] [c]	-	-	114	0.56 (0.46)	79522	0.83 (0.42)	0.27 (0.18-0.36) *

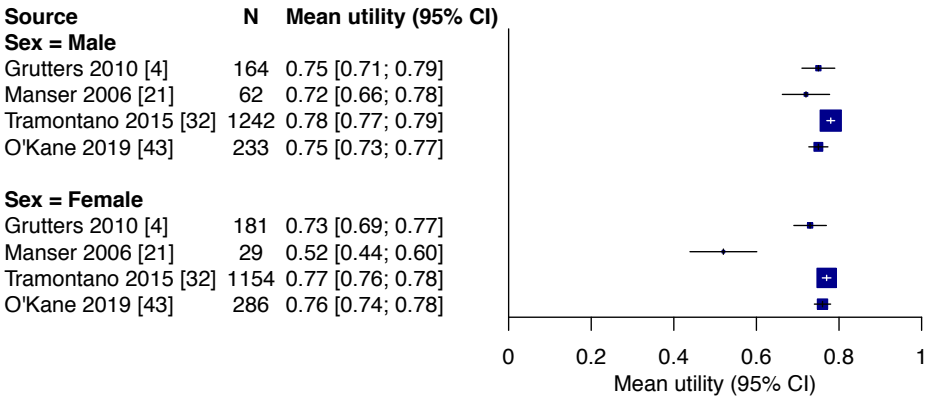
Abbreviations: SD= standard deviation; 95%CI = 95% confidence interval.
Superscript Arabic numerals refer to the list of references at the end of this appendix.
[a] Both studies used the EQ-5D instrument, applying a time-trade-off tariff.
[b] This study applied the Thai tariff to EQ-5D data from Thai persons. Controls were younger than the patient sample (mean age 44.4 years compared to 60.9 years for the patient sample).
[c] This study applied the United Kingdom tariff to EQ-5D data from persons from the United States. Controls were younger than the patient sample (mean age 42.8 years compared to 69.6 years for the patient sample).
* p<.001.



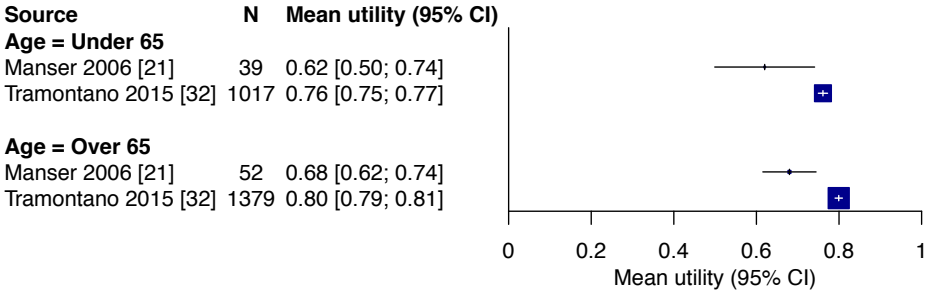
Supplementary Figure 1: Pooled results of studies reporting community and choice-based health state utility values for lung cancer, explicitly elicited using the EQ-5D-3L instrument, by stage. The size of the symbol representing the effect size in each study is relative to the weight it had in random effects meta-analysis. Not all studies included both stage I-II and stage III-IV cases. Not all studies that did include all stages stratified by stage. Arabic numerals between square brackets refer to the reference list in this appendix.



Supplementary Figure 2: Subgroup analysis of community and choice-based health state utility values for lung cancer by histology. Arabic numerals between square brackets refer to the reference list in this appendix. Abbreviations: NSCLC = non-small cell lung cancer; SCLC = small cell lung cancer.

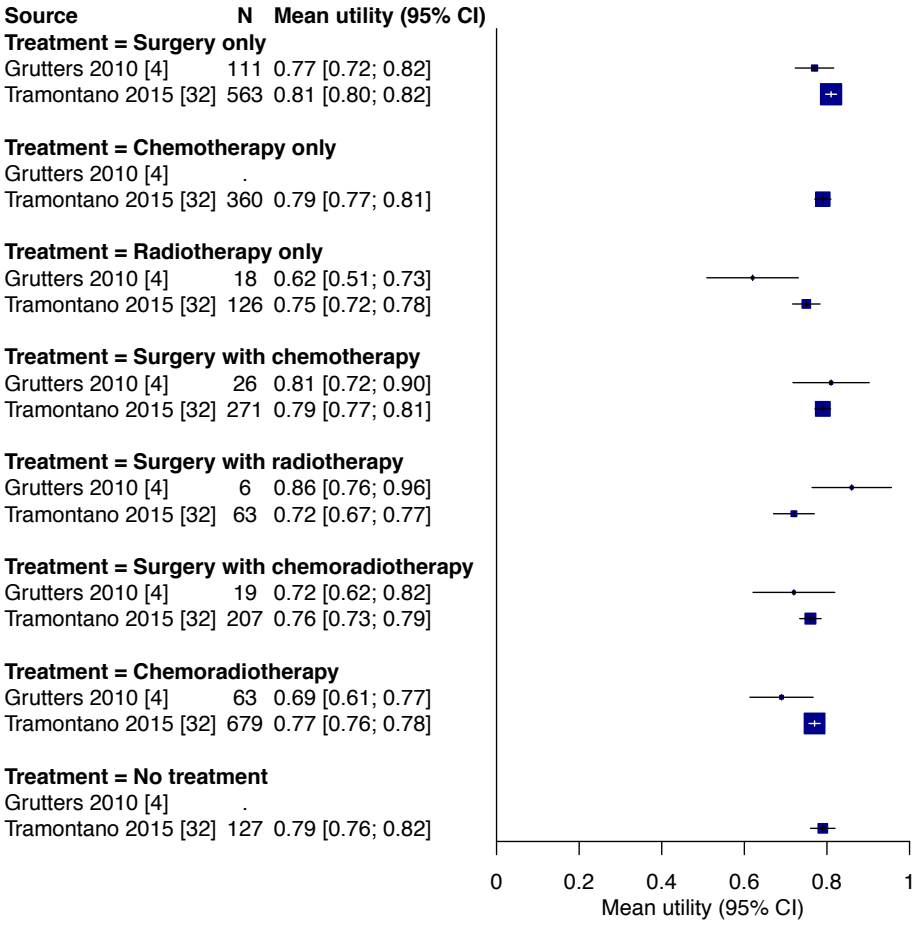


Supplementary Figure 3: Subgroup analysis of community and choice-based health state utility values for lung cancer by sex. Arabic numerals between square brackets refer to the reference list in this appendix.

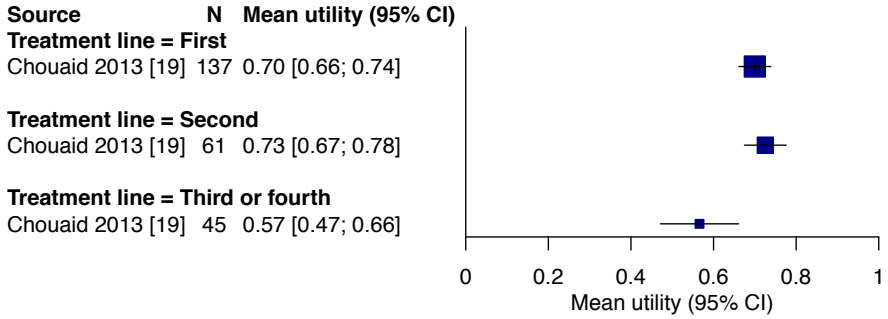


Supplementary Figure 4: Subgroup analysis of community and choice-based health state utility values for lung cancer by age. Please note that in Tramontano 2015, age 65 was included

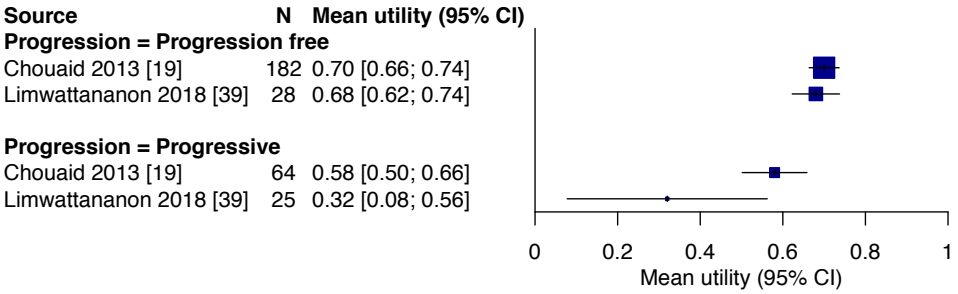
in the "over 65" category. In Manser 2006, age 65 was included in the "under 65" category. Arabic numerals between square brackets refer to the reference list in this appendix.



Supplementary Figure 5: Subgroup analysis of community and choice-based health state utility values for lung cancer by treatment modality. Manser 2006 did not report health state utility values for those receiving no treatment. In addition, Manser 2006 only included 2 patients in the stratum that received chemotherapy only. Those 2 patients had a perfect health state utility value, but no standard deviation was given. Therefore, these 2 patients were omitted from the current analysis. Arabic numerals between square brackets refer to the reference list in this appendix.



Supplementary Figure 6: Subgroup analysis of community and choice-based health state utility values for lung cancer by treatment line. Arabic numerals between square brackets refer to the reference list in this appendix.



Supplementary Figure 7: Subgroup analysis of community and choice-based health state utility values for lung cancer by progression status. Both studies included metastatic non-small cell lung cancer cases and used the EQ-5D instrument. Arabic numerals between square brackets refer to the reference list in this appendix.

