UNIVERSITAT DE BARCELONA

Assessing Value in Lung Cancer Treatment: A Detailed Cost-Benefit Analysis of Clinical Management Strategies

Rudith Guzmán Portillo

Assessing Value in Lung Cancer Treatment: A Detailed Cost-Benefit Analysis of Clinical Management Strategies

Doctoral thesis dissertation presented by:

Rudith Guzmán Portillo

To apply for the degree of doctor at the University of Barcelona.

Directed by

Dra. Ángela Guirao Montes, MD, PhD

Dr. Laureano Molins López-Rodó, MD, PhD

Tutor:

Dr. Laureano Molins López-Rodó, MD, PhD

Doctoral Program in Medicine and Translational Research

School of Medicine and Health Sciences

University of Barcelona

November 2023

Assessing Value in Lung Cancer Treatment: A Detailed Cost-Benefit Analysis of Clinical Management Strategies

Acknowledgments

In the odyssey that is the pursuit of a PhD, there are many moments that test our perseverance, courage, and determination. Standing at the conclusion of this journey, I am filled with immense gratitude for the people who have supported and guided me through the challenges and triumphs of these past years. This thesis would not have been possible without the unwavering love and encouragement of those who have walked beside me, and it is to them that I dedicate these words of acknowledgment.

First and foremost, I must express my heartfelt appreciation to my two exceptional directors, Dr. Laureano Molins and Dra. Ángela Guirao. Their wisdom, experience, and passion for medicine have been nothing short of inspiring. Dr. Molins, your ability to see the potential in every situation has been a beacon of hope and guidance, and I am eternally grateful for your patience and mentorship and for fostering an environment that encourages continuous learning and growth. Angela, your friendship and your keen eye for detail and ability to challenge me to reach greater heights have been pivotal in molding me into the surgeon I am today. You have both given me the wings to soar.

To my loving family – my mother, who has been my rock and the source of my strength, and my two brothers, who have always believed in me and supported me unconditionally – words cannot express the depths of my gratitude. Mom, your unwavering love and belief in me have been the foundation upon which I have built my dreams. Your selflessness and sacrifices have not gone unnoticed, and I am so grateful for everything you have done to make this journey possible. To my brothers,

thank you for being my cheerleaders, confidants, and best friends. You have carried me through even the darkest of times.

I would also like to extend my appreciation to my colleagues, who have become a second family to me. I would like to express my sincere gratitude to my esteemed surgery mentor Dr. Gimferrer, your unwavering guidance, expertise, and support throughout my journey in becoming a skilled surgeon have been invaluable. Thank you for sharing your wealth of knowledge, and for inspiring me to strive for excellence. David, thank you for your guidance, belief in my abilities and have consistently challenged and encouraged me to reach my full potential, pushing me beyond my limits and broadening my horizons.

Marc, your willingness to lend an ear, offer insightful advice, and collaborate on complex cases has been instrumental in my growth and development. Our shared experiences in the operating room have fostered a sense of camaraderie and mutual respect that I will always cherish, you have been steadfast companion throughout this challenging journey.

Leo and Pablo, your camaraderie, encouragement, and shared passion for our work have made the countless hours spent in the hospital not only bearable but enjoyable. I am honored to have shared this journey with such brilliant and dedicated individuals, and I look forward to watching each of you flourish in your respective fields. I am truly fortunate to have had the opportunity to learn from such remarkable professionals, and I will carry the lessons you've taught me throughout my career.

To my incredible circle of friends – you are my safe harbor in stormy seas, my companions on this voyage, and the ones who make life truly worth living. Thank you for the laughter, the tears, the late-night conversations, and the memories that we will cherish forever. Your love and friendship have been a balm to my soul, and I am eternally grateful for each and every one of you.

Last but certainly not least, I must express my deepest gratitude to Sebastien, my partner and my rock. Your unwavering love, understanding, and support have been my guiding star through tough times. Your belief in me, even when I doubted myself, has given me the strength to persevere and conquer the challenges that have come my way. I cannot imagine this journey without you by my side, and I am eternally grateful for your love and partnership. Thank you for dreaming with me, for believing in me, and for holding my hand every step of the way.

I am truly humbled by the love, support, and guidance that I have received from each of you throughout this journey. It is impossible to overstate the profound impact that you have had on my life and work, and I will carry your love and encouragement with me as I embark on the next chapter of my life. As I stand on the threshold of a new beginning, I am filled with the knowledge that I am not alone, and that I am surrounded by the support of those who have helped to shape me into the surgeon I am.

To my mother,

Thank you

Abbreviations

FNA: Fine Needle Aspiration.

AAPM: American Association of Physicists in Medicine.

AATS: American Association for Thoracic Surgery.

CBA: Cost-Benefit Analysis.

ACCP: American College of Chest Physicians.

CEA: Cost-Effectiveness Analysis.

CMA: Cost Minimization Analysis.

ACR: American College of Radiology.

ACRIN: American College of Radiology Imaging Network.

ACS: American Cancer Society.

CUA: Cost-Utility Analysis.

AECC: Asociación Española Contra el Cáncer. (SPAIN)

AEE or EE: Economic Analysis and Evaluation or Economic Evaluation.

AIS: Adenocarcinoma In Situ.

ASCO: American Society of Clinical Oncology.

DALY: Disability-Adjusted Life Years.

YLD: Years of Life with Disability.

YLG: Years of Life Gained.

PYLL: Potential Years of Life Lost.

CDCP: Centers for Disease Control and Prevention.

QOL: Quality of Life.

BD: Burden of Disease.

ECAC: European Code Against Cancer.

cTNM: Clinical Tumor Nodes Metastases Classification

pTNM: Pathological Tumor Nodes Metastases Classification

FDA: Food and Drug Administration.

GCO: Global Cancer Observatory.

GECP: Grupo Español de Cáncer de Pulmón. (SPAIN)

GLOBOCAN: Proyecto de la GCO. (SPAIN)

IARC: International Agency for Research on Cancer.

IASLC: International Association for the Study of Lung Cancer.

INAHTA: International Network of Agencies for Health Technology Assessment.

INC: Instituto Nacional del Cáncer. (SPAIN)

INE: Instituto Nacional de Estadística. (SPAIN)

MEDCAC: Medicare Evidence Development & Coverage Advisory Committee

MLND: Mediastinal Lymph Node Dissection.

MLNS: Mediastinal Lymph Node Sampling.

NCCN: National Comprehensive Cancer Network.

NCI: National Cancer Institute.

NICE: The National Institute for Health and Care Excellence.

NSCLC: Non-Small-Cell Lung Cancer

LC: Lung cancer

LDCT: Low-dose Computed Tomography

PET: Positron Emission Tomography

POMS: The Profile of Mood States.

PSA: Prostatic Specific Antigen.

QALY (Quality-Adjusted Life Year.

RATS: Robotic-Assisted Thoracic Surgery

REDECAN: Red Española de Registros de Cáncer. (SPAIN)

SBRT: Stereotactic Body Radiation Therapy.

SEOM: Sociedad Española de Oncología Médica. (SPAIN)

DANTE: Detection And screening of early lung cancer with Novel Imaging Technology.

DLCST: Danish Lung Cancer Screening Trial

ELCAP: Early Lung Cancer Action Project.

I-ELCAP: International Early Lung Cancer Action Project.

MILD: Multicentric Italian Lung Cancer Detection.

NELSON: Nederlands-Leuvens Longkanker Screenings Onderzoek

NLST: National Lung Cancer Trial.

P-ELCAP: Pamplona Early Lung Cancer Project.

PLCO: Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial.

PLuSS: Pittsburgh Lung Screening Study.

UKLS: UK Lung Cancer Screening.

Resumen

Título

Evaluación del valor del tratamiento del cáncer de pulmón: un análisis coste-beneficio detallado de las estrategias de manejo clínico

Introducción

El cáncer de pulmón representa un grave problema de salud debido a que, si bien es uno de los tipos de cáncer más comunes, también es el de mayor mortalidad. Esta alta mortalidad se debe al carácter asintomático de la enfermedad durante las primeras etapas de su desarrollo, lo que a su vez conduce a una detección tardía, cuando el cáncer ya se encuentra en un estadio avanzado; el tumor ya se ha diseminado y por lo tanto no puede tratarse con cirugía. Por tanto, la única posibilidad terapéutica depende del tratamiento sistémico, que tiene un peor pronóstico de la enfermedad además de un aumento del coste y de recursos.

Esta tesis doctoral expone la posibilidad de que el tratamiento quirúrgico del cancer de pulmón sea más rentable que el tratamiento médico.

Hipotesis

La hipótesis principal de esta tesis doctoral afirma que la cirugía para tratar el cáncer de pulmón es más costo-efectiva que el tratamiento médico. Se basa en dos ideas: primero, que la cirugía es más rentable que la terapia médica; segundo, que la resección quirúrgica, siguiendo las directrices del Comité Multidisciplinario de Cáncer, podría ser más económica que realizar biopsias pulmonares antes de la cirugía.

Objetivos

General

Resaltar la ventaja económica de la cirugía sobre las terapias médicas en el tratamiento del cáncer de pulmón.

Específicos

1. Demostrar que la cirugía para el cáncer de pulmón es clínica y económicamente más viable que las terapias médicas.
2. Probar que la resección quirúrgica, siguiendo las directrices del Comité Multidisciplinario de Cáncer, es más costo-efectiva que las biopsias pulmonares guiadas por TAC.

Metodos y Resultados

Análisis comparativo, observacional y retrospectivo incluye a 13.186 residentes en Cataluña diagnosticados con cáncer de pulmón por primera vez entre el 1 de enero de 2014 y el 31 de diciembre de 2016 en el sistema público de salud. Se excluyeron del análisis los pacientes tratados con quimio y radioterapia antes del 1 de enero de 2014 y con un diagnóstico de cualquier metástasis antes de la fecha de diagnóstico del cáncer de pulmón. Todos los pacientes incluidos fueron tratados médica o quirúrgicamente de acuerdo con las mejores prácticas y recomendaciones internacionales. El análisis se llevó a cabo hasta 30 meses después del diagnóstico de cáncer de pulmón . Las variables del estudio tienen como resultado la estimación del coste anual de cada opción terapéutica por enfermo , además del valor promedio del cálculo de coste beneficio. Este estudio real confirma que la cirugía es la mejor opción terapéutica para el cáncer de pulmón, ya que ofrece una mejor supervivencia y un retorno más rápido a las actividades diarias en comparación con los tratamientos médicos. Además, el tratamiento quirúrgico resulta en un menor uso de recursos sanitarios y menor coste para los contribuyentes. Los datos indican que un programa

de detección de cáncer de pulmón se equilibrará económicamente entre 3 y 6 años después de su implementación, generando ahorros en costos de salud a largo plazo.

Conclusiones

1. La intervención quirúrgica para el tratamiento del cáncer de pulmón, especialmente cuando se adhiere a las directrices del Comité Multidisciplinario de Cáncer (MCC), es tanto clínica como económicamente más eficiente en comparación con las terapias médicas. Esto fue evidente a través de mejores tasas de supervivencia, un retorno más rápido a la autonomía y un menor costo de la atención médica.
2. El uso de la cirugía minimamente invasiva, como método de abordaje quirúrgico puede impactar significativamente en la rentabilidad de los tratamientos para el cáncer de pulmón, asociándose con estancias hospitalarias más cortas y menores costos totales.
3. La implementación de programas de detección de cáncer de pulmón tiene el potencial de mejorar aún más la rentabilidad al permitir la identificación y el tratamiento tempranos de los pacientes, con puntos de equilibrio y ahorros en los costos de atención médica alcanzables en unos pocos años desde la iniciación del programa. Esta conclusión apunta hacia la necesidad de más investigaciones para refinar los procesos de selección de pacientes.

INDEX

1. Introduction

Lung cancer (LC) represents a serious health problem due to the fact that, while it is one of the most common cancer types, it is also the one with the highest mortality[1]. This high mortality is due to the asymptomatic nature of the illness during the early stages of its development, which in turn leads to a late detection, when the cancer is already in an advanced stage; the tumor has already spread and thus cannot be treated with surgery. As a result, the only therapeutical chance depends on systemic treatment, which has a worse prognosis of the disease as well as an increase in the expenditures of resources.

This MD thesis exposes the possibility that surgical LC treatment is more cost-effective than medical treatment.

1.1 Epidemiology

Cancer is expected to be the leading cause of death during the 21st century all over the world. This is caused by the fact that LC is both one of the most common cancer types and at the same time the one with the highest mortality, thus posing a serious health problem for both women and men.

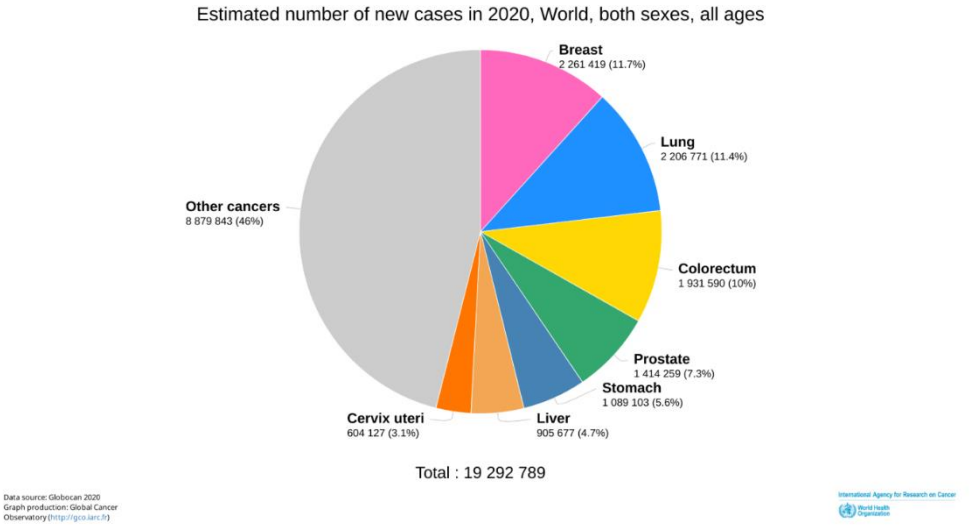
In 2020, deaths recorded worldwide from this disease represented 18% of all cancer deaths. In this sense, not only it was the most frequent cause of cancer death, but also led to more deceases than the sum of colon, breast, and prostate cancer combined. (Figure 1) [1,2].

This low survival rate is mostly due to a delay in LC diagnosis because of the asymptomatic nature of the illness. Consequently, about 30% of patients are diagnosed in stage III and around 40% already in stage IV, when the effectiveness of a curative treatment is minimal.[3]

In Spain, according to the Spanish Lung Cancer Group (GECP), only 16% of new cases are diagnosed before they spread to other parts of the body (Figure 2,3)[4]. Thus, 5-year

survival rate is currently at IA1, 85% for IA2, 80% for IA3, 58% for IB, 46% for IIA, 36% for IIB, 24% for IIIA, 9% for IIIB, and 13% for stage IV [5,6,7].

Due to the fact that tobacco is its most relevant risk factor, LC rates vary depending on the region, reflecting the evolution of the tobacco habit in each given area. At present, while we see a decline in LC rates in men because of the diminution in smoking habit, in women a rising trend in incidence is still observed.



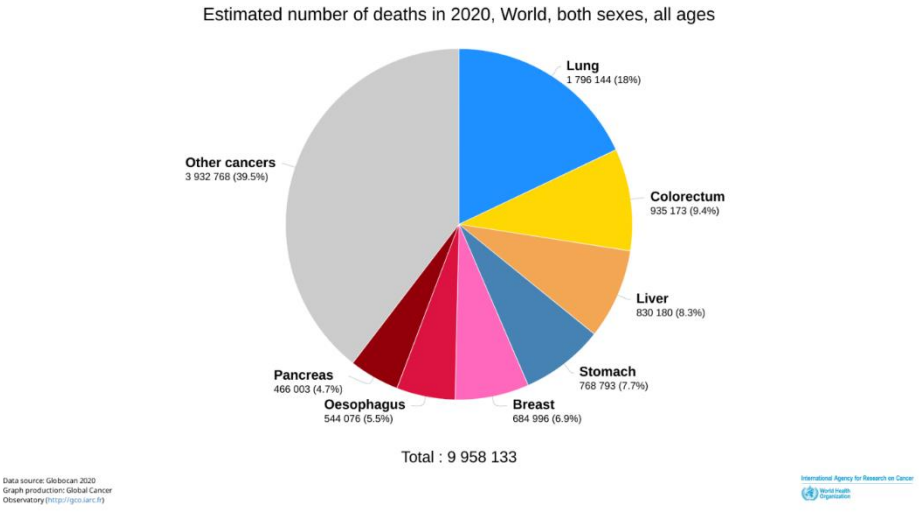


Figure 1: Pie Chart Present the estimated number of new cases in 2020. For world population, both sexes all ages. GLOBOCAN 2020.

Figure 2: Pie Chart Present the Distribution of Deaths due to Cancer in 2020. GLOBOCAN 2020.

Epidemiological information about LC is thus essential for raising awareness of the magnitude and consequences of the problem, and also for informing the action planning and resource allocation protocols devoted to provide effective care to patients.[9,10,11]

In 2018, using data provided by INE, GLOBOCAN projected an estimated linear increase in incidence from 60 cases per 100,000 inhabitants to 78 cases in 2040, reaching approximately 38,762 cases for that year [12](Figure 3).

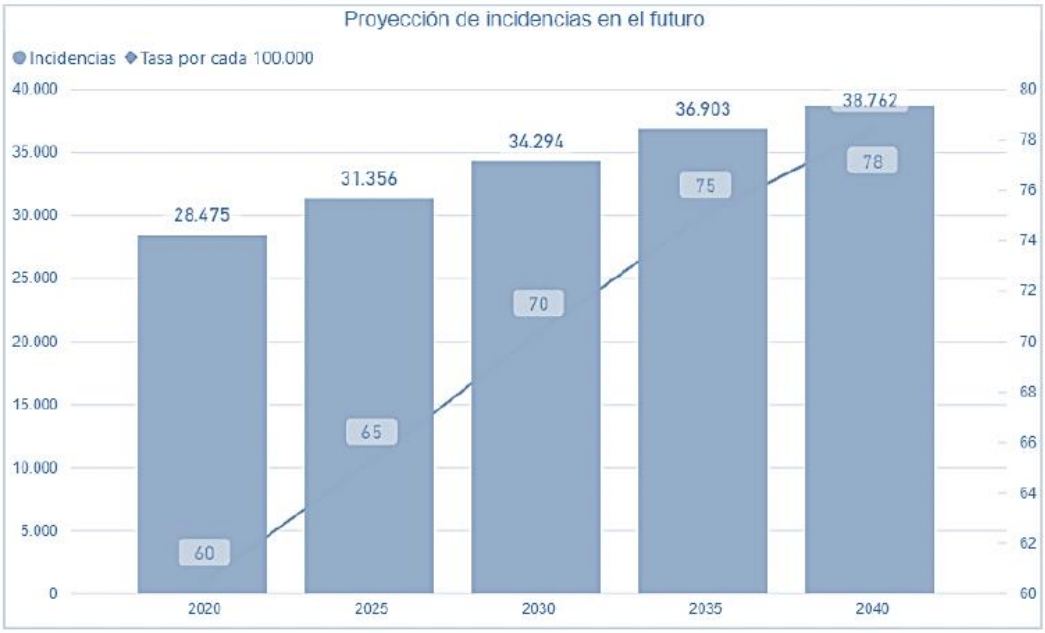


Figure 3. Projection of incidence of PC in Spain. GLOBOCAN 2019 - WHO

1.2 Lung cancer types

LC is classified into two groups: Small Cell Lung Cancer (SCLC) and Non Small Cell Lung Cancer (NSCLC)[13].

SCLC has the worst prognosis of all LC types, with a 2-year survival rate under 5%. It is the most dedifferentiated LC type, since it usually manifests as a mediastinal tumor with early metastatic nodes and distant blood metastasis. SCLC is a very high malignant LC type and only very little cases are eligible to radical treatment due to advanced stages at the moment of diagnosis. Its treatment consists of cisplatin and etoposide.

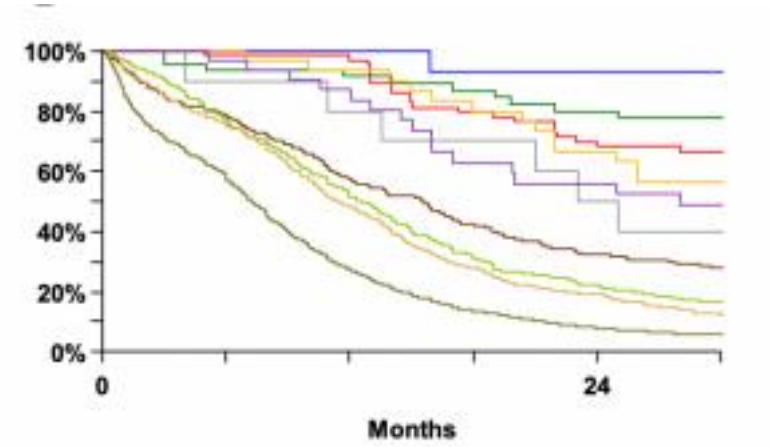
NSCLC is represented by three main different subtypes:

1. Adenocarcinoma: representing 40% of all LC peripheral tumors, they grow in the peripheral bronchi and when in an advanced stage can produce pneumonitis and atelectasis. Adenocarcinoma in situ and minimally invasive adenocarcinoma have very good disease-free survival rates after complete resection, with a five-year rate survival of almost 100%.
2. Squamous Carcinoma: 30% of all LC types, usually originates in the lobar or main bronchi and tends to advance towards the center.
3. Large cell carcinoma: 10% of all LC, it is located proximally and tends to early invasion of mediastinum with a rapid lethal spread.

1.3 Survival

LC survival is directly related to the development of the disease at the time of detection. Early stage detection LCs have a significantly greater chance of being cured. On the other hand, a more advanced stage of LC at the time of detection significantly reduces the chances of a cure. As a result, TNM stage at the moment of the diagnosis is currently the most important LC survival independent prognostic factor.

In the latest proposed TNM classification, a 12 -24 months survival rate of 90% is estimated for stage IA and 27 – 8% respectively for stage IV (Figure 4,5) [7].



cTNM Proposed	Events / N	MST	12 Month	24 Month
IA1	3 / 14	NR	100%	93%
IA2	27 / 67	NR	97%	68%
IA3	15 / 48	NR	91%	80%
IB	16 / 32	33.0	93%	67%
IIA	6 / 10	24.1	80%	50%
IIB	17 / 38	28.0	87%	56%
IIIA	191 / 254	15.6	58%	32%
IIIB	326 / 402	12.6	52%	22%
IIIC	330 / 400	11.4	48%	19%
IV	2620 / 2926	7.3	27%	8%

Figure 4 and 5. Survival graph of the different clinical stages used in the 8th edition of the TNM .

1.4 Mortality

Recent data from Europe shows that LC continues to be the leading cause of cancer deaths. According to data from 2020, LC cased 21.5% of all cancer deaths in men, which represents a decrease of -10.7% since 2012, and 13.7% of all cancer deaths in women, representing an increase of 5.1% since 2012[9]. (Figure 6). LC has a global mortality rate of 33.3/100,000 , causing over 183,400 deaths. In women, the rate was 14.6/100,000, corresponding to 92,300 deaths.

