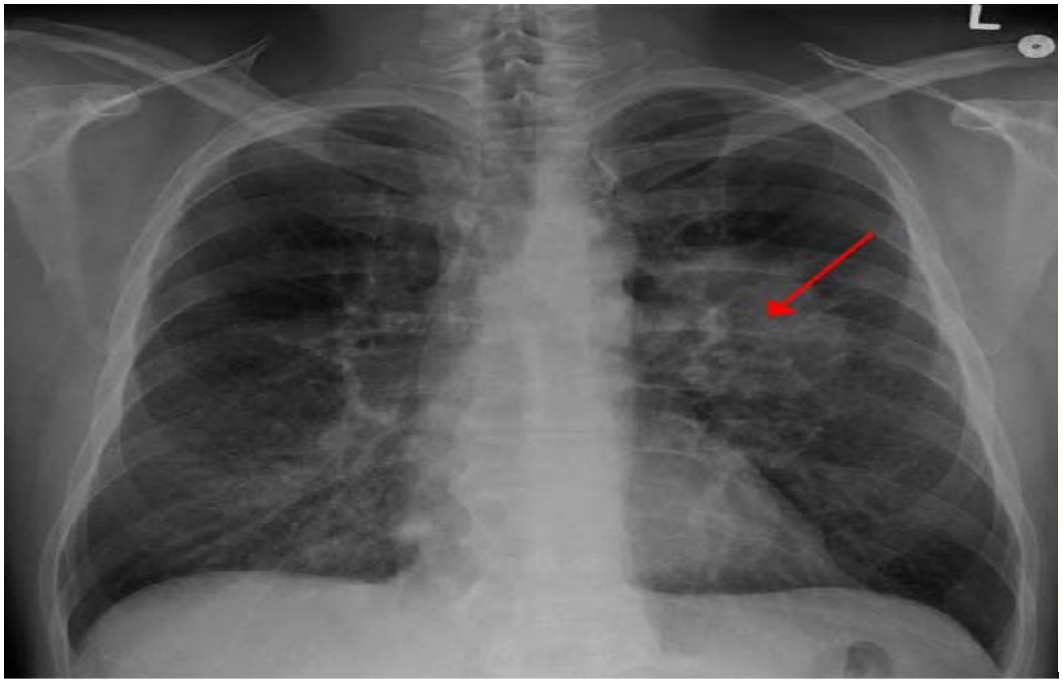
KCE REPORT 266

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

QUALITY INDICATORS FOR THE MANAGEMENT OF LUNG CANCER



KCE REPORT 266
HEALTH SERVICES RESEARCH

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FRANCE VRIJENS, LEEN VERLEYE, CINDY DE GENDT, VIKI SCHILLEMANS, JO ROBAYS, CÉCILE CAMBERLIN, CÉCILE DUBOIS, SABINE STORDEUR, DAVID JEGOU, GEERT SILVERSMIT, ELIZABETH VAN EYCKEN, ISABELLE WAUTERS, JAN VAN MEERBEECK

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Consultancy or employment for a company, an association or an organisation that may gain or lose financially due to the results of this report: Yolande Lievens (IWT grant, radiotherapy in SCLC)

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Disclaimer:

- **The external experts were consulted about a (preliminary) version of the scientific report. Their comments were discussed during meetings. They did not co-author the scientific report and did not necessarily agree with its content.**
- **Subsequently, a (final) version was submitted to the validators. The validation of the report results from a consensus or a voting process between the validators. The validators did not co-author the scientific report and did not necessarily all three agree with its content.**

- **Finally, this report has been approved by common assent by the Executive Board.**
- **Only the KCE is responsible for errors or omissions that could persist. The policy recommendations are also under the full responsibility of the KCE.**

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
2D	Two-dimensional
3D	Three-dimensional
95% CI	95% Confidence interval
ACE-27	Adult Comorbidity Evaluation-27
ALK	Anaplastic lymphoma kinase
ATC	Anatomical Therapeutical Chemical
AUC	Area under the curve
AZ	Algemeen ziekenhuis (general hospital)
BCR	Belgian Cancer Registry
cI, cII, etc	Clinical stage I, clinical stage II, etc.
CIRS	Cumulative illness rating scale
COPD	Chronic Obstructive Pulmonary Disease
CT	Computed tomography
DDD	Defined daily dose
DICA-DLSA	Dutch Institute for Clinical Auditing – Dutch Lung Surgery Audit
DLCO	Diffusing capacity of the lung for carbon monoxide
EBUS	Endobronchial ultrasound
EGFR	Epidermal growth factor receptor
EORTC	European Organisation for Research and Treatment of Cancer
EPAAC	European Partnership Action Against Cancer
EUS	Endoscopic ultrasonography
FEV1	Forced expiratory volume in 1 second
FNA	Fine needle aspiration
GDG	Guideline development group
GRADE	Grading of Recommendation, Assessment, Development and Evaluation
HIV/AIDS	Human immuno-deficiency virus / Acquired immune deficiency syndrome
HR	Hazard ratio

ICD-10-CM	International Classification of Diseases, 10th Revision, Clinical Modification
IGZ	Inspectie voor de Gezondheidszorg (The Netherlands)
IHC	Immunohistochemistry
IKNL	Integraal Kankercentrum Nederland
IMA – AIM	InterMutualistisch Agentschap – Agence Intermutualliste
IMRT	Intensity-modulated radiotherapy
INSZ – NISS	National Number for Social Security
K	Kappa statistic
KCE	Belgian Health Care Knowledge Centre
KSZ – BCSS	Kruispuntbank van de Sociale Zekerheid – Banque Carrefour de la Sécurité Sociale (Crossroads Bank for Social Security)
maxSUV	Maximum standardized uptake value
MDT	Multidisciplinary team
pI, pII	Pathological stage I, etc.
MRI	Magnetic resonance imaging
MZG – RHM	Minimale Ziekenhuisgegevens – Résumé Hospitalier Minimum
NA	Not applicable
NHS	National Health Service (United Kingdom)
NICE	National Institute for Health and Care Excellence (United Kingdom)
NOS	Not otherwise specified
NPV	Negative predictive value
NSCLC	Non small cell lung cancer
OR	Odds ratio
PET	Positron emission tomography
PFS	Progression free survival
PH	Proportional hazard
PPV	Positive predictive value

PS	Performance status
QI	Quality indicator
RIZIV – INAMI	Rijksinstituut voor ziekte- en invaliditeitsverzekering – Institut National d'Assurance Maladie Invalidité
ROC	Receiver Operating Characteristic
RT	Radiotherapy
SCLC	Small cell lung cancer
Se	Sensibility
SIGN	Scottish Intercollegiate Guidelines Network
Soncos	Stichting Oncologische Samenwerking (The Nederlands)
Sp	Specificity
TBNA	Transbronchial needle aspiration
TKI	Tyrosine kinase inhibitor
TNM	Tumour – Node – Metastasis
UK	United Kingdom
US(A)	United States (of America)
UZ	Universitair ziekenhuis (academic hospital)
VA	Alveolar volume
WHO	World Health Organization
X	Missing stage

SCIENTIFIC REPORT

1 HOW TO READ THIS REPORT?

This report consists of three separate documents.

1. The synthesis: contains a summary of the methodology, the main findings, discussion of results, strengths and weaknesses and the conclusions and recommendations

For each chapter, more details can be found in the following two documents:

2. The scientific report: contains a detailed description of the aim and general methodology of the report, description of the methods used for case-mix adjustment, the pilot study, descriptive statistics of the included population and the methodology and results of the volume-outcome analyses.

3. Supplementary document: contains a technical fiche for each quality indicator, with all results, discussion and conclusion. Billing codes that were used to calculate the indicators are listed at the end of this document.

2 AIM OF THE PROJECT

2.1 Introduction, aim of the project and target audience

In 2012, 8 142 lung cancers were newly diagnosed in Belgium. It is the leading cause of cancer death in males and the second in females. Worldwide, age-standardised 5-year net survival ranges between 10 and 20%, both in developed and developing countries. In both males and females, lung cancer presents most often in advanced stages and more than half of the patients die within the first year after diagnosis.[1, 2]

In cooperation with the College of Oncology, KCE published an evidence-based guideline for the diagnosis and treatment of small cell and non-small cell lung cancer in 2013.[3] Key elements for the treatment of early and locally advanced stage disease are surgery or (chemo) radiation after comprehensive (mediastinal) staging. For advanced disease that is not amenable to therapy with curative intent, chemotherapy or newer targeted therapies can be considered.

Since several years, KCE and the Belgian Cancer Registry (BCR) have been engaged together in quality improvement initiatives for cancer patients. An ideal integrative quality system in oncology starts with the development and implementation of clinical practice guidelines, followed by the development of a set of indicators aiming at measuring and improving quality of care. Individual feedback can be provided to all hospitals and lead to corrective actions to improve quality.[4] The first three steps of this improvement cycle (development of an evidence-based guideline, measurement of a set of quality indicators, individual feedback to centres) have already been successfully implemented for several cancers at a national level: rectum (in collaboration with PROCARE), breast, testis, oesophagus and stomach.[5-8]

Aim of this project

The aim of this project is to provide insight in patterns of care and outcomes of care for lung cancer patients in Belgium. Auditing processes and related outcomes can identify key areas for quality improvement. Auditing practice can reveal to what degree evidence-based recommendations are implemented, which outcomes are achieved in the Belgian population, which practices are associated with better outcomes and most importantly, what can be done to optimize lung cancer care in the future. Hospitals can benchmark their results against international and national results, identify best practices and that way, improve their own practice.

Target audience

The primary audience of this project are hospitals and caregivers that provide care for lung cancer patients. The results may also be of interest to other stakeholders, although their information needs may not fully be addressed. Patients for example may prefer other types of information, such as the quality of information delivery and patient experiences in a certain hospital.

Many indicators are analysed per individual centre to provide individual feedback and to gather information on possible reasons for and associated factors of variability between hospitals. However, this report does not intend to judge an individual hospital's overall practice or create a hospital ranking based on perceived quality. The data used in this report do not always allow precise and correct comparison between individual centres as they are extracted from administrative databases originally not intended for quality measurements, sample sizes are often small and residual confounding may exist after case-mix correction. Furthermore, hospitals may not be in control of the overall care pathway for all their patients. Avoiding a name-and-blame culture may encourage all caregivers involved to accept joint accountability and work together towards improvement of outcomes.