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General Discussion

This thesis investigates the interplay of early detection, treatment, and quality of life in lung cancer screening. As outlined in the introduction, this thesis focuses on two main research questions. Part I ("Lung cancer treatment") aims to answer the research question: "How does the implementation of lung cancer screening affect the demand for different treatment modalities?". Part II ("Benefits and harms of population-based screening programs") subsequently aims to answer the research question: "What are the benefits and harms of population-based lung cancer screening programs?". Each part is divided into three chapters, which cover different aspects relating to the two main research questions. This general discussion provides a summary and interpretation of the main findings of each chapter, and uses those to synthesize an answer to the main research questions. Subsequently, methodological considerations of the studies included in this thesis are discussed, followed by recommendations for future research and policies. Finally, a point-by-point summary of the overall conclusions and recommendations is provided.

Summary and interpretation of main findings

Part I: Lung cancer treatment

Chapter 1

Chapter 1 used the U.S. National Cancer Database (NCDB) to investigate which treatments lung cancer patients in the United States currently receive,[1] and whether these treatments are in concordance with clinical guidelines.[2,3] Guideline-concordant treatment was defined as the minimal treatments recommended by the guidelines. Non-surgical treatment options for potentially inoperable patients were included as part of the recommended treatments.

Among 441,812 U.S. lung cancer patients diagnosed between 2010-2014, only 62.1% received the minimally recommended treatments. In addition, 16.3% received treatment that was not guideline-concordant, and 21.6% received no treatment. The percentage receiving guideline-concordant treatment varied across clinical subgroups, defined by stage and histology, and was highest among early-stage non-small cell lung cancer (NSCLC) (76.2%) and lowest among advanced NSCLC (50.4%). For each clinical subgroup, as well as for the entire sample, multivariable logistic regression models were used to identify groups of patients that are less likely to receive guideline-concordant treatment.

After adjusting for potentially confounding patient, tumor, and health care provider characteristics, including comorbidity, age was the factor most strongly associated with the likelihood of receiving guideline-concordant treatment (e.g. age ≥80 years compared with <50 years: adjusted odds ratio = 0.12). In addition, black patients were less likely to receive guideline-concordant treatment than white patients (adjusted odds ratio = 0.78). Patterns of care among those receiving non-guideline-concordant treatment indicated possibilities for an increased uptake of certain treatments, such as stereotactic body radiation therapy (SBRT) for potentially inoperable patients with early-stage NSCLC.

Knowing which patients are at risk of receiving suboptimal treatment may be an important first step towards the development and testing of targeted interventions to improve lung cancer care.[4,5] In addition, awareness of this issue among individual medical doctors may increase the chance of identifying any unjustified concerns or inappropriate beliefs their patients may have regarding their treatment options.[6] Ensuring that all groups of lung cancer patients receive optimal treatment is especially important because the success of lung cancer screening will depend on the optimal treatment of cases detected at early stage. To address the disparities identified in chapter 1, more research should be conducted to identify the underlying reasons.[7] In addition, future lung cancer screening studies should account for existing treatment disparities. This is further elaborated on in the section "Incorporate racial disparities in lung cancer (screening) research" under the heading "Directions for future research and policy" below.

Chapter 2

Using the same NCDB, chapter 2 further investigated the uptake of SBRT among patients with early-stage NSCLC, as well as the uptake of minimally invasive surgery (MIS) and the rate of conversions from MIS to open surgery. We found that, between 2010-2014, the uptake of SBRT as the radiation modality increased substantially. Among those with stage IA NSCLC, SBRT uptake increased from 53.4% in 2010 to 73.0% in 2014. During the same period, the uptake of MIS as the surgical modality among stage IA cases increased from 28.7% to 48.6%, while the rate of conversions to open surgery decreased from 17.0% to 9.1%. For other early stages (i.e. stages IB-IIB), uptake of SBRT and MIS was lower, but time trends were similar.

These findings implicate that, although the uptake of SBRT and MIS are increasing, there is still room for improvement. Lung cancer screening guidelines state that optimal treatment of lung cancer cases detected at an early stage is essential.[8,9] This includes the use of SBRT and MIS.[8] Therefore, we anticipate that the uptake of SBRT and MIS will continue to increase along with the continuing implementation of lung cancer screening.

Chapter 3

Chapter 3 aimed to quantify how currently observed lung cancer treatment patterns will change due to the continued implementation of population-based lung cancer screening in the United States. The main underlying mechanism behind screening is a shift towards early stages, for which better treatment options are available. In addition, lung cancer screening may be more effective among women than among men,[10-12] at least in part because screening may more effectively identify certain histological subtypes of lung cancer that are more common among women, such as adenocarcinoma.[10] Therefore, the MISCAN-Lung model[13,14] was used to project how the gender, stage, histology, and age-specific incidence of lung cancer in the general U.S. population will change between 2015-2040 due to the implementation of screening in 2018. Then, the gender, stage, histology, and age-specific treatment patterns from the National Cancer Database were used to project the corresponding change in demand

for the different treatment modalities used in lung cancer care. By using real-world treatment data, this analysis acknowledges the fact that some patients do not receive the recommended treatments (for example due to patient preferences).

Assuming a 50% adherence to screening, implementing the 2014 United States Preventive Task Force (USPSTF) policy would increase the demand for lung cancer surgery by 37.0%, with a peak in the first years. Overall, radiotherapy use would decrease by 2.2%, and overall, chemotherapy use would decrease by 5.4%. Results were highly sensitive to screening adherence. A gradual buildup of screening uptake may spread the initial peak in surgical demand over time.

Currently, the median time between lung cancer diagnosis and onset of treatment in the United States ranges between 15-57 days (across 12 studies).[15] If, at some point in time, the capacity for lung cancer surgery would be insufficient, this delay could potentially increase. Therefore, to avoid unnecessary increases in waiting times for lung cancer surgery, surgical capacity planning should be an important part of the continuing implementation of lung cancer screening in the United States.

Answer to first main research question

Together, chapters 1-3 answer the first main research question ("How does the implementation of lung cancer screening affect the demand for different treatment modalities?"):

> *To ensure that lung cancer screening is effective, it is crucial that optimal treatment is available and provided, particularly for those diagnosed with early-stage lung cancer. Continuing the implementation of lung cancer screening in the United States will result in an overall increase in demand for lung cancer surgery, with a peak in the initial years. The magnitude of this peak will depend on the degree of screening uptake. If, at some point, surgical capacity would become constrained, a gradual buildup of screening uptake could be a strategy to avoid increases in waiting times for lung cancer surgery. Changes in demand for radiotherapy and chemotherapy due to screening will likely not cause any capacity issues. Addressing treatment disparities by age and race, which persist after adjusting for relevant patient, tumor, and health care provider characteristics, should be an important focus of future research and policy. The increasing uptake of SBRT and MIS as treatment modalities for early-stage NSCLC is expected to continue with the implementation of lung cancer screening.*

Part II: Benefits and harms of population-based screening programs

Chapter 4

In a population-based screening program, screening takes places far beyond the 1-5 screening rounds offered in the randomized controlled trials. [16-23] In addition, new persons become eligible for screening each year, whereas others become ineligible due

to age. In other words, screening takes place in a dynamic population. It is unclear how the decreasing smoking prevalence in the general U.S. population[24] affects the benefits and harms of lung cancer screening in such a dynamic population. Overdiagnosis is considered one of the main harms of cancer screening. Previous assessments of lung cancer overdiagnosis were based on modeling of a single birth cohort,[25] or on randomized controlled trials with an insufficient period of follow-up.[26] Chapter 4 provides a population-based estimate of lung cancer overdiagnosis,[27] accounting for the decreasing smoking prevalence in the general U.S. population.[24] In addition, Chapter 4 provides methodological guidance for future overdiagnosis studies.

The MISCAN-Lung model was used to project lung cancer incidence with and without screening in the general U.S. population between 2018-2040. The model was updated to account for changes in smoking behavior (and thus background lung cancer risk and screening eligibility) across the many birth cohorts that comprise the evaluated population. Three distinct methods were used to estimate the degree of overdiagnosis.

For several separate birth cohorts from the general U.S. population, the cumulative excess-incidence approach was used to show that overdiagnosis is less likely among younger birth cohorts than among older birth cohorts. For example, 5.9% of screen-detected cases were overdiagnosed in the 1990 birth-cohort, compared with 10.5% in the 1950 birth-cohort. This was associated with a lower background risk of lung cancer among younger cohorts, as well as a decreased screening eligibility (due to decreasing smoking trends). To assess the annual rate of overdiagnosis in the entire general U.S. population, two approaches were used: the annual excess-incidence approach and the microsimulation approach. Using the annual excess-incidence approach, overdiagnosis appeared absent between years 2029 and 2040. This occurred because the annual excess-incidence approach does not account for the decreasing background lung cancer risk and screening eligibility across birth cohorts. The microsimulation approach, which uses the underlying full individual life histories in the presence and absence of screening, showed that overdiagnosis was present in each year that screening occurred. Overdiagnosis increased from 7.1% to 9.5% of screen-detected cases between 2018–2040. During the same period, overdiagnosis decreased from 3.7% to 1.4% of all lung cancer cases.

To conclude, the cumulative excess-incidence approach may only be used to assess overdiagnosis in separate closed cohorts. Therefore, results from this commonly used approach are not representative for the entire general population. In addition, the annual excess-incidence approach does not account for smoking trends in the general population, and consequently provides biased overdiagnosis estimates. Given a carefully calibrated model, the microsimulation approach may be used to provide an estimate of the annual rate of overdiagnosis in the general population, accounting for trends in background risk and screening eligibility. These conclusions have implications for policy, because an assessment of overdiagnosis is often part of the decision to implement a particular screening program or not.[28]

Chapter 5

The main benefits of lung cancer screening are the number of averted lung cancer deaths, and the corresponding number of life-years gained. When assessing the number of life-years gained by screening, it is important to include an adjustment for the generally lower quality of life after receiving a diagnosis of lung cancer. Adjustment of life-years gained for quality of life takes place using health state utility values (HSUVs), and yields quality-adjusted life years (QALYs). Economic evaluations often use HSUVs from previous studies without assessing the relevance and validity of those HSUVs. Therefore, in chapter 5, the literature was systematically reviewed for published HSUVs for lung cancer.