Figure 6

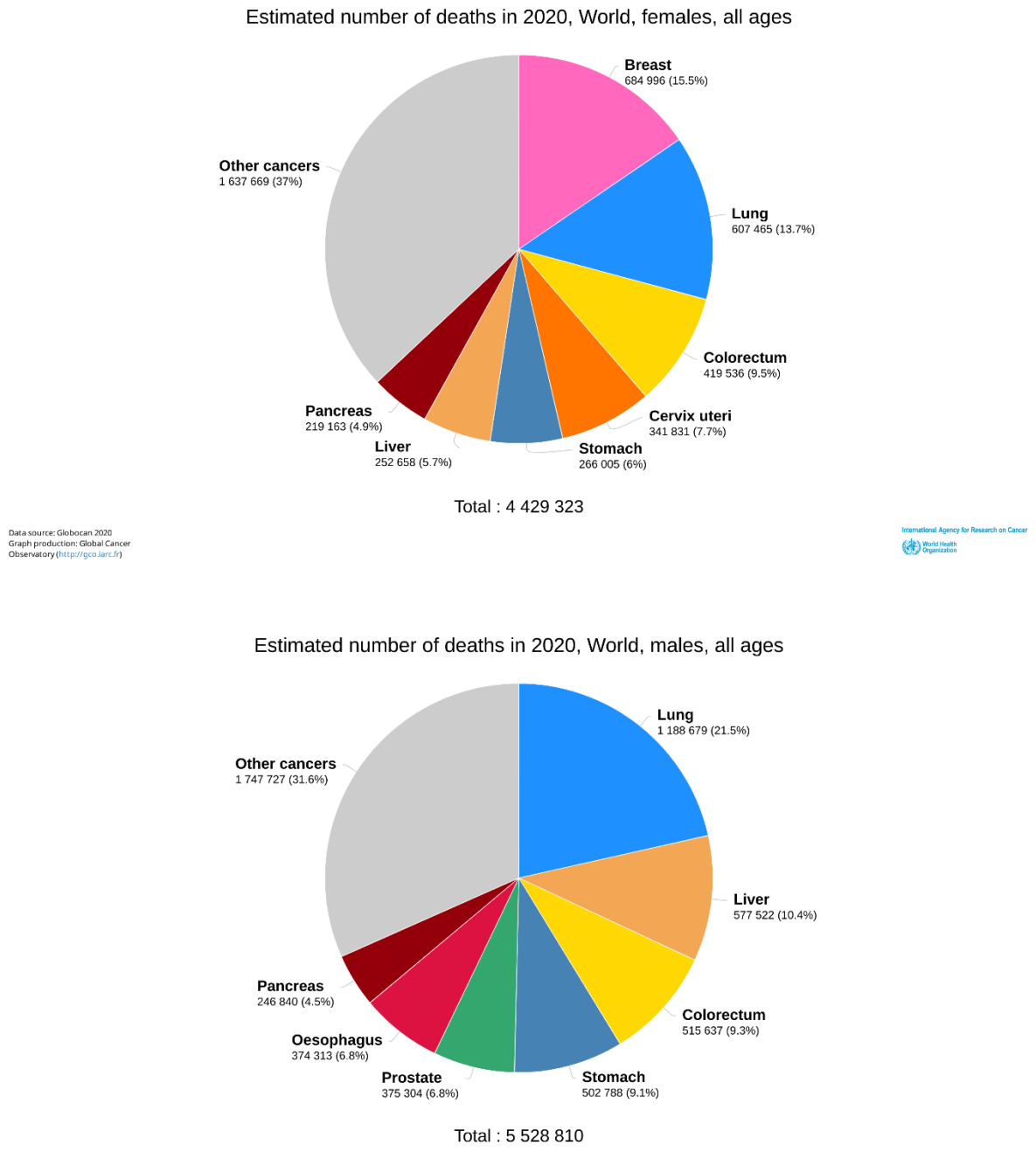


Figure 6. Estimated number of deaths in 2020, World, both sexes, all ages
Data source: Globocan 2020

All these figures highlight the greater mortal aggressiveness of LC compared to the other more common and less fatal tumors such as breast, colon or prostate cancer,

which are diagnosed in early stages in 100%, 89% and 65% of the cases, respectively, according to the American Cancer Society (ACS) 2015 [4].

1.5 Diagnosis

Without undervaluing the much-deserved importance of the very complex LC diagnostic algorithm, the reality is that CT is currently the basis of the diagnostic process.

It should also be noted that since there is currently no screening method for LC, CT is also assuming this role, thus resulting in a compounding importance of CT within the diagnosis process. (Figure 7 and 8).

Management of solid nodules smaller than 8 mm		
Nodule size	*Low-risk patient*	*High-risk patient*
≤4 mm	No follow-up needed	Follow-up at 12 months; if unchanged, no further follow-up
>4–6 mm	Follow-up CT at 12 months; if unchanged, no further follow-up	Initial follow-up CT at 6–12 months, then at 18–24 months if no change
>6–8 mm	Initial follow-up CT at 6–12 months then at 18–24 months if no change	Initial follow-up CT at 3–6 months, then at 9–12 and 24 months if no change
>8 mm	Follow-up CT at around 3, 9, and 24 months, dynamic contrast-enhanced CT, PET and/or biopsy	Same as for low-risk patient
Management of subsolid nodules – solitary pure ground-glass nodule		
Nodule size		
≤5 mm	No follow-up needed (obtain contiguous 1-mm-thick sections to confirm that nodule is truly a pure ground-glass nodule	
>5 mm	Initial follow-up CT at 3 months; if persistent annual CT for ≥3 years (FDG PET is of limited value, potentially misleading and therefore not recommended)	
Management of subsolid nodules – solitary part-solid nodule		
Solid component size		
<5 mm	Initial follow-up CT at 3 months; if persistent, annual CT for ≥3 years	
>5 mm	Initial follow-up CT at 3 months; if persistent, biopsy or surgical resection (consider PET/CT for part-solid nodules with a solid component >8 mm)	

Figure 7. Recommendations for the management of pulmonary nodules referring to the statements from the Fleischner Society. Radiology July 2017, 228-243

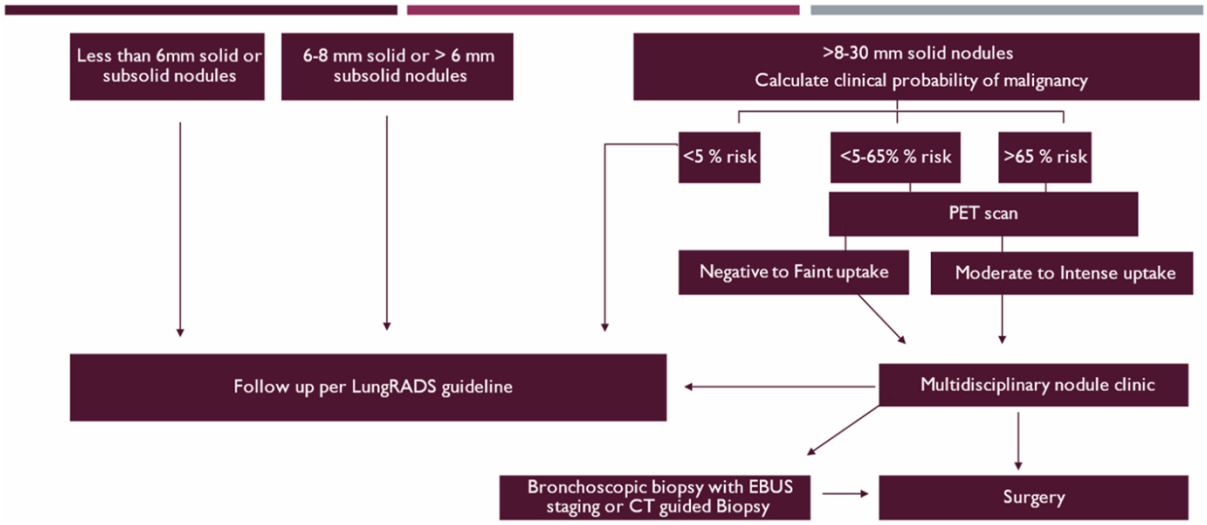


Figure 8. A proposed algorithm for Dominant lung nodule evaluation in a potential surgical candidate. Based on LungRADS and American College of Chest Physicians evidence-based clinical practice guidelines. Respiratory Medecine 214(2023)107277

1.5.1 Screening in Lung Cancer

As mentioned above, the importance of early detection of LC, and its subsequent treatment, makes screening a fundamental procedure. We can define screening as the application of a selection methodology on a population or groups of apparently non-sick people, with the goal of identifying, in an asymptomatic phase, those who are affected by the disease or at significant risk of developing the disease. This methodology includes questionnaires, tests, physical examination, and diagnostic tests[14].

A key indicator of the effectiveness of a screening technique is given by the significant decrease in mortality associated with the disease and not exclusively by the increase in survival but also of quality of life for the patients. Regarding LC, the core of screening would be to detect the highest number of cases in early stages, which favors their treatment and cure, thus reducing mortality[15].

The organization and development of a screening program must be based on a set of premises and criteria, which were established in the late 1960s by JM Wilson and YG Jungner in their well-known *Principles and Practices of Mass Screening of Diseases*[16].

The central idea underlying these principles is that a successful screening program must enable early detection and the consequent early treatment of the disease for those affected by the disease, while at the same time ensuring that no harm is caused to those not requiring treatment.

We can affirm without a doubt that LC represents a health problem of extraordinary magnitude both in individual and collective or social terms due to its prevalence and levels of mortality. But it also constitutes an important problem in economic and institutional terms, as it requires and implies adequate attention to budgetary and management resources by the Public Administration.[15] In light of these considerations, there is an urgent need to establish an effective LC screening protocol.

1.5.2 History of Lung Cancer Screening: From Chest X-Ray to Low-Dose Radiation Computed Tomography

The history of lung cancer screening has evolved from early large-scale chest X-ray (CXR) studies in the 1960s to the advanced low-dose radiation computed tomography (CT) scans we see today. In the 1960s, Brett's study in London highlighted that regular CXRs increased the detection of lung cancers but did not reduce mortality rates[17]. Further studies in the 1970s, including CXR and sputum cytology, echoed these findings. These studies, including the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) launched in the 1990s by the National Cancer Institute, confirmed that screening with CXR did not lead to a decrease in lung cancer mortality [18,19]. The advent of CT scans in the 1970s revolutionized medical radiology and rapidly became essential for capturing images of the entire body. It represented a significant leap in medical imaging. CT scans quickly gained popularity due to their efficacy in image-based diagnoses despite their high costs[20]. Advances like the helical computed

tomography in 1989 and multi-detector computed tomography (CTBD) in 1998 significantly improved imaging detection technology.

The development of CT scans allowed for early screening and detection of small nodules often associated with lung cancer. This resulted in high-resolution three-dimensional chest images that significantly improved lung cancer detection and screening processes. In the 1990s, the Early Lung Cancer Action Project (ELCAP) proved that CT scans were more efficient in detecting small non-calcified nodules, hence enabling early, potentially curable lung cancer detection[21]. This finding led to the widespread adoption of CTBD and resulted in the International Early Lung Cancer Action Project (I-ELCAP). The I-ELCAP, involving 38 institutions in five countries, confirmed the ability of CT scans to detect small malignant tumors, improving survival and cure prospects. It significantly stimulated the push for lung cancer screening with CT[22].

In 2011, the National Lung Screening Trial (NLST), involving over 50,000 participants, revealed that those undergoing CT had a lower risk of dying from lung cancer than those examined with X-ray. This finding, along with the results from I-ELCAP, triggered the widespread acceptance of screening programs by medical institutions in the US and Europe. This led to various clinical practice guidelines for lung cancer screening, and in 2013, the US Preventive Services Task Force recommended screening for certain high-risk groups.

Despite initial opposition from the Medicare Evidence Development & Coverage Advisory Committee (MEDCAC) due to concerns about high false-positive rates and other issues, Medicare decided to cover LC screening for specific high-risk patients in 2015.

1.5.2.1 Randomized studies in Europe

Starting in the 2000s, various studies were initiated and developed in Europe, favored by the process and preliminary results of the NLST. Among them, we have:

Multicentric Italian Lung Detection (MILD), which began as an observational study in 2000 in Milan, aimed at determining the capabilities of low-dose computed tomography (LDCT) in one year and the selective use of Positron Emission Tomography (PET). This study continued in 2005, randomized and comparing annual and biennial LDCT with observation. It included 4,099 participants, 1,190 in the annual study group, 1,186 in the biennial group, and 1,723 in the control group. The LDCT arm showed a 39% lower risk of LC mortality at 10 years compared to the control arm, and a 20% reduction in overall mortality. Likewise, a significant benefit of LDCT was observed beyond the fifth year of detection, with a 58% reduction in the risk of LC mortality and a 32% reduction in overall mortality. Later, the same group concluded that there was no evidence of a protective effect of annual or biennial LDCT[23].

The Danish Lung Cancer Screening Trial (DLCST), which was conducted from 2004 to 2006, highlighted the potential of annual LDCT screening in LC detection by following over 4,000 smoking and non-smoking participants. Crucially, a higher incidence of early-stage LC was identified in the screened group compared to the control, leading to minimal invasive treatment options. Although there were no significant differences in LC mortality between the groups, the benefits were more pronounced in high-risk subgroups such as those with COPD, smokers over 35, and elderly individuals. This emphasizes the transformative power of early detection facilitated by screening and its potential in impacting treatment approaches and outcomes.[24]

The UK Lung Cancer Screening (UKLS) was a randomized controlled study aimed at early lung cancer detection in 4,055 high-risk participants aged 50 to 75 using LDCT. Participants were identified through a detailed questionnaire based on the Liverpool

Lung Project predictive risk model. The pilot study demonstrated that early detection allowed curative treatment in over 80% of cases and was cost-effective with a cost per quality-adjusted life year (QALY) under the funding threshold set by the National Institute for Health and Care Excellence (NICE). However, while the benefits were substantial, the trial did not provide definitive results on mortality benefits, a critical aspect for cost-effectiveness evaluation.[24]

The NELSON trial, the largest lung cancer screening study in Europe, was pivotal in demonstrating the efficacy of CT screening. It involved over 15,000 high-risk participants from the Netherlands and Belgium. The study detected 209 lung cancers, primarily stage I adenocarcinomas. Interestingly, women were diagnosed at an earlier stage than men. Overall, the trial showed a significant reduction in lung cancer deaths at 10 years - 24% in men and 33% in women, compared to the control group[25].

In the case of Spain, **the International Early Lung Cancer Action Program with CT screening (P-IELCAP) in Pamplona,** marked a milestone in lung cancer screening. Conducted from 2000 to 2014, it involved nearly 3,000 participants, mostly men with smoking history, and detected 60 cancers, primarily Stage I adenocarcinomas. It demonstrated the feasibility and potential of CT screening for early lung cancer detection and underscored the importance of considering high-risk factors like COPD and emphysema in such programs[26].

Despite its rapid expansion in the US and the aforementioned trials and action plans, the reality is that lung cancer screening is still under debate in Europe. While the European Society of Radiology and the European Respiratory Society endorse it within well-regulated medical centers and a consensus statement in 2017 urged strategic planning for quality CT screening programs in Europe, there are still criticisms regarding its impact in quality of life, cost effectiveness and potential fallibility.

1.5.2.2 Controversies of Lung Cancer Screening

The main criticisms or objections to LC screening programs are focused on 3 basic considerations, namely: a) the risks of radiation, b) the risk of overdiagnosis and False Positives and c) cost-effectiveness and economic feasibility of a large-scale implementation, taking into account its potential psychosocial impacts and patients' quality of life.

a) Risks of Radiation

While ionizing radiation exposure in CT-based lung cancer screening stirs concerns about induced cancer, evidence suggests that the risk is minimal. Studies estimate that only 0.6%-3.2% of cancers among older patients could be radiation-attributed, and doses below 50-100 mSv pose low to non-existent risk. With the American Association of Physicists in Medicine firmly opposing high-risk estimations, it seems that the actual risk lies in the continual exposure to environmental radiation exceeding 2-3 mSv annually, a dose equivalent to 1-3 CT scans[27].

That said, despite the uncertainty surrounding the accumulated risk from multiple CT scans, the benefits of early detection far outweigh these potential risks. Scientific progress is continually reducing radiation exposure, and when balancing years of life gained, survival, and mortality reduction against the marginal radiation risk, the evidence leans heavily towards CT screening [28,29,30]. Thus, the benefits of screening, especially with technological advancements minimizing radiation exposure, largely overshadow the slight potential risk[31].

b) Overdiagnosis

It is essential to differentiate between overdiagnosis and false positives. The latter refers to an incorrect diagnosis, a diagnostic error where the patient does not have the clinically diagnosed disease; overdiagnosis is a failure in prognosis, in the anticipated prediction aimed at avoiding the effects of cancer on quality and life expectancy.

Detecting LC at an early stage has the invaluable possibility of significantly reducing mortality. In addition to detecting aggressive tumors, the process will also detect indolent tumors that may not produce clinical symptoms. In any screening, there is a risk of detecting tumors that, if not diagnosed, would not cause the individual's death. These cases, called overdiagnosis, negatively affect the importance and impact of detection because they result in additional economic costs, anxiety, and morbidity associated with the detection and treatment of the disease. That is why overdiagnosis becomes a factor of doubt about screening programs[32].

Overdiagnosis refers to tumors that would not have been perceived if the patient had not participated in an early detection program. It includes those tumors or lesions, small and with a slow growing rate, that could remain asymptomatic throughout the patient's life if they had not been detected in a screening program. It also includes those tumors that, even though they are malignant, do not determine the cause of their death[33]. In this sense, we can specify two types of overdiagnosis:

a) Detection of a preclinical disease that is in the process of regression or not progressing.
b) Detection of a preclinical disease that, although in progress, does not advance at a pace that would allow appreciable symptoms to appear before the patient's death. This type of overdiagnosis occurs mainly in patients with slow-growing tumors and whose life expectancy is small due to their age and/or morbidity.

In general terms, each of the definitions can lead to different estimates of overdiagnosis. [34]

Overdiagnosis is an inherent bias in screening that distorts an objective reading of its results, overvaluing its effectiveness. In the same sense, a tumor detected in the screening process that was not very aggressive can be considered, with the aggravating factor that positive survival results would be wrongly altered by the behavior of the tumor itself.

Nevertheless, it is crucial to point out that, unlike prostate cancer screening, in which many diagnosed tumors will not affect the patient's survival, in lung cancer screening, the vast majority have aggressive behavior if not removed when diagnosed early [35].

In the NLST study, it was estimated that just over 18% of the tumors diagnosed in the CT screening group were overdiagnosed. However, this high rate was in part due to a relatively short follow-up period of around 6.5 years. A subsequently developed model informed that this rate was actually overestimated[36].

Around 80% of the then considered overdiagnosed cancers were identified as bronchioloalveolar carcinoma (BAC), a pathology now reclassified as in situ adenocarcinoma, which is easily diagnosed with CT and is currently associated with a good prognosis[37]. The same model determined that with lifelong follow-up, the estimated rate of non-BAC overdiagnosis in the NLST would be less than 5%.

The continuous decrease in overdiagnosis is a challenge for science, technology, and professionals associated with LC detection processes. The application of additional treatments to reduce deaths from causes other than LC, together with adherence to updated principles and protocols for managing nodules established in the eighth edition of the staging manual (TNM), can significantly reduce overdiagnosis, minimizing risks and harm to participants and increasing the effectiveness and efficiency of screening[38].

While overdiagnosis certainly has important negative effects, it is also true that diagnosing a nodule as LC and then failing to monitor its evolution and define a treatment plan is also unreasonable and unethical. In this sense, the I-ELCAP study showed that patients with LC in stage I and detected in screening died from this disease because they were not treated[39].

c) Cost-Effectiveness

The consideration of an economic perspective to evaluate healthcare constitutes a dimension of growing and progressive acceptance in the formulation of policies and in the planning of healthcare in many countries around the world. The use of Cost-Effectiveness Analysis (CEA) has become an important element in the decision-making process on issues related to the allocation of scarce resources to the healthcare sector, as it is a useful tool for comparing relative costs and benefits between different health alternatives.

A key element, due to its importance in decision-making, to establish LC Screening with LDCT as a strategy for planned action against a disease with significant consequences for public health, refers to the costs and effectiveness of the Screening process.

Thanks to the unquestionable achievements and results of this detection technique, as described above, there is currently less discussion about its effectiveness. However, in recent times, the discussion of the costs of a massive screening program has become a constant in the scientific and academic world in the face of the need for public policies on LC, with a special focus on QALYs and their ability to measure health.

In the early studies on the impact of a disease on the health of a population or a specific social sector, only the magnitude or indices of mortality, potential years of life lost, etc. were addressed. Thus, only the main causes of death were analyzed, ignoring a significant number of disabilities associated with the disease. Although mortality-based rates are useful, they do not provide sufficient information to serve as a basis for adequate analysis of the health of a population or the comparative impact of a health intervention (Figure 9), as they do not record the effects of chronic diseases, injuries, and disability on the health status of the population considered [39], thus leaving out the potential impacts on quality of life.

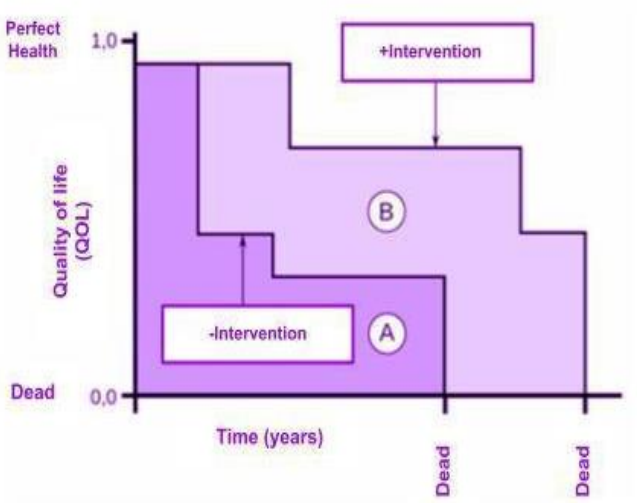


Figure 9. Relationship of QALYs based on an intervention.

QALYs, first used by Zeckhauser and Shepard in 1976, are a key measure of health status combining quantity and quality of life. They are widely used in economic evaluations and regulatory institutions for cost-effectiveness studies. A QALY equals to one full health year, with lower health status resulting in less than 1 QALY per year, and death equating to zero QALYs. QALYs reflect individuals' preferences for life quality resulting from medical interventions, calculated by multiplying the change in utility value by the treatment's duration.

QALYs assume health as a function of life duration and quality. Determining QALYs involves multiplying the utility value associated with a health status by the years lived in that state. For instance, one full health year is 1 QALY, while a less optimal health state (e.g., bedridden, utility value of 0.5) equals 0.5 QALYs. QALYs are pivotal for personal decisions, health program evaluations, and setting priorities for new programs, providing a solution for the lack of comparative data in health program utility evaluation.[40,41].

1.5.3 Economic Analysis and Evaluation (EAE)

Health systems require producing health services of adequate quality in response to a potentially unlimited demand within a framework of scarce resources. In this sense, economic analysis represents a valuable tool to improve the efficiency of budget allocation processes among the different levels of health care.

In practical terms, an economic evaluation is defined as a comparative analysis of alternative courses of action in terms of their costs and consequences. We consider AEE as a quantitative technique that allows evaluating programs that are generally funded by the public sector. Using economic evaluation as a tool, and not as an end in itself, serves to improve the impact of a given health action, by carefully allocating the available resources.

There are various types of economic evaluations in health; however, all must compare at least two intervention alternatives in terms of their costs and effectiveness. This comparison will be primarily influenced by the definition of the study and whether the focus is placed on a) the societal impact, b) the health system, or c) the perspective of the patient[42].

According to the indicators that are compared, we can identify four types of complete economic evaluations:

Cost-minimization analysis (CMA) compares only the costs of two alternative interventions under the assumption that both lead to an equivalent health outcome or benefit.

Cost-effectiveness analysis (CEA) assumes that the benefits of the different strategies being evaluated are not necessarily equivalent and thus compares those using different measuring scales in terms of morbidity, mortality, or quality of life units. Some of the units used are deaths avoided, years of life gained, or changes in quality of life indicators, all referring to the health provided by each strategy.

Cost-utility analysis (CUA) simplifies the approach of CEA by synthesizing the outcome into a single unit that represents both the quantity and the quality of life obtained as

a result of an intervention, so that different interventions for different health problems can be compared by a single indicator. We have already addressed the most well-known and used units for measuring benefits in CUA, which are quality-adjusted life years (QALYs).

Cost-benefit analysis (CBA) expresses the results of a given intervention in monetary terms with reference to net monetary gain or cost-benefit ratio, in order to enable comparisons between different alternatives. The fact that both benefits and costs are expressed in the same unit facilitates that the results are analyzed not only from the health perspective but also in relation to other programs of social impact.

1.5.3.1 Cost-effectiveness of Lung Cancer Screening with LDCT

It is vital to analyze the link between effectiveness and cost in the immense challenge of early detection of lung cancer in order to achieve a significant reduction in the number of deaths and an increase in quality-adjusted life years. There are three important dimensions that allow for increased effectiveness of lung cancer screening and, consequently, a significant decrease in cost.

The first dimension refers to significant qualitative advances in the selection of patients to participate in the screening process, thus optimizing the number of screened patients in order to avoid unnecessary tests. This includes taking into account risk factors such as the presence of respiratory conditions associated with COPD and emphysema in addition to the inclusion criteria of the NLST. As an immediate outcome, this would place smokers with the aforementioned conditions as priority candidates for a screening program.