For that reason, all analyses are performed and reported anonymously. The anonymous reporting also creates the possibility for honest and constructive evaluation of the results with focus on quality improvement rather than competition between hospitals or detrimental discussions about interpretation of the results and assigning responsibility. Even less-than-perfect quality measurements can be informative and guide quality improvement, but using the same quality measurements as the basis for selective referral, pay-for-quality or public reporting of hospital rankings could be problematic.[9, 10]

2.2 Measuring quality

Donabedian's model to evaluate quality includes three categories: structure, process and outcome indicators of quality.

Structure indicators relate to the attributes of the settings in which care occurs. This includes material resources (such as facilities, equipment, and financing), human resources (such as the number and qualifications of personnel) and the organizational structure (such as medical staff, organization, methods of peer review, and methods of reimbursement).[11]

Process denotes what is actually done in giving and receiving care, i.e. the practitioner's activities in making a diagnosis, recommending or implementing treatment, or other interaction with the patient.[11]

'Outcome' measures attempt to describe the effects of care on the health status of patients and populations.[11]

The value-based health care framework of Porter et al. highly praises comprehensive outcome measurement to drive quality improvement. The complete set of all outcomes is what really matters to the patients. Measured outcomes should reflect the quality of the whole care cycle, rather than outcomes of a single intervention, a single speciality or a single care episode. Measuring outcomes that are the result of a whole care cycle enforces all caregivers involved to accept joint accountability and work together towards quality improvement.[10]

However, data for comprehensive outcome measurement is often lacking, especially if retrospective databases are used. Data used to evaluate process indicators are more commonly available in administrative databases. Moreover, process indicators are more easily 'actionable', they show what precisely can be done differently to improve outcomes, under the condition that the effectiveness of the measured processes is supported by evidence.[10, 11]

3 OVERVIEW OF THE METHODOLOGY

This chapter presents an overview of the methodology followed to identify, select, measure and interpret quality indicators related to the diagnosis and treatment of lung cancer. This methodology was already applied in previous quality of care projects: rectal cancer (pilot project),[7] breast cancer,[5] testicular cancer[8] and oesophageal and stomach cancer.[6]

The methodology is split up into a sequence of seven steps summarized in Table 1 and described below.

Table 1 – General methodology: overview

Step	Action
1	Identification of target population
2	Setting up a list of potentially interesting indicators, based on lists of indicators published in peer-reviewed articles and official reports from international agencies. Additional indicators are formulated based on the Belgian clinical guideline
3	Operationalization of indicators (technical definition)
4	Development of an algorithm to assign patients to a centre
5	Pilot test leading potentially to changes in algorithm and technical definition
6	Measurement of QIs, at national level and by centre
7	Interpretation of results

Step 1: Identification of target population

The target population is composed of all patients diagnosed with a lung cancer during a 2-year period (2010-2011). To be included, all cancer patients have to be confirmed by a histopathological exam.

Step 2: Setting up a list of potentially interesting indicators

This second step is mainly based on published lists of quality indicators in peer-reviewed papers and on official reports published by international healthcare agencies.

Possible quality indicators were identified from the following sources:

- List of indicators published by other (national or international) healthcare agencies (grey literature)
- Peer-reviewed articles describing and measuring quality indicators (indexed literature)

This preliminary list of quality indicators resulting from the literature search was complemented by quality indicators derived from the recommendations of the KCE guideline. To this end, most individual recommendations were translated in at least one quality indicator. Quality indicators were only searched for 'strong' recommendations according to the GRADE scoring system.

From the long list of possible indicators, relevant and measurable indicators were selected. Further details on the selection of quality indicators can be found in chapter 4.

Step 3: Operationalization of indicators (technical definition)

For each indicator, a technical fiche was written, with key information on the indicator:

- rationale for selecting the indicator and bibliographic source
- operational definition
- nomenclature codes (if appropriate) to capture the indicator in the Belgian administrative databases (billing data) and time intervals
- sensitivity analyses and subgroup analyses
- limitations

All technical fiches are presented in a separate document (supplement).

Step 4: Development of an algorithm to assign patients to a hospital centre

Patients with lung cancer can receive care in more than one centre during the course of their disease. To be able to evaluate variability between centres, to measure a possible volume-outcome relationship and to provide individual feedback to centres, every patient needs to be assigned to a centre for each part of his treatment (the surgery can be performed in another centre than the radiotherapy).

First, an algorithm was designed to assign patients to the centre where diagnosis and staging procedures were performed and where clinical decisions regarding treatment were taken. If patients were referred for their treatment, they remained assigned to the original diagnostic centre. Second, to evaluate the outcomes of surgery and radiotherapy, patients were also assigned to a surgical centre or radiotherapy centre, if appropriate.

More details on the development of algorithms can be found in chapter 6.

Step 5: Pilot test in 6 hospitals to validate the algorithm and the technical definitions of indicators

To test the validity of the algorithm for assigning patients to a centre and the technical definitions of the indicators, a two-step pilot test was organized in six hospitals.

In the first step, a list of assigned patients was sent to each pilot centre, to identify missing patients or patients wrongly assigned to the centre. In the second step, centres received their individual indicators results and validated them using information available in the medical files of the hospital.

Feedback received from the centres was discussed during a meeting with all participating centres; algorithm and technical definitions were adapted if needed. More details on the pilot test can be found in chapter 6.

Step 6: Measurement of QIs, at national level and by centre

All selected QIs were measured at a national level and by diagnostic, surgery or radiotherapy centre, if appropriate. All analyses were performed by the BCR.

Step 7: Interpretation of results

Based on steps 5 and 6, conclusions were discussed with the expert panel. Recommendations for quality improvement were formulated and further discussed with all stakeholders.

4 SELECTING QUALITY INDICATORS: PROCESS AND RESULTS

4.1 Identification of possible quality indicators

4.1.1 Literature search

Both Ovid Medline (see Appendix 1.1.1 for search strategy) and grey literature were searched to identify published and validated quality indicators for lung cancer (NSCLC and SCLC).

The following sources were considered to identify grey literature, typically quality reports published by other (national or international) agencies:

1. http://www.healthcareimprovementscotland.org
2. http://www.qualitymeasures.ahrq.gov
3. http://www.nice.org.uk
4. http://www.iknl.nl
5. http://www.clinicalaudit.nl
6. http://www.soncos.org
7. http://www.eortc.org
8. http://www.jointcommission.org
9. http://www.nhs.uk
10. http://www.zorgvooruitkomst.nl
11. http://www.igz.nl

The main searches were conducted in June 2014.

4.1.2 Addition of guideline-based quality indicators

The list of quality indicators resulting from the literature search was complemented by quality indicators derived from the recommendations of the KCE lung cancer guideline. To this end, most individual recommendations were translated in at least one quality indicator, with focus on 'strong' recommendations according to the GRADE scoring system (see Table 2).

Table 2 – Strength of recommendations according to the GRADE system

Grade	Definition
Strong	The desirable effects of an intervention clearly outweigh the undesirable effects (the intervention is to be put into practice), or the undesirable effects of an intervention clearly outweigh the desirable effects (the intervention is not to be put into practice)
Weak	The desirable effects of an intervention probably outweigh the undesirable effects (the intervention probably is to be put into practice), or the undesirable effects of an intervention probably outweigh the desirable effects (the intervention probably is not to be put into practice)

Source: Andrews JC, Schunemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. J Clin Epidemiol. 2013;66(7):726-35.

4.1.3 Selection process and search results

Medline search revealed 779 citations of possible interest. First selection based on title abstract left 67 papers for full text evaluation. Finally, 30 selected papers reported quality indicators that were reported in a list of indicators for further assessment. The included publications are listed in Table 3.

Table 3 – Included publications reporting quality indicators for lung cancer diagnosis, staging, treatment and follow-up

First author	Year	Reference
Allen [12]	2011	Allen JW, Farooq A, O'Brien TF, Osarogiagbon RU. Quality of surgical resection for nonsmall cell lung cancer in a US metropolitan area. Cancer. 2011;117(1):134-42.
Aumann [13]	2013	Aumann K, Kayser G, Amann D, Bronsert P, Hauschke D, Palade E, et al. The format type has impact on the quality of pathology reports of oncological lung resection specimens. Lung Cancer. 2013;81(3):382-7.
Brunelli [14]	2009	Brunelli A, Berrisford RG, Rocco G, Varela G, European Society of Thoracic Surgeons Database C. The European Thoracic Database project: composite performance score to measure quality of care after major lung resection. Eur J Cardiothorac Surg. 2009;35(5):769-74.
Caldarella [15]	2012	Caldarella A, Amunni G, Angiolini C, Crocetti E, Di Costanzo F, Di Leo A, et al. Feasibility of evaluating quality cancer care using registry data and electronic health records: a population-based study. Int J Qual Health Care. 2012;24(4):411-8.
Cassivi [16]	2008	Cassivi SD, Allen MS, Vanderwaerdt GD, Ewoldt LL, Cordes ME, Wigle DA, et al. Patient-centered quality indicators for pulmonary resection. Ann Thorac Surg. 2008;86(3):927-32.
Cerfolio [17]	2011	Cerfolio RJ, Bryant AS. Optimal care of patients with non-small cell lung cancer reduces perioperative morbidity. J Thorac Cardiovasc Surg. 2011;141(1):22-33.
Chien [18]	2008	Chien CR, Tsai CM, Tang ST, Chung KP, Chiu CH, Lai MS. Quality of care for lung cancer in Taiwan: a pattern of care based on core measures in the Taiwan Cancer Database registry. J Formos Med Assoc. 2008;107(8):635-43.
Conron [19]	2007	Conron M, Phuah S, Steinfort D, Dabscheck E, Wright G, Hart D. Analysis of multidisciplinary lung cancer practice. Intern Med J. 2007;37(1):18-25.
Evans [20]	2013	Evans WK, Ung YC, Assouad N, Chyjek A, Sawka C. Improving the quality of lung cancer care in Ontario: the lung cancer disease pathway initiative. J Thorac Oncol. 2013;8(7):876-82.
Fasola [21]	2012	Fasola G, Rizzato S, Merlo V, Aita M, Ceschia T, Giacomuzzi F, et al. Adopting integrated care pathways in non-small-cell lung cancer: from theory to practice. J Thorac Oncol. 2012;7(8):1283-90.
Freixinet [22]	2011	Freixinet JL, Varela G, Molins L, Rivas JJ, Rodriguez-Paniagua JM, de Castro PL, et al. Benchmarking in thoracic surgery. Eur J Cardiothorac Surg. 2011;40(1):124-9.
Gephardt [23]	1996	Gephardt GN, Baker PB. Lung carcinoma surgical pathology report adequacy: a College of American Pathologists Q-Probes study of over 8300 cases from 464 institutions. Arch Pathol Lab Med. 1996;120(10):922-7.
Gould [24]	2008	Gould MK, Ghaus SJ, Olsson JK, Schultz EM. Timeliness of care in veterans with non-small cell lung cancer. Chest. 2008;133(5):1167-73.