After screening almost 6000 titles and abstracts, and more than 450 full text articles, 51 studies reporting mean or median lung cancer-specific HSUVs and a measure of variance were identified. Twenty-seven of these studies used community and choice-based methods to elicit HSUVs, as recommended by most international guidelines.[29] These studies were further analyzed. The pooled HSUV across the studies that included all stages of lung cancer was 0.68. Among stage I-II lung cancer, the pooled HSUV was 0.78. Finally, the pooled HSUV among stage III-IV lung cancer was 0.69. In a sensitivity analysis, only the methodologically most comparable studies were included, which used the EQ-5D instrument and applied the tariff matching the country of quality of life respondents. In that sensitivity analysis, stage-specific HSUVs varied substantially by the country in which the study was conducted. However, studies providing such stage-and country-specific HSUVs were only identified for 8 countries. Therefore, pooling of stage-and country-specific HSUVs was not possible. A subgroup analysis concluded that the HSUVs for metastatic NSCLC decreased significantly during the last year of life, ranging from 0.83 at ≥360 days from death to 0.56 at <30 days from death. Based on a limited number of studies, other subgroup analyses indicated that for patients with metastatic NSCLC, HSUVs may decrease during the third or fourth treatment line and when disease progresses.

Therefore, chapter 5 concluded that, for most countries, the pooled stage-specific HSUVs across the literature may provide the best available evidence. For those countries with available high-quality studies with stage and country-specific HSUVs, those HSUVs may be used instead. In addition, (proportionally) adjusting for the decreased HSUVs in the last year of life may be appropriate, particularly for those with metastatic NSCLC. If required, further stratification of HSUVs for metastatic NSCLC by treatment line or progression status may be considered. By providing the state-of-the-art in lung cancer HSUVs, chapter 5 will enhance the reliability and validity of future economic evaluations. This is topical because in the near future, many such economic evaluations will be conducted regarding lung cancer screening and new immunotherapy agents.

Chapter 6

In chapter 4, the main harm of lung cancer screening, overdiagnosis, was assessed for the entire general U.S. population, which includes non-screening eligible individuals. This perspective is often appropriate when making policy decisions. However,

for shared decision making in clinical practice, it is more important to know the expected benefits and harms of screening among eligible individuals. Although decision aids with such estimates have been previously developed, these were based on the 3 screening scans offered in the National Lung Screening Trial (NLST).[30-32] However, in practice, eligible individuals are asked to consider up to 25 screening scans. In addition, existing decision aids do not account for potential differences in screening effect by age and gender. Therefore, chapter 6 assessed the benefits and harms of participating in population-based lung cancer screening for 55, 60, 65, 70, and 75-year-old men and women meeting the USPSTF eligibility criteria in 2020. The QALYs gained by screening were adjusted using the HSUVs identified in chapter 5.

The key benefit of screening, the number of lung cancer deaths averted, was projected to be 41 per 1000 eligible 55-year-old men in 2020 (M55), compared with 25 per 1000 eligible 75-year-old men in 2020 (M75), 49 per 1000 eligible 55-year-old women in 2020 (W55), and 30 per 1000 eligible 75-year-old women in 2020 (W75). Per lung cancer death averted, the projected number of life-years gained was 13.5 (M55), 7.1 (M75), 13.7 (W55), and 7.7 (W75). Thus, screening those eligible at older ages from 2020 would result in fewer lifetime benefits than screening those eligible at younger ages from 2020 (also accounting for birth-cohort-specific smoking trends and life-expectancy). In addition, women would experience more benefits from screening, compared with similarly-aged men.

When adjusting for quality of life, the number of QALYs gained per lung cancer death averted was approximately a quarter to a third lower than the number of life-years gained per averted lung cancer death (depending on age and sex). For example, 10.0 QALYs would be gained per averted lung cancer death (M55) when using the pooled stage-specific HSUVs from chapter 5, compared with 13.5 life-years (M55). Using the HSUVs from the most high-validity U.S.-based study identified in chapter 5 resulted in similar QALYs gained per averted lung cancer death. For example, 10.4 QALYs would be gained per averted lung cancer death (M55) when using HSUVs from the most high-validity study, compared with 10.0 (M55) when using the pooled HSUVs.

The key harm of screening, the lifetime percentage of screen-detected cases that would be overdiagnosed, ranged from 6.7% (M55) to 13.9% (W75). Overdiagnosis was more likely among older eligible individuals (regardless of sex) and among women (compared with similarly aged men). The key adverse event, the number of biopsies or bronchoscopies for screening findings that are ultimately not lung cancer, was projected to range from 21 (M75 and W75) to 72 (W55). Adverse events were less likely among older eligible individuals, but more likely among women.

To conclude, screening older eligible individuals from 2020 leads to fewer benefits, fewer adverse events, but more overdiagnosis, compared with screening 55-year-old eligible individuals from 2020. In addition, compared with similarly-aged men, women experience more benefits, more adverse events, and more overdiagnosis. Per lung cancer death averted, the number of QALYs gained is approximately a quarter to a third lower than the number of life-years gained. The QALYs gained were fairly robust to the choice of HSUVs. The findings presented in Chapter 6 indicate the need to personalize the information discussed in shared decision making by age and sex. Personalized shared decision making conversations may be facilitated by using the presented graphical decision aids.

Answer to second main research question

Together, chapters 4-6 answer the second main research question ("What are the benefits and harms of population-based lung cancer screening programs?"):

> *The main harm of lung cancer screening is overdiagnosis. When screening all U.S. individuals meeting the USPSTF eligibility criteria from 2018-2040, overdiagnosis among screen-detected cases will increase from 7.1% to 9.5%, whereas overdiagnosis among all lung cancer cases will decrease from 3.7% to 1.4%. This is due to decreasing smoking trends across birth cohorts, which reduces the background lung cancer risk and screening eligibility over time in the general U.S. population. It is important to use appropriate methods to account for these trends. For shared decision making in clinical practice, the benefits and harms of lung cancer screening were assessed among men and women eligible for screening in the calendar year 2020. Using that perspective, the expected lifetime benefits of screening and the number of adverse events decrease with advancing age (accounting for smoking trends across birth cohorts), whereas overdiagnosis increases. In addition, compared with similarly-aged men, women experience more benefits, more adverse events, and more overdiagnosis. The number of QALYs gained per lung cancer death averted is approximately a quarter to a third lower than the number of life-years gained, regardless of the choice of HSUVs. Shared decision making discussions prior to lung cancer screening should preferably be personalized by age and sex. This may be facilitated by using the age and sex-specific graphical decision aids presented in this thesis.*

Methodological considerations

Causal inference and observational data

In chapter 1, logistic regression models were used to investigate which groups of patients are less likely to receive guideline-concordant treatment. These multivariable models were corrected for potential confounding factors identified in previous studies. The NCDB comprises up to 70% of incident cancer cases in the United States, and chapter 1 included all clinical subgroups of lung cancer. Therefore, these findings are more generalizable than earlier studies. Nevertheless, it is important to realize that the NCDB data are observational. Therefore, the findings in chapter 1 do not allow for firm conclusions regarding causality. In chapter 1, this is reflected by using language such as "associated with", instead of "caused".

Recently, some investigators have argued that causal inference using observational data may still be possible when using specific methods.[33] In short, these investigators argue that there are 2 main types of observational studies: those that aim to predict the value of an outcome, and those that aim to make causal inferences.[33] When causal inference is the aim, investigators could draw "directed acyclic graphs".[34] In such graphs, the relations between all factors that are related to either the exposure variable or outcome variable should be indicated by a directed

arrow, based on previous literature. Then, statistical models should only control for those variables that are identified as a "confounder", strictly defined as a variable that has a unidirectional causal effect on both the exposure and outcome variable.

Although these efforts to improve causal inference based on observational data are important developments, it is worth mentioning several additional considerations. First, studies using observational data are not limited to prediction modeling and causal inference.[35] Often, the most appropriate aim is to identify associations, while correcting for potential confounding factors. Second, the proposed criteria for identifying confounders are very strict. As was the case in chapter 1, there is often insufficient evidence to determine all the interrelations of potentially influential variables in "directed acyclic graphs". In particular, the directions of previously identified associations are often unknown. In that case, imposing a strict statistical model structure based on assumed interrelations may actually introduce bias.[36] In chapter 1, a more pragmatic definition of a confounder was used instead: a variable that is associated with the exposure of interest, and that also plausibly affects the outcome of interest.[37]

Perhaps more important than to prove the causality of the associations identified in chapter 1, is attempting to identify the underlying reasons.[7] This is further elaborated on in the section "Incorporate racial disparities in lung cancer (screening) research" under the heading "Directions for future research and policy" below.

Differences in treatment of screen-detected and clinically detected cancer

In chapter 3, it was assumed that screen-detected and non-screen detected lung cancers receive the same treatment, given similar stage, histology, age, and gender. However, in practice, persons participating in screening programs may be healthier than average (i.e. the so-called "healthy volunteer effect").[38] Therefore, persons with a screen-detected lung cancer may receive surgery relatively more often than persons with clinically detected lung cancer. Indeed, lung cancer surgery was more prevalent among cases in the low-dose computed tomography screening (LDCT) arm of the NLST than among cases in the NCDB with a similar stage.[39,40] Therefore, Chapter 3 included a sensitivity analysis, in which stage-specific treatment patterns from the LDCT arm of the NLST were applied to screen-detected cases instead of treatment patterns from the NCDB. Using these alternative treatment patterns for screen-detected cases, the increase in surgical demand due to screening was more pronounced. However, it should be noted that the NLST was conducted in a highly controlled environment. Therefore, surgical use in the LDCT arm of the NLST may be an upper bound. Early detection of lung cancer by screening will only be effective if treatment is optimal. Therefore, it is important that, as more representative data become available, future studies monitor whether surgical use differs between screen-detected cancers and non-screen detected cancers.