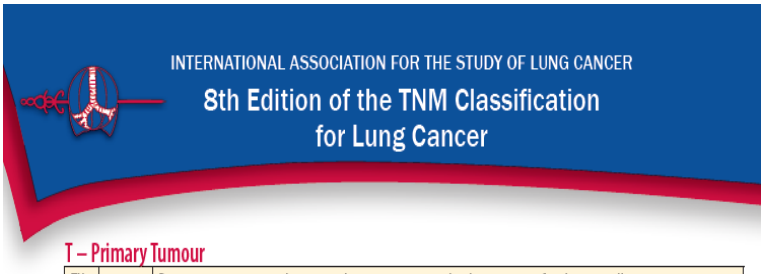
The second dimension includes scientific and technological advances in the field of radiology and imaging, thus improving results and allowing for more targeted screening actions. These are fundamental for the early detection of lung cancer, as demonstrated by the example of the use of computed tomography versus conventional radiography[42]. Similarly, as we have already noted, LDCT has allowed for

the precise relationship between an important risk factor such as emphysema and lung cancer, potentially improving the selection protocol for a screening program[43].

The third dimension includes the synergy that develops from information and communication between health sectors and institutions, in relation to their nature and purposes. It is in this area where, due to its importance in the design and formulation of policies and decisions on public health, what is known as Health Technology Assessment (HTA) emerges.

1.6 Classification and Staging

In collaboration with the International Academy of Pathology (IAP) and the International Association for the Study of Lung Cancer (IASLC), the World Health Organization (WHO) updated and published a new classification of lung cancer[50]. (Figure 10 and 11)



T – Primary Tumour

TX		Primary tumour cannot be assessed, or tumour proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0		No evidence of primary tumour
Tis		Carcinoma in situ
T1		Tumour 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)[1]
	T1mi	Minimally invasive adenocarcinoma[2]
	T1a	Tumour 1 cm or less in greatest dimension[1]
	T1b	Tumour more than 1 cm but not more than 2 cm in greatest dimension[1]
	T1c	Tumour more than 2 cm but not more than 3 cm in greatest dimension[1]
T2		Tumour more than 3 cm but not more than 5 cm; or tumour with any of the following features[3] • Involves main bronchus regardless of distance to the carina, but without involving the carina • Invades visceral pleura • Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, either involving part of the lung or the entire lung
	T2a	Tumour more than 3 cm but not more than 4 cm in greatest dimension
	T2b	Tumour more than 4 cm but not more than 5 cm in greatest dimension
T3		Tumour more than 5 cm but not more than 7 cm in greatest dimension or one that directly invades any of the following: chest wall (including superior sulcus tumours), phrenic nerve, parietal pericardium; or associated separate tumour nodule(s) in the same lobe as the primary
T4		Tumours more than 7 cm or one that invades any of the following: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina; separate tumour nodule(s) in a different ipsilateral lobe to that of the primary

N – Regional Lymph Nodes

NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2		Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3		Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene or supraclavicular lymph node(s)

M- Distant Metastasis

M0		No distant metastasis
M1		Distant metastasis
	M1a	Separate tumour nodule(s) in a contralateral lobe; tumour with pleural or pericardial nodules or malignant pleural or pericardial effusion[4]
	M1b	Single extrathoracic metastasis in a single organ[5]
	M1c	Multiple extrathoracic metastases in one or several organs

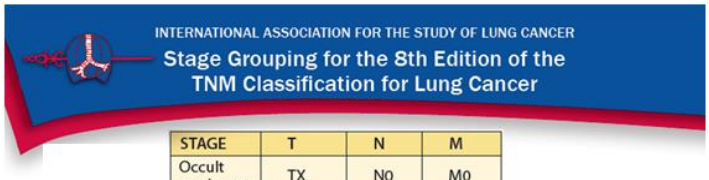
[1]The uncommon superficial spreading tumour of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified as T1a.

[2]Solitary adenocarcinoma (</= 3 cm), with a predominantly lepidic pattern and </= 5 mm invasion in greatest dimension in any one focus.

[3]T2 tumours with these features are classified T2a if 4 cm or less, or if size cannot be determined and T2b if greater than 4 cm but not larger than 5 cm.

[4]Most pleural (pericardial) effusions with lung cancer are due to tumour. In a few patients, however, multiple microscopic examinations of pleural (pericardial) fluid are negative for tumour, and the fluid is non-bloody and is not an exudate. Where these elements and clinical judgement dictate that the effusion is not related to the tumour, the effusion should be excluded as a staging descriptor.

[5]This includes involvement of a single distant (non-regional) node.



STAGE	T	N	M
Occult carcinoma	TX	N0	M0
0	Tis	N0	M0
IA1	T1mi	N0	M0
	T1a	N0	M0
IA2	T1b	N0	M0
IA3	T1c	N0	M0
IB	T2a	N0	M0
IIA	T2b	N0	M0
IIB	T1a	N1	M0
	T1b	N1	M0
	T1c	N1	M0
	T2a	N1	M0
	T2b	N1	M0
	T3	N0	M0
IIIA	T1a	N2	M0
	T1b	N2	M0
	T1c	N2	M0
	T2a	N2	M0
	T2b	N2	M0
	T3	N1	M0
	T4	N0	M0
	T4	N1	M0
IIIB	T1a	N3	M0
	T1b	N3	M0
	T1c	N3	M0
	T2a	N3	M0
	T2b	N3	M0
	T3	N2	M0
	T4	N2	M0
IIIC	T3	N3	M0
	T4	N3	M0
IVA	Any T	Any N	M1a
	Any T	Any N	M1b
IVB	Any T	Any N	M1c

Figure 10 and 11. IASLC 8th LC staging classification

1.6.1 Treatment alternative for LC

Upon establishing the staging, the treatment plan for LC can be developed. Surgery is the primary treatment for early-stage (I-II) LC in operable patients, offering a five-year survival rate of approximately 60-80% for stage I and 30%-50% for stage II in non-small cell lung cancer (NSCLC) patients[51].

1.6.1.1 Minimal Invasive Surgery

Video-assisted thoracic surgery (VATS) and Robotic-Assisted Thoracic Surgery (RATS) are minimally invasive surgical approaches that have gained significant attention in recent years. VATS is performed by making small incisions in the chest and using a special camera and instruments to perform the surgery. It results in less postoperative pain, shorter hospital stays, and quicker recovery times compared to traditional open surgery.

RATS, a further evolution of minimally invasive surgery provides enhanced dexterity, precision and control for the surgeon, making complex procedures easier. It also offers 3D high-definition visualization, further facilitating the surgeon's work.

Both techniques have shown promising results in treating early-stage lung cancer, leading to comparable survival outcomes as open surgery but with fewer complications and quicker recovery [52].(Figure 12).

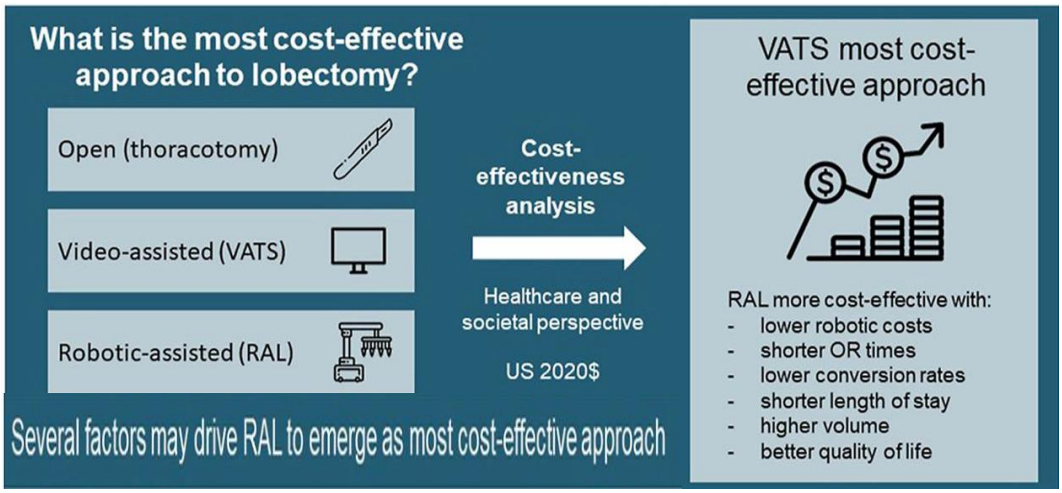


Figure 12. Cost-effectiveness analysis of Minimal Invasive Surgery Lobectomy for Non-small Cell Lung Cancer.

1.6.2 Radiotherapy

If surgery is not feasible or is refused, stereotactic body radiotherapy (SBRT) could be an alternative[53].

1.6.3 Chemotherapy and immunotherapy

Adjuvant chemotherapy based on platinum is advised for completely resected stage II NSCLC lesions. For stage I NSCLC patients, the benefits of adjuvant chemotherapy remain unclear.

1.6.4 Complex treatment strategies

Most LC patients (over 70%) are diagnosed at advanced stages (III and IV), when curative surgery cannot already be offered and making treatment strategies diverse and dependent on the specific stage and condition of the disease. These strategies can include combinations of surgery, radiotherapy, chemotherapy, and immunotherapy.

For unresectable stage IIIA and IIIB NSCLC patients, platinum-based chemotherapy with concurrent radiotherapy is standard in fit patients. Durvalumab, an anti-PDL-1, has shown to improve overall survival when administered for one year in patients with PDL-1 superior to 1%.

Stage IV NSCLC accounts for 40% of all new diagnoses. Treatment planning depends on several factors, including comorbidity, general condition, histology, and molecular genetic features of the tumor. Standard first-line treatment involves immune checkpoint inhibitors in patients with PDL-1 superior to 50%, targeted therapy in adenocarcinomas with molecular alterations, and chemotherapy for remaining patients [54,55].

Final summary of the current situation

LC is one of the deadliest forms of cancer, and it is responsible for a significant number of deaths worldwide. The disease is often diagnosed in advanced stages, which makes

it difficult to treat and reduces the chances of survival. However, recent studies have shown that lung cancer screening is more cost-effective than medical treatment in advanced cases.

We state that CT screening for lung cancer is undoubtedly an effective procedure for the early detection of this disease and the consequent reduction in mortality. Before CT screening, no treatment or intervention had achieved such a positive impact on lung cancer mortality.

Lung cancer screening involves the use of low-dose computed tomography (LDCT) to detect lung cancer in its early stages. The screening is recommended for individuals who are at high risk of developing lung cancer, such as smokers and former smokers. The LDCT scan is a non-invasive procedure that takes only a few minutes to complete, and it is relatively inexpensive compared to medical treatment.

On the other hand, medical treatment for advanced lung cancer is costly and often involves a combination of surgery, chemotherapy, and radiation therapy. These treatments are not only expensive but also have significant side effects that can affect the quality of life of the patient. Moreover, the success rate of medical treatment for advanced lung cancer is relatively low, and the chances of survival are significantly reduced.

Surgical treatment of early-stage lung cancer has been proven to be the most effective treatment option. With a success rate with surgical treatment of around 80-90%, significantly higher than other treatment options such as chemotherapy or radiotherapy. This means that most patients who undergo surgical treatment for early-stage lung cancer are completely cured of the disease. In addition, the earlier the stage of the cancer, the higher the chances of a complete cure. Surgical treatment is the only option that provides a complete cure for lung cancer in its early stages.

Surgical treatment also has a lower risk of recurrence than other treatment options. This means that patients who undergo surgical treatment for early-stage lung cancer

have a lesser chance of developing a new cancer in the same place, and as a it offers greater long-term survival rates compared to other treatment options. Not only that, but the overall survival rate of patients who undergo surgical treatment for early-stage lung cancer is significantly higher than those who receive other treatments.

Early diagnosis is thus essential for the best possible outcome of lung cancer treatment, and patients who are diagnosed with early-stage lung cancer should consider surgical treatment as their primary treatment option.

In conclusion, CT screening for lung cancer represents a paradigm shift in the treatment of this pathology and consequently future research must aim to improve the selection of the population at risk of developing lung cancer and to refine the relevant protocols for its detection and diagnosis, which avoid or minimize the negative effects associated.

We share the idea that the time has come to design, organize, and implement a Massive Lung Cancer Screening Program in our country, which addresses a problem of vast dimensions and dramatic consequences in terms of health, quality of life, and mortality for a significant number of citizens in today's Spain and offer the opportunity to received early treatment for the patients.

Of course, this program will be marked by the virtues and shortcomings of our National Health System and the always limited financial resources of the National Budget. Limitations and shortcomings should never be arguments for not taking on the challenge. The challenge is to promote the program and overcome our own limitations and shortcomings. A program with that objective and scope, even with the shortcomings mentioned, will always be ethically, socially, and humanly preferable to inaction in the face of the problem of lung cancer in our country.

2. Research Hypotheses

Primary Hypothesis

The primary proposition that underscores this doctoral research contends that surgical intervention, both as a diagnostic and therapeutic tool, in the treatment of LC, provides superior cost-effectiveness compared to medical treatment.

This central hypothesis is further subdivided into two distinct yet interlinked hypotheses, each forming the crux of the two original papers incorporated in this thesis.

Specific hypotheses

1. The cost-effectiveness of surgical intervention in LC treatment is superior to that of medical therapy.

2. Surgical resection as diagnostic therapeutic intervention of lung cancer (LC), when decided by the Multidisciplinary Cancer Committee (MCC) guidelines, could potentially result in substantial economic savings compared to the approach of conducting lung biopsies before surgery.

3. Objectives

General

The overarching objective of this doctoral thesis is to underscore the economic advantage of adopting surgical intervention as the primary mode of lung cancer (LC) treatment over medical therapies.

Specific objectives

This broad objective is segmented into two interrelated, yet distinct, focused objectives. Each of these aims to serve as the centerpiece of the two original papers incorporated in this thesis.

1. To establish that surgical intervention for LC treatment is not only clinically viable but also more economical when compared to medical therapies.
2. To elucidate that surgical resection of LC, adhering to the guidelines set forth by the Multidisciplinary Cancer Committee, provides a more cost-effective approach than those dictated by CT-guided lung biopsy results.

These objectives will be addressed through rigorous research and analysis, striving to provide an in-depth understanding of the economic considerations of different LC treatment modalities.

4. Results

The results of this PhD thesis have been published in the form of two original papers in peer reviewed international journals, one in the second quartile of the field: European Journal of Cancer Prevention (impact factor from JCR 2020: 2.497) and the other in the third quartile of the field: Cirugía Española (Impact factor from de JCR 2023:2.242).

These two papers are printed below.

4.1 Original Paper 1

Outcomes and cost of lung cancer patients treated surgically or medically in Catalunya: cost-benefit implications for lung cancer screening programs.

Guzman R, Guirao À, Vela E, Clèries M, García-Altés A, Sagarra J, Magem D, Espinas JA, Grau J, Nadal C, Agusti À, Molins L.

Eur J Cancer Prev. 2020

Outcomes and cost of lung cancer patients treated surgically or medically in Catalunya: cost–benefit implications for lung cancer screening programs

Rudith Guzman[a], Àngela Guirao[a], Emili Vela[b], Montserrat Clèries[b], Anna García-Altés[c,d], Joan Sagarra[a], David Magem[d–f], Josep A. Espinas[g], Jaume Grau[a], Cristina Nadal[h], Àlvar Agusti[a,i–k] and Laureano Molins[a,i–k]

Lung cancer screening programs with computed tomography of the chest reduce mortality by more than 20%. Yet, they have not been implemented widely because of logistic and cost implications. Here, we sought to: (1) use real-life data to compare the outcomes and cost of lung cancer patients with treated medically or surgically in our region and (2) from this data, estimate the cost–benefit ratio of a lung cancer screening program (CRIBAR) soon to be deployed in our region (Catalunya, Spain). We accessed the Catalan Health Surveillance System (CHSS) and analysed data of all patients with a first diagnosis of lung cancer between 1 January 2014 and 31 December 2016. Analysis was carried forward until 30 months (*t*=30) after lung cancer diagnosis. Main results showed that: (1) surgically treated lung cancer patients have better survival and return earlier to regular home activities, use less healthcare related resources and cost less tax-payer money and (2) depending on incidence of lung cancer identified and treated in the program (1–2%), the return on investment for CRIBAR is expected to break even at 3–6 years, respectively, after its launch. Surgical treatment of lung cancer is cheaper and offers better outcomes. CRIBAR is estimated to be cost-effective soon after launch. *European Journal of Cancer Prevention* 29: 486–492 Copyright © 2019 Wolters Kluwer Health, Inc. All rights reserved.

European Journal of Cancer Prevention 2020, **29**:486–492

Keywords: cost–benefit, early stages, smoking, survival

[a]Hospital Clinic, [b]Unitat d'informació i Coneixement. Servei Català de la Salut (CatSalut), [c]Catalan Health System Observatory, Agència de Qualitat i Avaluació Sanitàries de Catalunya (AQuAS), [d]CIBER de Epidemiología y Salud Pública (CIBERESP), [e]Institut d'Investigació Biomèdica (IIB Sant Pau), [f]Divisió d'Innovació i Cartera de Serveis Sanitaris. Servei Català de la Salut, Barcelona, Spain, [g]Pla Director Oncologia, Departament de Salut, Generalitat de Catalunya, [h]Departament de Salut, Generalitat de Catlunya, [i]Universitat de Barcelona, [j]Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona and [k]CIBER Enfermedades Respiratorias (CIBERES), Spain

Correspondence to Angela Guirao, Respiratory Institute, Hospital Clínic, Villarroel 170, Escala 1, Planta 3, 08036 Barcelona, Spain
Tel: +34 93 227 1701; fax: +34 93 227 9868; e-mail: GUIRAO@clinic.cat

Received 17 September 2019 **Accepted** 4 November 2019

Introduction

Lung cancer is the first cause of cancer death in the world, both in men and females (Malvezzi *et al.*, 2017). Yet, it can be cured by surgical removal (Asamura *et al.*, 2017; Pérez-Martínez *et al.*, 2018; Waller, 2018). Unfortunately, this occurs only in a minority of patients because, in practice, about three quarters of patients are diagnosed when lung cancer is advanced (Postmus *et al.*, 2017) and surgery cannot be offered. Early lung cancer diagnosis is, therefore, in addition to primary prevention, of paramount importance.

In 2011, the National Lung Screening Trial (NLST) showed that the use of low-dose helical computed tomography (CT) was effective to detect early lung cancer and, as a result, mortality was reduced by 20% (Aberle *et al.*, 2011). Just a few days ago, the results of the NELSON study (a European equivalent to the NLST) confirmed these results (De Koning *et al.*, 2018).

Several international societies have recommended the implementation of CT screening programs for lung cancer (Kauczor *et al.*, 2015; Garrido *et al.*, 2017; Oudkerk *et al.*, 2017; Pedersen *et al.*, 2017). Yet, because this recommendation faces significant logistic hurdles and has important economic implications (Cressman *et al.*, 2014; Chin *et al.*, 2015; Oudkerk *et al.*, 2017; Wade *et al.*, 2018), lung cancer screening programs have not been widely adopted. Here, we reasoned that a detailed analysis and comparison of the cost and outcomes of lung cancer patients treated in early stages (surgically) or advanced stages (medically) in real-life may provide relevant background information in this setting. Accordingly, in this study, we sought to: (1) use real-life data to quantify the outcomes and cost of lung cancer patients treated medically (because they were not surgical candidates) or surgically (sometimes combined with other medical treatments) from 2014 to 2016 in our region (Catalunya, Spain), which enjoys

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (www.eurjcancerprev.com).

DOI: 10.1097/CEJ.0000000000000566

a publically funded health care system that covers all residents in the region and (2) use this real-life derived data to estimate the cost–benefit ratio of a lung cancer screening program (CRIBAR) soon to be deployed in our region.

Materials and methods

Study design and ethics

This retrospective, observational, comparative analysis includes 13.186 residents in Catalunya (Spain) diagnosed of lung cancer (see ICD-9-CM codes in Supplementary Table S1, Supplemental digital content 1, *http://links.lww.com/EJCP/A271*) for the first time between 1 January 2014 and 31 December 2016 ($t=0$) in the public healthcare system. Patients treated with chemo and radiotherapy before 1 January 2014 and with a diagnosis of any metastasis before the date of lung cancer diagnosis were excluded from the analysis. All included patients were treated medically or surgically according to best practice international recommendations (Reck *et al.*, 2013; Hirsch *et al.*, 2017). Analysis was carried forward until 30 months ($t=30$) after the diagnosis of lung cancer ($t=0$).

Because we used anonymized administrative databases for analysis, we did not obtain signed informed consent from each patient. Likewise, because this analysis includes all the population served by the Catalan Health Care system (not a random sample), formal sample size calculation is not required.

Sources of information

The Catalan Health Surveillance System (CHSS) includes detailed information on the use of healthcare resources of this population at individual level, including primary care attention, hospitalization, sociosanitary resources use, emergency care, mental healthcare and dispensed medication. Besides, it also includes information on hospital outpatient clinic, radiotherapy sessions, dialysis utilization, outpatient rehabilitation, nonemergency sanitary transport and home respiratory therapies (oxygen, noninvasive ventilation and others). The CHSS incorporates an automatic validation system that checks for internal consistency and, periodically, there are external audits to guarantee the quality and validity of the stored information, which is then used to pay healthcare providers. The CHSS does not include the care type and cost of lung cancer treatment provided by private healthcare companies (~15% of the total activity in the region for lung cancer), which is not accessible.

Analysis of real-life data

In each patient, we analysed the following variables: (1) demographics at $t=0$; (2) vital status from $t=0$ until $t=30$ months by Selwood analysis, as reported earlier (Vela *et al.*, 1999); (3) place of residence (home, hospital, nursing home, long-term care facility), which was analysed in 7-day periods from $t=0$ until $t=30$; (4) drug dispensation (Supplementary Table S2, Supplemental digital content 1, *http://links.lww.com/EJCP/A271*) from 12 months before $t=0$ until $t=30$; (5) annual healthcare resources utilization (HCRU), including primary care, emergency care, day-hospital visits, hospitalization events, long-term care needs and nonurgent sanitary transport use from $t=0$ until $t=30$. The annual rate of HCRU per person/year was calculated using the time at risk of each patient during each of these time periods, which finished either when the patient died or the study was censored (31 December 2016). This rate was estimated as total HCRU during the time period considered over the total number of patients/year; and, finally, (6) annual cost (€) per patient, as reported elsewhere (Vela *et al.*, 2017). Costs were calculated as the average value (€) per patient and category (surgical vs. medical treatment) during a given period of time, according to the Catalan Health System (Catsalut) tariffs.

Estimation of CRIBAR cost/benefit

Because CRIBAR will use the same inclusion and exclusion criteria, and three-year follow-up protocol, than those of the NLST (Aberle *et al.*, 2011), we anticipate a similar lung cancer detection rate (1–2%). On the other hand, as detailed in the on-line supplement, Supplemental digital content 1, *http://links.lww.com/EJCP/A271*, we estimated a total population to screen of 1.193 residents in three reference areas of our hospital. As a result, we anticipated total *cost* of CRIBAR for 3 years for these patients in our healthcare system context of 1 427 871 € (Supplementary Table S3, Supplemental digital content 1, *http://links.lww.com/EJCP/A271*).

To estimate the potential *benefits* of CRIBAR, we used life-years gained (LYG) (Torrance and Feeny, 1989) in two different efficacy scenarios (lung cancer incidence during screening of 1 or 2%), according to the results of the NSLT (Aberle *et al.*, 2011). To do so, we used the actual survival of surgical and medical patients at $t=30$ determined in our real-life analysis detailed above; survival after 5 and 10 years was estimated from the literature (Goldstraw *et al.*, 2016). We then applied a value of 30 000€ per LYG (and a discount rate of 3%) according to the most common value used to assign a societal value to LYG in Spain (Sacristán *et al.*, 2002), although this value varies between countries (Neumann *et al.*, 2014),

Statistical analysis

Results are presented as mean ± SD or proportion, as appropriate. Chi-square test (for categorical variables) and Student's t test (for continuous variables) were used to explore differences between groups. Given the observational nature of this study, no correction for multiple testing was applied. The threshold for statistical significance was set at a two-sided α-value of 0.05. All analyses were performed in R (version 3.4.3).

Results

Characteristics of patients at the time of lung cancer diagnosis ($t=0$)

Table 1 compares the main demographic and clinical characteristics at the time of lung cancer diagnosis ($t=0$) in patients treated medically ($n=10\,866$; 82.4%) or surgically ($n=2230$; 17.6%). Males predominate in both groups and surgical patients tended to be slightly younger (about 4 years). Comorbidities were prevalent in both groups.

Outcomes

As expected, survival after lung cancer diagnosis was higher ($P<0.001$) in surgical patients (Fig. 1, Table 2). Besides, surgically treated patients regained autonomy and returned home after $t=0$ much sooner than those treated medically (Table 2).