First author	Year	Reference
Hermens [25]	2006	Hermens RP, Ouwens MM, Vonk-Okhuijsen SY, van der Wel Y, Tjan-Heijnen VC, van den Broek LD, et al. Development of quality indicators for diagnosis and treatment of patients with non-small cell lung cancer: a first step toward implementing a multidisciplinary, evidence-based guideline. Lung Cancer. 2006;54(1):117-24.
Jakobsen [26]	2009	Jakobsen E, Palshof T, Osterlind K, Pilegaard H. Data from a national lung cancer registry contributes to improve outcome and quality of surgery: Danish results. Eur J Cardiothorac Surg. 2009;35(2):348-52; discussion 52.
Komaki [27]	2013	Komaki R, Khalid N, Langer CJ, Kong FM, Owen JB, Crozier CL, et al. Penetration of recommended procedures for lung cancer staging and management in the United States over 10 years: a quality research in radiation oncology survey. Int J Radiat Oncol Biol Phys. 2013;85(4):1082-9.
Kramer [28]	2006	Kramer GW, Legrand CL, van Schil P, Uitterhoeve L, Smit EF, Schramel F, et al. Quality assurance of thoracic radiotherapy in EORTC 08941: a randomised trial of surgery versus thoracic radiotherapy in patients with stage IIIA non-small-cell lung cancer (NSCLC) after response to induction chemotherapy. Eur J Cancer. 2006;42(10):1391-8.
Krzyzanowska [29]	2011	Krzyzanowska MK, Barbera L, Elit L, Razzaq A, Saskin R, Yeritsyan N, et al. Identifying population-level indicators to measure the quality of cancer care for women. Int J Qual Health Care. 2011;23(5):554-64.
Li [30]	2013	Li X, Scarfe A, King K, Fenton D, Butts C, Winget M. Timeliness of cancer care from diagnosis to treatment: a comparison between patients with breast, colon, rectal or lung cancer. Int J Qual Health Care. 2013;25(2):197-204.
Mainz [31]	2009	Mainz J, Hansen AM, Palshof T, Bartels PD. National quality measurement using clinical indicators: the Danish National Indicator Project. J Surg Oncol. 2009;99(8):500-4.
Ost [32]	2014	Ost DE, Niu J, L SE, Buchholz TA, Giordano SH. Quality gaps and comparative effectiveness in lung cancer staging and diagnosis. Chest. 2014;145(2):331-45.
Ouwens [33]	2007	Ouwens MM, Hermens RR, Termeer RA, Vonk-Okhuijsen SY, Tjan-Heijnen VC, Verhagen AF, et al. Quality of integrated care for patients with nonsmall cell lung cancer: variations and determinants of care. Cancer. 2007;110(8):1782-90.
Ouwens [34]	2010	Ouwens M, Hermens R, Hulscher M, Vonk-Okhuijsen S, Tjan-Heijnen V, Termeer R, et al. Development of indicators for patient-centred cancer care. Support Care Cancer. 2010;18(1):121-30.
Perez [35]	2008	Perez G, Porta M, Borrell C, Casamitjana M, Bonfill X, Bolibar I, et al. Interval from diagnosis to treatment onset for six major cancers in Catalonia, Spain. Cancer Detect Prev. 2008;32(3):267-75.
Pourcel [36]	2013	Pourcel G, Ledesert B, Bousquet PJ, Ferrari C, Viguier J, Buzyn A. Delais de prise en charge des quatre cancers les plus frequents dans plusieurs regions de France en 2011 et 2012. Bull Cancer. 2013;100(12):1237-50.

First author	Year	Reference
Powell [37]	2008	Powell AA, Schultz EM, Ordin DL, Enderle MA, Graham BA, Partin MR, et al. Timeliness across the continuum of care in veterans with lung cancer. J Thorac Oncol. 2008;3(9):951-7.
Ryoo [38]	2014	Ryoo JJ, Malin JL, Ordin DL, Oishi SM, Kim B, Asch SM, et al. Facility characteristics and quality of lung cancer care in an integrated health care system. J Thorac Oncol. 2014;9(4):447-55.
Tanvetyanon [39]	2009	Tanvetyanon T. Quality-of-care indicators for non-small cell lung cancer. Cancer Control. 2009;16(4):335-41.
Tanvetyanon [40]	2011	Tanvetyanon T, Corman M, Lee JH, Fulp WJ, Schreiber F, Brown RH, et al. Quality of care in non-small-cell lung cancer: findings from 11 oncology practices in Florida. J Oncol Pract. 2011;7(6):e25-31.
Wouters [41]	2010	Wouters MW, Siesling S, Jansen-Landheer ML, Elferink MA, Belderbos J, Coebergh JW, et al. Variation in treatment and outcome in patients with non-small cell lung cancer by region, hospital type and volume in the Netherlands. European Journal of Surgical Oncology. 2010;36(1).

Results of the grey literature search are listed here, by country:

Scotland

1. http://www.healthcareimprovementscotland.org/our_work/cancer_care_improvement/programme_resources/cancer_qpis.aspx: Lung cancer Quality Performance Indicators

United Kingdom

2. http://www.nice.org.uk/guidance/QS17/chapter/List-of-quality-statements

The Netherlands

3. http://www.iknl.nl/docs/default-source/Palliatieve-zorg-in-de-ziekenhuizen/tumorspecifiek-kwaliteitskader-longcarcinoom-1-0-iknl-20130926.pdf,
4. https://www.iknl.nl/docs/default-source/KIB-rapportages/definities-van-de-parameters-.pdf?sfvrsn=0
5. https://www.iknl.nl/docs/default-source/KIB-rapportages/portfolio_kib_longkanker.pdf?sfvrsn=2
6. http://www.clinicalaudit.nl/sites/default/files/20140127_DLSA_indicatoren.pdf
7. http://www.clinicalaudit.nl/sites/default/files/20140127_DLRA_indicatoren.pdf, http://dlra.clinicalaudit.nl/jaarrapportage/2013/#dica_rapportages_dlra
8. http://www.soncos.org/Nieuws.html: Normeringrapport SONCOS, versie: 26 Februari 2014
9. http://www.santeon.nl/; http://www.zorgvooruitkomst.nl/uitkomstenboek2013.pdf http://www.zorgvooruitkomst.nl/uitkomstenboek2014.pdf

The United States of America (USA)

10. http://www.qualitymeasures.ahrq.gov/search/search.aspx?term=lung+cancer

4.2 Selection of quality indicators

All indicators identified in the above mentioned sources were first merged in a long list of indicators. The first long list contained 287 possible indicators.

Based on scoping and feasibility considerations (use of administrative data), the following categories of QIs were excluded:

- Patient reported outcomes
- QIs addressing the quality of palliative care
- QIs addressing the quality of radiotherapy planning
- QIs related to structure (except volume-outcome relationship)
- QIs related to screening for lung cancer
- Process indicators related to surgical audits

In a next step, indicators that referred to the same concept were grouped in a single indicator as much as possible. Furthermore, indicators were rephrased for clarity and consistency. Finally, indicators that were not in agreement with Belgian clinical recommendations were adjusted or removed.

This step resulted in a list of 120 indicators of possible interest.

The list of 120 indicators was used as starting point for the assessment of indicators by the panel of clinicians.

In a first step, each member of the panel was asked to score each quality indicator on its relevance. To be relevant, an indicator needs to reflect an important health issue or an aspect of the health system functioning that matters to the health of the population group in question and assist in monitoring health system performance and be meaningful to stakeholders.

The panel of 19 experts used a five point scale to score the relevance of each quality indicator:

5 = considerable priority (must be included)

4 = moderate priority (would be good if it were included)

3 = some priority (may be included)

2 = little priority (likely not to be included)

1 = no priority (do not bother)

There was also space for remarks about each QI, or addition of new items. Each panel member received one vote. Belgian Cancer Registry and KCE also received one vote each.

Scores received from the expert panel were summarized and indicators were categorized based on the following scheme:

- '**green**': ≥ 70% of assessors scored 4 or 5, priority to be included
- '**orange**': between 50 and 70% of assessors scored 4 or 5, may be included but further discussion is needed
- '**red**': less than 50% of assessors scored of 4 or 5, likely not to be included.

Simultaneously, all indicators were judged for their measurability with available data by experts from KCE (two votes) and from BCR (one vote). Final decision was taken by consensus.

Based on the results of the scoring exercise, final decision on inclusion or exclusion of indicators was taken by consensus during two meetings (held on 3/10/2014 and 4/11/2014) with the clinical expert panel, KCE and BCR.

Scores received from the panel of clinical experts and data experts are summarized in Table 4 and Table 5. For the quality indicators regarding end-of-life care and overdiagnosis and overtreatment, it became apparent that the scoring rules could not be easily applied.