Modeling assumptions

The assessments of benefits and harms of population-based lung cancer screening in this thesis were based on analyses conducted using the MISCAN-Lung model. As with any statistical model, the validity of the estimates depends on the validity of the model structure and calibration. Hence, the commonly used aphorism "all models are wrong, but some are useful". The structure of the MISCAN-Lung model was discussed in several chapters in this thesis.[27,39] In addition, the model structure and calibration of key parameters was more elaborately described in previous publications.[13,14] In short, key assumptions regarding unobservable parameters, such as the preclinical duration of disease, were carefully calibrated to data of the NLST and Prostate, Lung, Colorectal, and Ovarian Cancer Screening (PLCO) trials.[13,14] At this point, MISCAN-Lung is considered a well-established and validated model, which has been used to inform the USPSTF recommendations for lung cancer screening.[25,28]

Nevertheless, it is worth discussing the potential effect of two model assumptions on the findings presented in this thesis. First, the MISCAN-Lung model, which uses the U.S. National Cancer Institute's Smoking History Generator,[24] accounts for changes in smoking behavior across birth cohorts. However, the model assumes that these smoking patterns are unaffected by screening. In reality, however, current lung cancer screening recommendations emphasize that lung cancer screening should be complemented with smoking cessation interventions.[28,41-43] Recently, Cancer Intervention and Surveillance Modeling Network (CISNET) investigators assessed the potential impact of adding smoking cessation counseling to lung cancer screening, under varying hypothetical rates of screening uptake and smoking quitting probabilities.[44] The CISNET investigators found that complementing lung cancer screening (with a 30% adherence to screening) with a hypothetical smoking cessation intervention with a moderate 10% quitting probability would increase the number of averted lung cancer deaths by 14%, and the number of life-years gained by 81%. This effect could be even greater with a higher screening uptake and quit probability. Therefore, the projected benefits due to screening presented in this thesis may be even larger if successful smoking cessation strategies are implemented concurrently. Nevertheless, the actual magnitude of the effect of joint screening and smoking cessation counseling in clinical practice is currently unknown, and the optimal cessation intervention is unclear.[45] In addition, it has been suggested that a negative screening result may provide some screenees with a false sense of reassurance, thus potentially lowering the smoking quit rates.[46] However, this effect was not present in the Netherlands-Leuvens Longkanker Screenings Onderzoek (NELSON) trial.[47] More research is needed to assess the interplay of lung cancer screening and smoking cessation interventions in a population setting.

Second, rates of adverse events in MISCAN-Lung were modeled using data from the NLST. However, currently other nodule follow-up algorithms are recommended, such as Lung-RADS.[41] Such new nodule management algorithms generally use volumetric nodule assessment, and indeterminate nodule categories for which follow-up screening is a safe approach. Therefore, Lung-RADS may greatly reduce the number of false-positive screening results.[48] Therefore, rates of adverse events projected by MISCAN-Lung may in practice turn out to be less frequent. However,

Lung-RADS may misidentify some lung cancers as benign, thereby decreasing the screening sensitivity, and ultimately the benefits due to screening.[48] Unfortunately, there is currently insufficient real-world data to correctly include Lung-RADS in the MISCAN-Lung model.

Directions for future research and policy

Optimizing current lung cancer screening programs

The second part of this thesis focused on the benefits and harms of population-based lung cancer screening. These chapters were based on lung cancer screening programs using the 2014 USPSTF eligibility criteria, which are based on age, the number of accumulated pack-years, and the time since quitting smoking.[28] Although smoking history and age are the most important risk factors for lung cancer, there are additional risk factors. These include chronic obstructive pulmonary disease,[49,50] a positive family history for lung cancer,[51] and exposure to occupational or environmental factors such as air pollution,[52,53] industrial chemicals,[52] asbestos,[52,54] and radon.[52,55] Therefore, several multivariable models have been developed to predict an individual's risk of lung cancer or lung cancer death.[56–58]

In a retrospective analysis of the NLST and PLCO data, these models had superior sensitivity and specificity for predicting 6-year lung cancer incidence (>79.8% and >62.3%, respectively), compared with the NLST criteria (71.4% and 62.2%, respectively).[59] A subsequent study investigated the benefits and harms of lung cancer screening programs that use these risk models to select individuals for screening.[60] Compared with the current USPSTF criteria, selection of eligible individuals using risk models averted more lung cancer deaths, but yielded only modestly more life-years, while overdiagnosis increased (given a similar number of screening examinations). These findings could mostly be explained by the fact that risk-based criteria selected older individuals for screening than the current pack-year based USPSTF criteria. This happens because lung cancer risk continues to increase with age, whereas the current pack-year based criteria stop screening after 15 years of smoking cessation. Excluding individuals with a life expectancy less than 5 years from screening reduced overdiagnosis by 65.1–67.3%, while retaining the life-years gained. However, in practice, it is difficult to accurately predict an individual's life expectancy. These studies show that selection of individuals for screening by using risk models may increase the benefits of screening, but may also increase the harms.

The 2014 USPSTF recommendations have been found to be cost-effective, given a willingness-to-pay threshold of $100,000 per QALY gained.[61] As risk-based strategies avert more lung cancer deaths (given a similar number of screens), cost-effectiveness may be more favorable. However, the moderate effect on the life-years gained could mitigate the cost-effectiveness of risk-based screening strategies. In addition, the increased selection of elderly individuals for screening could increase treatment costs, as more chronic treatment for inoperable elderly patients may be required. However, the cost-effectiveness of a screening strategy can be influenced by the interplay of many factors. Thus, the cost-effectiveness of risk-based screening strategies should

be investigated in future modeling studies. To limit the influence of specific model assumptions on the outcomes, these studies should preferably include and compare projections from several independently developed models.

In the NELSON trial, the individual risk of developing lung cancer was dependent on earlier screening results.[62] A recently updated version of one of the previously assessed lung cancer risk prediction models incorporates information on previous screening results.[63] Including previous screening results significantly improved model discrimination for lung cancer incidence (area under the curve: 0.761 compared with 0.687). The authors suggest that the screening interval could be tailored to the individual's personal lung cancer risk and previous screening findings, but acknowledge that further validation of such approaches in prospective studies is necessary. An important multicenter European implementation trial, named 4-IN-THE-LUNG-RUN, will prospectively investigate the effect of one such approach: tailoring an individual's screening interval to the baseline screening results.[64]

More research is necessary to identify the optimal approach to tailor screening intervals to individual persons. Possibly, less intensive screening may be appropriate for those with an initial negative screening result. Furthermore, the screening interval could possibly be further tailored as a person undergoes subsequent screens. In addition, the net benefit of lung cancer screening among certain eligible persons (e.g. those with a low annual lung cancer risk) is preference-sensitive.[65] Possibly, patient preferences may also help identify eligible individuals for whom less intensive screening (or not screening) is an appropriate option. Such approaches can be investigated by carefully conducted modeling studies.

Prioritizing efforts to increase the uptake of screening

Although lung cancer screening has been recommended in the United States since 2013, only a limited portion of eligible individuals are actually screened.[66,67] In the United States, potential screenees need to be assessed for eligibility and counseled on the benefits and harms by clinicians.[42] In the typical mandatory shared decision making appointment, the time spent discussing lung cancer screening is typically only a minute.[68] These findings point to time constraints among clinicians. Also, physician's knowledge on current lung cancer screening guidelines appears to show gaps.[69] Although new risk-based approaches may increase the benefits of screening, they are more complex than current screening guidelines. Data on more variables needs to be collected to assess eligibility (and possibly the screening interval), which could increase time constraints. Furthermore, some primary care providers feel that they lack proper understanding of risk models, and believe that risk-based screening may unnecessarily confuse potential screenees.[70] These factors may hinder an increase in screening uptake.

Therefore, it could be worthwhile to initially focus efforts on increasing the uptake of the current recommendations, even if these are imperfect. Sometimes, less (complexity) is more.[71] Increasing the uptake of screening on the short term is especially important because the number of screening eligible individuals in the United States is expected to decrease in coming years due to decreasing smoking trends.[39,72] In other

words, if screening uptake remains low, an important window of opportunity could be missed, thus potentially mitigating the additional long-term benefits of risk-based screening programs. A first step towards increasing screening uptake could be to use qualitative methods to identify physician's informational needs and barriers to recommend and implement screening. Then, effective educational material could be developed to increase physician's knowledge on lung cancer screening, and even more importantly, their acceptance and recommendation of lung cancer screening policies. Additionally, these educational materials could be used to train navigators, whom may alleviate physician's time constraints. The combined training and use of primary care physicians and navigators may particularly increase the uptake of lung cancer screening.[73]

Incorporate racial disparities in lung cancer (screening) research

In chapter 1, racial disparities were identified in the use of guideline-concordant treatment for lung cancer.[1] A recent study by CISNET investigators showed that, given a similar lung cancer risk, current USPSTF eligibility criteria select relatively fewer black persons than white persons for screening.[74] In addition, a recent study showed that, compared with white lung cancer patients, black lung cancer patients are less likely to be eligible for lung cancer screening according to the current USPSTF recommendations (56% compared with 32%).[75] This was mostly due to the lower median number of pack-years among black lung cancer patients compared with white lung cancer patients (25.8 compared with 48.0, respectively). In other words, a substantial proportion of black lung cancer patients did not meet the minimum 30 pack-years criterion. The authors suggest that lowering the pack-years criterion to 20 pack-years may be appropriate for black persons. This statement is supported by the finding in an older study that black smokers have a significantly higher lung cancer risk than smokers of other races, given a similar number of cigarettes smoked per day.[76] Another possible approach would be to use lung cancer risk prediction models that include race to select individuals for screening.