Healthcare resources utilization

Table 3 presents the HCRU rates by medical and surgical patients before and after the diagnosis of lung cancer ($t=0$), as well as their rate ratio. HCRU after $t=0$ was most often higher in medical patients (higher rate ratio).

Cost assessment

Figure 2 shows that the average annual cost of medical and surgical patients during the year that preceded lung cancer diagnosis was similar but, at $t=30$, cost was 36% lower in surgical patients.

Table 1 Main clinical characteristics of participants by type of treatment received (medical vs. surgical)

	Medical treatment		Surgical treatment		
	N	%	*N*	%	*P* value
Cases	10866	82.4	2320	17.6	
Sex					0.007
Men	8410	77.4	1735	74.8	
Women	2456	22.6	585	25.2	
Age, years					<0.001
0–44 years	262	2.4	69	3.0	
45–64	3550	32.7	948	40.9	
65–74	3098	28.5	857	36.9	
75–84	2828	26.0	432	18.6	
85 or more	1128	10.4	14	0.6	
COPD	3820	35.2	902	38.9	<0.001
Diabetes	2800	25.8	545	23.5	0.024
Cardiac failure	1434	13.2	136	5.9	<0.001
Ischaemic Illness	1648	15.2	270	11.6	<0.001
Stroke	1408	13.0	199	8.6	<0.001
Chronic renal failure	1484	13.7	196	8.4	<0.001
Dementia	373	3.4	21	0.9	<0.001
Depression	1697	15.6	418	18.0	0.005
Nursing home	134	1.2	8	0.3	<0.001
Risk strata high (Dueñas-Espín *et al.*, 2016; Vela *et al.*, 2018)	3322	30.6	521	22.5	
Medium	4414	40.6	1,160	50.0	<0.001
Low	2255	20.8	493	21.2	
Basal	875	8.0	146	6.3	

COPD, chronic obstructive pulmonary disease.

Cost–benefit analysis

As detailed in Table 4 and presented graphically in Fig. 3, depending on the efficiency of the screening program (1 or 2% detection of incident lung cancer), we estimated that the cost–benefit ratio of CRIBAR will break even between 3 and 6 years after launch and will generate healthcare cost savings thereafter.

Discussion

This real-life study confirms previous studies that show that the best therapeutic option for a lung cancer patients is the surgical removal of the tumour (Speicher *et al.*, 2016; Couñago *et al.*, 2018) because lung cancer patients treated surgically here have better survival and return earlier to regular home activities than those treated medically (Fig. 1). It also shows that lung cancer patient treated surgically uses less healthcare related resources and cost less tax-payer money (Fig. 2). Using these real-life data, we estimated that the cost–benefit ratio of a lung cancer screening program in our region will break even between 3 and 6 years after launching and will generate healthcare cost savings thereafter (Fig. 3).

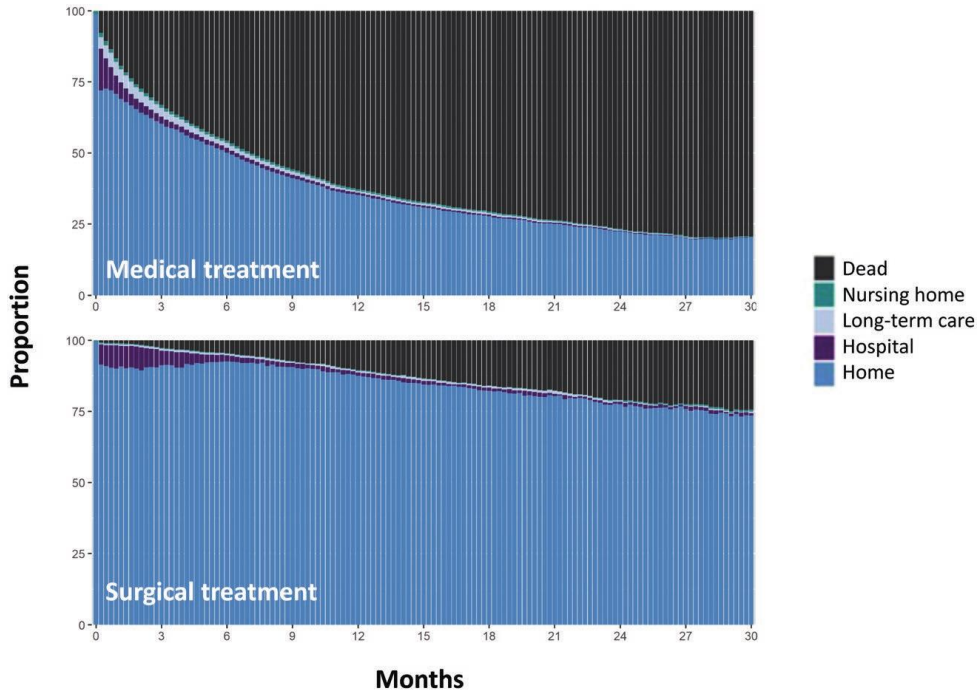
Previous studies

The publication of the NLST results in 2011 (Aberle *et al.*, 2011) generated a great deal of interest to explore the cost-effectiveness of lung cancer screening programs. Initially, most studies used mathematical models in data bases of private healthcare insurance companies. All of them concluded that lung cancer screening programs were highly cost-effective, in line with other accepted cancer screening interventions (McMahon *et al.*, 2011; Pyenson *et al.*, 2012; Villanti *et al.*, 2013). More recently, Black *et al.* (2014) investigated the cost-effectiveness of the original NLST program and reported that screening for lung cancer with low-dose CT would cost about 81 000 USD (about 70 000€) per quality-adjusted life-years gained. Importantly, though these authors also reported that modest changes in some of their assumptions may greatly alter this figure, they eventually concluded that 'the determination of whether screening outside the trial will be cost-effective will depend on how screening is implemented' (Black *et al.*, 2014). This is, precisely, the goal of our study.

Interpretation of current observations

Several observations of our analysis deserve specific discussion. First, not surprisingly (but reassuringly) our real-life analysis confirmed that surgery is the best (and cheapest) therapeutic option (both in terms of survival, speed of recovery and cost) for lung cancer (Figs. 1 and 2, Table 2). Second, according to CHSS, the prevalence of lung cancer in the general population of Catalunya is 0.14%. This figure is well below that reported in the NLST (1–2%), indicating that an identical lung cancer screening program in our region has great potential to

Fig. 1



AQ9 Survival and place of residence of lung cancer patients treated medically (top panel) or surgically (bottom panel). For further explanations, see text.

Table 2 Survival and place of residence at different times after lung cancer diagnosis (*t*=0) in patients treated medically or surgically

	Medical treatment				Surgical treatment			
	t=3	*t*=12	*t*=24	*t*=30	*t*=3	*t*=12	*t*=24	*t*=30
Dead (%)	33.1	62.7	76.6	79.3	2.7	10.5	20.9	24.4
Living at home (%)	60.4	35.3	22.6	20.3	91.3	87.6	77.5	73.6
Long-term care facility/hospitalized (%)	6.5	2.0	0.8	0.4	6.0	1.9	1.6	2.0

't' indicates number of months after lung cancer diagnosis (*t*=0).

identify, diagnose, operate and cure many asymptomatic lung cancer patients. Third, our analysis shows that the return on investment will break even between 3 and 6 years after launching CRIBAR and that it will generate significant health-care cost savings thereafter (Table 4, AQ6 Fig. 3). All in all, these observations clearly support the implementation of lung cancer screening programs in our healthcare system, as proposed by a recent European Union position statement [7].

On the other hand, however, the cost–benefit ratio of any screening program depends critically on the technology used to screen for the presence of the disease of interest as well as the characteristics of the population to be screened (Molina *et al.*, 2016; Carozzi *et al.*, 2017). The NSLT included asymptomatic men and women, 55–74 years of age, with a history of >30 pack-years of cigarette smoking and who were either current smokers or had been smokers within the previous 15 years (Aberle *et al.*, 2011). Very recently, extended follow-up results during more than 11 years confirmed the original observations (National Lung Screening Trial Research, 2019). It is possible, however, that the inclusion of other lung cancer-related markers, such as circulating tumour markers (Molina *et al.*, 2016; Guida *et al.*, 2018), abnormal spirometry (de-Torres et al., 2015, 2016) or others can contribute

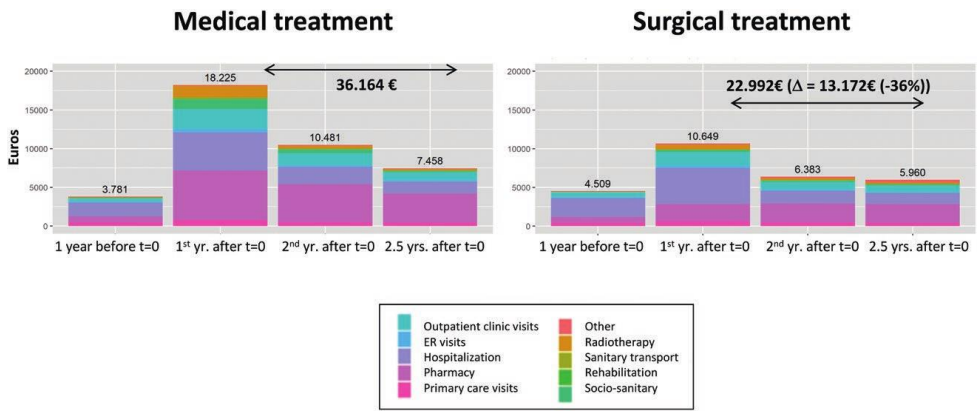
	12/30/19	4 Color Fig(s): F1-3	18:55	Art: EJCP063843

Table 3 **Health-care resources utilization rate per 100 patients and year (and ratio rate between medical and surgical patients), during the year before *t*=0 and the first two years after it**

	First year before *t*=0				First year after *t*=0				Second year after *t*=0			
	Medical	Surgical	Ratio rate (M/S)	*P* value	Medical	Surgical	Ratio rate (M/S)	*P* value	Medical	Surgical	Ratio rate (M/S)	*P* value
Primary care visits	1490.7	1266.3	1.177	<0.001	2471.9	2048	1.207	<0.001	1650.1	1477.8	1.117	<0.001
Out-patient visits	414.8	750.0	0.553	<0.001	1731.7	1753.8	0.987	0.048	1136.2	1090.5	1.042	0.001
ER visits	189.0	119.9	1.576	<0.001	370.2	214	1.73	<0.001	216.4	139.3	1.553	<0.001
Day-hospital sessions	57.1	91.7	0.623	<0.001	902.7	436	2.07	<0.001	509.7	200.2	2.546	<0.001
Hospitalization	89.1	101.4	0.879	<0.001	200.9	190.5	1.054	0.006	100.2	71.6	1.399	<0.001
Long-term care facility	20.0	1.8	10.994	<0.001	144.5	17.2	8.396	<0.001	66.3	18.7	3.539	<0.001
Nonemergency transport	105.7	47.7	2.217	<0.001	673.7	234.7	2.87	<0.001	283.6	153.7	1.845	<0.001
Radiotherapy sessions	–	–	–	–	76.3	23.9	3.192	<0.001	18.4	11.6	1.597	<0.001
Drug dispensations	1576.5	1602.2	0.984	0.005	2438.9	1704.1	1.431	<0.001	1672.9	1343.8	1.245	<0.001
Cancer drugs	–	–	–	–	2666.1	932.2	2.86	<0.001	2550.4	678.4	3.759	<0.001
Anxiolytics	840.8	833.6	1.009	0.28	396.2	321.3	1.233	<0.001	353.8	304.7	1.161	<0.001
Sedatives	357.4	337.5	1.059	<0.001	149.8	120.2	1.246	<0.001	132.3	123.8	1.069	0.064
Antidepressive	587.3	605.7	0.97	0.001	224	210.2	1.066	<0.001	246	229.1	1.074	0.006
Opioids	387.2	273.3	1.417	<0.001	1049.4	418.8	2.506	<0.001	846.8	327.5	2.586	<0.001
Analgesics	1484.7	1082.5	1.371	<0.001	2024.4	1418.4	1.427	<0.001	1629.5	845.2	1.928	<0.001

M, medical; S, surgical.

Fig. 2



Mean annual cost (€) per patient before and after the diagnosis of lung cancer in patients treated medically (left panel) or surgically (right panel). For further explanations, see text.

to better define the population to screen, and as a result, can improve the cost–benefit ratio of future lung cancer screening programs. This is a hypothesis that requires future prospective research.

Strengths and limitations

The fact that we analysed real life data from the entire population of patients with lung cancer ($n=13.186$) served by the Catalan Health Service followed up for 30 months is a clear strength of our analysis. On the other hand, however, there are some limitations that deserve specific comment. First, data on private healthcare information (about 15% of total activity in Catalunya) are not included in the public databases used for our analysis and could not therefore be accessed. Second, there is a relative paucity of clinical information in the administrative databases accessed. In particular, we lack information on the clinical stage of lung cancer at diagnosis. Likewise, we miss information on specific causes of death in both groups. Finally, some surgical patients (stage IIIA) might have received neoadjuvant chemotherapy. Unfortunately, we do not know the precise figure, but in any case, in our analysis, its cost has been attributed to the surgical group, so real differences between groups would have been larger in favour of the surgical group.

Conclusion

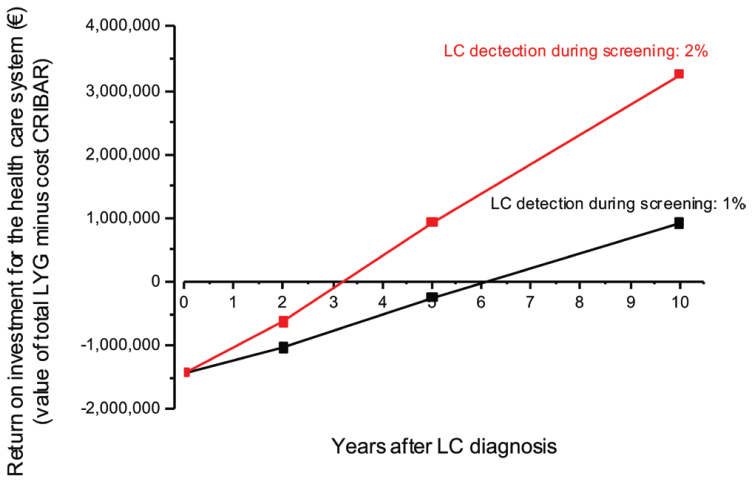
Using real-life data, our study confirms that surgical treatment of lung cancer is cheaper and offers better

Table 4 Cost–benefit analysis of CRIBAR

Number of patients identified by screening	*N*=12 (1% incidence of lung cancer)	*N*=24 (2% incidence of lung cancer)
2 years		
Survival surgical patients	79%	79%
Survival medical patients	23%	23%
LYG	13.4	26.7
Economic value of LYG	401 040.00 €	802 080.00 €
Return on investment (Value LYG – cost CRIBAR)	−1 026 831.03 €	−625 791.03 €
5 years		
Survival surgical patients	76%	76%
Survival medical patients	10%	10%
LYG	39.4	78.7
Economic value of LYG	1 180 800.00 €	2 361 600.00 €
Return on investment (Value LYG – cost CRIBAR)	−247 071.03 €	933 728.97 €
10 years		
Survival surgical patients	72%	72%
Survival medical patients	7%	7%
LYG	78.0	156.0
Economic value of LYG	2 340 000.00 €	4 680 000.00 €
Return on investment (value LYG – cost CRIBAR)	912 128.97 €	3 252 128.97 €

LYG, Life-years gained.

Fig. 3



Estimated return on investment over 10 years after the launch of CRIBAR assuming a 1% (black lines) or 2% (red lines) lung cancer detection (Aberle *et al.*, 2011). For further explanations, see text.

outcomes and shows that lung cancer screening programs in our region are highly likely to be cost-effective within a few years after launching.

Acknowledgements

This work was supported, in part, by SEPAR 2018 and Cerca Program (Generalitat de Catalunya).

Conflicts of interest

There are no conflicts of interest.

References

Asamura H, Aokage K, Yotsukura M (2017). Wedge resection versus anatomic resection: extent of surgical resection for stage I and II lung cancer. *Am Soc Clin Oncol Educ Book* **37**:426–433.

Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, Fagerstrom R M, *et al.*; National Lung Screening Trial Research Team (2011). Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med* **365**:395–409.

Black WC, Gareen I F, Soneji SS, Sicks JD, Keeler EB, Aberle DR, *et al.*; National Lung Screening Trial Research Team (2014). Cost-effectiveness of CT screening in the national lung screening trial. *N Engl J Med* **371**:1793–1802.

Carozzi FM, Bisanzi S, Carrozzi L, Falaschi F, Lopes Pegna A, Mascalchi M, *et al.*; ITALUNG Working Group (2017). Multimodal lung cancer screening using

the ITALUNG biomarker panel and low dose computed tomography. Results of the ITALUNG biomarker study. *Int J Cancer* **141**:94–101.

Couñago F, Rodriguez de Dios N, Montemuiño S, Jové-Teixidó J, Martin M, Calvo-Crespo P, *et al.* (2018). Neoadjuvant treatment followed by surgery versus definitive chemoradiation in stage IIIA-N2 non-small-cell lung cancer: a multi-institutional study by the oncologic group for the study of lung cancer (Spanish Radiation Oncology Society). *Lung Cancer* **118**:119–127.

Cressman S, Lam S, Tammemagi MC, Evans WK, Leighl NB, Regier DA, *et al.*; Pan-Canadian Early Detection of Lung Cancer Study Team (2014). Resource utilization and costs during the initial years of lung cancer screening with computed tomography in Canada. *J Thorac Oncol* **9**:1449–1458.

Chin J, Syrek Jensen T, Ashby L, Hermansen J, Hutter JD, Conway PH (2015). Screening for lung cancer with low-dose CT–translating science into medicare coverage policy. *N Engl J Med* **372**:2083–2085.

de-Torres JP, Marín JM, Casanova C, Pinto-Plata V, Divo M, Cote C, *et al.* (2016). Identification of COPD patients at high risk for lung cancer mortality using the COPD-LUCSS-DLCO. *Chest* **149**:936–942.

de-Torres JP, Wilson DO, Sanchez-Salcedo P, Weissfeld JL, Berto J, Campo A, *et al.* (2015). Lung cancer in patients with chronic obstructive pulmonary disease. Development and validation of the COPD lung cancer screening score. *Am J Respir Crit Care Med* **191**:285–291.

Dueñas-Espín I, Vela E, Pauws S, Bescos C, Cano I, Cleries M, *et al.* (2016). Proposals for enhanced health risk assessment and stratification in an integrated care scenario. *BMJ Open* **6**:e010301.

Garrido P, Sánchez M, Belda Sanchis J, Moreno Mata N, Artal Á, Gayete Á, *et al.* (2017). Reflections on the implementation of low-dose computed tomography screening in individuals at high risk of lung cancer in Spain. *Arch Bronconeumol* **53**:568–573.

Goldstraw P, Chansky K, Crowley J, Rami-Porta R, Asamura H, Eberhardt W E, *et al.*; International Association for the Study of Lung Cancer Staging and Prognostic Factors Committee, Advisory Boards, and Participating Institutions; International Association for the Study of Lung Cancer Staging and Prognostic Factors Committee Advisory Boards and Participating Institutions (2016). The IASLC lung cancer staging project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer. *J Thorac Oncol* **11**:39–51.

De Koning CVDA H, Ten Haaf K, Oudkerk M (2018). Effects of volume CT lung cancer screening: mortality results of the Nelson randomised-controlled population based trial. Proceedings of the IASLC 19th World Conference on lung cancer; 09-25-2018; Toronto.

Guida F, Sun N, Bantis LE, Muller DC, Li P, Taguchi A, *et al.*; Integrative Analysis of Lung Cancer E, Risk Consortium for Early Detection of Lung C (2018). Assessment of lung cancer risk on the basis of a biomarker panel of circulating proteins. *JAMA Oncol* **4**:e182078.

Hirsch FR, Scagliotti GV, Mulshine JL, Kwon R, Curran WJJr, Wu YL, Paz-Ares L (2017). Lung cancer: current therapies and new targeted treatments. *Lancet* **389**:299–311.

Kauczor HU, Bonomo L, Gaga M, Nackaerts K, Peled N, Prokop M, *et al.* (2015). ESR/ERS white paper on lung cancer screening. *Eur Respir J* **46**:28–39.

Malvezzi M, Carioli G, Bertuccio P, Boffetta P, Levi F, La Vecchia C, Negri E (2017). European cancer mortality predictions for the year 2017, with focus on lung cancer. *Ann Oncol* **28**:1117–1123.

McMahon PM, Kong CY, Bouzan C, Weinstein MC, Cipriano LE, Tramontano AC, *et al.* (2011). Cost-effectiveness of computed tomography screening for lung cancer in the United States. *J Thorac Oncol* **6**:1841–1848.

Molina R, Marrades RM, Augé JM, Escudero JM, Viñolas N, Reguart N, *et al.* (2016). Assessment of a combined panel of six serum tumor markers for lung cancer. *Am J Respir Crit Care Med* **193**:427–437.

National Lung Screening Trial Research T (2019). Lung Cancer Incidence and Mortality with Extended Follow-up in the National Lung Screening Trial. *J Thorac Oncol* **14**:1732–1742.

Neumann PJ, Cohen JT, Weinstein MC (2014). Updating cost-effectiveness–the curious resilience of the $50,000-per-QALY threshold. *N Engl J Med* **371**:796–797.

Oudkerk M, Devaraj A, Vliegenthart R, Henzler T, Prosch H, Heussel CP, *et al.* (2017). European position statement on lung cancer screening. *Lancet Oncol* **18**:e754–e766.

Pedersen JH, Rzyman W, Veronesi G, D'Amico TA, Van Schil P, Molins L, *et al.* (2017). Recommendations from the European Society of Thoracic Surgeons (ESTS) regarding computed tomography screening for lung cancer in europe. *Eur J Cardiothorac Surg* **51**:411–420.

Pérez-Martínez O, Vidal-García I, Montero-Martínez C, Provencio M, Ruano-Ravina A (2018). Description and survival of stage I and II lung cancer patients. *Arch Bronconeumol* **54**:420–426.

Postmus PE, Kerr KM, Oudkerk M, Senan S, Waller DA, Vansteenkiste J, *et al.* (2017). Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* **28**(Suppl_4):iv1–iv21.

Pyenson BS, Sander MS, Jiang Y, Kahn H, Mulshine JL (2012). An actuarial analysis shows that offering lung cancer screening as an insurance benefit would save lives at relatively low cost. *Health Aff (Millwood)* **31**:770–779.

Reck M, Heigener DF, Mok T, Soria JC, Rabe KF (2013). Management of non-small-cell lung cancer: recent developments. *Lancet* **382**:709–719.

Sacristán JA, Oliva J, Del Llano J, Prieto L, Pinto JL (2002). What is an efficient health technology in spain?. *Gac Sanit* **16**:334–343.

Speicher PJ, Fitch ZW, Gulack BC, Yang CJ, Tong BC, Harpole DH, *et al.* (2016). Induction chemotherapy is not superior to a surgery-first strategy for clinical N1 non-small cell lung cancer. *Ann Thorac Surg* **102**:884–894.

Torrance GW, Feeny D (1989). Utilities and quality-adjusted life years. *Int J Technol Assess Health Care* **5**:559–575.

Vela E, Clèries M, Rué M (1999). The use of treatment modality specific analysis according to Selwood in epidemiological studies. *Nephrol Dial Transplant* **14**:412–415.

Vela E, Cleries M, Vella VA, Adroher C, Garcia-Altes A (2017). Population-based analysis of the healthcare expenditure in Catalonia (Spain): what and who consumes more resources?. *Gac Sanit*.

Vela E, Clèries M, Vella VA, Adroher C, García-Altés A (2019). Population-based analysis of the healthcare expenditure in Catalonia (Spain): what and who consumes more resources?. *Gac Sanit* **33**:24–31.

Vela E, Tényi Á, Cano I, Monterde D, Cleries M, Garcia-Altes A, *et al.* (2018). Population-based analysis of patients with COPD in Catalonia: a cohort study with implications for clinical management. *BMJ Open* **8**:e017283.

Villanti AC, Jiang Y, Abrams DB, Pyenson BS.(2013). A cost-utility analysis of lung cancer screening and the additional benefits of incorporating smoking cessation interventions. *PLoS One* **8**:e71379.

Wade S, Weber M, Caruana M, Kang YJ, Marshall H, Manser R, *et al.* (2018). Estimating the cost-effectiveness of lung cancer screening with low dose computed tomography for high risk smokers in Australia. *J Thorac Oncol*

Waller DA (2018). Surgical management of lung cancer with multiple lesions: implication of the new recommendations of the 8(th) edition of the TNM classification for lung cancer. *J Thorac Dis* **10**(Suppl 22):S2686–S2691.