For 35 indicators there was consensus that the indicator was relevant and should be included. Unfortunately, 14 of them were not measurable with available data and had to be excluded (Table 4). For another 43 indicators, the vote indicated that the indicator was considered as relevant, but there was no clear consensus. Final decision was taken during the meetings through further discussion. Sixteen of these indicators were excluded because they were not measurable with available data. The reasons for which QI were not measurable are reported in Appendix 1.1.2.

Twenty-three indicators were considered relevant by only a minority of clinical experts and were excluded.

Table 4 – QI evaluation by the panel of 19 clinicians and 3 data experts (relevance and measurability)

Score	Interpretation	Selection based on relevance	Selection based on measurability
> 70%	QI needs to be included	35	21
50-70%	QI needs to be discussed	43	27
< 50%	QI needs to be excluded	23	-

Table 5 – QI for which scoring conventions were insufficiently clear

QI	Interpretation	Selection based on relevance	Selection based on measurability
End of life	QI needs to be discussed	6	4
Overdiagnosis and overtreatment	QI needs to be discussed	13	9
TOTAL		**120**	**61**

During two further discussion rounds, the large list of 61 QIs that were relevant and measurable was further scrutinized and consequently reduced. This phase allows to consider 32 indicators (see Appendix 1.1.3). The most important reasons for exclusion of indicators that initially were voted relevant by more than 50% of the experts were: overlap between indicators (e.g. several indicators on timeliness of treatment) or expected lack of room for improvement (e.g. CT-scan of the thorax before start of treatment). Quality indicators were grouped as much as possible and exact formulation and patient selection were further refined.

Two indicators had to be excluded from the list as they turned out to be technically not measurable (indicators 31 and 32 in Appendix 1.1.3)

The final list of included indicators is composed of 21 quality indicators, listed in Table 6.

These quality indicators will allow to assess the structure (S), the process (P) and the outcomes (O).

Table 6 – Final selection of quality indicators

Category	Quality Indicator	S/O/P
Generic indicator	(A) 1-year observed survival after a diagnosis of lung cancer	O
	(B) 1-year relative survival after a diagnosis of lung cancer	
Diagnosis and staging	Proportion of lung cancer patients who was discussed during a multidisciplinary team meeting (MDT)	P
	Time from incidence date to first active treatment (curative intent or palliative intent)	P
	(A) Proportion of lung cancer patients with histopathological confirmation of the diagnosis of lung cancer	P
	(B) Proportion of lung cancer patients with histopathological confirmation of the diagnosis of lung cancer in whom the tumour type was identified	
	(C) Proportion of NSCLC patients for whom the subtype has been identified	
	Proportion of stage IV non squamous NSCLC patients in whom (EGFR) mutation analysis was performed	P
	(A) Proportion of cI-III NSCLC who had PET-CT prior to first treatment with curative intent	P
	(B) Proportion of cIII lung cancer patients who had brain imaging (CT or MRI) before first treatment with curative intent	
	(A) Proportion of clinical stage II-III NSCLC patients who had (minimally) invasive mediastinal staging before treatment with curative intent	P
	(B) Proportion of clinical stage II-III NSCLC patients who had mediastinoscopy where the mediastinoscopy was preceded by EBUS or EUS before treatment with curative intent	
	(A) Proportion of lung cancer patients who have their clinical TNM stage reported to the Belgian Cancer Registry	P
	(B) Proportion of patients treated with surgery with curative intent who have the pathological TNM stage reported to the Belgian Cancer Registry	

Treatment NSCLC	Proportion of patients with NSCLC who received surgical resection for stage cI-II, chemoradiation for stage cIII and chemotherapy or targeted therapy for stage cIV (A) cStage I-II (B) cStage III (C) cStage IV	P
	Proportion of pT1-T3 pN1-2 M0 NSCLC patients who are treated with adjuvant chemotherapy after resection	P
	Proportion of NSCLC patients who have FEV1 and DLCO performed before surgery	P
	Proportion of clinical stage III NSCLC patients receiving concurrent or sequential chemoradiotherapy, based on all patients who received radiotherapy	P
	Proportion of clinical stage III NSCLC operated patients who were discussed in MDT before start of treatment	P
	Proportion of NSCLC patients receiving anti EGFR treatment who were previously tested for EGFR-mutation	P
	Proportion of NSCLC patients for whom performance status was assessed (WHO performance status) at presentation	P
Treatment SCLC	Proportion of patients with SCLC who received chemoradiation (concurrent or sequential) for cI-III patients and platinum-etoposide combination first-line chemotherapy for cIV patients.	P
End-of-life	Proportion of lung cancer patients who received chemotherapy, targeted therapy or palliative radiotherapy within 2 weeks of death	P
Safety and Complications	Proportion of lung cancer patients who died within 60 days after primary treatment, by treatment modality (surgery and radiotherapy)	O
Overdiagnosis and overtreatment	Proportion of early stage NSCLC patients who had a bone scintigraphy performed after a PET-CT	P
	Proportion of patients with pathological stage IA NSCLC who received adjuvant chemotherapy	P

5 DATA SOURCES

5.1 Data selection and linkage

For the calculation of the selected quality indicators for lung cancer care, cancer registry data were linked with health insurance data.

5.1.1 Primary selection

All invasive lung cancers that were diagnosed between January 1, 2010 and December 31, 2011 for patients with an official residence in Belgium at time of diagnosis, were selected from the Belgian Cancer Registry (BCR) database. To be included, patients needed to be registered in the BCR database with their unique National Number for Social Security (NISS — INSZ). Tumours with an ICD-10 code C34 (Malignant neoplasm of bronchus and lung) were selected. This resulted in the selection of 15 783 cancers from 15 746 unique patients.

5.1.2 Linkage of cancer registry data with health insurance data

Since 2009, the Belgian Cancer Registry is authorised[a] to link data from the BCR database with data on cancer-related diagnostic and therapeutic procedures and pharmaceuticals, which are obtained from all seven Belgian sickness funds via the Intermutualistic Agency (IMA — AIM). Via this linkage procedure, the Belgian Cancer Registry receives for each registered patient, health insurance data starting from January 1 of the year preceding the incidence year, until December 31 of the fifth year after the incidence year (further mentioned as IMA — AIM data). At the start of this study, IMA — AIM data until the end of 2012 were available at the Cancer Registry. Because at least one year of follow-up could be guaranteed for each individual patient, it was decided that the available IMA — AIM data were sufficient to calculate the selected process indicators.

From the originally selected 15 746 patients, 15 529 (98.6%) could be linked to the IMA — AIM database. Patients for whom no information was available in the IMA — AIM database were probably not affiliated to one of the Belgian sickness funds or had an invalid National Number for Social Security (NISS — INSZ).

5.1.3 Vital status

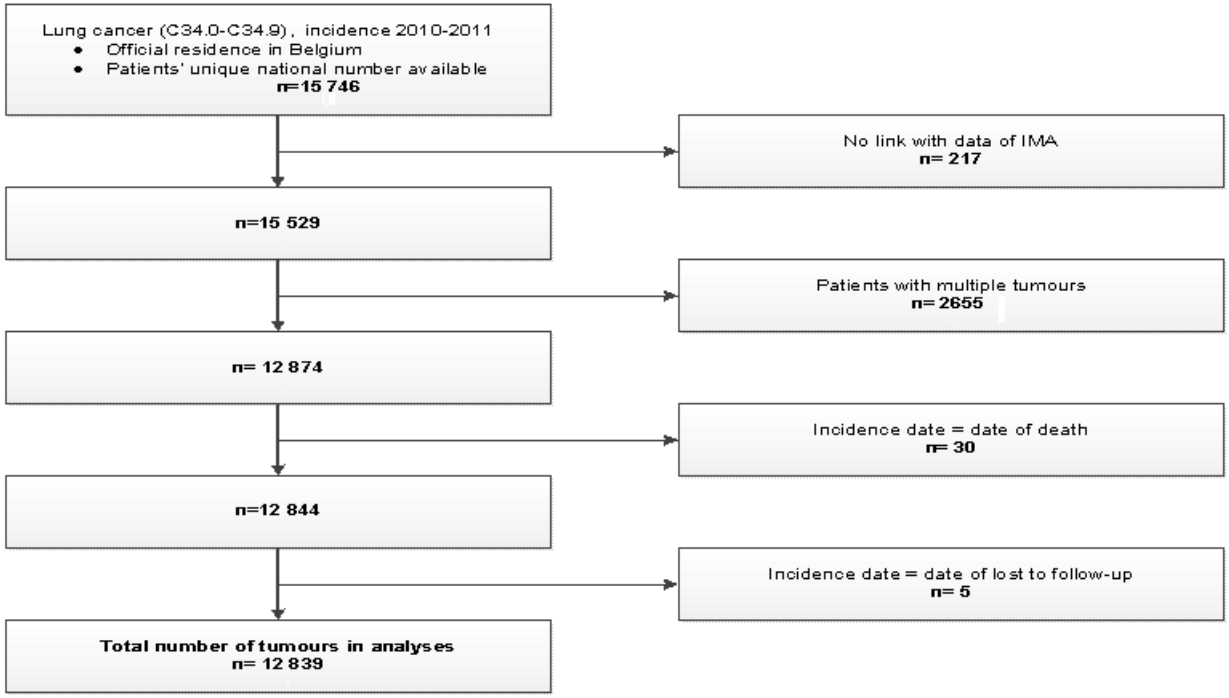
The vital status was retrieved from the Crossroad Bank of Social Security (Kruispuntbank van de Sociale Zekerheid — Banque Carrefour de la Sécurité Sociale) based on the patients' unique social security number (NISS — INSZ). Using this active follow-up method, patients were followed up until December 31st 2014.

5.1.4 Additional data selection

From the 15 746 patients with a lung cancer who were originally selected from the BCR database, 2 907 patients were excluded from further analysis (see Figure 1).

[a] Beraadslaging nr 09/071 van 15 september 2009, laatst gewijzigd op 18 februari 2014, met betrekking tot de mededeling van persoonsgegevens door de verzekeringsinstellingen aan de Stichting Kankerregister in het kader van artikel 45 quinquies van het KB nr. 78 van 10 november 1967 betreffende de uitoefening van de gezondheidsberoepen / Délibération n°09/071 du 15 septembre 2009, modifiée le 18 février 2014, relative à la communication de données à caractère personnel par les organismes assureurs à la Fondation Registre du Cancer dans le cadre de l'article 45quinquies de l'AR n° 78 du 10 novembre 1967 relatif è l'exercice des professions des soins de santé.