These studies show that, given current practice, black persons with a high risk of lung cancer are less likely to be selected for lung cancer screening, and additionally, if lung cancer is detected, black patients are less likely to receive optimal treatment. It is important that future research investigates ways to address these disparities. An important first step would be to conduct (qualitative) studies to identify the underlying reasons for the identified disparities. Also, future lung cancer screening and treatment modeling efforts could explicitly incorporate race. Using such race-specific models, different strategies to mitigate racial disparities could be assessed. For example, the comparative effectiveness of the two suggested methods to tailor screening eligibility to race could be assessed.

Assess the joint impact of immunotherapy and screening

Chapter 1 showed that between 2010-2014, rates of lung cancer surgery, radiotherapy, and chemotherapy remained stable. Chapter 2 considered more granular treatment patterns among early-stage NSCLC, and showed that the uptake of MIS and SBRT as treatment modalities increased during the same period. As outlined in the introduction of this thesis, new therapies have more recently been introduced: targeted therapy and immunotherapy. Targeted therapies act on specific molecular features expressed by some, but not all, lung cancers. These therapies include epidermal growth factor receptor (EGFR) inhibitors (e.g. erlotinib, afatinib and gefitinib)[77-79] and anaplastic lymphoma kinase (ALK) inhibitors (e.g. crizotinib and ceritinib).[80,81] Immunotherapy agents help the immune system to identify and target lung cancer cells, or the blood supply they need to grow. In lung cancer care, these include vascular endothelial growth factor (VEGF) inhibitors (e.g. bevacizumab),[82] protein programmed cell death 1 (PD-1) inhibitors (e.g. pembrolizumab and nivolumab),[83,84] protein programmed cell death-ligand 1 (PD-L1) inhibitors (e.g. atezolizumab),[85] and ROS1 inhibitors (e.g. crizotinib and entrectinib).[86]

The use of these agents outside of clinical trials is still very recent; the first immunotherapy agent to be approved by the U.S. Food and Drug Administration for the first-line treatment of certain advanced lung cancer cases was pembrolizumab, in October 2016. Important lung cancer treatment databases, such as the NCDB used in this thesis, usually lag several years. Therefore, the use of targeted and immunotherapy agents could not be assessed in this thesis. Nevertheless, this is, and will remain a very active area of research. At first, the recommendation of targeted and immunotherapy agents was limited to the palliative treatment of specific advanced NSCLC patients (depending on the expression of EGFR, ALK, and PD-L1). However, the use of some of these agents has already shifted from second-line treatment to first-line treatment. In addition, current studies are investigating the effect of adjuvant or neoadjuvant treatment with targeted and immunotherapy agents for operable early-stage and locally advanced NSCLC, and as consolidation therapy after concurrent chemoradiation for inoperable locally advanced NSCLC.[87,88]

These developments may complement and interact with lung cancer screening efforts. As the uptake of lung cancer screening in the United States will continue to increase, there will be a shift towards diagnosis at earlier stages (see chapter 3 in this thesis).[39] Targeted and immunotherapy agents are currently provided mainly to patients with advanced NSCLC, potentially prolonging their survival. Because these agents are very expensive, their increased use may increase the cost-effectiveness of lung cancer screening. However, if the (neo)adjuvant use of targeted and immunotherapies in early-stage NSCLC indeed proves effective, this effect may be mitigated. It is important that future (modeling) studies assess the relative contributions of new therapeutics and the continuing uptake of lung cancer screening in reducing the lung cancer burden. Also, the cost-effectiveness and budget impact of each of these developments alone and combined should be assessed. Such studies can help policy makers make important decisions, for example regarding reimbursements and prioritization.

Initiate a high-quality international study of health state utility values

By providing the state-of-the-art in HSUVs for lung cancer, chapter 5 will enhance the validity of future health economics modeling efforts. Nevertheless, chapter 5 also identified important areas where additional research is needed. Most importantly, although a large number of studies was identified, many studies were found to be of insufficient quality. In many of the included studies, HSUVs were not the primary endpoint. Therefore, reporting of the methodology of HSUV elicitation was often limited. In addition, there was substantial variation in stratification variables, coding, and reporting across the identified studies. Therefore, we could not pool results by other variables than stage, while age, sex, treatment, and time since diagnosis could be factors influencing HSUVs. Some authors have used meta-regression in an attempt to pool HSUVs from markedly different patients, elicited using different methods, but this approach can lead to false positive associations.[89] Only two of the studies identified in Chapter 5 included a matched control group of the general population. Including a matched control group is important because members of the general population do not have a perfect health.[90] Finally, many identified studies did not apply the choice-based tariff of the country in which patient's quality of life scores were collected. This important because applying a different tariff to quality of life scores from the same patients can leads to large variations in HSUVs.[91]

An important step towards overcoming these issues would be to conduct a study (or series of studies) across multiple countries, in which health-related quality of life is measured in nationally representative samples of lung cancer patients (e.g. by age, stage, sex and histology), and in which societal preferences are elicited using the EQ-5D instrument with the choice-based tariff that matches the country of the responding patients. This study should collect data on the treatment received, and measure HSUVs at the moment of diagnosis, and at subsequent fixed time intervals. Because a choice-based EQ-5D tariff is not available for many countries, this study should be preceded by the elicitation of such a tariff from a matched (at least by age and sex) sample of members of the general population. This sample could then also be asked to rate their own health-related quality of life, thus serving as a control group to the lung cancer patients. It would be important that the entire resulting dataset would be made available in open access. That way, investigators of future health economic evaluations can tailor the data to the needs of their model, instead of relying on selected findings presented in a published manuscript.

Assess the benefits and harms of lung cancer screening in the Netherlands

The research in this thesis was focused on the United States, where lung cancer screening has been recommended since 2013.[28] In Europe, discussions regarding a possible implementation of lung cancer screening have been ongoing for several years.[92] In recent years, the European position has been to start planning for a possible implementation, but to await the results of the NELSON trial before making a final decision.[92] Now that the final mortality results the NELSON have been published, showing a significant 24% lung cancer mortality reduction compared

with no screening,[11] European countries will likely face important implementation questions. Many studies have been conducted regarding the optimal lung cancer screening policy in the United States. However, the results from those studies do not necessarily translate directly to other countries. First, demographics and smoking rates vary across countries.[93] Second, as detailed elsewhere in this discussion, there are some important differences between the performance of the NELSON trial and the NLST trial, on which most U.S.-based work was based. Third, treatment patterns may differ across countries. Therefore, an important step would be to recalibrate the MISCAN-Lung model to individual-level data from the NELSON trial, and to use Dutch smoking and treatment data as input. Then, the optimal lung cancer screening policy for the Netherlands can be determined, as well as the treatment capacity required for a successful implementation.

Overall conclusions and recommendations

The results of the different chapters in this thesis lead to the following conclusions:

- In the United States, lung cancer treatment disparities by race and age persist, despite adjusting for important patient, tumor, and healthcare provider characteristics. Addressing these disparities is topical because the success of lung cancer screening depends on optimal treatment of cases detected at an early stage.
- Between 2010-2014, the uptake of stereotactic body radiation therapy and minimally invasive surgery in the United States increased substantially, while the rate of conversions to open surgery decreased. These trends are expected to continue with the increasing uptake of lung cancer screening.
- The continued implementation of lung cancer screening in the United States will substantially increase the demand for lung cancer surgery, especially in the first years. A gradual buildup of screening uptake can spread this peak over time, thus potentially avoiding unnecessary increases in waiting times for lung cancer treatment.
- Future rates of overdiagnosis due to lung cancer screening in the general U.S. population will be affected by the reducing smoking behavior, which affects the background risk of lung cancer and screening eligibility. Using appropriate methods to account for these trends is crucial.
- Future comparative effectiveness studies of lung cancer screening and treatment should use methodologically appropriate health state utility values to calculate the quality-adjusted life-years gained by the intervention.
- The mandatory shared decision making conversation prior to lung cancer screening should preferably include the use of age and sex-specific graphical decision aids.

Based on the research conducted in this thesis, the following suggestions for future research and policy are suggested:

- Prioritizing the identification of ways to increase the low uptake of the current lung cancer screening recommendations in the United States.

- Optimization of current lung cancer screening policies, for example by risk stratification.
- Exploring potential strategies to address racial disparities in lung cancer screening eligibility and treatment.
- Assessing the relative contributions of new lung cancer therapeutics and screening on reducing the lung cancer burden.
- Initiating a high-quality international study of health state utility values for lung cancer to address gaps in the current literature.
- Quantifying the benefits and harms of implementing lung cancer screening in the Netherlands, and identifying the optimal policy.

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Summary

General introduction

Smoking is the main risk factor for lung cancer. Therefore, primary prevention (smoking cessation) is potentially the most effective method of preventing lung cancer. However, despite the successes of tobacco control policies since the 1960s, lung cancer is still the leading cause of cancer deaths worldwide. When patients present with symptoms, their lung cancer has often metastasized to distant sites. Currently, there are no curative treatment options for metastasized lung cancer. The goal of secondary prevention (screening) is to identify lung cancer before it presents with symptoms, in which case the disease is presumably in an earlier stage, thus enabling better treatment options. In 2011, the U.S. National Lung Screening Trial showed that three annual low-dose computed tomography screens, among high-risk current and former smokers, can reduce lung cancer mortality by 20%. The benefit of lung cancer screening was recently confirmed by the Dutch-Belgian randomized lung cancer screening trial, which found a 24% lung cancer mortality reduction. In the United States, annual lung cancer screening has been recommended since 2013, for persons aged 55-80 with a smoking history of at least 30 pack-years, that currently smoke or quit less than 15 years ago. Despite this recommendation, the uptake of lung cancer screening in the United States remains low. In Europe and the United Kingdom, many countries have been debating a possible implementation of lung cancer screening. In the meantime, many topics of debate remain.