4.2 Original Paper 2

A look ahead to promote the early detection of lung cancer: Technical and cost implications of a confirmed diagnosis before surgery

Guzman R., Angela Guirao, Leandro Grando, Marc Boada, David Sanchez, Nestor Quiroga, Pablo Paglialunga, Laureano Molins

Cirugia Española 2023

CIRENG 2892g 1
ARTICLE IN PRESS
CIR ESP. 2023;xx(xx):xxx–xxx

CIRUGÍA ESPAÑOLA
www.elsevier.es/cirugia

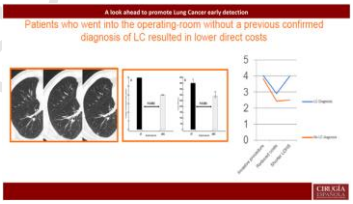
Graphical Abstract

A look ahead to promote the early detection of lung cancer: technical and cost implications of a confirmed diagnosis before surgery

CIR ESP. 2023;xx(xx): pp. xxx–xxx

Rudith Guzmán,[a,*] Angela Guirao,[a,b,c] Leandro Grando,[a] Marc Boada,[a,b] David Sanchez,[a,b] Nestor Quiroga,[a] Pablo Paglialunga,[a] Laureano Molins [a,b,c]

[a] *Respiratory Institute, Hospital Clínic de Barcelona, Spain*
[b] *University of Barcelona, Spain*
[c] *Institut d'Investigacions Biomediques August Pi i Sunyer (IDIBAPS), Barcelona, Spain*



CIRENG 2892 1–8
ARTICLE IN PRESS
CIR ESP. 2023;xx(xx):xxx–xxx

CIRUGÍA ESPAÑOLA
www.elsevier.es/cirugia

Original article

A look ahead to promote the early detection of lung cancer: technical and cost implications of a confirmed diagnosis before surgery

Rudith Guzmán,[a,*] Angela Guirao,[a,b,c] Leandro Grando,[a] Marc Boada,[a,b] David Sanchez,[a,b] Nestor Quiroga,[a] Pablo Paglialunga,[a] Laureano Molins[a,b,c]

[a] Respiratory Institute, Hospital Clínic de Barcelona, Spain
[b] University of Barcelona, Spain
[c] Institut d'Investigacions Biomediques August Pi i Sunyer (IDIBAPS), Barcelona, Spain

ARTICLE INFO

Article history:
Received 21 December 2022
Accepted 16 March 2023
Available online xxx

Keywords:
Cost effectiveness
Lung cancer
Minimal invasive thoracic surgery

ABSTRACT

Objective: To compare the costs and length of hospital stay among patients with a confirmed diagnosis of lung cancer (LC) prior to surgery versus those without confirmation.
Methods: This retrospective, single-center study was conducted in patients who underwent a surgical procedure for LC, with or without a pathologically confirmed LC diagnosis prior to surgery, between March 2017 and December 2019. The main outcomes were costs and length of hospital stay (LOS).
Results: Among the 269 patients who underwent surgery for lung cancer between March 2017 and December 2019, 203 (75.5%) patients underwent surgery due to a histopathological diagnosis, and 66 (24.5%) because of a Multidisciplinary Cancer Committee indication. The unadjusted mean cost was significantly lower in Group II (patients with surgery based on Multidisciplinary Cancer Committee criteria) (€2,581.80 ± €1,002.50) than in Group I (patients with histopathological diagnosis) (€4,244.60 ± €2,008.80), $P < 0.0001$. Once adjusted for covariables, there was a mean difference of −€1,437.20 in the costs of Group II, $P < 0.0001$.

Unadjusted mean hospital stay was significantly longer in Group I (5.6 days) than in Group II (3.5 days).
Conclusions: The results suggest that indicating surgical resection of lung cancer based on Multidisciplinary Cancer Committee criteria, rather than performing CT-guided percutaneous lung biopsy, may result in a significant decrease in cost and length of hospital stay.

* *Corresponding author.*
E-mail address: rudithgp@gmail.com (R. Guzmán).
http://dx.doi.org/10.1016/j.cireng.2023.03.013

Please cite this article in press as: Guzmán R, et al. A look ahead to promote the early detection of lung cancer: technical and cost implications of a confirmed diagnosis before surgery. Cir Esp. 2023. http://dx.doi.org/10.1016/j.cireng.2023.03.013

CIRENG 2892 1–8
ARTICLE IN PRESS
2 CIR ESP. 2023;xx(xx):XXX–XXX

Una mirada al futuro para promover la detección temprana del Cáncer de Pulmón: implicaciones técnicas y económicas de tener un diagnóstico confirmado antes de la cirugía

Palabras clave:
Cribado del cáncer de pulmón
Coste-efectividad
Cáncer de pulmón
Cirugía torácica video-asistida

RESUMEN

Objetivo: Comparar los costes y la duración de la estancia hospitalaria entre los pacientes con un diagnóstico confirmado de cáncer de pulmón (CP) antes de la cirugía frente a los que no lo tienen.

Métodos: Estudio retrospectivo y unicéntrico realizado en pacientes que se sometieron a un procedimiento quirúrgico de CP, con o sin diagnóstico de CP confirmado patológicamente antes de la cirugía, entre marzo de 2017 y diciembre de 2019. Los principales resultados fueron los costes y la duración de la estancia hospitalaria (LOHS).

Resultados: Entre los 269 pacientes sometidos a cirugía por cáncer de pulmón entre marzo de 2017 y diciembre de 2019, 203 (75,5%) pacientes se operan por diagnóstico histopatológico y 66 (24,5%) por indicación del Comité Oncológico Multidisciplinar. El coste medio no ajustado fue significativamente menor en el Grupo II (pacientes con intervención quirúrgica basada en criterios del Comité Multidisciplinar del Cáncer) (2.581,8 ± 1.002,5€) que en el Grupo I (pacientes con diagnóstico histopatológico) (4.244,6€ ± 2.008,8), $p < 0,0001$. Una vez ajustados por covariables, hubo una diferencia media de −1.437,2€ en los costes del Grupo II, $p < 0,0001$.

La estancia hospitalaria media no ajustada fue significativamente mayor en el Grupo I (5,6 días) que en el Grupo II (3,5 días).

Conclusiones: Los resultados sugieren que indicar la resección quirúrgica del cáncer de pulmón basándose en los criterios del Comité Multidisciplinar del Cáncer, en lugar de realizar una biopsia pulmonar percutánea guiada por TAC, puede suponer una disminución significativa del coste y de la duración de la estancia hospitalaria.

Q5 Introduction

Lung cancer remains the leading cause of cancer incidence and mortality worldwide.[1–3] For both sexes combined, lung cancer is the most commonly diagnosed cancer (11.6% of the total cases) and the leading cause of cancer death (18.4% of the total cancer deaths).[2] In Spain, lung cancer was responsible of 22,930 deaths (20.3% of total cancer deaths) in 2020 year.[4]

Lung cancer remains as one of the cancers with the poorest prognosis, mainly due to the fact that most patients are diagnosed at an advanced stage.[5] Surgery represents a valuable strategy for treating lung cancer patients with curative purposes.[6–9] Unfortunately, this strategy is only feasible for a minority of patients, since approximately three quarters of lung cancer patients present when the disease is in advanced stages.[10]

Early detection would be, therefore, a valuable strategy for diagnosing disease at an earlier, asymptomatic, and potentially curable stage. According to the results of the National Lung Cancer Screening Trial (NLST), low-dose computed tomography (CT) was associated with earlier lung cancer detection, which led to a 20% reduction in lung cancer-related death and an overall all-cause mortality reduction of 6.7%.[11] Additionally, the Dutch-Belgian NELSON trial recently confirmed that screening for lung cancer with low radiation dose CT reduces lung cancer mortality.[12]

Despite their relevance, several issues should be addressed for translating these findings into clinical practice. "Who should be screened"; "How often screening should be performed"; and "For how long" are key questions that need an answer.

Moreover, screening programs entail significant logistic and economic implications. A health economic evaluation of the NLST found that CT screening was associated with an incremental cost-effectiveness ratio (ICER) of $52,000/life-year gained or $81,000/quality-adjusted life year (QALY) gained.[13] In a previous study published by our group, surgical treatment was associated with better clinical outcomes and was identified as the most cost-effective lung cancer therapeutic strategy. These results provided evidence supporting the implementation of screening programs in a real setting.[14]

Special consideration merits the solitary pulmonary nodules, which represent a common problem and are usually a diagnostic challenge. Additionally, implementation of CT screening programs may entail an increase in solitary pulmonary nodules prevalence.[15]

Among the different methods for obtaining lung tissue before resection, CT-guided percutaneous lung biopsy is widely used.[16–18] An alternative strategy is collecting a tissue sampling at the time of surgery. While the patient is under general anesthesia, a small tissue sample is resected and sent to histopathological evaluation. Surgery resumes once diagnosis has been established. If malignancy is diagnosed the

Please cite this article in press as: Guzmán R, et al. A look ahead to promote the early detection of lung cancer: technical and cost implications of a confirmed diagnosis before surgery. Cir Esp. 2023. http://dx.doi.org/10.1016/j.cireng.2023.03.013

CIRENG 2892 1–8
ARTICLE IN PRESS
CIR ESP. 2023;xx(xx):xxx–xxx

patient undergoes a surgical resection; while cases of benign disease typically led to conclusion of the surgery.[19]

Because the most cost-effective approach has not been established yet, we have considered whether it was necessary to have the diagnosis before the patient enters the operating room.

This study aimed to compare the costs attributed directly to the surgical procedure between patients who underwent surgery with a prior histopathological diagnosis of lung cancer and those who went to the operating room with a diagnosis of suspected lung cancer according to Multidisciplinary Cancer Committee criteria.

Methods

Retrospective and single center study.

The study protocol was approved by the Institutional Review Board of the Hospital, which waived the need for written informed consent of the participants.

Patients

The study sample included all the patients who underwent a surgical procedure for lung cancer, independently of diagnosis, between March 2017 and December 2019. The surgical indication was established by the multi-disciplinary LC Committee in our Institution. The study was approved by the Institutional Ethics Board of our institution.

Multidisciplinary cancer committee criteria

Comprises a core group of specialists from disciplines including medical oncology, pulmonologist, radiation oncology, radiology, haematology, pathology, nuclear medicine, thoracic surgery and nursing. Regular meetings provide a forum for this core group to discuss patient cases in terms of key radiographic and pathological findings; diagnostic and/or therapeutic options and the best approach for each patient; integration of evidence-based guidelines focus on Diagnosis: pathology and molecular testing, Disease staging and treatment options used as criteria; and communication of clinical trial findings.

Direct costs

Cost analysis was carried out from the perspective of the regional health System Catalonian Institute of Health (CIH).

Cost per hospital day and, therefore, total costs for hospitalization were calculated according to the information supplied by the Hospital.

Besides the cost of the procedure, the different items considered in the model included cost of personnel, equipment, hospital stay, consumables, drugs, laboratory tests, other medical supplies, structure, and perioperative complications.

The data have been considered as a whole and an individualized analysis of the different cost items has not been carried out, beyond the hospital stay.

Other costs, such as transport services, food services, other non-medical materials, etc. have not been taken into account in this study.

Study groups

Subjects were divided into two groups: [I] patients with a histopathology diagnosis before surgery, by using CT-guided fine needle aspiration; [II] Patients with a low-dose CT positive screening result according to the NLST protocol (any non-calcified nodule with a maximum diameter $\geq$4 mm),[11] but without a histopathological diagnosis prior to the surgery. According to the Multidisciplinary Cancer Committee criteria, that comprises a core group of specialists from disciplines including medical oncology, radiation oncology, radiology, pneumonology pathology, nuclear medicine, thoracic surgery, and nursing.Patients were selected for undergoing therapeutic diagnostic surgery based on their clinical and radiologic characteristics.

Study parameters

For patients in group I, data collected included demographics; lung cancer stage, according to the 8th edition of the tumor, node and metastasis (TNM) classification system[20]; tumor stage; smoking habit; comorbidities; diagnosis; neoadjuvant and adjuvant therapy; forced expiratory volume in 1 s (FEV_1), performance access; lung excision procedure; lobectomy procedure site; days of hospital stay; and total cost per patient.

For patients in group II, demographics; smoking habit; histopathological diagnosis (at the time of surgery); TNM classification system[20]; tumor stage; FEV_1; Chronic obstructive pulmonary disease (COPD) stage, according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) committee classification[21]; performance access; lobectomy procedure site; days of hospital stay; and total cost per patient were assessed.

Statistical analysis

Main outcome was the mean cost. Secondary outcome was the length of hospital stay.

Statistical analysis

A standard statistical analysis was performed using the MedCalc® Statistical Software version 19.7.1 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2021) and the SPSS IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp.

Descriptive statistics number (percentage), mean [standard deviation (SD)], mean [95% confidence interval (95% CI)], mean [standard error (SE)], median (95% CI), or median [interquartile range (IqR)] were used, as appropriate.

Data were tested for normal distribution using a D'Agostino-Pearson test.

The one-way ANOVA test or the Kruskal-Wallis test were used to compare differences between groups. Post hoc analysis for pair wise comparisons were done with the Scheffé's method (ANOVA) or the Conover method (Kruskal-Wallis). The Mann–Whitney U test was used in the evaluation of the pre surgery clinical and demographic parameters between groups.

The analysis of covariance (ANCOVA) was used in the evaluation of the total costs and day of hospital stay between study groups. The model included "Study group" as a factor

Please cite this article in press as: Guzmán R, et al. A look ahead to promote the early detection of lung cancer: technical and cost implications of a confirmed diagnosis before surgery. Cir Esp. 2023. http://dx.doi.org/10.1016/j.cireng.2023.03.013

CIRENG 2892 1–8
ARTICLE IN PRESS
4
CIR ESP. 2023;xx(xx):XXX–XXX

and age, sex, smoking habit, TNM, tumor stage, FEV_1, and performance access as covariates.

Categorical variables were compared using a Chi-square test and a Fisher's exact test, as needed. P value of < 0.05 was considered significant.

Results

Among the 269 patients who underwent a surgical procedure for lung cancer between March 2017 and December 2019, 203 (75.5%) patients went into the theater with a histopathological diagnosis and 66 (24.5%) ones with Multidisciplinary Cancer Committee indication.

Median age was 68 years (IqR: 61.0–74.0 years) and 70.0 years (IqR: 62.0–74.0) years in the Groups I and II, respectively (Hodges–Lehmann median difference: 1.0 years; 95%CI: −2.0–3.0 years; p = 0.6375). The proportion of women was 36.9% (75/203) in Group I and 30.3% (20/66) in Group II, p = 0.3306. Table 1 summarizes the main presurgical demographic and clinical characteristics.

Regarding diagnosis, adenocarcinoma was the most frequently diagnosed cancer in both groups; followed by squamous cell in the Group I and Lepidic adenocarcinoma in group II (Table 2). In the Group II, 8 (12.1%) patients had a final histopathological diagnosis of benign lesions.

The Tables 3 and 4 show the tumor stage.

Unadjusted mean cost was significantly lower in the Group II (patients with surgical intervention based on Multidisci-

Table 1 – Demographic and clinical characteristics of the study sample.

	Group I (n = 203)	Group II (n = 66)	p[a]
Age, years			
Median (IqR)	68.0 (61.0–74.0)	70.0 (62.0–74.0)	0.6375
Sex, n (%)			
Women	75 (36.9)	20 (30.3)	0.3276
Men	128 (63.1)	46 (69.7)	
BMI, Kg/m^2			
Median (IqR)	25.2 (23.3–27.8)	Missing	N.A.
Comorbidities, n (%)			N.A.
Yes	97 (47.8)	Missing	
No	106 (52.2)		
COPD, n (%)	N.A.		N.A.
None		33 (50.0)	
Gold I		6 (9.1)	
Gold II		22 (33.3)	
Gold III		4 (6.1)	
Missing		1 (1.5)	
Neoadjuvant therapy, n (%)		N.A.	N.A.
None	172 (84.7)		
CT	8 (3.9)		
CT + RT	8 (3.9)		
Missing data	15 (7.4)		
Adjuvant therapy		N.A.	N.A.
None	135 (66.5)		
CT	37 (18.2)		
CT + RT	29 (14.3)		
Missing data	2 (1.0)		
FEV_1, (%)			0.4042
Median (IqR)	83.0 (69.0–90.0)	84 (66.8–97.3)	
Smoking habit, n (%)			0.0290[b]
Never smoked	12 (5.9)	9 (13.6)	
Current smoker	54 (26.6)	23 (34.8)	
Past smoker[c]	128 (63.1)	34 (55.1)	
Unknown	9 (4.4)	0 (0.0)	
LPS, n (%)			0.0439
Culmen	0 (0.0)	2 (3.0)	
RUL	65 (37.8)	24 (36.4)	
RML	6 (3.5)	4 (6.1)	
RLL	34 (19.8)	12 (18.2)	
LUL	46 (26.7)	10 (15.2)	
LLL	21 (12.2)	14 (21.2)	

IqR, Interquartile range; BMI, Body mass index; COPD, Chronic obstructive pulmonary disease; CT, Chemotherapy; RT, Radiotherapy; FEV_1, Forced expiratory volume in 1 s; LPS, Lobectomy procedure site; RUL, Right upper lobule; RML, Right middle lobule; RLL, Right lower lobule; LUL, Left upper lobule; LLL, Left lower lobule; NA, Not applicable.
[a] Mann–Whitney U test.
[b] Chi–squared test.
[c] Stopped >1month before surgery.

Please cite this article in press as: Guzmán R, et al. A look ahead to promote the early detection of lung cancer: technical and cost implications of a confirmed diagnosis before surgery. Cir Esp. 2023. http://dx.doi.org/10.1016/j.cireng.2023.03.013

CIRENG 2892 1–8
ARTICLE IN PRESS
CIR ESP. 2023;xx(xx):XXX–XXX

Table 2 – Overview of the histopathological diagnosis.

	Diagnosis	N (%)
Group I	Adenocarcinoma	95 (50.0)
	Carcinoma in situ*	11 (5.8)
	Large cells	7 (3.7)
	Mixed	6 (3.2)
	Squamous cells	64 (33.7)
	Neuroendicrine	7 (3.7)
Group II	Adenocarcinoma	23 (34.8)
	Lepidic adenocarcinoma	20 (30.3)
	Atypical carcinoid	3 (4.5)
	Typical carcinoid	1 (1.5)
	Large cells	2 (3.0)
	Small cells	1 (1.5)
	Squamous cells	8 (12.1)
	Granuloma	2 (3.0)
	Hamartoma	1 (1.5)
	Sclerosing neumocitoma	1 (1.5)
	Pleomorphic sarcoma	1 (1.5)
	Pulmonary infarction	1 (1.5)
	Benign tumor	2 (3.0)

plinary Cancer Committee criteria) (2,581.8 ± 1,002.5€; 95% CI: 2,335.3–2,828.2) than in the Group I (patients with histopathological diagnosis) (4,244.6€ ± 2,008.8; 95% CI: 3,966.6–4,522.6), $p < 0.0001$. Once adjusted by covariates, there was a mean difference of −1,437.2€ (standard error of the mean: 291.2€; 95% CI: −2,010.8 to −863.7€) in the Group II costs, $p < 0.0001$ (Fig. 1).

Table 3 – Lung cancer stage, according to the 8th edition of the tumor, node and metastasis (TNM) classification system.

TNM	Group 1	Group 2	P
T1aN0M0	8 (4.0)	6 (10.3)	<0.0001
T1bN0M0	52 (26.9)	21 (36.2)	
T1bN1M0	2 (1.0)	0 (0.0)	
T1bN2M0	3 (1.5)	1 (1.7)	
T1bNXM0	1 (1.0)	0 (0.0)	
T1cN0M0	16 (8.0)	19 (32.8)	
T1cN0M1c	0 (0.0)	1 (1.7)	
T1cN1M0	4 (2.0)	0 (0.0)	
T2aN0M0	19 (9.5)	1 (1.7)	
T2aN0Mo	0 (0.0)	3 (5.2)	
T2aN1M0	3 (1.5)	1 (1.7)	
T2aN2M0	8 (4.0)	0 (0.0)	
T2bN0M	0 (0.0)	2 (3.4)	
T2bN0M0	12 (6.0)	1 (1.7)	
T2bN0M1b	1 (0.5)	0 (0.0)	
T2bN1M0	4 (2.0)	0 (0.0)	
T2bN1M1b	1 (0.5)	0 (0.0)	
T2N1M0	0 (0.0)	1 (1.7)	
T3N0M0	23 (11.5)	0 (0.0)	
T3N1M0	10 (5.0)	1 (1.7)	
T3N2M0	7 (3.5)	0 (0.0)	
T4N0M0	13 (6.5)	0 (0.0)	
T4N1M0	8 (4.0)	0 (0.0)	
T4N2M0	1 (0.5)	0 (0.0)	
T4N2MO	1 (0.5)	0 (0.0)	
T4NXM0	1 (0.5)	0 (0.0)	
TXN0M0	1 (0.5)	0 (0.0)	
TXNXM0	1 (0.5)	0 (0.0)	

P value was calculated by using Chi-squared test.

Table 4 – Lung cancer stage.

Stage	Group I (n = 196)	Group II (n = 66)	P value
Benign	0 (0.0)	8 (12.1)	<0.0001
IA1	8 (4.1)	6 (9.1)	
IA2	52 (26.5)	21 (31.8)	
IA3	17 (8.7)	19 (28.8)	
IB	1 (0.5)	5 87.6)	
IIA	12 (6.1)	3 (4.5)	
IIB	49 (25.0)	1 (1.5)	
IIIA	46 (23.5)	2 (3.0)	
IIIB	9 (4.6)	0 (0.0)	
IVA	2 (1.0)	0 (0.0)	
IVB	0 (0.0)	1 (1.5)	

Unadjusted mean hospital stay was significantly longer in the Group I (mean 5.6 days; 95% CI: 5.4–5.8 days) than in the Group II (3.5 days; 95% CI: 3.4–3.7 days), (Mean difference 2.1 days; 95% CI: 1.7–2.5 days, $p < 0.0001$). Once adjusted by covariates, as compared to Group II, Group I was associated with a significantly higher length of hospital stay (mean difference 1.7 days; 95% CI: 1.3–2.1 days; $p < 0.0001$).

In our study, performance access was significantly associated with both length of hospital stay and total costs. Unadjusted mean of hospital stay and costs were 4.6 ± 1.5 days and 3,456.1 ± 1854.9€, respectively, in patients who underwent video-assisted thoracoscopic surgery (VATS) versus 6.0 ± 1.6 days and 4,511.3 ± 1938.6€, respectively, in patients who underwent open thoracotomy, $p < 0.0001$ each, respectively.

Moreover, after adjusting by covariates (age, sex, smoking habit, TNM, tumor stage, FEV_1, lobectomy procedure site, and study group) VATS was associated with a significantly shorter hospital stay (mean difference: −0.75 days; 95% CI: −1.13 to −0.37 days); $p = 0.0001$) and lower total costs (mean difference: −503.1€; 95% CI: −1,003.4 to −2.8; $p = 0.0487$) (adjusted by age, sex, age, sex, smoking habit, TNM, tumor stage, FEV_1, lobectomy procedure site, length of hospital stay, and study group).

Discussion

The results of the current study suggested that indicating lung cancer surgical resection based on the Multidisciplinary Cancer Committee criteria, instead of performing CT-guided percutaneous lung biopsy, may result in a significant decrease in cost and length of hospital stay.

These results disagree from those reported by Barnett et al.,[19] who found that in patients with solitary pulmonary nodules, pre-surgical CT guide percutaneous lung biopsy was the most effective strategy.

Nevertheless, the results of our study were in agreement with those published by Cho et al.,[22] who found that in nodular ground-glass opacities with high suspicious of malignancy, surgery resection without previous tissue histopathological diagnosis was more cost-effective and reduced the length of hospital stay.