Figure 1 – Selection of cancer patients



Excluded patients were the following:

1. 217 patients for whom no link could be made with the IMA — AIM database.
2. 2 655 patients with multiple invasive tumours registered in the BCR database, which is considered to be complete as from 1999 for Flanders and as from 2004 for Brussels and Wallonia, and for the whole of Belgium until 2011 at time of data selection for this study (currently until 2013). At the time of data selection, tumours that were diagnosed until the end of 2011 could be taken into account. Multiple tumours can be diagnosed before or after the main lung tumour. This exclusion criterion ensures that the population included in the analysis consists only of patients with one single tumour, and that oncological treatments are given for that specific tumour.
3. 30 patients whose incidence date is the same as the date of death: quality of care can obviously not be evaluated for those patients, as no care was given.
4. 5 patients whose incidence date is the date of lost to follow-up: these are patients who live in Belgium at time of diagnosis, but did move abroad when first checked for their vital status at the Crossroad Bank of Social Security (Kruispuntbank – Banque Carrefour).

A total of 2 907 patients are excluded from the analysis (18.7%), the main reason for exclusion being the presence of multiple tumours (16.8% of patients). The resulting population included in the present report consists of 12 839 patients diagnosed in 2010-2011 with a lung cancer.

6 PILOT STUDY: VALIDATION OF INDICATOR RESULTS BY SIX HOSPITALS

6.1 Introduction and general method

For this project, quality indicators for lung cancer care were calculated at the national and hospital level. Calculation was based on a linkage of cancer registry data (BCR data) and administrative data (financial claims data) from the health insurance companies (IMA — AIM data). Because it remains impossible to unambiguously link diagnoses to the health insurance data, a subproject was initiated to validate the indicator results. The main research question of the validation project was "*Do quality indicator results differ when they are calculated using cancer registry data linked to health insurance data compared to when they are calculated using data that are available at the hospital (e.g. medical files, financial data,…), and can a possible difference in results be considered as acceptable?*".

During a first phase of the validation, it was tested whether it is possible (based on BCR and IMA — AIM data) to identify for each hospital a complete list of patients diagnosed with lung cancer. Both completeness and validity of the BCR and IMA — AIM data, as well as the algorithm to assign patients to one diagnostic hospital (Figure 2) were evaluated during this phase. In the second phase, it was evaluated whether quality of care indicators can correctly be calculated using BCR and IMA — AIM data.

Members of the expert panel composed specifically for this project were asked to participate with their hospitals in this validation. A selection of six hospitals was made; taking into account academic versus non-academic hospitals, the volume of the hospitals and their geographical location. To have a comparable and manageable workload, a sub-selection of patients was made (based on incidence years) for the higher volume hospitals. A small fee was provided to the participating hospitals.

The following hospitals participated to the pilot phase:

- Cliniques universitaires Saint-Luc
- Clinique et Maternité Sainte-Elisabeth
- Institut Jules Bordet
- AZ Delta (Campus Heilig Hart)
- UZ Antwerpen
- UZ Leuven

After the validation process, results of this validation were discussed between the KCE, the BCR and the participating hospitals (per hospital one medical specialist and one data manager were invited to take part in this meeting). Results of this validation procedure were presented anonymously (at this meeting and in this report) for reasons of privacy and confidentiality (for patients and hospitals). Below, the results of the six hospitals are per quality indicator reported in a different order (Hospital A-F). Hospital A always represents the hospital with the best result for the concerning indicator. Consequently, Hospital A for one indicator is not necessarily the same hospital for the other indicators.

6.2 Validation of the algorithm to assign patients to a diagnostic centre

6.2.1 Method

Each of the six hospitals received a list of the patients selected for their hospital, ranging from 51 to 127 patients per hospital and a total number of 574 patients for the six hospitals together. These lists were constructed using a proposed algorithm to assign patients to one diagnostic hospital (Figure 2) and were based on the IMA — AIM data. Next to the unique number for Social Security of each patient, a coded patient ID was provided and the priority rule that was used to assign each individual patient to the hospital was defined. Furthermore, the date of diagnosis, the sublocalisation and histological type of a patient's tumour were provided. For each diagnostic test taken into account in the algorithm, the date of the test as found in the IMA — AIM database was provided as well as a variable indicating whether the test was performed within the defined timeframe or not. Hospital representatives were asked to verify whether each of these patients are known in their hospital in the context of lung cancer, and whether they could identify additional patients who were erroneously not included in the hospital list (due to missing data in the cancer registry data or incorrectly assigned to another hospital). Additionally, it was asked to verify if the rule used to assign the patients was correct.

Figure 2 – Algorithm to assign patients to one diagnostic hospital

To define 'the diagnostic hospital' the hospital in which the following diagnostic procedures took place were taken into account, in hierarchical order:

- a bronchoscopy
- a biopsy
- a lung function test
- a CT

Only diagnostic tests within 3 months before until 3 months after the day of incidence were considered, and if one of these tests occurred more than once within the defined timeframe, only the one closest to incidence date was retained.

The following rules were respected to define one 'diagnostic hospital' per patient. The order in which they are stated, indicates the priority between the rules (1 = highest priority; 4 = lowest priority).

		Cumulative % of patients assigned
1.	The hospital where bronchoscopy took place	77%
2.	The hospital where biopsy took place	83%
3.	The hospital where a lung function test took place	91%
4.	The hospital where CT took place	99%

6.2.2 Results

Figure 3 shows the correctness of the patient lists per hospital. A range of 90% to 100% of patients per hospital was correctly assigned. Although the correct hospital was identified, participating hospitals sometimes used another rule than was defined by the BCR based on administrative databases. Though, this occurred very infrequently (maximum 3 patients per hospital). Reasons were:

- Inconsistency between health insurance data versus hospital data, due to misclassification or missing billing data.
- No bronchoscopy took place because an EBUS took place.

In reality, the rule to assign patients to the hospitals was, incorrectly, more often questioned by the hospitals because other nomenclature codes for biopsy and bronchoscopy (e.g. EBUS, mediastinoscopy) were used by the hospitals than those included in the patient assignment algorithm.

For the six hospitals together, eight patients were excluded from the hospital list (but remained included in the study). Different reasons for this kind of exclusion were found:

- Three patients should have been assigned to another hospital because of a correction in the incidence date based on extra information reported by the hospital.
- Four patients should have been assigned to another hospital because of missing information in the IMA — AIM database (more information was available in the medical files).
- One patient should have been assigned to another hospital because the patient underwent multiple similar diagnostic tests. The first test (closest to incidence date) was negative, but the second was positive and there was no exchange of information between the two hospitals. Consequently, the patient was not known to have lung cancer in the first hospital.

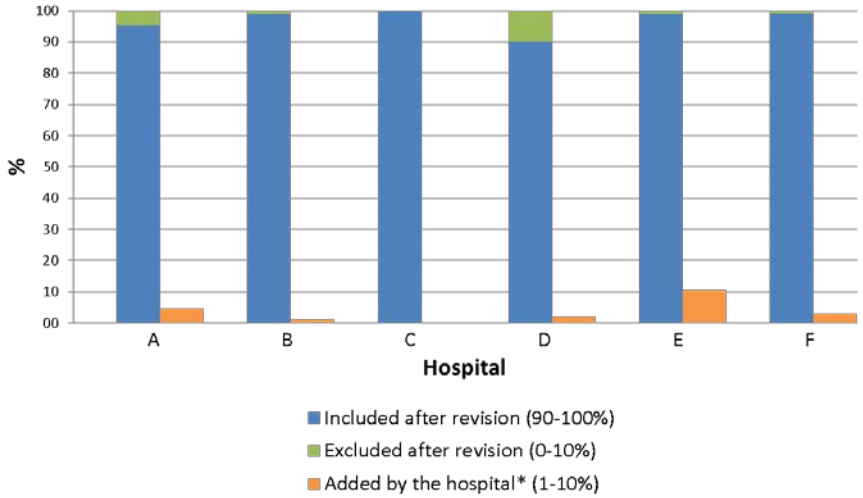
For the six hospitals together, six patients had to be excluded from the study:

- Three of them because they had multiple tumours, which were previously not reported to the BCR.
- Two patients had to be excluded because they were registered with an incorrect incidence date, while the correct incidence date was outside the study period.
- One tumour was wrongfully registered as an invasive lung cancer.

Twenty-one patients were added by the hospitals to their patient lists (a range from 1% to 10%):

- Four tumours were previously not reported in the BCR database.
- For three tumours, the incidence date was incorrect in the BCR database.
- Two tumours were registered in the BCR database with another topography (outside C34).
- Seven patients were erroneously considered as not having their official residence in Belgium (this error was already corrected in the BCR database since the end of 2014, but this was after data extraction for this project).
- The correct centre could not been identified based on IMA — AIM data for one patient.
- For four patients no IMA — AIM data were available.

Figure 3 – Correctness of the patient list by hospital



Note: Original patient lists as selected by the Belgian Cancer Registry ranged from 51 to 127 patients per hospital.
** Not available for hospital C*

Though the algorithm was technically considered as correct by everyone, a general remark of one of the participating hospitals was that the algorithm to assign patients to one diagnostic hospital resulted in a much lower volume for their hospital compared to what the hospital itself would report as its diagnostic volume. This was caused by the referral pattern of this hospital; patients were always referred to another hospital for bronchoscopy/EBUS and lung function tests. Since the hospital where bronchoscopy took place had the most important role in the assignment algorithm, many patients were assigned to another hospital, while all other diagnostics and treatment decisions based on test results were done in the participating hospital. Although this seems to be a rather specific situation, hospitals not participating in the validation procedure may have similar problems.

6.2.3 Conclusion

The overall quality of the assignment algorithm can be considered as good. However, correctly assigning patients to a hospital strongly depends on the exhaustiveness and quality of the data delivery to the Cancer Registry. Additionally, misclassifications and non-specific nomenclature codes for medical acts/procedures in the IMA — AIM data are barriers to optimally assign a hospital to each patient.