This thesis deals with two of these topics. The first part of this thesis (Chapters 1-3) investigates which treatments lung cancer patients in the United States received before the implementation of screening, and how these treatment patterns change as a result of the implementation of lung cancer screening. In the second part of this thesis (Chapters 4-6), the benefits and harms of population-based lung cancer screening in the United States are investigated from different perspectives.

Part I: Lung cancer treatment

Chapter 1

Using the U.S. National Cancer Database, Chapter 1 assessed treatment patterns among 441,812 U.S. individuals diagnosed with lung cancer between 2010-2014. Overall, 21.6% of cases did not receive any first course treatment. Only 62.1% of cases received guideline-concordant treatment. Black patients and elderly patients were less likely to receive guideline-concordant treatment, despite adjustment for relevant patient, tumor, and healthcare provider characteristics. The remaining 16.3% of cases received less intensive treatment than recommended. Treatment patterns among these cases suggested possibilities for an increased uptake of certain treatments, such as stereotactic body radiation therapy (SBRT) for potentially inoperable patients with early-stage non-small cell lung cancer (NSCLC).

Chapter 2

Chapter 2 used the NCDB to assess the uptake of SBRT as the radiation modality among early-stage NSCLC cases in the United States. Among those with stage IA NSCLC, the use of SBRT as the radiation modality increased from 53.4% in 2010 to 73.0% in 2014. Uptake of SBRT was lower among stages IB-IIB, although time trends were similar to those among stage IA. Chapter 2 also assessed the uptake of minimally invasive surgery (MIS) among surgically treated patients with early-stage NSCLC. Between 2010-2014, the uptake of MIS among cases with stage IA NSCLC increased from 28.7% to 48.6%. During the same period, the rate of conversions from MIS to open surgery decreased from 17.0% to 9.1%. The uptake of MIS was lower among stages IB-IIB than among stage IA, while the rate of conversions was higher.

Chapter 3

Chapter 3 extended the MISCAN-Lung microsimulation model with gender, stage, histology, and age-specific lung cancer treatment patterns from the NCDB. The extended model was used to assess the change in demand for the different lung cancer treatment modalities due to the implementation of lung cancer screening in the United States. Under the base-case assumption of 50% adherence to the current United States Preventive Task Force recommendations between 2018-2040, the implementation of lung cancer screening would increase the demand for lung cancer surgery by 37.0%. There would be a large initial peak in demand for lung cancer surgery in the first years, which could be mitigated by a gradual build-up of screening uptake. Overall, radiotherapy use and chemotherapy use would slightly decrease.

Part II: Benefits and harms of population-based screening programs

Chapter 4

Chapter 4 used three different methods to estimate the degree of overdiagnosis due to lung cancer screening in the United States. Using the cumulative excess-incidence approach, the lifetime percentage of screen-detected cases that was overdiagnosed ranged from 10.5% in the 1950 birth-cohort to 5.9% in the 1990 birth-cohort. The microsimulation approach was used to project the annual rate of overdiagnosis in the entire general U.S. population between 2018-2040. This population is composed of many different birth cohorts. Using this approach, overdiagnosis increased from 7.1% of screen-detected cases in 2018 to 9.5% of screen-detected cases in 2040. During the same period, the percentage of all lung cancer cases (both clinically and screen-detected cases) that was overdiagnosed decreased from 3.7% to 1.4%. These changes in overdiagnosis across birth cohorts and over time are due to decreasing smoking trends, which reduce the background risk of lung cancer and the percentage of screening-eligible individuals over time. We showed that the third method, the

annual excess-incidence approach, does not correctly account for these trends, thus producing biased overdiagnosis estimates.

Chapter 5

Chapter 5 reviewed the literature for lung cancer specific health state utility values (HSUVs), which are used to calculate the number of quality-adjusted life years (QALYs) gained by screening. The literature review focused on HSUVs elicited using community and choice-based methods. Twenty-seven of these studies were identified. The pooled HSUV was 0.68 for all stages, 0.78 for stages I-II, and 0.69 for stages III-IV. A sensitivity analysis included only the methodologically most comparable studies, which calculated HSUVs using the tariff matching the country of origin of responding patients. Such studies were identified for 8 countries, and HSUVs varied by stage and country. A subgroup analysis showed that HSUVs for metastatic NSCLC decreased significantly throughout the last year of life. Finally, subgroup analyses indicated that HSUVs for metastatic NSCLC may differ by treatment line and progression status.

Chapter 6

Chapter 6 assessed the benefits and harms of participating in population-based lung cancer screening among those eligible according to the United States Preventive Task Force criteria in 2020. Using the pooled HSUVs from chapter 5 resulted in similar QALYs gained compared with using the HSUVs from the most high-validity U.S. based study. Compared with screening 55-year-old eligible individuals from 2020, screening older eligible individuals from 2020 leads to fewer benefits, fewer adverse events, but more overdiagnosis. Furthermore, compared with similarly-aged men, women experience more benefits, more adverse events, and more overdiagnosis. These findings indicate the need to tailor the information discussed in the mandatory shared decision making visit by age and sex. Therefore, chapter 6 provided age and sex-specific graphical decision aids.

General discussion

The general discussion of this thesis provides an overview of the overall conclusions that can be derived from these chapters. First, lung cancer treatment disparities by race and age persist, despite adjusting for important patient, tumor, and healthcare provider characteristics. Second, the uptake of SBRT and VATS in the United States increased substantially between 2010-2014, while the rate of conversions to open surgery decreased. Addressing disparities by race and age, as well as continuing the increasing uptake of new treatment modalities, will contribute to a successful implementation of lung cancer screening. Third, the implementation of lung cancer screening in the United States will substantially increase the demand for lung cancer surgery, especially in the first years. A gradual buildup of screening uptake can spread

this peak over time. Fourth, it is important to use appropriate methods to adjust overdiagnosis estimates for reducing smoking trends in the general population. Fifth, it is important to use methodologically appropriate HSUVs to calculate the quality-adjusted life-years gained by lung cancer screening. Finally, shared decision making prior to lung cancer screening should preferably take place using age and sex-specific graphical decision aids.

The general discussion of this thesis also provides recommendations for future research. First, the identification of ways to increase the currently low uptake of lung cancer screening in the United States should take priority. Second, efforts to optimize eligibility criteria and screening intervals should be continued. Third, strategies to overcome racial disparities in lung cancer screening eligibility and subsequent treatment should be explored. Fourth, the relative contributions of new lung cancer therapeutics (immunotherapy) and lung cancer screening to the reduction of lung cancer burden should be assessed. Fifth, an international study on lung cancer specific HSUVs should be initiated, addressing current gaps in knowledge. Finally, a modeling study should assess the lung cancer screening strategy with the optimal balance between benefits and harms in the Netherlands.

Dutch Summary

(Samenvatting)

Algemene inleiding

Roken is de belangrijkste risicofactor voor longkanker. Daarom is primaire preventie (stoppen met roken) in potentie de belangrijkste manier om longkanker te voorkomen. Sinds de jaren '60 is veel voortgang geboekt met anti-rookbeleid. Desondanks blijft longkanker wereldwijd de belangrijkste oorzaak van kankersterfte. Op het moment dat patiënten klachten krijgen en een arts bezoeken, is de longkanker vaak al uitgezaaid. Momenteel zijn er geen curatieve behandelingsmogelijkheden voor uitgezaaide longkanker. Het doel van secundaire preventie (screening) is om longkanker op te sporen voordat het klachten veroorzaakt. In dat geval is de ziekte vaak minder ver gevorderd, waardoor er betere behandelingsopties zijn. In 2011 toonde de Amerikaanse National Lung Screening Trial aan dat de sterfte aan longkanker met 20% kan worden teruggebracht door huidige en voormalige rokers met een hoog risico drie screenings te laten ondergaan middels low-dose computed tomography scans. Onlangs werden deze bevindingen ruimschoots bevestigd door het Nederlands-Leuvens Longkanker ScreeningsONderzoek (NELSON). In de Verenigde Staten wordt sinds 2013 jaarlijkse longkankerscreening aanbevolen voor 55 tot 80-jarige personen, die minstens 30 pakjaren hebben gerookt en niet langer dan 15 jaar geleden gestopt zijn met roken. Ondanks deze aanbeveling wordt in de Amerikaanse praktijk slechts een beperkt deel van deze doelgroep daadwerkelijk gescreend. In Europa en het Verenigd Koninkrijk wordt de invoering van een structureel longkankerscreeningsprogramma al een aantal jaar overwogen. Intussen zijn er nog veel longkankerscreenings-gerelateerde onderwerpen waarover het laatste woord nog niet is gesproken.

In dit proefschrift werden twee van deze onderwerpen behandeld. In het eerste deel (hoofdstukken 1-3) werd onderzocht welke behandelingen longkankerpatiënten in de Verenigde Staten momenteel krijgen. Vervolgens werd onderzocht hoe deze behandelingspatronen veranderen door de invoering van longkankerscreening. In het tweede deel van dit proefschrift werden de gunstige en schadelijke effecten van een longkankerscreeningsprogramma in de Verenigde Staten onderzocht vanuit verschillende perspectieven.