Although it has been published that CT-guided fine needle aspiration may save money by preventing unneeded surgery,[23] this was based on the assumption that rates of resection of nonmalignant lung nodules are high. In addition, collecting a

Please cite this article in press as: Guzmán R, et al. A look ahead to promote the early detection of lung cancer: technical and cost implications of a confirmed diagnosis before surgery. Cir Esp. 2023. http://dx.doi.org/10.1016/j.cireng.2023.03.013

CIRENG 2892 1–8
ARTICLE IN PRESS
6 CIR ESP. 2023;xx(xx):XXX–XXX

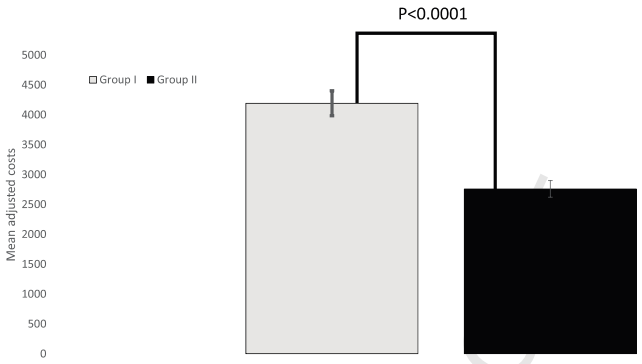


Fig. 1 – Mean adjusted direct costs per patient. Vertical bars represent the standard error of the mean. The model included "Study group" as a factor and age, sex, smoking habit, TNM, tumor stage, FEV_1, and performance access as covariates.

tissue sampling at the time of surgery may be associated with lengthening of the operating room time in approximately 45 min.[19] However, despite this fact, and after adjusting by different covariates, in our study this strategy was more cost-effective than CT-guided fine needle lung biopsy.

Current guidelines emphasize a systematic approach to pulmonary nodules evaluation, with probability assessment based on clinical and radiographic characteristics.[17,24,25] Pulmonary nodules may be classified according to their probability of malignancy. Those with a high probability of malignancy should be evaluated aggressively and considered for surgical resection.[24] Low-dose chest CT scanning has been suggested as a screening tool, especially in the presence of high-risk factors for lung cancer. Although this procedure has been associated with a significant reduction in lung cancer-related mortality rates,[11,12] it might be affected by a large rate of false positives.[11] However, the use of validated clinical malignancy probability models can help to discriminate benign from malignant nodules, guiding clinicians and patients when making management decisions.[26] And going further, and look into the future, we mustn't forget about artificial intelligence (AI). It is being increasingly used in the diagnosis and treatment of lung cancer. AI algorithms can help in image analysis for the early detection of lung cancer through CT scans, making it more accurate and efficient compared to manual interpretation. Additionally, AI can assist in the analysis of molecular and genetic data, helping to personalize treatment plans and predicting patients' response to various therapies. However, it's important to note that AI is not a substitute for human expertise and judgment in medical decision-making and should be used as an aid.

On average, approximately 25 % of the thoracic surgical procedures performed during the various randomized controlled lung cancer screening trials were done for benign nodules.[27] Nevertheless, in our study, only 8 (12.1%) had a confirmed histopathological diagnosed of benignity. It should be highlighted that the definition of a positive screening result may differ substantially among the different protocols, which critically impacts on the number of false-positive scans.

Although in Group II, benign processes were associated with lower costs (Hodges–Lehmann median difference: 319.4€; 95% CI: −215.0–863.0€), such a difference was not statistically significant (p = 0.3163).

In a previous study, we have found that implementation of lung cancer screening programs is beneficial for both patients and health care systems.[14] Additionally, it has been observed that survival time decreases significantly with progression of disease, with a 5-year survival time declining from 50 % for clinical stage IA to 43%, 36%, 25%, 19%, 7% and 2% for stages IB, IIA, IIB, IIIA, IIIB and IV, respectively.[28]

VATS lobectomy for patients with early-stage lung cancer is a standard surgical treatment, and is associated with lower morbidity and improved survival rates compared with open thoracotomy.[29] Additionally, VATS is potentially more cost-effective than thoracotomy.[30,31] Although in our study, VATS was performed in subjects with less advanced cancer stages, after adjusting by different covariates, including age, sex, tumor stage, FEV_1, lobectomy procedure site, and study group, VATS was associated with lower costs and shorter hospital stay than open thoracotomy.

Among the different limitations of the current study, its retrospective design may be the most important one. Selection bias and confounding factors are inherent to retrospective studies. As second limitation, the accuracy of the Multidisciplinary Cancer Committee criteria has not been assessed. Nevertheless, in the current study 58 (87.9%) patients had a confirmed histopathological diagnosed of malignancy. In fact, Multidisciplinary Cancer Committee approach may be the best way for managing cancer patients, especially the more complex cases. However, it should be noted that requires behavior changes and specific logistic requirements.[32–35] Additionally, our study took into account only the direct medical costs related to lung cancer treatment. Other costs, such as transportation services, food expenses, non-medical

Please cite this article in press as: Guzmán R, et al. A look ahead to promote the early detection of lung cancer: technical and cost implications of a confirmed diagnosis before surgery. Cir Esp. 2023. http://dx.doi.org/10.1016/j.cireng.2023.03.013

CIRENG 2892 1–8
ARTICLE IN PRESS
CIR ESP. 2023;xx(xx):xxx–xxx

materials, and working time lost, were not considered. However, providing comprehensive data on expenditures of lung cancer care is highly complex because treatment strategies and survival need to be taken into consideration.

Despite these limitations, this study suggests that indicating lung cancer surgery based on Multidisciplinary Cancer Committee criteria is more costs effective than do it based on pre-surgical CT guide biopsy. Additionally, our study also found that independently of the cancer stage and demographic variables, VATS was associated with lower costs than open thoracotomy.

Further studies are needed for establishing the positive and negative likelihood ratios of our Multidisciplinary Cancer Committee criteria, as well as their positive and negative predictive values.

Author contribution

All authors met the ICMJE authorship criteria. All authors made substantial contributions to conception, design, analysis and interpretation of data, contributed to writing the article, provided critical revision of the manuscript, and approved the final version.

Availability of materials and data

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of interest

None of the authors have any conflict of interest to declare.

Ethics declaration

"All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The local ethics committee waived the need for written informed consent of the participants for the study".

Ethics approval

This study was approved by the local ethics committees and was performed with the principles of the Declaration of Helsinki.

Acknowledgements

Statistics assistance was provided by Antonio Martinez (MD) of Ciencia y Deporte ltd.

REFERENCES

1. Malvezzi M, Carioli G, Bertuccio P, Boffetta P, Levi F, La Vecchia C, et al. European cancer mortality predictions for the year 2017, with focus on lung cancer. Ann Oncol. 2017;28(5):1117–23. http://dx.doi.org/10.1093/annonc/mdx033.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424. http://dx.doi.org/10.3322/caac.21492. Epub 2018 Sep 12. Erratum in: CA Cancer J Clin. 2020 Jul;70(4):313.
3. Babar L, Modi P, Anjum F. Lung cancer screening. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020. 2021 Jan. Available in: https://www.ncbi.nlm.nih.gov/books/NBK537283/ Last accessed March 12, 2021
4. Spanish Society of Medical Oncology. [Cancer figures in Spain in 2021 year]. Available in: https://seom.org/images/Cifras_del_cancer_en_Espnaha_2021.pdf Last accessed March 12, 2021.
5. National Cancer Institute SEER stat fact sheets: lung and bronchus cancer. Available in: http://seer.cancer.gov/statfacts/html/lungb.html Last accessed March 12, 2021.
6. Asamura H, Aokage K, Yotsukura M. Wedge resection versus anatomic resection: extent of surgical resection for stage I and II lung cancer. Am Soc Clin Oncol Educ Book. 2017;37:426–33. http://dx.doi.org/10.1200/EDBK_179730.
7. Pérez-Martínez O, Vidal-García I, Montero-Martínez C, Provencio M, Ruano-Ravina A. Description and survival of stage I and II lung cancer patients. Arch Bronconeumol. 2018;54(8):420–6. http://dx.doi.org/10.1016/j.arbres.2018.02.007. English, Spanish.
8. Waller DA. Surgical management of lung cancer with multiple lesions: implication of the new recommendations of the 8th edition of the TNM classification for lung cancer. J Thorac Dis. 2018;10 Suppl 22:S2686–91. http://dx.doi.org/10.21037/jtd.2018.04.159.
9. Rosen JE, Keshava HB, Yao X, Kim AW, Detterbeck FC, Boffa DJ. The natural history of operable non-small cell lung cancer in the national cancer database. Ann Thorac Surg. 2016;101(5):1850–5. http://dx.doi.org/10.1016/j.athoracsur.2016.01.077.
10. Postmus PE, Kerr KM, Oudkerk M, Senan S, Waller DA, Vansteenkiste J, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28 suppl_4:iv1–21. http://dx.doi.org/10.1093/annonc/mdx222.
11. National Lung Screening Trial Research Team, Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, Fagerstrom RM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011;365(5):395–409. http://dx.doi.org/10.1056/NEJMoa1102873.
12. de Koning HJ, van der Aalst CM, de Jong PA, Scholten ET, Nackaerts K, Heuvelmans MA, et al. Reduced lung-cancer mortality with volume CT screening in a randomized trial. N Engl J Med. 2020;382(6):503–13. http://dx.doi.org/10.1056/NEJMoa1911793.
13. Black WC, Gareen IF, Soneji SS, Sicks JD, Keeler EB, Aberle DR, et al. Cost-effectiveness of CT screening in the National Lung Screening Trial. N Engl J Med. 2014;371(19):1793–802. http://dx.doi.org/10.1056/NEJMoa1312547.
14. Guzman R, Guirao À, Vela E, Clèries M, García-Altés A, Sagarra J, et al. Outcomes and cost of lung cancer patients treated surgically or medically in Catalunya: cost-benefit

Please cite this article in press as: Guzmán R, et al. A look ahead to promote the early detection of lung cancer: technical and cost implications of a confirmed diagnosis before surgery. Cir Esp. 2023. http://dx.doi.org/10.1016/j.cireng.2023.03.013

CIRENG 2892 1–8
ARTICLE IN PRESS
8 CIR ESP. 2023;xx(xx):XXX–XXX

implications for lung cancer screening programs. Eur J Cancer Prev. 2020;29(6):486–92. http://dx.doi.org/10.1097/CEJ.0000000000000566.
15. Gould MK, Tang T, Liu IL, Lee J, Zheng C, Danforth KN, et al. Recent trends in the identification of incidental pulmonary nodules. Am J Respir Crit Care Med. 2015;192(10):1208–14. http://dx.doi.org/10.1164/rccm.201505-0990OC.
16. Callister ME, Baldwin DR, Akram AR, Barnard S, Cane P, Draffan J, et al. British Thoracic Society guidelines for the investigation and management of pulmonary nodules. Thorax. 2015;70 Suppl 2:ii1–54. http://dx.doi.org/10.1136/thoraxjnl-2015-207168. Erratum in: Thorax. 2015 Dec;70(12):1188.
17. MacMahon H, Naidich DP, Goo JM, Lee KS, Leung ANC, Mayo JR, et al. Guidelines for management of incidental pulmonary nodules detected on CT images: from the fleischner society 2017. Radiology. 2017;284(1):228–43. http://dx.doi.org/10.1148/radiol.2017161659.
18. Bueno J, Landeras L, Chung JH. Updated fleischner society guidelines for managing incidental pulmonary nodules: common questions and challenging scenarios. Radiographics. 2018;38(5):1337–50. http://dx.doi.org/10.1148/rg.2018180017.
19. Barnett J, Belsey J, Tavare AN, Saini A, Patel A, Hayward M, et al. Pre- surgical lung biopsy in management of solitary pulmonary nodules: a cost effectiveness analysis. J Med Econ. 2019;22(12):1307–11. http://dx.doi.org/10.1080/13696998.2019.1665322.
20. Detterbeck FC, Boffa DJ, Kim AW, Tanoue LT. The eighth edition lung cancer stage classification. Chest. 2017;151(1):193–203. http://dx.doi.org/10.1016/j.chest.2016.10.010.
21. The global initiative for chronic obstructive lung disease-GOLD. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: 2020 report. Available in: GOLD-2020-FINAL-ver1.2-03Dec19_WMV.pdf (goldcopd.org) Last accessed March 13, 2021.
22. Cho J, Ko SJ, Kim SJ, Lee YJ, Park JS, Cho YJ, et al. Surgical resection of nodular ground-glass opacities without percutaneous needle aspiration or biopsy. BMC Cancer. 2014;14:838. http://dx.doi.org/10.1186/1471-2407-14-838.
23. Barta JA, Henschke CI, Flores RM, Yip R, Yankelevitz DF, Powell CA. Lung cancer diagnosis by fine needle aspiration is associated with reduction in resection of nonmalignant lung nodules. Ann Thorac Surg. 2017;103(6):1795–801. http://dx.doi.org/10.1016/j.athoracsur.2016.11.055.
24. Gould MK, Donington J, Lynch WR, Mazzone PJ, Midthun DE, Naidich DP, et al. Evaluation of individuals with pulmonary nodules: when is it lung cancer? Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 Suppl):e93S–120S. http://dx.doi.org/10.1378/chest.12-2351.
25. Baldwin DR, Callister ME, Guideline Development Group. The British Thoracic Society guidelines on the investigation and management of pulmonary nodules. Thorax. 2015;70(8):794–8. http://dx.doi.org/10.1136/thoraxjnl-2015-207221.
26. Choi HK, Ghobrial M, Mazzone PJ. Models to estimate the probability of malignancy in patients with pulmonary nodules. Ann Am Thorac Soc. 2018;15(10):1117–26. http://dx.doi.org/10.1513/AnnalsATS.201803-173CME.
27. Detterbeck FC, Mazzone PJ, Naidich DP, Bach PB. Screening for lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 Suppl):e78S–92S. http://dx.doi.org/10.1378/chest.12-2350.
28. Goldstraw P, Crowley J, Chansky K, Giroux DJ, Groome PA, Rami-Porta R, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. J Thorac Oncol. 2007;2(8):706–14. http://dx.doi.org/10.1097/JTO.0b013e31812f3c1a. Erratum in: J Thorac Oncol. 2007 Oct;2(10):985.
29. Whitson BA, Groth SS, Duval SJ, Swanson SJ, Maddaus MA. Surgery for early- stage non-small cell lung cancer: a systematic review of the video-assisted thoracoscopic surgery versus thoracotomy approaches to lobectomy. Ann Thorac Surg. 2008;86(6):2008–16. http://dx.doi.org/10.1016/j.athoracsur.2008.07.009. discussion 2016-2018.
30. Fang HY, Hsiao FY, Huang HC, Lin YS, Chen CY, Shieh SH, et al. Cost and effectiveness of video-assisted thoracoscopic surgery for clinical stage I non-small cell lung cancer: a population-based analysis. J Thorac Dis. 2014;6(12):1690–6. http://dx.doi.org/10.3978/j.issn.2072-1439.2014.10.27.
31. Bendixen M, Kronborg C, Jørgensen OD, Andersen C, Licht PB. Cost-utility analysis of minimally invasive surgery for lung cancer: a randomized controlled trial. Eur J Cardiothorac Surg. 2019;56(4):754–61. http://dx.doi.org/10.1093/ejcts/ezz064.
32. Quint LE, Reddy RM, Lin J, Arenberg DA, Speers C, Hayman JA, et al. Imaging in thoracic oncology: case studies from Multidisciplinary Thoracic Tumor Board (part 1 of 2 part series). Cancer Imaging. 2013;13(3):429–39. http://dx.doi.org/10.1102/1470-7330.2013.0037.
33. Denton E, Conron M. Improving outcomes in lung cancer: the value of the multidisciplinary health care team. J Multidiscip Healthc. 2016;9:137–44. http://dx.doi.org/10.2147/JMDH.S76762.
34. Specchia ML, Frisicale EM, Carini E, Di Pilla A, Cappa D, Barbara A, et al. The impact of tumor board on cancer care: evidence from an umbrella review. BMC Health Serv Res. 2020;20(1):73. http://dx.doi.org/10.1186/s12913-020-4930-3.
35. Madariaga ML, Lennes IT, Best T, Shepard JO, Fintelmann FJ, Mathisen DJ, Gaissert HA, MGH Pulmonary Nodule Clinic Collaborative. Multidisciplinary selection of pulmonary nodules for surgical resection: diagnostic results and long-term outcomes. J Thorac Cardiovasc Surg. 2020;159(4):1558–66. http://dx.doi.org/10.1016/j.jtcvs.2019.09.030. e3.

Please cite this article in press as: Guzmán R, et al. A look ahead to promote the early detection of lung cancer: technical and cost implications of a confirmed diagnosis before surgery. Cir Esp. 2023. http://dx.doi.org/10.1016/j.cireng.2023.03.013

5. Discussion

5.1 Summary of Main Results

The first study compared the demographic and clinical characteristics of patients, as well as health care resources required, in order to provide medical (n = 10 866; 82.4%) or surgical (n = 2230; 17.6%) treatments for lung cancer. Surgically treated patients demonstrated better survival rates, a quicker return to daily activities and lower healthcare costs. Furthermore, we performed a cost-benefit analysis of the lung cancer screening program implemented in the region of Catalunya Spain, revealing that the cost–benefit ratio of said program is expected to break even between 3 to 6 years after launch and will generate healthcare cost savings subsequently.

Our second study focused on analyzing the clinical outcomes and cost-effectiveness of 269 lung cancer patients who underwent surgical procedures from March 2017 to December 2019. Of these, 203 patients were operated based on a histopathological diagnosis (Group I), while 66 patients were selected based on Multidisciplinary Cancer Committee indications (Group II). We found that patients in Group II had a significantly lower unadjusted mean cost (2,581.8±1,002.5 €) compared to Group I (4,244.6 €±2,008.8), and also experienced shorter hospital stays. Moreover, when adjusted for various covariates, video-assisted thoracoscopic surgery (VATS) was associated with a further significant reduction in both hospital stay duration and total costs.

In combination, the results of these two studies provide strong evidence that surgical intervention, particularly when adhering to Multidisciplinary Cancer Committee guidelines, is not only a clinically superior treatment option for lung cancer but also a more cost-effective one. This becomes even more evident when considering the impact of VATS and the implementation of lung cancer screening programs.

5.2 Mass LC Screening programs and Its Limitations: A Cost-Effectiveness Analysis

The experience and results of the National Lung Screening Trial (NLST) influenced the dissemination and application of low-dose computed tomography (LDCT) and LC screening. This new reality raised the possibility of large-scale screening programs based on clearly defined criteria (Seijo)[56], which significantly improve the effectiveness of detection.

However, cost-effectiveness of implementing such large-scale programs is still in debate, and in the recent years multiple studies have addressed this issue with varying conceptual and methodological approaches with regards to how to measure cost-effectiveness and to what intervention alternative should be taken into consideration when comparing the results of such screening programs.

Some published studies have estimated the cost per QALY of LC screening using LDCT. For example, a compelling study by MEDICARE based on a mathematical model and conducted in the United States with a population of Medicare beneficiaries over 65 years old and at high risk of LC, concluded that the annual cost of screening a patient would be $241, implying a monthly expenditure of $1 per insured person and $19,000 per year of life gained. This screening would qualify as a high cost-effectiveness intervention, even surpassing colon and breast cancer screening programs. The study concluded that "if all eligible Medicare beneficiaries had been consistently screened and treated since the age of 55, approximately 358,134 additional individuals with current or past LC would be alive in 2014."[57]

Another study concerning the organization and execution of a large-scale LC screening in the United States aimed to assess its budgetary impact and the profitability of LDCT detection before it became effective [58]. The authors used data from the 2009 National Health Interview Survey, CMS, and NLST to conduct an economic analysis of LDCT screening, which included a budgetary impact model and an estimation of additional costs per LC death avoided attributed to screening. According to the authors, LDCT

screening would add $1.3 to $2.0 billion to annual national health care expenditures for screening uptake rates of 50% to 75%, respectively. However, LDCT detection would prevent up to 8,100 premature LC deaths at a 75% detection rate. The additional cost of screening tests to prevent one LC death reached $240,000.

In another study by Braithwaite, it was calculated that screening all registered U.S. citizens using the NLST inclusion criteria would save around $1.3 billion per year in LC treatments. Based on this savings, the cost per quality-adjusted life year (QALY) would be close to $35,000 [59].

The pan-Canadian study conducted between 2008 and 2011 with 2,059 high-risk LC participants concluded that "the average cost to evaluate individuals at high risk for developing LC using LDCT and the average initial cost of treatment with curative intent were lower than the average cost per person of treating advanced-stage LC, which rarely results in a cure."[60]

In Europe, health care costs and the cost of a reasonable QALY are much lower than in North America. Therefore, the cost-effectiveness ratio is also more favorable than in the United States.

The United Kingdom's LC Detection Pilot Trial, the UK Lung Cancer Screening RCT Pilot Trial, demonstrated that the cost per QALY attributable to population screening could be £8,466, approximately €12,000 [61]. The initial estimation of the incremental cost-effectiveness ratio of single LDCT screening according to the UKLS protocol was £8,466 per quality-adjusted life year gained (CI £5,542 to £12,569). Their conclusions indicated that it is possible to detect LC at an early stage and administer potentially curative treatment in more than 80% of cases, and that the economic analysis suggests that the intervention would be cost-effective, but this must be confirmed using data on the reduction of LC mortality.

Regarding the relationship between high-risk patients and cost-effectiveness in the context of LC screening, it is relevant to mention the study by Vaibhav Kumar et al. [62]

which addresses the notion that LC detection in individuals with higher risk of mortality improves screening efficiency. Consequently, it proposes to quantify the value of risk-targeted selection for LC detection compared to the eligibility criteria of the National Lung Screening Trial (NLST).

Utilizing a multi-state prediction model applied to a population of current and former smokers eligible for lifetime screening, the research team aimed to measure: incremental 7-year mortality, life expectancy, quality-adjusted life years (QALYs), and cost and profitability of low-dose computed tomography (LDCT) screening versus chest radiography in each decile of lung cancer (LC) mortality risk. The study's results were as follows:

1. Participants with a higher risk of LC mortality were older and had more comorbid conditions and higher detection-related costs.
2. Incremental LC mortality benefits during the first 7 years ranged between 1.2 and 9.5 LC deaths avoided per 10,000 person-years for the lowest to highest risk deciles, respectively.
3. However, the gradient of benefits between risk groups diminished in terms of life years and QALYs.
4. Incremental cost-effectiveness ratios (ICERs) were similar across all risk deciles, ranging from $75,000 per QALY in the lowest risk decile to $53,000 in the highest risk decile.

Ultimately, the study's conclusions were that while risk selection as an approach to screening can improve efficiency in terms of early LC mortality per person screened, the gains in efficiency are attenuated and moderated in terms of life years, QALYs, and cost-effectiveness.

LDCT is an expensive technique, and the potential number of candidates for screening is significant; however, it is essential to consider the impact of LC and its treatment on patients' quality of life and survival[63].

Screening costs could also be reduced by prioritizing patients with additional risk factors, such as emphysema and chronic obstructive pulmonary disease (COPD)-related symptoms detected by LDCT [64].

5.3 The Case of Spain

The European Respiratory Society (ERS) suggested in its white paper of 2015 that member countries should adopt the National Lung Screening Trial (NLST) inclusion criteria for implementing a massive lung cancer (LC) screening program. In Spain, however, there is no definitive estimation determining the number of individuals in our population who meet these inclusion criteria yet. In this context, the large-scale screening studies of IBERPOC and EPISCAN in Spain can serve as a reference for this purpose [65,66].

According to IBERPOC data, 13.8% of Spaniards aged 50 to 80 years meet the NLST smoking criteria (IPA ≥ 30), indicating that over one and a half million people would be eligible for an LC screening program[67]. This number would be reduced by the exclusion of those who do not meet minimum adherence levels, those who should be excluded due to functional reasons and ailments, and those who have quit smoking for more than 15 years. The number of screening candidates after this reduction would be around 500,000.

Assuming that between 10 and 15% of candidates would require an interval low-dose computed tomography (LDCT) based on annual results, we can estimate that the over 550,000 annual LDCT scans would be required across all Spain. On this topic, it is worth mentioning that hospitals within the Madrid Health Service alone performed 556,687 scans in 2015 [68].

In order to validate this assumption, our study analyzed data provided by the Catalan Health Surveillance System on patients diagnosed with LC and who received medical or surgical treatment between 2014 and 2016. The goal of the study was to evaluate the costs associated with each treatment plan during the first 30 months after

diagnosis and, using this cost evaluations as a reference, to estimate the cost-benefit ratio of an LC screening program with LDCT in this population.

Our results demonstrated that:

1. Patients with LC who underwent surgical treatment had better survival and returned to their regular activities sooner, used fewer healthcare-related resources and thus generating a lower financial impact on taxpayers, and ;
2. Based on the incidence of LC identified and treated in the program (1-2%), the return on investment is expected to be reached within 3-6 years, respectively, after implementation.

In conclusion, we assume that surgical treatment is more cost-effective and offers better outcomes, which is consistent with the international literature.

In the white paper mentioned above, the European Respiratory Society (ERS) recommends that hospitals with multidisciplinary teams experienced in the management of pulmonary nodules and with expertise in detection, diagnosis, and treatment of lung cancer (LC) should assume the organization and implementation of massive LC screening programs.