A shortcoming of the algorithm is that EBUS seems to have an important role in the centre assignment of the patients.

Additionally, it became clear that the referral pattern for individual hospitals was not adequately captured by the algorithm. Therefore, a new algorithm to assign the patients to the different centres was set up. In this new algorithm, EBUS and the multidisciplinary team (MDT) meeting were additionally taken into account to assign a patient to one diagnostic hospital (Table 7).

Table 7 – Procedures (with timeframe) used in the new algorithm to assign patients to one diagnostic hospital

Procedure	Timeframe
1. MDT meeting	-1m < incidence date < +6m
2. Bronchoscopy	-3m < incidence date <+3m
➔ **When no bronchoscopy: EBUS**	-3m < incidence date < +3m
3. Biopsy	-3m < incidence date < +3m
4. Lung function test	-3m < incidence date < +3m
5. CT	-3m < incidence date < +3m

Using these five procedures (Table 7), a new algorithm was built to take the referral patterns between the hospitals better into account and to give higher priority to the hospital where most of the patient's diagnostic tests were performed (Table 8).

Table 8 – New algorithm to assign patients to one diagnostic hospital

Priority rule	Cumulative percentage of patients assigned
1. Only one hospital known for these 5 procedures	97.9%
2. Multiple hospitals involved in these procedures → hospital that occurs most often	98.5%
If multiple hospitals were involved with the same number of procedures:	
3. Hospital of MDT meeting	99.0%
4. Hospital of bronchoscopy (or EBUS when no bronchoscopy)	99.0%
5. Hospital of biopsy	99.1%
6. Hospital of lung function test	99.1%
7. Hospital of CT	99.1%

With this new algorithm, a patient that was referred to another hospital for one or two diagnostic tests, but with the majority of tests in the referring hospital, was assigned to this referring hospital. As such, referring a patient to another hospital for a diagnostic test no longer had any impact on the referring hospital's volume. Additionally, the new role of EBUS (besides bronchoscopy) and the MDT meeting in the algorithm, makes the algorithm more complete. For most of the hospitals these adaptations had few consequences on their patient lists. Though, for a limited number of hospitals it had a substantial impact.

6.3 Validation of indicator results

6.3.1 Method

After consultation of clinical experts, we selected 32 quality indicators (QI) for lung cancer care. Twenty-one of them were calculable based on the available BCR and IMA — AIM data. Because some of these remaining indicators could only be calculated in a national context (not centre specific, e.g. treatment at the end of life) or were more complex to calculate (e.g. survival), seventeen indicators only were considered during the second phase of the validation. For each indicator, a short description of the indicator was provided to the participating hospitals, the operational definition and a flowchart on how to calculate the indicator.

The indicator results, calculated by the BCR, were sent to the hospitals, together with all detailed patient information that was taken into account in the calculation. The hospitals' representatives were asked to discuss the indicator results for their hospitals during a MDT meeting. They were asked to evaluate whether these results were as expected, taking into account the case mix and the daily practices of the hospital. If the result of an indicator corresponded to their expectations, this had to be reported to the BCR and no further action was needed. Though, in case that an indicator result was considered incorrect, they were asked to first validate the theoretical calculation of the indicator as explained in the flowchart. If they agreed with the definition of the numerator and denominator but did not agree with the indicator result, the patient list with detailed information on how that specific indicator was calculated had to be consulted. A (selection) of patients was then verified to check whether the information retrieved from the IMA — AIM database, was in line with the information in the patients' medical file. It was stressed that the detailed patient lists and medical files should only be consulted in case of disagreement or doubt about the indicator result.

For this second phase of the validation, the new algorithm to assign patients to one diagnostic hospital was used. This way indicator results were immediately evaluated for the selected patients as it would be for the final publication.

To estimate the influence on the indicator results from patients incorrectly assigned to the hospital (e.g. because of an incorrect incidence date), these patients remained included in the calculations by the BCR. If the hospital representatives would try to recalculate the indicator result based on their individual patient information, they were asked to take into account the additional patients they correctly added to their patient lists during the first phase.

6.3.2 Results

It is important to mention that all results obtained during the validation study are reported in figures following a descending slope, hospital A scoring highest for the indicator and hospital F scoring lowest for this indicator. In this way, participating hospitals cannot be identified.

6.3.2.1 Quality indicators related to data registration

Quality Indicator DR-1: TNM reported to BCR

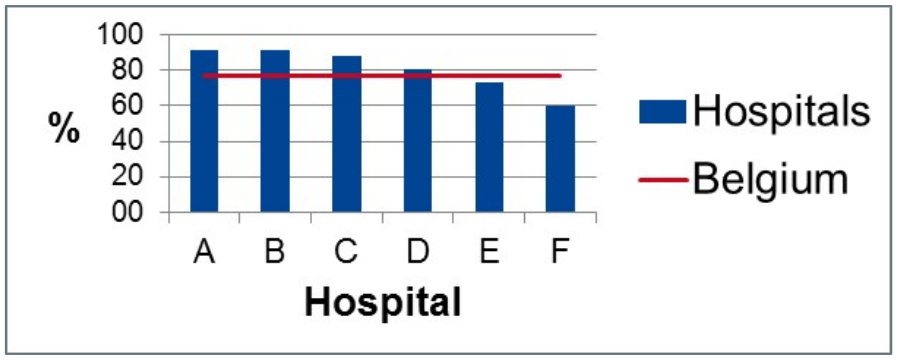
Quality Indicator DR-1 (A):

Description: Proportion of lung cancer patients who have their clinical TNM stage reported to the Belgian Cancer Registry (Figure 4)

Numerator: Number of lung cancer patients who have their clinical TNM stage reported to the BCR

Denominator: All patients diagnosed with lung cancer

Figure 4 – Proportion of lung cancer patients who have their clinical TNM stage reported to the BCR: Results of the validating hospitals



Comments of the validating hospitals: All hospitals agreed with their results and indicated that they want to improve them in the future. One of the hospitals informed us that they did not report tumours with a clinical stage IV to the Belgian Cancer Registry when they were not discussed during the multidisciplinary team meeting. Though, action had already been taken to prevent this in the future.

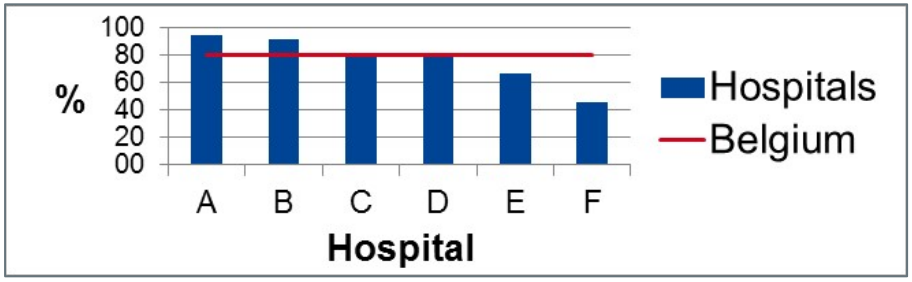
Quality Indicator DR-1 (B):

Description: Proportion of patients treated with surgery with curative intent who have their pathological TNM stage reported to the Belgian Cancer Registry (Figure 5)

Numerator: Number of lung cancer patients treated with surgery with curative intent, who have their pathological TNM stage reported to the BCR

Denominator: Number of lung cancer patients treated with surgery with curative intent

Figure 5 – Proportion of patients treated with surgery with curative intent who have their pathological TNM stages reported to the BCR: results of the validating hospitals



Comments of the validating hospitals: All hospitals agreed with their results and indicated that they wanted to improve them in the future. One of the hospitals mentioned the importance of combining the information of the pathology report and the surgical reports. The latter is only available in the hospitals.

Quality Indicator DS-8: Performance status reported to BCR

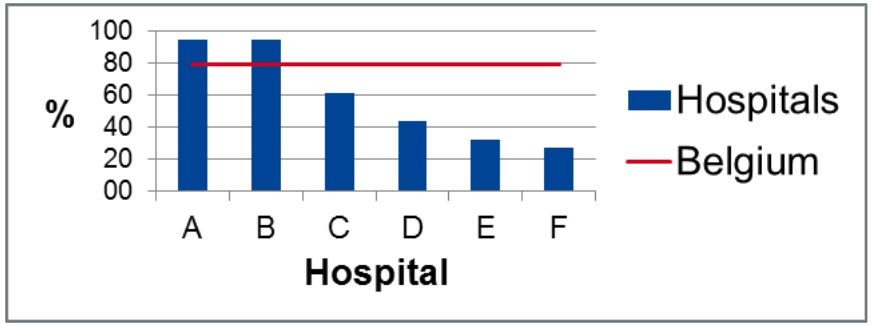
Description: Proportion of NSCLC patients for whom performance status was assessed (WHO performance status) at presentation and reported to the BCR (Figure 6)

Numerator: Number of NSCLC patients for whom performance status (WHO) was reported to BCR

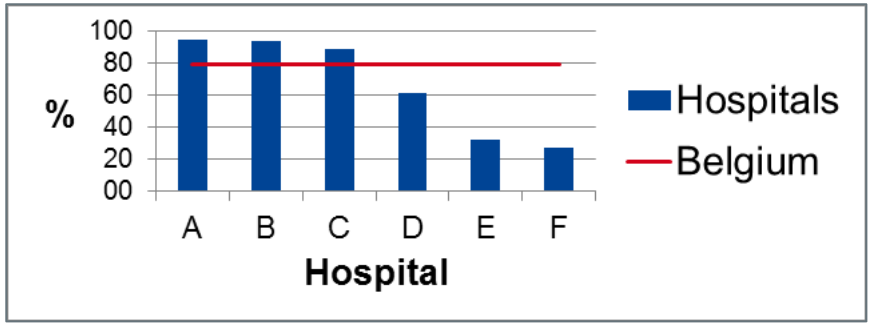
Denominator: All NSCLC patients

Figure 6 – Proportion of NSCLC patients for whom performance status was assessed at presentation and reported to the BCR: original and new results of the validating hospitals

Original results



New results



Comments of the validating hospitals on their original results: Two hospitals reported that the assessment of the performance status was done, but not reported to the BCR for all of their patients. Another hospital reported that its indicator result seemed too low.