Deel I: Behandeling van longkanker

Hoofdstuk 1

In hoofdstuk 1 werd de initiële behandeling van 441812 longkankerpatiënten uit de Amerikaanse National Cancer Database onderzocht. Deze personen werden tussen 2010 en 2014 gediagnosticeerd. Een aanzienlijk deel (21.6%) van deze patiënten kreeg geen initiële behandeling. Slechts 62.1% kreeg de behandeling die door de richtlijnen wordt aanbevolen. Ondanks een correctie voor relevante patiënt-, tumor-, en behandelaarsgebonden factoren, hadden Afro-Amerikaanse patiënten en ouderen minder kans om de aanbevolen behandeling te krijgen. De resterende 16.3% van de patiënten kreeg wel een behandeling, maar deze was minder intensief dan aanbevolen door de richtlijnen. De behandelingspatronen binnen deze laatste groep suggereerden dat sommige behandelingen vaker gegeven zouden kunnen worden, zoals stereotac-

tische radiotherapie (SBRT) voor patiënten met een niet-kleincellig longcarcinoom (NSCLC) in een vroeg stadium die niet in aanmerking komen voor een operatie.

Hoofdstuk 2

In hoofdstuk 2 werd wederom de Amerikaanse National Cancer Database gebruikt om specifieker te kijken naar de behandelingen van patiënten die tussen 2010-2014 gediagnosticeerd werden met een vroeg stadium (stadium I-II) NSCLC. Onder patiënten met een stadium IA NSCLC, die behandeld werd met radiotherapie, nam het gebruik van stereotactische bestraling (stereotactic body radiation therapy - SBRT) toe van 53.4% in 2010 naar 73.0% in 2014. Deze percentages waren lager onder patiënten met een stadium IB-IIB NSCLC, maar de relatieve toename over de tijd was vergelijkbaar. In hoofdstuk 2 werd daarnaast onderzocht welk deel van de operaties onder patiënten met een vroeg stadium NSCLC gebeurde middels een minimaal invasieve operatie (een kijkoperatie of een robot-geassisteerde operatie). Onder patiënten met een stadium IA NSCLC nam dit percentage tussen 2010 en 2014 toe van 28.7% naar 48.6%, terwijl het aantal minimaal invasieve operaties dat uiteindelijk toch werd afgemaakt als een open operatie (conversies) binnen dezelfde periode afnam van 17.0% naar 9.1%. Het aandeel minimaal invasieve operaties was lager onder patiënten met een stadium IB-IIB NSCLC, maar het aantal conversies was hoger.

Hoofdstuk 3

In hoofdstuk 3 werd het MISCAN-Long microsimulatiemodel uitgebreid met geslachts-, stadium-, histologie-, en leeftijdsspecifieke behandelingsgegevens uit de Amerikaanse National Cancer Database. Het model werd vervolgens gebruikt om te voorspellen hoe de vraag naar verschillende longkankerbehandelingen zal veranderen door de invoering van longkankerscreening in de Verenigde Staten. Als 50% van de personen die tussen 2018 en 2040 voor longkankerscreening in aanmerking komen (volgens de criteria van de United States Preventive Task Force (USPSTF)) ook daadwerkelijk gescreend wordt, zal de vraag naar longkankeroperaties met 37% toenemen. Het grootste deel van deze toegenomen vraag zal in de eerste jaren plaatsvinden. Deze piek in vraag naar longkankerchirurgie kan verlicht worden door het aantal gescreende personen in de eerste jaren gelijkmatig op te bouwen. Het gebruik van radiotherapie en chemotherapie zal door longkankerscreening iets afnemen.

Deel II: Gunstige en schadelijke effecten van een longkankerscreeningsprogramma

Hoofdstuk 4

In hoofdstuk 4 werden drie methoden vergeleken om overdiagnose door longkankerscreening in de Verenigde Staten te kwantificeren. De *cumulative excess*

incidence methode werd gebruikt om het percentage door screening gevonden longkankers dat overgediagnosticeerd was te schatten binnen enkele losse geboortecohorten. Binnen het cohort dat in 1950 werd geboren was dat percentage 10.5% en binnen het cohort dat in 1990 werd geboren was dat percentage 5.9%. De microsimulatie-methode werd gebruikt om het jaarlijkse percentage overdiagnose tussen 2018 en 2040 te schatten onder de algemene Amerikaanse bevolking. Deze algemene bevolking is opgebouwd uit een groot aantal verschillende geboortecohorten. Middels de microsimulatie-methode bleek dat het percentage door screening gevonden longkankers dat overgediagnosticeerd was toenam van 7.1% in 2018 tot 9.5% in 2040. Tijdens dezelfde periode nam het percentage van alle longkankers (zowel door screening als klinisch gevonden) dat overgediagnosticeerd was af van 3.7% naar 1.4%. De verschillen in overdiagnose tussen de geboortecohorten en over de tijd konden verklaard worden doordat rookgedrag afneemt. Daardoor wordt het risico op longkanker steeds kleiner. Ook komen er steeds minder mensen in aanmerking voor longkankerscreening. Ten slotte toont hoofdstuk 4 aan dat de derde methode, de *annual excess-incidence* methode, niet corrigeert voor deze trends. Daarom is deze methode niet geschikt om overdiagnose in de algemene bevolking te kwantificeren.

Hoofdstuk 5

In hoofdstuk 5 werd de literatuur over longkanker-specifieke *health state utility values* (HSUVs) op een rij gezet. HSUVs worden gebruikt om het aantal *quality-adjusted life years* (QALYs) te berekenen dat door screening wordt gewonnen. De literatuurreview richtte zich specifiek op HSUVs die berekend zijn vanuit een maatschappelijk perspectief, met behulp van op keuzen gebaseerde methoden. Er werden 27 van dit soort studies gevonden. De gepoolde HSUV voor alle longkankerstadia was 0.68. Voor stadium I-II was de gepoolde HSUV 0.78 en voor stadium III-IV 0.69. In een sensitiviteitsanalyse werden alleen de methodologisch meest vergelijkbare studies meegenomen. Deze studies gebruikten het EQ-5D instrument om HSUVs te berekenen. Daarbij pasten zij het *tarief* van het juiste land toe. Dergelijke studies werden voor slechts 8 landen gevonden. Binnen deze studies varieerden HSUVs per stadium en land. Een subgroepanalyse toonde aan dat HSUVs voor gemetastatseerd NSCLC lager werden gedurende het laatste levensjaar. Ten slotte suggereerde subgroepanalyses dat HSUVs voor gemetastaseerd NSCLC mogelijk verschillen naar lijn van behandeling en progressiestatus.

Hoofdstuk 6

In hoofdstuk 6 werden de gunstige en schadelijke effecten berekend van deelname aan het door de USPSTF aanbevolen longkankerscreeningsprogramma. Dit werd apart berekend voor mannen en vrouwen van verschillende leeftijden, die in het jaar 2020 voor screening in aanmerking kwamen. Zowel de gepoolde HSUVs uit hoofdstuk 6 als de HSUVs van de meest valide Amerikaanse studie werden gebruikt om het aantal gewonnen QALYs te berekenen. Beide HSUVs leverden vergelijkbare resultaten op.

Vergeleken met 55-jarige personen die in 2020 in aanmerking komen voor screening, ondervinden oudere personen die in 2020 in aanmerking komen voor screening minder voordelen van deelname aan screening. Tevens ondervinden zij minder nadelige gevolgen. De kans op overdiagnose is onder oudere personen echter groter. Vergeleken met mannen met dezelfde leeftijd, ondervinden vrouwen meer voordelen van screening. Tevens ondervinden zij vaker nadelige gevolgen en is de kans op overdiagnose groter. Deze bevindingen wijzen erop dat de informatie die voorafgaand aan het screenen – tijdens *shared decision making* – met patiënten wordt besproken, bij voorkeur gepersonaliseerd moet zijn naar leeftijd en geslacht. Daarom werden in hoofdstuk 6 leeftijds- en geslachtsspecifieke (grafische) beslishulpen gepresenteerd.

Algemene discussie

De algemene discussie van dit proefschrift geeft een overzicht van de belangrijkste conclusies die op basis van de verschillende hoofdstukken getrokken kunnen worden. Ten eerste krijgen Afro-Amerikaanse patiënten met longkanker en ouderen geen optimale behandeling, ondanks correctie voor relevante patiënt-, tumor-, en behandelaarsgebonden factoren. Ten tweede nam het gebruik van SBRT en minimaal invasieve chirurgie in de Verenigde Staten substantieel toe tussen 2010 en 2014, terwijl het aantal conversies naar open chirurgie gedurende dezelfde periode afnam. Het aanpakken van de geobserveerde ongelijkheden in longkankerbehandeling en het toenemende gebruik van SBRT en minimaal invasieve chirurgie, zullen bijdragen aan een succesvolle voortzetting van de invoering van longkankerscreening in de Verenigde Staten. Ten derde zal de voortgezette invoering van longkankerscreening in de Verenigde Staten zorgen voor een substantiële toename in de vraag naar longkankerchirurgie, met een uitgesproken piek in de eerste jaren. Deze piek in vraag naar longkankerchirurgie kan verlicht worden door het aantal gescreende personen in de eerste jaren gelijkmatig op te bouwen. Ten vierde is het belangrijk om de juiste methoden toe te passen om de hoeveelheid overdiagnose door longkankerscreening in de algemene bevolking te kwantificeren, omdat gecorrigeerd moet worden voor afnemend rookgedrag. Ten vijfde is het belangrijk om methodologisch juiste HSUVs te gebruiken om de gezondheidswinst door longkankerscreening uit te kunnen drukken in *quality-adjusted life years.* Ten slotte is het aan te bevelen om bij *shared decision making* voorafgaand aan longkankerscreening een leeftijds- en geslachtsspecifieke beslishulp te gebruiken.