In Spain, 78 public health network hospitals meet these requirements [67]. Consequently, based on the ERS proposal, the implementation of a massive LC screening program in our country would entail performing over 7,000 LDCT scans per center per year, which would result in an additional cost to the national health budget of around €120 million. These estimations are on the assumptions that 75% of the cost of a screening program is attributed to LDCT scans and that each scan in our country costs around €150.

While cost and resource allocation might be possible, the ERS white paper anticipate that the real problem might not so much be the cost but rather the capacity for absorb

this additional workload, as it is challenging for the current hospital network to handle such a large number of examinations.

In this light, the authors of the ERS proposal suggest an alternative and more restrictive inclusion criteria that could potentially reduce the number of LDCT scans to fewer than 3,000 per center per year, based on the prevalence data of chronic obstructive pulmonary disease (COPD) from the EPISCAN study. This would represent an acceptable increase of 5-10% in the activity of high-complexity hospitals integrated into the public network, which currently perform an average of 30-50,000 LDCT scans annually.

5.4 False Positives and overdiagnosis

One of the key concerns regarding the future of screening is the potential impact of a high false positive rate, since an incorrect diagnosis, while not providing any benefit to the patient, can generate anxiety and significantly increase the costs and rates of morbidity and mortality among asymptomatic individuals participating in a screening process.

It is essential to differentiate between overdiagnosis and false positives. The latter refers to an incorrect diagnosis, a diagnostic error where the patient does not have the clinically diagnosed disease, while overdiagnosis is a failure in prognosis, in the anticipated prediction aimed at avoiding the effects of cancer on quality and life expectancy.

In this context, the primary goal of a large-scale LDCT screening should not only be the detection of pulmonary nodules, but maybe more importantly a subsequent accurate evaluation in terms of malignancy. This is due to the fact that the high sensitivity of LDCT can lead the detection of a significant number of small nodules with various shapes, many of which are benign. The lack of a precisely defined criteria for positivity can be a source of errors in the classification of malignancy for many detected nodules.

Consequently, it is essential evaluation and classification protocols are defined in order to reduce the number and rate of false positives [69].

The experience has shown that considering only nodule diameter and radiological opinion leads to a significant number of false positives, and when the criteria are expanded to include volume and growth parameters, the results change positively. The different definitions of nodule positivity based on linear size or volume will undoubtedly affect the number and rate of false positives. Likewise, they will have consequences on radiation exposure rates, invasive and non-invasive interventions, benign surgical resections, and the impact on the quality of life of participating patients [70].

In the NLST and NELSON studies, researchers used different criteria in the measurements and cut-off points for detected nodules in order to assess their predictive value but also their false positive rates. In the NLST, nodule diameter was established as the measurement technique, while in the NELSON study, volume and growth were considered. The NELSON study went even further to introduce a third evaluation outcome, the indeterminate, with the clear purpose of reducing the number of false positives.

While sensitivity and negative predictive ability seem to be consistent between both protocols, the results were much different terms of specificity, where the volume-based approach resulted in high specificity rate, and thus a much lower false positive rate.

More specifically, 24.2% of the LDCT scans performed in the NLST study were considered positive. Of those, the vast majority of these findings, generally nodules with a diameter of ≥ 4mm, were false positives (96.4%).

In contrast, the NELSON study was able to obtain a much lower false positive rate by combining the 4mm diameter threshold of the NLST with additional diagnostic tests for nodules with a volume of 500mm³ or greater, or an equivalent diameter of 9.8mm,

as well as a biopsy for small nodules that showed growth in the follow-up LDCT after volumetric analysis. This procedure resulted in a mere 1% of screenings being considered false positives.

In addition, the I-ELCAP study proposed that additional tests were required for the baseline screening round when the nodule size was between 5 and 8mm, depending on the nodule's consistency and whether it was solid or not. Furthermore, an increase in nodule size would determine the need for a biopsy. The study also demonstrated, post hoc, that raising the diameter limit of nodules to 6mm significantly reduced the number and rate of false positives without affecting the number and rate of true positives.

Another important result of the I-ELCAP study pertains to the necessary rigor of the nodule evaluation protocol, as it revealed that over 90% of the decided biopsies were positive, indicating that a high rate of false positives does not necessarily imply a high rate of useless diagnostic tests [72].

Regarding nodule detection management, Horeweg et al. interesting study[71] using data from the NELSON study, they addressed the probability of developing lung cancer within two years following a LDCT scan, controlling for diameter, volume, and doubling time as covariates, and, as a result, proposed thresholds for management protocols. They concluded, in accordance to other studies on the matter, that nodule management protocols based on these thresholds were more effective than the simulated nodule management protocol of the American College of Chest Physicians (ACCP). Figure 13.

In conclusion, due to its negative impacts in patients' quality of life but also the cost-benefit ratio and profitability of the screening process, one of the major challenge of a LDCT-based screening program is to increase specificity and improve the treatment of patients diagnosed with positive nodules.

We can assert that the I-ELCAP, NELSON and other studies have demonstrated that using a more restrictive positivity threshold significantly reduces the rate of false positives, potentially reaching only between 1% and 2% of total screenings. Additionally, the use of linear and volumetric measurements and short-term LDCT follow-up appear to be key factors in this reduction [73].

However, there are other areas that offer possibilities for improving lung cancer detection processes refer to two fundamental areas, such as 1) refining qualitative selection criteria based on risk factor assessment to achieve optimal population selection and 2) optimizing the management of patients with indeterminate nodules by improving diagnostic decision-making algorithms.

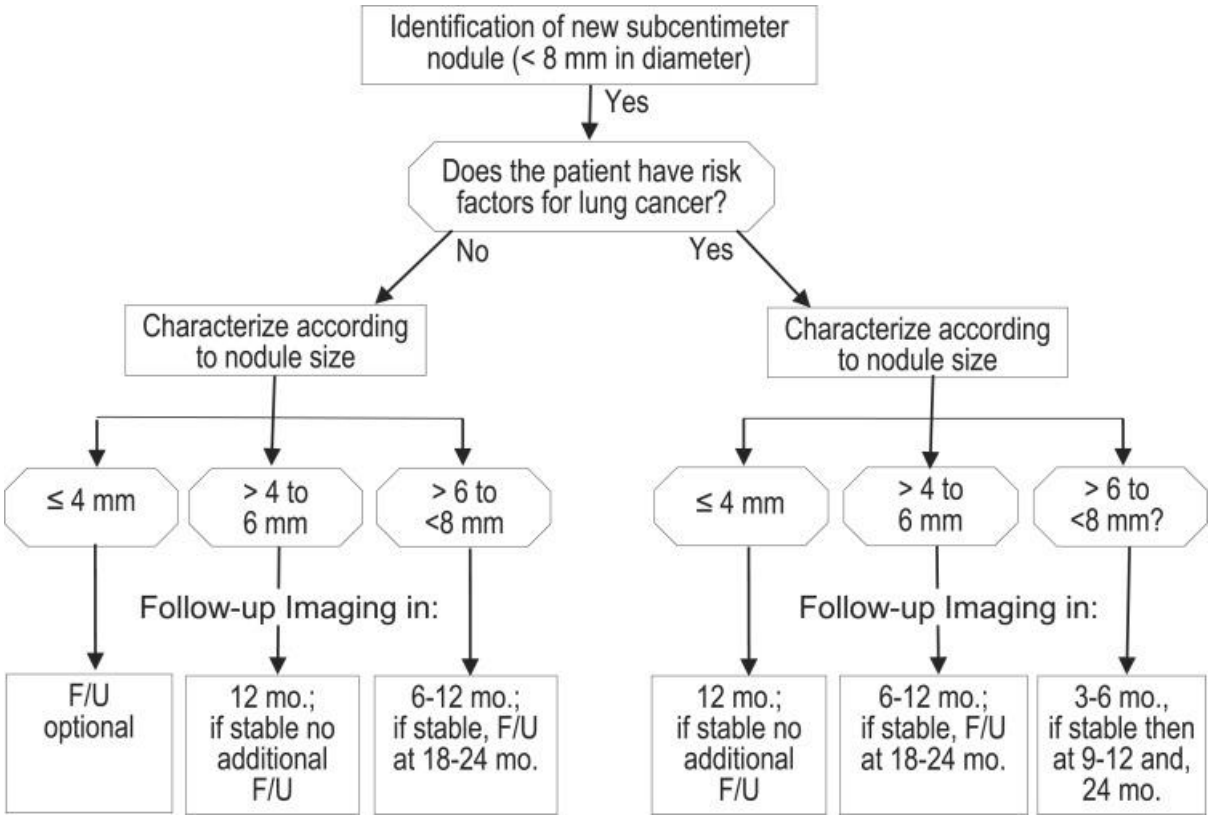


Figure 13. ACCP Management algorithm for individuals with solid nodules measuring < 8 mm in diameter. F/U =follow-up. Chest, 2013,143, e93S-e120S.

5.5 Qualitative Improvement of Selection Criteria

In the study by Katki HA et al.[74], the authors aimed at comparing the modeled outcomes of two lung cancer screening selection strategies: 1) risk-based selection, focusing on selecting individuals at higher risk using all available information regarding on lung cancer risk factors and 2) USPSTF guidelines, following the recommendations of the United States Preventive Services Task Force (USPSTF), which focus solely on a targeted subgroup of smokers and former smokers aged 55 to 80 and 55 to 77, respectively, with at least 30 pack-years and ex-smokers who quit less than 15 years ago.

The authors concluded that, among a cohort of American smokers aged 50 to 80, selecting individuals with using the risk-based approach over the USPSTF subgroup approach was associated with a higher number of deaths prevented at 5 years (20%), along with a 17% reduction in the number of patients needed to prevent one lung cancer death (NNC), 162 162 versus 194 for the USPSTF model.

The decrease in this indicator refers to an increase in screening effectiveness, as well as a decrease in false positives and diagnostic procedures due to mortality reduction, which in turn to increased process efficiency, that is, effectiveness with an appropriate cost level.

In another study from 2018, Katki HA and his team[75] selected nine lung cancer risk models and applied them to various U.S. screening populations. At the end of their study, four models - Bach, PLCOM2012, LCRAT, and LCDRAT - predicted risk more accurately and obtained better results in selecting smokers with the highest risks for LDCT lung cancer detection, regardless of their subgroup.

In the NLST, similar benefits to a risk-based selection approach were found. The study focused on high-consumption smokers aged 55 to 74 at enrollment, with more than 30 pack-years, as well as ex-smokers who quit less than 15 years. After six years of follow-up, lung cancer mortality was reduced by an overall of 20% (21). However, 88%

of the prevented deaths occurred among the 60% of participants at the highest risk, while only 1% of prevented deaths occurred among the 20% of participants at the lowest risk.

The study by Oluf Dimitri R et al., set to prove the hypothesis that the validated HUNT lung cancer risk-based model would perform better when applied to the Danish DLCST screening study than the U.S. NLST criteria and the Dutch-Belgian NELSON criteria. Since the DLCST measured only five of the seven variables included in the validated HUNT lung cancer model, a reduced model was applied again to this cohort, using the same statistical methodology as in the original HUNT study, but only based on age, pack-years, smoking intensity, time since quitting, and sex-adjusted body mass index (BMI. The results showed that the HUNT model outperforms the NLST and NELSON criteria in all measures of predictive performance, as demonstrated in the DLCST.

In addition to proving their hypothesis, the authors concluded that, unlike the sole use of age, pack-years, and quitting time as selection criteria, which forces the classification of patients within subgroups, a risk prediction model classifies each individual according to a weighted average of many variables and outputs a risk threshold. This approach, while improving predictive performance, also allows the medical community and public health authorities to determine the risk threshold that would make screening more cost-effective[77] and so would enable the implementation of these programs at a large-scale.

In conclusion, risk-based selection more accurately delineates the benefits and harms of screening by including detailed information on all lung cancer risk factors [76], which can lead to not only to lower false positive rates and mortality reduction, but also to a higher cost-effective protocol.

5.6 Psychosocial impact and quality of life

There is limited knowledge on the psychosocial effects associated with incidental detection of lung nodules, indicating a need for comprehensive screening processes that allow for the collection and systematization of relevant data.

In LC, emotional effects often relate to poor prognosis, personal attribution for smoking habits, and disease symptoms. Studies suggest that about half of patients with malignant diseases suffer from psychological disorders, with depression and adjustment disorders being common. In addition, the pre-surgical anxiety experienced by patients can influence their post-intervention wellbeing, affecting pain tolerance and rehabilitation progress.

Despite a decrease in symptoms of anxiety and depression over time, overall distress persists throughout the disease's clinical course, indicating a need for ongoing psychological support.

Consequently, providing patients with adequate information can reduce fear levels, improving their experience and potentially their outcomes.

While studies show that participating in a randomized controlled trial for lung cancer screening has negative psychosocial consequences for seemingly healthy participants in both the screening and control groups, the reasons for that negative impact are not caused by LDCT, but by a general lack of attention towards physical, psychosocial, and emotional issues in current screening processes, affecting not only patient wellbeing but also adherence to these programs.

In summary, we emphasize the psychosocial impact and quality of life considerations in patients undergoing early detection procedures for LC. The development of comprehensive guidelines to address these issues could improve the overall health-related quality of life for patients involved in the screening process.

5.7 Computer-Aided Detection and Diagnosis (CAD) and Artificial Intelligence

Some of the technological tools that are currently in discussion are computer-aided diagnosis (CAD) that facilitate the interpretation of LDCTs, the inclusion of Artificial Intelligence (AI) in decision making algorithms and the use of biological and genetic biomarkers that help with effective early detection of lung cancer, optimization of participant selection or accurate classification of lung nodules, in order to minimize the potential false positives derived from indeterminate lung nodules.

Within the framework of strategies to reduce false positives by overcoming their causes in the LDCT process, the incorporation of computer-aided detection of lung nodules, or CAD (Computer-Aided Diagnosis), has gained significant importance.

This technology is currently a relevant area of research in medical imaging and diagnostic radiology.

5.8 Multidisciplinary Committee in LC

As we mentioned in our second paper the multidisciplinary committee approach in managing LC is crucial, as early detection, diagnosis, and intervention are fundamental to improving patient outcomes and increasing cost-effectiveness. This integrative approach typically involves a team of experts who collaborate and make collective decisions based on a comprehensive understanding of the global patient's condition.

Early-stage LC diagnosis often allows for surgical intervention, which, while invasive, often lead to better outcomes and can be more cost-effective than treatments required for advanced-stage LC. As a result, since early detection through diligent screening procedures allows for more efficient use of resources, as the potential for surgical intervention eliminates the need for more extensive treatments, the critical role of the radiologist in early detection through the analysis of screening imaging cannot be overstated.

However, the cost-effectiveness of early-stage intervention isn't merely a matter of resource allocation. Patients benefit significantly from this approach as well. Early diagnosis and intervention often result in improved quality of life and longer survival rates. Here, the role of the multidisciplinary team extends beyond diagnosis to the comprehensive management of the patient's care. (Figure 13.)

The multidisciplinary committee also plays a pivotal role in decision-making. Each professional brings a unique perspective and expertise to the table, ensuring the most informed decisions are made for each patient, thus not only increasing the accuracy of diagnoses but also allowing for the development of personalized treatment. This individualized approach often results in more effective treatment, further enhancing cost-effectiveness.

Figure 14. Proposed Lung nodule workflow proposed by the multidisciplinary committee.

5.9 Cost-effectiveness of diagnostic- therapeutically surgery

The findings from our series emphasize the importance of early detection and cost-effective treatment strategies in lung cancer management (Figure 14). Early-stage lung cancer detection through screening programs allows for more accurate patient

selection for surgical intervention and reduces the number of unnecessary surgeries and associated costs.

Our first paper highlights the cost-effectiveness of surgical treatment, particularly Minimal Invasive Surgery (MIS) lobectomy, compared to medical treatment for early-stage LC. Early detection programs can improve patient outcomes and reduce the economic burden on healthcare systems by identifying and treating LC in its earlier stages.

However, as mentioned before, there are two main problems with large-scale lung cancer screening that have to be potential to thwart these improvements in cost effectiveness: indeterminate cases and false positives.

Firstly, one of the main limitations of lung cancer screening is the nature of an early detection program, in which suspicious lesions are almost always small, may not be anatomically located in peripheral or accessible areas, and/or have a partially solid consistency. This could make it difficult or even impossible to obtain a preoperative diagnosis through a transthoracic or endoscopic puncture. As a result, the biopsy obtained in the operating room would ultimately confirm the diagnosis.

Having a high proportion of undiagnosed patients reaching the operating room, along with the described false-positive rate, suggests that a proper risk assessment, compliance with a diagnostic algorithm, and a consensus decision from an expert multidisciplinary committee are crucial in the performance of a screening program. Unnecessary invasive procedures should be limited for the program to be successful.

However, the fact is that our series demonstrated certain limitations in obtaining a preoperative diagnosis. These indeterminate cases, which require diagnostic surgery, call for the smallest possible pulmonary resection that allows for an adequate intraoperative diagnosis and the subsequent definition of the extent of the radical therapeutic pulmonary resection. All this, under the described characteristics (small, central, and/or partially solid lesions), poses an extraordinary challenge in minimally

invasive surgery to locate the lesion. Preoperative marking of lesions can be very helpful and should be a tool that every screening program should have. It represents a growing clinical need and a challenge that comes with the development and increase of effective technique alternatives [84,85].

In our series, lobectomy has been considered the "gold standard" for pulmonary resection in patients with adequate functional tests and confirmed malignancy diagnosis. It would be interesting and convenient to know if, in the context of a screening program and at an early stage at diagnosis, sub-lobar resections (wedge resections or segmentectomies) would ultimately yield better or equal survival outcomes than lobectomy. Two randomized controlled trials attempt to answer these questions (CALGB 140503 and JCOG0802/WJOG4607L) [78,79].

In this context, we believe that VATS may provide an opportunity. There is currently a general consensus based on multiple studies that recognize VATS as the preferred method for surgical intervention in early stages of the disease. This preference is mainly due to VATS being associated with a significant reduction in perioperative morbidity and mortality compared to traditional open thoracotomy [52].

In 2016, Bendixen et al. demonstrated in a randomized study that VATS is associated with less postoperative pain and better quality of life than anterolateral thoracotomy during the first year after surgery [82]. Preliminary results from the VIOLET trial [83], a multicenter randomized trial in the United Kingdom led by Dr. Eric Lim, showed that patients who underwent VATS had a significant reduction in postoperative complications and stayed in the hospital one day less compared to patients who received open surgery. However, oncological outcomes were similar.

All studies suggest that VATS should be the preferred surgical approach for diagnostic and therapeutic pulmonary resection in lung cancer management, especially in a screening program where most patients are diagnosed at early stages. In the case for patients with clinical stage I lung cancer, VATS segmentectomy has resulted in lower

complication rate, shorter hospital stays, and no differences in overall survival terms[80,81].

Secondly, another important problem in in lung cancer screening and the purpose of our study is the false-positive that reaches the operating room. The candidate who not only meets suspicion criteria through the findings of a LDCT with an indeterminate pulmonary nodule (IPN), but also other complementary diagnostic tests carried out within the diagnostic algorithm, which are not capable of ruling out or defining malignancy, and therefore indicate diagnostic surgery.

In order to combat this issue, it is essential to define a fine-tuned and rigorous protocol for evaluation and control of pulmonary nodules allows for early-stage lung cancer diagnosis with a reduced false-positive rate and avoids unnecessary invasive tests, reducing anxiety and psychological effects associated with a less relevant screening finding. The progressive advancement of the effectiveness and efficiency of screening, ensuring the continuous reduction of negative effects through evidence-based algorithms and protocols, is a permanent challenge and the necessary path.

We strongly agree with current European guidelines that suggest that any lung cancer screening program with LDCT should ensure comprehensive care quality and be led by an expert multidisciplinary team, which would be responsible for implementing the protocol for evaluation of control of pulmonary nodes mentioned before. The team should include surgeons experienced in minimally invasive procedures and be equipped with technical and/or technological tools that allow intraoperative localization of small nodules.

Furthermore, the use of MCC criteria for determining surgical intervention and MIS for resection of lung tumors may improve the management of LC by reducing costs and hospital stays without compromising patient outcomes. Figure 15.

Both of our studies suggest that using MCC criteria for surgical intervention and MIS for resection of lung tumors may improve the management of LC by reducing costs

and hospital stays without compromising patient outcomes. The combined approach of early detection, MCC criteria for surgical intervention, and MIS for tumor resection could lead to more accurate patient selection for surgery, reduced rates of unnecessary surgeries, shorter hospital stays, and overall reduced costs for treatment.

In summary, our results show that lung cancer screening with LDCT is effective for detecting the disease in early stages, and that most patients achieve long-term survival after surgical resection.

In terms of diagnosis, morbidity and mortality, and survival, the outcomes of our surgical patients are comparable with other international studies. These results demonstrate once again that lung cancer screening with LDCT is, for now, the only evidence-based method capable of achieving early detection of lung cancer, allowing surgical treatment with curative intent and probability in a high percentage of patients, being a highly cost-effective option.

A possible limitation of our study is that it is based on data from a single center; therefore, our population, resources, and staff characteristics may limit the generalization of our results. However, we believe that surgery for LC is quite standardized across all centers and that others will likely achieve similar results. Additionally, the increasing investment towards MIS, including new approaches such as robotic surgery, leads to better outcomes in terms of improving immediate postoperative morbidity and patients' quality of life undergoing these interventions.

Despite their limitations, including the retrospective nature of both studies and the lack of assessment of the accuracy of the MCC criteria, the findings from both articles provide valuable insights into the potential benefits of early detection. Further research is needed to establish the positive and negative likelihood ratios of the MCC criteria and their predictive values. Additionally, prospective, randomized controlled trials comparing the combined use of early detection, MCC criteria, and MIS to

traditional approaches in lung cancer management would help elucidate the potential benefits of this approach.

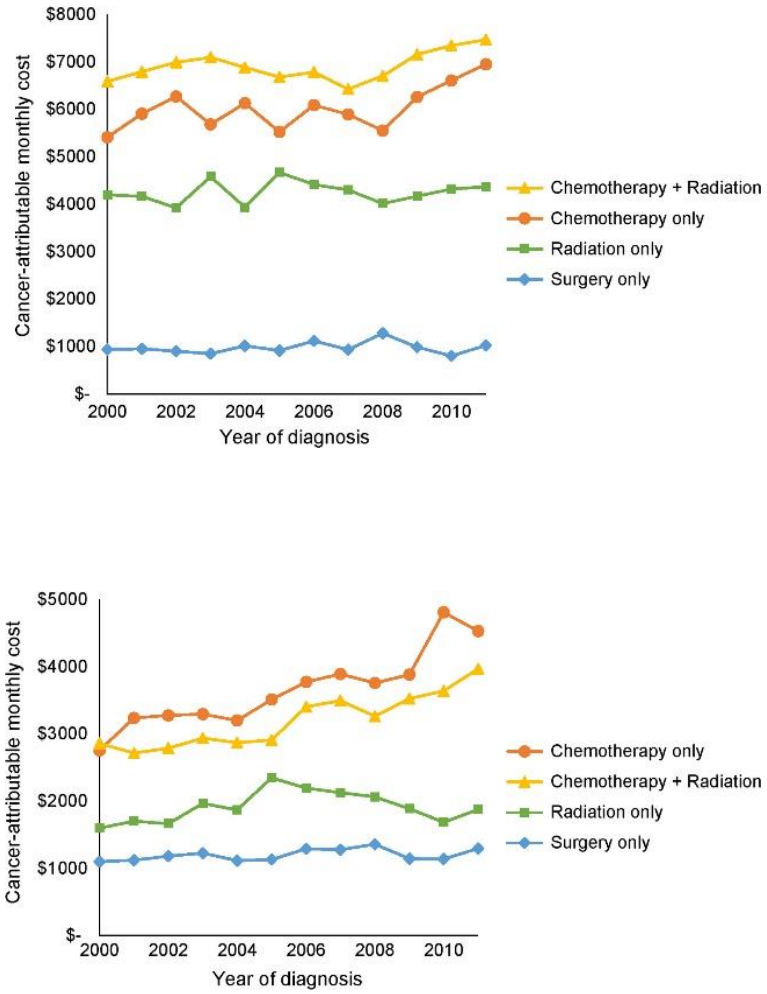


Figure15. ***Superior.*** *Average monthly cancer-attributable costs are presented for the initial phase, by treatment strategy. Costs ranged from $802 per month for patients who received surgery to $7469 per month for patients who received chemotherapy plus radiation.*

Inferior*. Average monthly cancer-attributable costs are presented for the continuing phase, by treatment strategy. Costs ranged from $1100 per month for patients who received surgery to $4809 per month for patients who were treated with chemotherapy*

6. Conclusions

The conclusions of this Doctoral Thesis are that:

1. Surgical intervention for lung cancer treatment, particularly when adhering to Multidisciplinary Cancer Committee (MCC) guidelines, is both clinically and economically more efficient compared to medical therapies. This was evident through better survival rates, quicker return to autonomy, and lower cost of care.