The calculation of this indicator was revised based on this last comment. This led to the detection of a programming error, influencing the result of only a few hospitals. The indicator was recalculated and presented with the new results to the hospitals participating in the validation phase. Based on these new results, there were no more comments.

Quality Indicator DS-2: Pathological diagnosis and subtype

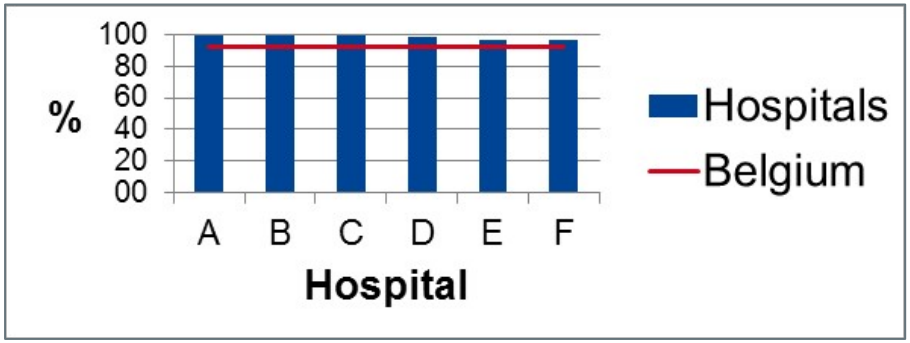
Quality Indicator DS-2 (A):

Description: Proportion of lung cancer patients with histopathological confirmation of the lung cancer diagnosis (Figure 7)

Numerator: Number of lung cancer patients with histopathological confirmation of the lung cancer diagnosis

Denominator: All patients with a diagnosis of lung cancer

Figure 7 – Proportion of lung cancer patients with histopathological confirmation of the diagnosis of lung cancer: results of the validating hospitals



Comments of the validating hospitals: All hospitals agreed with their results

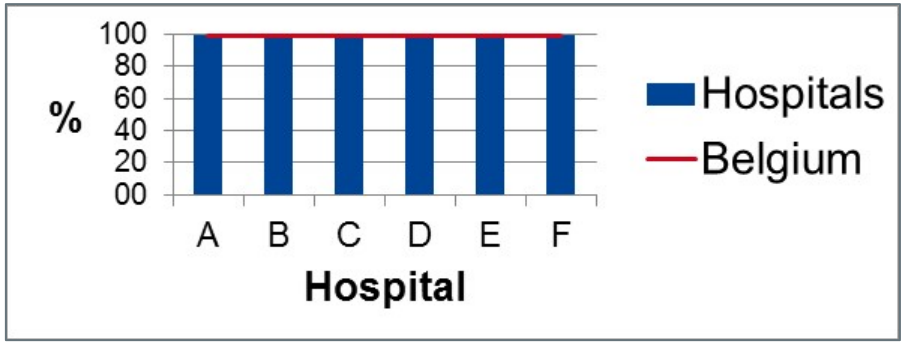
Quality Indicator DS-2 (B):

Description: Proportion of lung cancer patients in whom the tumour type is identified (Figure 8)

Numerator: Number of lung cancer patients who had tumour type identified (SCLC, NSCLC or other specified lung cancer)

Denominator: All patients with a diagnosis of lung cancer with histopathological confirmation

Figure 8 – Proportion of lung cancer patients in whom the tumour type is identified: results of the validating hospitals



Comments of the validating hospitals: All hospitals agreed with their results.

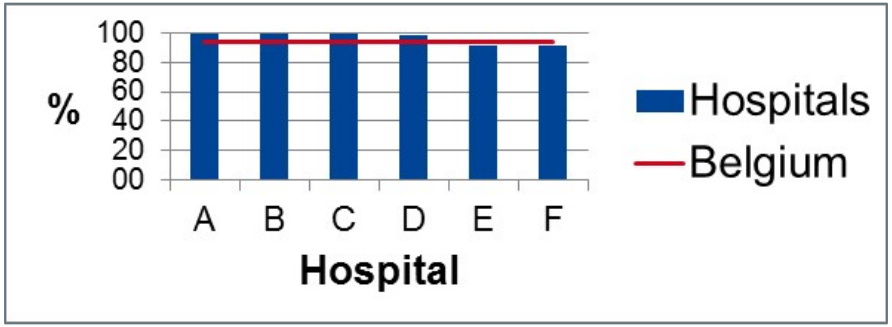
Quality Indicator DS-2 (C):

Description: Proportion of NSCLC patients for whom the subtype has been identified (Figure 9)

Numerator: Number of NSCLC patients who had tumour subtype identified

Denominator: All patients with a diagnosis of non-small cell lung cancer

Figure 9 – Proportion of NSCLC patients for whom the subtype has been identified: results of the validating hospitals



Comments of the validating hospitals: One hospital evaluated its result as too high. A possible reason for the disagreement is that the BCR received also information from the pathological anatomy laboratories and/or from other hospitals and all available information was combined to calculate the indicators.

6.3.2.2 *Quality indicators related to Multidisciplinary team (MDT) meeting*

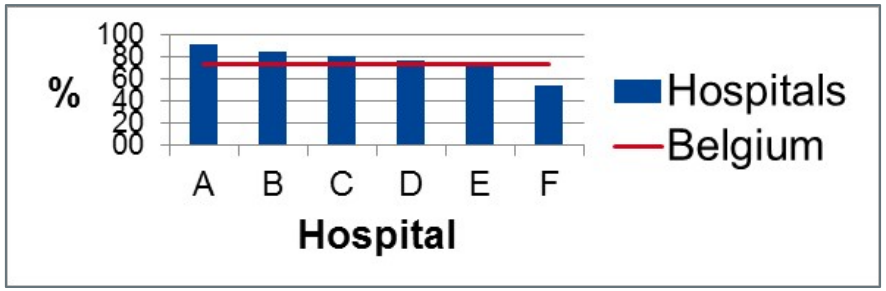
Quality Indicator DS-11: MDT meeting

Description: Proportion of lung cancer patients that was discussed during a MDT meeting (Figure 10)

Numerator: Number of patients diagnosed with lung cancer who were discussed during the multidisciplinary team meeting between 1 month before incidence date and 6 weeks after incidence date

Denominator: All patients diagnosed with lung cancer

Figure 10 – Proportion of lung cancer patients that was discussed during a multidisciplinary team meeting: results of the validating hospitals



Comments of the validating hospitals: Three hospitals considered their results as too low. One hospital mentioned that stage IV patients were often not discussed in any MDT meeting, and that patients diagnosed by the general practitioner or patients who needed to be discussed already at time of admission were not discussed in any MDT meeting.

From previous projects on quality indicators it is known that more patients are discussed during a MDT meeting than what can be derived from IMA — AIM data. This is mainly caused by billing rules for MDT meetings; the number of MDT meetings is limited to maximum one per year, so patients might have been discussed multiple times during MDT meetings, but it is possible that the one which was invoiced is outside the defined timeframe and is consequently not taken into account in the numerator of this indicator. Misclassifications remain also possible in administrative data.

Quality Indicator DS-12: Pre-operative MDT meeting

Description: Proportion of clinical stage III NSCLC surgically treated patients who were discussed in MDT meeting before start of treatment (Table 9)

Numerator: Number of patients who were discussed in MDT meeting before start of treatment

Denominator: all cIII NSCLC patients with surgery with curative intent within 9 months of incidence date

Table 9 – Proportion of clinical stage III NSCLC surgically treated patients who were discussed in MDT meeting before start of treatment: results of the validating hospitals

Hospital	Numerator/Denominator
A	4/5
B	3/5
C	4/4
D	3/3
E	3/3
F	0/0

Comments of the validating hospitals: One hospital argued that the sample size was not representative.

All agreed that the small sample size for all hospitals makes a comparison between hospitals inappropriate. Therefore, it is decided to not compare hospitals on this indicator.

The MDT meeting billing problems discussed for indicator DS-11 are also relevant for this indicator. As such, the real proportion of MDT meetings would probably be higher.

6.3.2.3 *Quality indicators on diagnosis and staging*

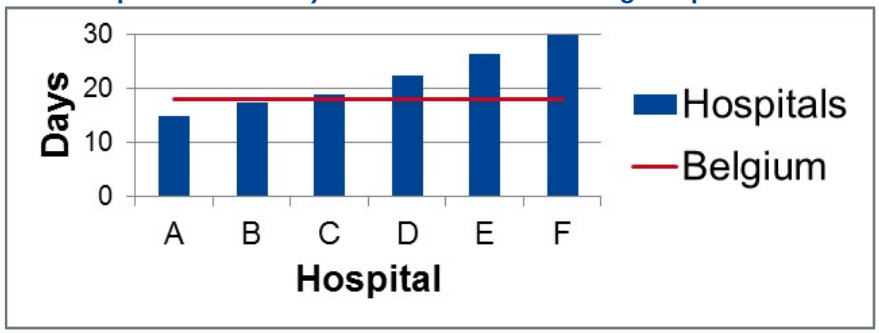
Quality Indicator DS-1: Time delay between diagnosis and first treatment

Description: Time from incidence date to first active treatment (curative intent or palliative intent) (Figure 11)

Calculation: Median number of days between the incidence date and the first day of active treatment

Included in analysis: all lung cancer patients who received treatment within 9 months of incidence date.

Figure 11 – Time from incidence date to first active treatment (curative intent or palliative intent): results of the validating hospitals



Comments of the validating hospitals: Several hospitals disagreed with the start date of the treatment on patient level, especially for the start date of radiotherapy. The reason for this was that the start date of radiotherapy cannot always directly be derived from IMA – AIM data (only the end date is always available) and it was arbitrary decided to estimate the start date of radiotherapy as 30 days before the end date. Though, since the indicator concerns the median time from incidence to start active treatment, errors on patient level disappeared on hospital level. However, a very small overestimation of the median time remains possible.