In de algemene discussie van dit proefschrift worden tevens aanbevelingen gedaan voor vervolgonderzoek. Ten eerste is het belangrijk dat er manieren worden gevonden om het aantal voor screening in aanmerking komende personen in de Verenigde Staten dat daadwerkelijk wordt gescreend te vergroten. Ten tweede moet er meer onderzoek worden gedaan naar de optimale criteria om personen voor screening te selecteren en naar het optimale screeningsinterval. Ten derde moeten er strategieën ontwikkeld en getest worden om rassenongelijkheid in de selectie van personen voor longkankerscreening en in de behandeling van longkanker tegen te gaan. Ten vierde wordt het aanbevolen om te onderzoeken wat de relatieve bijdragen van nieuwe behandelingen (immunotherapie) en longkankerscreening zijn aan het

verminderen van de ziektelast door longkanker. Ten vijfde wordt het aanbevolen om een internationaal onderzoek op te starten, waarin de huidige hiaten in de kennis over longkanker-specifieke HSUVs worden opgevuld. Ten slotte wordt het aanbevolen om middels een modelleerstudie te onderzoeken welke longkankerscreeningsstrategie de beste balans tussen gunstige en schadelijke effecten zal geven in Nederland.

About the Author

Erik Ferdinand Blom was born on July 30th 1990, in Nieuwegein, the Netherlands. During his bilingual secondary education at the Anna van College in Nieuwegein, he completed a two-year extracurricular honors program in the exact sciences at the Junior College Utrecht (part of the University of Utrecht). After completing secondary education *cum laude,* he was accepted to study Medicine at the University of Utrecht, the Netherlands. Throughout his medical studies, he served as a student-assistant, teaching various subjects to fellow students (including anatomy – see the preface to this thesis). In addition, he completed an internship in Ophthalmology at the Himalaya Eye Hospital in Pokhara, Nepal, and subsequently travelled extensively across South-East Asia and Australia. During the final year of his studies, he completed his research internship at the department of Public Health of the University of Utrecht (Julius Center). After obtaining his medical degree, he travelled extensively across Brazil and Argentina. Subsequently, he briefly worked on a large IT project at the University of Utrecht, designing and providing training on the use of a new electronic medical record to all staff of the department of Radiology. Then, his affection for medicine and science led him to initiate a PhD at the department of Public Health of the Erasmus Medical Center in Rotterdam, the Netherlands. During this 4 year period, his research focused on the early detection, treatment, and quality of life of lung cancer. He was a participating member of the U.S. based Cancer Intervention and Surveillance Modeling Network (CISNET), a consortium that uses statistical modeling to assess strategies and policies for the prevention, screening, and treatment of cancer. This thesis is the synthesis of these 4 years of scientific work.

PhD Portfolio

Name PhD student: E.F. Blom	**PhD period:** 2016-2020
Erasmus MC Department: Public Health	**Promotor:** Prof. dr. Harry J. de Koning
Research School: NIHES	**Supervisor:** dr. Kevin ten Haaf

1. PhD training	**Year**	**Workload**	
		Hours	**ECTS**
Courses at the Netherlands Institute for Public Health (NIHES)			
ESP25 Health Economics	2016	20	0.7
CC02 Biostatistical Methods I: Basic Principles	2016	160	5.7
HS05 Planning and Evaluation of Screening	2017	39	1.4
EWP02 Advanced Topics in Decision-making in Medicine	2019	67	2.4
Other courses			
Biomedical English Writing and Communication	2017	84	3
Seminars and workshops			
Seminars at MGZ	2016-2020	120	4.3
Cancer Intervention and Surveillance Modeling Network (CISNET) Webinars	2016-2020	3	0.1
Course “Time management” (Erasmus MC, department of Public Health)	2016	8	0.3
Course “Scientific Integrity” (Erasmus MC)	2017	8	0.3
Medical Business Masterclass 2017	2017	14	0.5
Symposium “Immuno-oncologie: nieuwe ontwikkelingen en optimale inzet van immunotherapie in de praktijk”	2017	3	0.1
Symposium ISOQOl-NL “Big data and PROMs in Healthcare”	2017	6	0.2
Teaching workshop “Omgaan met groepen” (Desiderius School)	2018	8	0.3

International conferences

Semi-annual Cancer Intervention and Surveillance Modeling Network (CISNET) meetings at various locations in the United States	2016-2020	252	9
17th World Conference on Lung Cancer, Vienna, Austria	2016	32	1.2
18th World Conference on Lung Cancer, Toronto, Canada	2018	32	1.2
International Cancer Screening Network Conference 2019, Rotterdam, the Netherlands	2019	24	0.9
20th World Conference on Lung Cancer, Barcelona, Spain	2019	32	1.2

Presentations

Presentations on ongoing projects at Semi-annual Cancer Intervention and Surveillance Modeling Network (CISNET) meetings at various locations in the United States	2016-2020	28	1
VO meeting, Erasmus MC, department of Public Health. Oral presentation "Modeling lung cancer treatment".	2017	8	0.3
Invited speaker at the Tobacco, Lung and Modeling Interest Group, University of Michigan School of Public Health. Oral presentation "Lung Cancer Treatment in the Context of Screening"	2017	8	0.3
18th World Conference on Lung Cancer, Toronto, Canada. Oral presentation "Patterns of Lung Cancer Care in the United States: Developments and Disparities"	2018	28	1
18th World Conference on Lung Cancer, Toronto, Canada. Poster presentation "Treatment Capacity Required for Full-Scale Implementation of Lung Cancer Screening in the United States"	2018	14	0.5
Journal Club, Erasmus MC, department of Public Health. Oral presentation "Recruitment of Participants for Lung Cancer Screening"	2019	16	0.6

VO meeting, Erasmus MC, department of Public Health. Oral presentation "Trends in Lung Cancer Risk and Screening Eligibility Affect Overdiagnosis Estimates".	2019	6	0.2
International Cancer Screening Network Conference 2019, Rotterdam, the Netherlands. Oral presentation "Trends in Lung Cancer Risk and Screening Eligibility Affect Overdiagnosis Estimates"	2019	28	1

2. Teaching	**Year**	**Workload**	
		Hours	**ECTS**
Supervising Community Project	2017	40	1.4
VO Betaalbaarheid van de zorg	2019	16	0.6

3. Other	**Year**	**Workload**	
		Hours	**ECTS**
MISCAN education and documentation working group	2016-2019	157	5.6
Assisted with case and Erasmus MC representation at Landelijke Econometristendag (LED) 2018	2018	8	0.3
Responsible for content of website for International cancer Screening Conference 2019, Rotterdam, the Netherlands	2018-2019	28	1
Peer reviewing for Chest	2019	24	0.9
Peer reviewing for Nature Scientific Reports	2019	6	0.2
Assisted with case and Erasmus MC representation at Landelijke Econometristendag (LED) 2019	2019	8	0.3
Assisted with case and Erasmus MC representation at Landelijke Econometristendag (LED) 2020	2020	8	0.3
TOTAL		**1343**	**48.3**

List of Publications

In this thesis

Blom EF, ten Haaf K, Arenberg DA, de Koning HJ. Disparities in Receiving Guideline-Concordant Treatment for Lung Cancer in the United States. Ann Am Thorac Soc 2020;17(2):186-194.

Blom EF, ten Haaf K, Arenberg DA, de Koning HJ. Uptake of minimally invasive surgery and stereotactic body radiation therapy for early stage non- small cell lung cancer in the USA: an ecological study of secular trends using the National Cancer Database. BMJ Open Resp Res 2020;7(1):e000603.

Blom EF, ten Haaf K, Arenberg DA, de Koning HJ. Treatment capacity required for full-scale implementation of lung cancer screening in the United States. Cancer 2019;125(12):2039-2048.

Blom EF, ten Haaf K, de Koning HJ. Trends in lung cancer risk and screening eligibility affect overdiagnosis estimates. Lung Cancer 2020;139:200-206.

Blom EF, ten Haaf K, de Koning HJ. Systematic Review and Meta-Analysis of Community- and Choice-Based Health State Utility Values for Lung Cancer. PharmacoEconomics 2020.

Other publications

Ten Haaf K, Bastani M, Cao P, Jeon J, Toumazis I, Han SS, Plevritis SK, Blom EF, Kong CY, Tammemagi MC, Feuer EJ, Meza R. de Koning HJ. A comparative modeling analysis of risk-based lung cancer screening strategies. J Natl Cancer Inst 2020;112(5):djz164.

Criss SD, Cao P, Bastani M, Ten Haaf K, Chen Y, Sheehan DF, Blom EF, Toumazis I, Jeon J, de Koning HJ, Plevritis SK, Meza R, Kong CY. Cost-Effectiveness Analysis of Lung Cancer Screening in the United States: A Comparative Modeling Study. Ann Intern Med 2019;171(11):796-804.

Blom EF, Gunning MN, Kleinrensink NJ, Lokin AS, Bruijnzeel H, Smit AL, Grolman W. Influence of Ossicular Chain Damage on Hearing After Chronic Otitis Media and Cholesteatoma Surgery: A Systematic Review and Meta-analysis. JAMA Otolaryngol Head Neck Surg 2015;141(11):974-982.

Blom EF. Decentrale selectie van aanstaande medisch studenten: een verbetering? Medisch-onderwijskundige verdieping. Utrecht: Expertisecentrum voor Onderwijs en Opleidingen UMC Utrecht; 2015. p. 16–24. ISBN 978-94-6228-734-1.

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Dear dr. ten Haaf, dear Kevin. Thank you for your guidance and supervision during the past 4 years. I have learned a great deal from you. For example, you have taught me to compile the results of complex analyses into a compelling and (relatively) easy-to-follow narrative, which is a skill I will probably benefit from for the rest of my life. Your attention to detail is remarkable and you always managed to identify potential improvements to our work.

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