2. The implementation of lung cancer screening programs has the potential to further enhance cost-effectiveness by allowing for earlier identification and treatment of patients, with break-even points and healthcare cost savings achievable within a few years of the program's initiation. This conclusion points towards the need for further research to refine patient selection processes.

3. The use of video-assisted thoracoscopic surgery (VATS) as a method of surgical access can significantly impact the cost-effectiveness of lung cancer treatments, associating with shorter hospital stays and lower total costs.

7. References

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide:Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136(5):E359-E386. doi:10.1002/ijc.29210
2. Naghavi M, Wang H, Lozano R, et al. Global, regional, and national age-sex specific allcause and cause-specific mortality for 240 causes of death, 1990-2013: A systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015. doi:10.1016/S0140-6736(14)61682-2
3. Grupo Español de Cancer de Pulmón (GECP). Las “notas” de 2015 de Cáncer de Pulmón: Situación Del Tumor En España. Spain; 2015. https://www.gecp.org/las-notasde-2015-de-cancer-de-pulmon-situacion-del-tumor-en-espana/.
4. Siegel RL, Miller KD JA. Cancer statistics, 2015. CA Cancer J Clin. 2015;Jan-Feb65(1):5-29. doi:doi: 10.3322/caac.21254.
5. Siegel RL, Miller KD, Jemal A, et al. Cancer statistics, 2015. CA Cancer J Clin. 2015;Jan-Feb 65(1):5-29. doi:doi: 10.3322/caac.21254.
6. Groome PA, Bolejack V, Crowley JJ, 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. J Thorac Oncol. 2007;2(8):694-705. doi:10.1097/JTO.0b013e31812d05d5
7. Goldstraw P, Chansky K, Crowley J, et al. The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer. J Thorac Oncol. 2016;11(1):39-51.doi:10.1016/j.jtho.2015.09.009
8. Shlomi D, Ben-Avi R, Balmor GR, Onn A, Peled N. Screening for lung cancer: Time for large-scale screening by chest computed tomography. Eur Respir J. 2014;44(1):217-238. doi:10.1183/09031936.00164513
9. International Agency for Research in Cancer, (IARC). Research Cancer Statistics Resources. Databases. Globocan 2012. https://gco.iarc.fr/. Accessed February 19, 2020.

10. Sociedad Española de Oncología Médica (SEOM). Las Cifras de Cáncer En España .; 2020. https://seom.org/seomcms/images/stories/recursos/Cifras_del_cancer_2020.pdf. Accessed February 19, 2020.
11. Cancer burden statistics and trends across Europe | ECIS. https://ecis.jrc.ec.europa.eu/. Accessed February 19, 2020.
12. REDECAN - Red Española de Registros de Cáncer. http://www.redecan.es/redecan.org/es/index.html Accessed February 19, 2020.
13. De Koning HJ, Van Der Aalst CM, ten Haaf K OM. Effects of Volume CT Lung Cancer Screening: Mortality Results of the NELSON Randomised-Controlled Population Based Trial. In: IASLC WCLC 2018. Toronto; 2018.
14. Gatta G, Mallone S, van der Zwan JM, et al. Cancer survival in Europe 1999-2007 by country and age: Results of EUROCARE-5 - A population-based study. Lancet Oncol. 2014;15(1):23-34. doi:10.1016/S1470-2045(13)70546-1
15. Francisci S, Minicozzi P, Pierannunzio D, et al. Survival patterns in lung and pleural cancer in Europe 1999-2007: Results from the EUROCARE-5 study. Eur J Cancer. 2015;51(15):2242-2253. doi:10.1016/j.ejca.2015.07.033
16. Rami-Porta R, Ball D, Crowley J, et al. The IASLC lung cancer staging project: Proposals for the revision of the T descriptors in the forthcoming (seventh) edition of the TNM classification for lung cancer. J Thorac Oncol. 2007;2(7):593-602. doi:10.1097/JTO.0b013e31807a2f81
17. Shi CL, Zhang XY, Han BH, He WZ, Shen J, Chu TQ. A clinicopathological study of resected non-small cell lung cancers 2 cm or less in diameter: A prognostic assessment. Med Oncol. 2011;28(4):1441-1446. doi:10.1007/s12032-010-9632-y
18. James D. Brierley, Anil K. D'Cruz, Martin F. Fey, Raphael Pollock JBV y SH, Huang. UICC Manual of Clinical Oncology. 9th Editio. (John Wiley & Sons L, ed.). John Wiley & Sons, Ltd.; 2015. doi:10.1002/9781119013143
19. Reporte Asociación Española Contra el Cancer, 2018. http://observatorio.aecc.es/. Accessed March 30, 2020.
20. Globocan 2020. International Agency for Research in Cancer (IARC). Research Cancer Statistics Resources. Databases. http://www.iarc.fr.

21. Gómez Raposo C, De Castro Carpeño J, González Barón M. Factores etiológicos del cáncer de pulmón: Fumador activo, fumador pasivo, carcinógenos medioambientales y factores genéticos. Med Clin (Barc). 2007;128(10):390-396. doi:10.1157/13099973
22. Peto R, Darby S, Deo H, Silcocks P, Whitley E, Doll R. Smoking, smoking cessation, and lung cancer in the UK since 1950: Combination of national statistics with two casecontrol studies. Br Med J. 2000;321(7257):323-329. doi:10.1136/bmj.321.7257.323
23. Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to smoking: 50 Years' observations on male British doctors. Br Med J. 2004;328(7455):1519-1528. doi:10.1136/bmj.38142.554479.ae
24. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Tobacco Smoke and Involuntary Smoking.; 2004. http://monographs.iarc.fr/. Accessed March 13, 2020.
25. de Koning HJ, van der Aalst CM, de Jong PA, et al. Reduced Lung-Cancer Mortality with Volume CT Screening in a Randomized Trial. N Engl J Med. 2020;382(6):503-513. doi:10.1056/NEJMoa1911793
26. Carrion Valero F, Hernandez Hernandez JR. [Passive smoking in adults]. Arch Bronconeumol. 2002;38(3):137-146.
27. Hackshaw AK, Law MR, Wald NJ. The accumulated evidence on lung cancer and environmental tobacco smoke. Br Med J. 1997;315(7114):980-988. doi:10.1136/bmj.315.7114.980
28. Hecht SS, Carmella SG, Murphy SE, Akerkar S, Brunnemann KD, Hoffmann D. A Tobacco-Specific Lung Carcinogen in the Urine of Men Exposed to Cigarette Smoke. N Engl J Med. 1993;329(21):1543-1546. doi:10.1056/NEJM199311183292105
29. Hecht SS. Tobacco smoke carcinogens and lung cancer. J Natl Cancer Inst. 1999;91(14):1194-1210. doi:10.1093/jnci/91.14.119
30. Cáncer ocupacional y ocupaciones con cáncer | Prevencionar. http://prevencionar.com/2018/03/20/cancer-ocupacional-y-ocupaciones-con-cancer Accessed March 13, 2020.
31. De Matteis S, Consonni D, Bertazzi PA. Exposure to occupational carcinogens and lung cancer risk. Evolution of epidemiological estimates of attributable fraction. Acta

Biomed. 2008;79 Suppl 1:34-42. http://www.ncbi.nlm.nih.gov/pubmed/18924308 Accessed March 13, 2020.

32. Kreuzer M, Boffetta P, Whitley E, et al. Gender differences in lung cancer risk by smoking: a multicentre case-control study in Germany and Italy. Br J Cancer. 2000;82(1):227-233. doi:10.1054/bjoc.1999.0904
33. Prescott E, Osler M, Hein HO, et al. Gender and smoking-related risk of lung cancer. The Copenhagen Center for Prospective Population Studies. Epidemiology. 1998;9(1):79-83. http://www.ncbi.nlm.nih.gov/pubmed/9430273 Accessed March 13, 2020.
34. Schwartz AG, Swanson GM. Lung carcinoma in African Americans and whites: A population-based study in Metropolitan Detroit, Michigan. Cancer. 1997;79(1):45-52. doi:10.1002/(SICI)1097-0142(19970101)79:1<45::AID-CNCR7>3.0.CO;2-L
35. Tucker MA, Murray N, Shaw EG, et al. Second primary cancers related to smoking and treatment of small-cell lung cancer. Lung Cancer Working Cadre. J Natl Cancer Inst. 1997;89(23):1782-1788. doi:10.1093/jnci/89.23.1782
36. Bobba RK, Holly JS, Loy T, Perry MC. Scar carcinoma of the lung: a historical perspective. Clin Lung Cancer. 2011;12(3):148-154. doi:10.1016/j.cllc.2011.03.011
37. Li X, Hemminki K. Familial multiple primary lung cancers: a population-based analysis from Sweden. Lung Cancer. 2005;47(3):301-307. doi:10.1016/j.lungcan.2004.07.048
38. Vestbo J, Hurd SS, Agustí AG, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease GOLD executive summary. Am J Respir Crit Care Med. 2013;187(4):347-365. doi:10.1164/rccm.201204-0596PP
39. Neumann PJ, Cohen JT, Weinstein MC. Updating Cost-Effectiveness — The Curious Resilience of the $50,000-per-QALY Threshold. N Engl J Med. 2014. doi:10.1056/nejmp1405158
40. Pyenson BS, Henschke CI, Yankelevitz DF, Yip R, Dec E. Offering lung cancer screening to high-risk medicare beneficiaries saves lives and is cost-effective: an actuarial analysis. Am Heal drug benefits. 2014;7(5):272-282. http://www.ncbi.nlm.nih.gov/pubmed/25237423. Accessed July 28, 2019.
41. Goulart BHL, Bensink ME, Mummy DG, Ramsey SD. Lung cancer screening with lowdose computed tomography: costs, national expenditures, and cost-effectiveness.

J Natl Compr Canc Netw. 2012;10(2):267-275 .
http://www.ncbi.nlm.nih.gov/pubmed/22308519. Accessed July 28, 2019.

42. Mauchley DC, Mitchell JD. Current Estimate of Costs of Lung Cancer Screening in the United States. Thorac Surg Clin. 2015;25(2):205-215. doi:10.1016/j.thorsurg.2014.12.005
43. Cressman S, Lam S, Tammemagi MC, et al. Resource utilization and costs during the initial years of lung cancer screening with computed tomography in Canada. J Thorac Oncol. 2014;9(10):1449-1458. doi:10.1097/JTO.0000000000000283
44. Facey K, Topfer EL, Chan L. Health Technology Assessment (HTA) Glossary. Heal Technol Assessment First edtion. 2006.
45. Seijo LM, Peled N, Ajona D, et al. Biomarkers in Lung Cancer Screening: Achievements, Promises, and Challenges. J Thorac Oncol. 2019;14(3):343-357. doi:10.1016/j.jtho.2018.11.023
46. Massion PP, Healey GF, Peek LJ, et al. Autoantibody Signature Enhances the Positive Predictive Power of Computed Tomography and Nodule-Based Risk Models for Detection of Lung Cancer. J Thorac Oncol. 2017;12(3):578-584 . doi:10.1016/j.jtho.2016.08.143
47. Ajona D, Okrój M, Pajares MJ, et al. Complement C4d-specific antibodies for the diagnosis of lung cancer. Oncotarget. 2018;9(5):6346-6355. doi:10.18632/oncotarget.23690
48. Montani F, Jacopo Marzi M, Dezi F, et al. miR-Test: A Blood Test for Lung Cancer Early Detection. J Natl Cancer Inst. 2015;107(6):63. doi:10.1093/jnci/djv063
49. Sozzi G, Boeri M, Rossi M, et al. Clinical utility of a plasma-based miRNA signature classifier within computed tomography lung cancer screening: A correlative MILD trial study. J Clin Oncol. 2014;32(8):768-773. doi:10.1200/JCO.2013.50.4357
50. International Association for the Study of Lung Cancer Strategic Screening Advisory C. Staging Handbook in Thoracic Oncology 2nd ed, 2017.
51. Howington JA, Blum MG, Chang AC, Balekian AA, Murthy SC. Treatment of stage I and II non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013: 143(5 Suppl): e278S-e313S.

52. Lim E, Batchelor T, Shackcloth M, et al. Study protocol for VIdeo assisted thoracoscopic lobectomy versus conventional Open LobEcTomy for lung cancer, a UK multicentre randomised controlled trial with an internal pilot (the VIOLET study). BMJ Open. 2019;9(10):e029507. doi:10.1136/bmjopen-2019-029507
53. Rowell NP, O'Rourke N P. Concurrent chemoradiotherapy in non-small cell lung cancer. Cochrane Database Syst Rev 2004(4): CD002140.
54. Group NM-aC, Arriagada R, Auperin A, Burdett S, Higgins JP, Johnson DH, Le Chevalier T, Le Pechoux C, Parmar MK, Pignon JP, Souhami RL, Stephens RJ, Stewart LA, Tierney JF, Tribodet H, van Meerbeeck J. Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data. Lancet 2010: 375(9722): 1267-1277.
55. Winton T, Livingston R, Johnson D, Rigas J, Johnston M, Butts C, Cormier Y, Goss G, Inculet R, Vallieres E, Fry W, Bethune D, Ayoub J, Ding K, Seymour L, Graham B, Tsao MS, Gandara D, Kesler K, Demmy T, Shepherd F, National Cancer Institute of Canada Clinical Trials G, National Cancer Institute of the United States Intergroup JBRTI. Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. N Engl J Med 2005: 352(25): 2589-2597.
56. Seijo LM, Trujillo JC, Zulueta JJ. Screening in Lung Cancer: The Latest Evidence. Arch Bronconeumol. January 2019. doi:10.1016/j.arbres.2019.04.019
57. Pyenson BS, Henschke CI, Yankelevitz DF, Yip R, Dec E. Offering lung cancer screening to high-risk medicare beneficiaries saves lives and is cost-effective: an actuarial analysis. Am Heal drug benefits. 2014;7(5):272-282. http://www.ncbi.nlm.nih.gov/pubmed/25237423. Accessed July 28, 2019.
58. Goulart BHL, Bensink ME, Mummy DG, Ramsey SD. Lung cancer screening with lowdose computed tomography: costs, national expenditures, and cost-effectiveness. J Natl Compr Canc Netw. 2012;10(2):267-275 . http://www.ncbi.nlm.nih.gov/pubmed/22308519. Accessed July 28, 2019.
59. Mauchley DC, Mitchell JD. Current Estimate of Costs of Lung Cancer Screening in the United States. Thorac Surg Clin. 2015;25(2):205-215. doi:10.1016/j.thorsurg.2014.12.005

60. Cressman S, Lam S, Tammemagi MC, et al. Resource utilization and costs during the initial years of lung cancer screening with computed tomography in Canada. J Thorac Oncol. 2014;9(10):1449-1458. doi:10.1097/JTO.0000000000000283
61. Field JK, Duffy SW, Baldwin DR, et al. UK Lung Cancer RCT Pilot Screening Trial: Baseline findings from the screening arm provide evidence for the potential implementation of lung cancer screening. Thorax. 2016. doi:10.1136/thoraxjnl-2015-207140
62. Kumar V, Cohen JT, Van Klaveren D, et al. Risk-targeted lung cancer screening: A cost effectiveness analysis. doi:10.7326/M17-1401
63. Villanti AC, Jiang Y, Abrams DB, Pyenson BS. A Cost-Utility Analysis of Lung Cancer Screening and the Additional Benefits of Incorporating Smoking Cessation Interventions. PLoS One. 2013. doi:10.1371/journal.pone.0071379
64. Sanchez-Salcedo P, Wilson DO, De-Torres JP, et al. Improving selection criteria for lung cancer screening: The potential role of emphysema. Am J Respir Crit Care Med.2015;191(8):924-931. doi:10.1164/rccm.201410-1848OC
65. Peña VS, Miravitlles M, Gabriel R, et al. Geographic variations in prevalence and underdiagnosis of COPD: Results of the IBERPOC multicentre epidemiological study. Chest. 2000. doi:10.1378/chest.118.4.981
66. Soriano JB, Miravitlles M, Borderías L, et al. [Geographical variations in the prevalence of COPD in Spain: relationship to smoking, death rates and other determining factors]. Arch Bronconeumol. 2010;46(10):522-530. doi:10.1016/j.arbres.2010.06.008
67. Instituto Nacional de Estadística. Cifras de población y datos demográficos. http://www.ine.es. Accessed July 28, 2019.
68. Observatorio de resultados - Portal de Salud de la Comunidad de Madrid. http://observatorioresultados.sanidadmadrid.org/HospitalesResultados.aspx. Accessed October 21, 2020.
69. Guzman R, Guirao A, Vela E, et al. Outcomes and cost of lung cancer patients treated surgically or medically in Catalunya. Eur J Cancer Prev. 2020;29:486-492. doi:10.1097/cej.0000000000000566
70. McWilliams A, Tammemagi MC, Mayo JR, et al. Probability of Cancer in Pulmonary Nodules Detected on First Screening CT. N Engl J Med. 2013;369(10):910-919. doi:10.1056/NEJMoa1214726

71. Horeweg N, van Rosmalen J, Heuvelmans MA, et al. Lung cancer probability in patients with CT-detected pulmonary nodules: A prespecified analysis of data from the NELSON trial of low-dose CT screening. Lancet Oncol. 2014;15(12):1332-1341. doi:10.1016/S1470-2045(14)70389-4
72. Yip R, Henschke CI, Yankelevitz DF, Smith JP. CT Screening for Lung Cancer: Alternative Definitions of Positive Test Result Based on the National Lung Screening Trial and International Early Lung Cancer Action Program Databases. Radiology. 2014. doi:10.1148/radiol.14132950
73. Yousaf-Khan U, Van Der Aalst C, De Jong PA, et al. Final screening round of the NELSON lung cancer screening trial: The effect of a 2.5-year screening interval. Thorax. 2017;72(1):48-56. doi:10.1136/thoraxjnl-2016-20865
74. Katki HA, Kovalchik SA, Berg CD, Cheung LC, Chaturvedi AK. Development and validation of risk models to select ever-smokers for ct lung cancer screening. JAMA - JAm Med Assoc. 2016;315(21):2300-2311. doi:10.1001/jama.2016.6255
75. Katki HA, Petito LC, Cheung LC, et al. Implications of 9 risk prediction models for selecting ever-smokers for CT lung-cancer screening. Ann Intern Med. 2018;169(1):10-19.
76. Kovalchik SA, Tammemagi M, Berg CD, et al. Targeting of low-dose CT screening according to the risk of lung-cancer death. N Engl J Med. 2013;369(3):245-254. doi:10.1056/NEJMoa1301851
77. Røe OD, Markaki M, Tsamardinos I, et al. “Reduced” HUNT model outperforms NLST and NELSON study criteria in predicting lung cancer in the Danish screening trial. BMJ Open Respir Res. 2019;6(1). doi:10.1136/bmjresp-2019-000512
78. Nakamura K, Saji H, Nakajima R, et al. A Phase III randomized trial of lobectomy versus limited resection for small-sized peripheral non-small cell lung cancer (JCOG0802/WJOG4607L). Jpn J Clin Oncol. 2009;40(3):271-274. doi:10.1093/jjco/hyp156
79. Altorki NK, Wang X, Wigle D, et al. Perioperative mortality and morbidity after sublobar versus lobar resection for early-stage non-small-cell lung cancer: post-hoc analysis of an international, randomised, phase 3 trial (CALGB/Alliance 140503). Lancet Respir Med. 2018;6(12):915-924. doi:10.1016/S2213-2600(18)30411-9

80. Ghaly G, Kamel M, Nasar A, et al. Video-Assisted Thoracoscopic Surgery Is a Safe and Effective Alternative to Thoracotomy for Anatomical Segmentectomy in Patients With Clinical Stage I Non-Small Cell Lung Cancer. In: Annals of Thoracic Surgery. Vol 101. ; 2016:465-472. doi:10.1016/j.athoracsur.2015.06.112
81. Lex JR, Naidu B. In patients with resectable non-small-cell lung cancer, is video-assisted thoracoscopic segmentectomy an appropriate alternative to video-assisted thoracoscopic lobectomy? Interact Cardiovasc Thorac Surg. 2016;23(5):826-831. doi:10.1093/icvts/ivw202
82. Bendixen M, Jørgensen OD, Kronborg C, Andersen C, Licht PB. Postoperative pain and quality of life after lobectomy via video-assisted thoracoscopic surgery or anterolateral thoracotomy for early stage lung cancer: a randomised controlled trial. Lancet Oncol. 2016;17(6):836-844. doi:10.1016/S1470-2045(16)00173-X
83. Lim E, Batchelor T, Shackcloth M, et al. Study protocol for VIdeo assisted thoracoscopic lobectomy versus conventional Open LobEcTomy for lung cancer, a UK multicentre randomised controlled trial with an internal pilot (the VIOLET study). BMJ Open. 2019;9(10):e029507. doi:10.1136/bmjopen-2019-029507
84. Petersen RH, Hansen HJ, Dirksen A, Pedersen JH. Lung cancer screening and videoassisted thoracic surgery. J Thorac Oncol. 2012;7(6):1026-1031. doi:10.1097/JTO.0b013e31824fe942

8. Annexes

AUTORIZATION FOR THE PRESENTATION OF THE THESIS

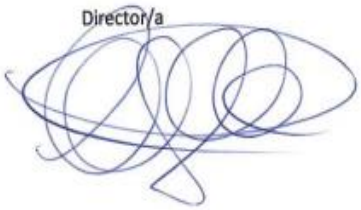
The Dr **ÁNGELA GUIRAO MONTES**, Professor / Investigator/ at the **HOSPITAL CLINIC DE BARCELONA I UNIVERSITAT DE BARCELONA** with Identity Card/Passport: **44423042-Z**, and The Dr **LAUREANO MOLINS LÓPEZ-RODÓ**, Professor / Investigator/ at the **HOSPITAL CLINIC DE BARCELONA AND UNIVERSITAT DE BARCELONA** with Identity Card/Passport: **46111382-Q**.

DECLARE THAT:

The thesis memory presented by Mr./Ms. **RUDITH LIUTMILA GUZMÁN PORTILLO** with title **"ASSESSING VALUE IN LUNG CANCER TREATMENT: A DETAILED COST-BENEFIT ANALYSIS OF CLINICAL MANAGEMENT STRATEGIES"**, has been developed under my/us supervision and I/we authorize the deposit for being defended and judged by a tribunal.

Signed on the day **09.11.2023**.

Director/a



Director

Versió/Versión/Version 0.3
Data/Fecha/Date 29.09.2022

DECLARATION OF AUTHORSHIP OF THE THESIS

The doctoral candidate Mr/ **RUDITH LIUTMILA GUZMÁN PORTILLO** with Identity card/Passport: **Y3205869M.**

DECLARE THAT

Is the author of the doctoral thesis entitled **"ASSESSING VALUE IN LUNG CANCER TREATMENT: A DETAILED COST-BENEFIT ANALYSIS OF CLINICAL MANAGEMENT STRATEGIES".**

Signed on the day **09.11.2023.**

The candidate

Versió/Versión/Version 0.3
Data/Fecha/Date 29.09.2022

STATEMENT OF THE DOCTORAL CANDIDATE AND DIRECTOR/S OF ORIGINALITY AND GOOD PRACTICES OF THE THESIS

Dr **ÁNGELA GUIRAO MONTES** Professor/Researcher at the **HOSPITAL CLINIC DE BARCELONA I UNIVERSITAT DE BARCELONA** with Identity card/Passport: **44423042-Z**; Dr **LAUREANO MOLINS LÓPEZ-RODÓ**, Professor/Researcher at the **HOSPITAL CLINIC DE BARCELONA AND UNIVERSITAT DE BARCELONA**, with Identity card/Passport: **46111382-Q**, and the doctoral candidate **RUDITH LIUTMILA GUZMÁN PORTILLO** with Identity card/Passport: **Y3205869M**.

DECLARE THAT

The doctoral thesis entitled **"ASSESSING VALUE IN LUNG CANCER TREATMENT: A DETAILED COST-BENEFIT ANALYSIS OF CLINICAL MANAGEMENT STRATEGIES"**, is original, containing own results and information, without plagiarism from other thesis, publications or research from other authors. They also confirm that ethical codes and good practices have been followed for its preparation

They declare that they consent that the thesis may be submitted to procedures to verify its originality.

Signed on the day **09.11.2023**.

Director

Director

Candidate

Versió/Versión/Version 0.3
Data/Fecha/Date 29.09.2022