For this reason this indicator was recalculated with the new refined algorithm to better estimate the start date of radiotherapy based on the cases whose start dates of radiotherapy were available in IMA – AIM data.

Quality Indicator DS-9: mutation analysis EGFR for stage IV patients

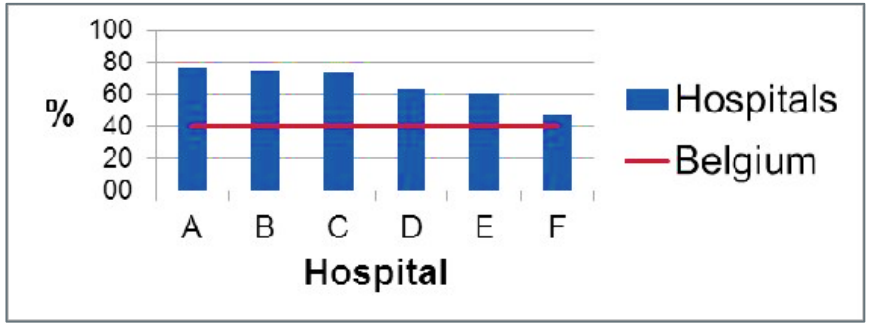
Description: Proportion of stage IV non squamous cell NSCLC patients in whom (EGFR) mutation analysis was performed (Figure 12)

Numerator: Number of patients in whom (any) mutation analysis was performed within 9 months of incidence date

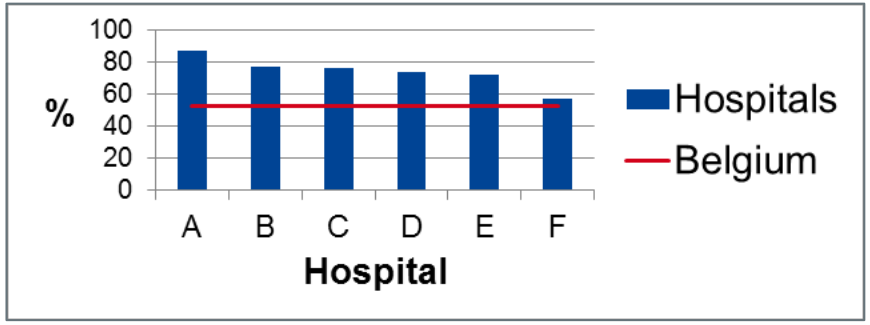
Denominator: All combined stage IV non squamous cell NSCLC patients

Figure 12 – Proportion of stage IV non squamous cell NSCLC patients in whom (EGFR) mutation analysis was performed: results of the validating hospitals: original and new results

Original results



New results



Comments of the validating hospitals: One hospital considered its result as too low.

Two reasons can be found for a disagreement. First, it should be noted that the nomenclature changed in 2010, which might have caused some billing problems (use of wrong nomenclature codes). Second, the data used for this project are older than the current guidelines, and with current medical practice in mind, results for 2010-2011 were judged low by the hospital representatives. (During the incidence years 2010-2011, performing a mutation analysis was not yet routine practice.)

To take these comments into account, the indicator was recalculated taking only the incidence year 2011 into account and new results were presented to the hospitals participating in the validation phase. Everyone agreed to report the results for 2011 as a baseline measurement instead of a quality indicator.

Quality Indicator DS-3 and DS-4: PET-CT and brain imaging before treatment with curative intent

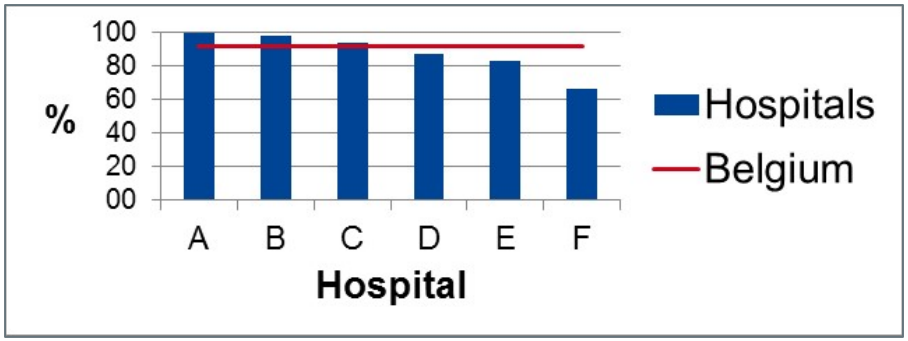
Quality Indicator DS-3:

Description: Proportion of clinical stage I-III NSCLC patients who had PET-CT prior to treatment with curative intent (Figure 13)

Numerator: Number of clinical stage I-III NSCLC patients in whom a PET-CT was obtained before the start of treatment with curative intent (< 3 months before start of treatment).

Denominator: All clinical stage I-III NSCLC patients who received treatment with curative intent within 9 months of incidence date

Figure 13 – Proportion of clinical stage I-III NSCLC patients who had PET-CT prior to treatment with curative intent: results of the validating hospitals



Comments of the validating hospitals: Three hospitals commented that their results were too low. One of them suggested that its lower score could be explained by the fact that the PET-CT was performed in another hospital. However, all PET-CT scans were taken into account, irrespective of the hospital where they were performed.

An explanation for the lower scores could be problems with the calculated start date for radiotherapy (a disagreement with the start date of radiotherapy was reported, see DS02). Therefore, also for this indicator, a more advanced method to estimate the start date of radiotherapy was developed afterwards and the indicator could be recalculated.

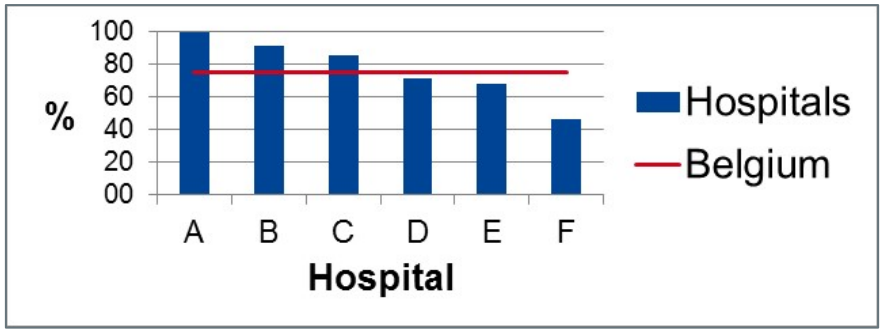
Quality Indicator DS-4:

Description: Proportion of clinical stage III lung cancer patients who had brain imaging (CT or MRI) before treatment with curative intent (Figure 14)

Numerator: number of clinical stage III lung cancer patients in whom brain imaging by CT or MRI was obtained before the start of first treatment with curative intent (< 3 months before start of treatment)

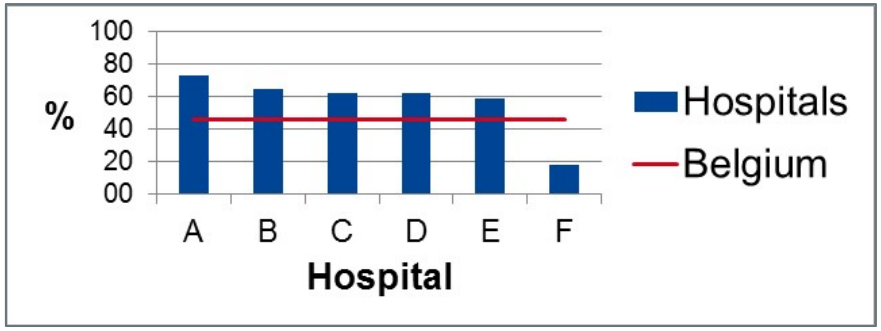
Denominator: All clinical stage III lung cancer patients who received treatment with curative intent within 9 months of incidence date

Figure 14 – Proportion of clinical stage III lung cancer patients who had brain imaging (CT or MRI) before treatment with curative intent: Results of the validating hospitals



Comments of the validating hospitals: Two hospitals considered their scores as too low. After a validation of the individual patient information, a disagreement in the start date of radiotherapy was reported (see DS02). Therefore, also for this indicator, a more advanced method to estimate the start date of radiotherapy was developed afterwards and the indicator could be recalculated.

Figure 15 – Proportion of clinical stage II-III NSCLC patients who had (minimally) invasive mediastinal staging before treatment with curative intent: results of validating hospitals



Comments of the validating hospitals: Four hospitals argued that their scores were too low. Two possible reasons for these lower scores can be put forward. The first reason was that in the original calculation, mediastinal staging on the day of surgery was not taken into account for the indicator. This was changed. A second reason was a disagreement in the start date of radiotherapy (see DS-1). Therefore, also for this indicator, a more advanced method to estimate the start date of radiotherapy was developed afterwards and the indicator could be recalculated.

Quality Indicator DS-5 (B):

Description: Proportion of clinical stage II-III NSCLC patients who had mediastinoscopy preceded by EBUS or EUS before treatment with curative intent (Table 10)

Numerator: Number of cstage II-III NSCLC patients for whom EBUS or EUS were performed before the mediastinoscopy

Denominator: All clinical stage II-III NSCLC patients who had a mediastinoscopy before treatment with curative intent

Table 10 – Proportion of clinical stage II-III NSCLC patients who had mediastinoscopy preceded by EBUS or EUS before treatment with curative intent: results of the validating hospitals

Hospital	Numerator/Denominator
A	2/10
B	3/5
C	1/2
D	1/1
E	0/0
F	0/0

Comments of the validating hospitals: One hospital considered its result as too high. However, it should be noted that the small numbers made the indicator hard to interpret.

All agreed that the small sample size for all hospitals makes a comparison between hospitals inappropriate. Therefore, it is decided to not compare hospitals for this indicator.

Additionally, also for this indicator a problem might occur concerning the start date of radiotherapy. Therefore, a more advanced method to estimate the start date of radiotherapy was developed afterwards and the indicator could be recalculated (see DS02).

6.3.2.4 Quality indicators related to treatment of NSCLC

Quality Indicator TRT-1: Guideline-concordant treatment NSCLC

All hospitals reported to have a problem with the description of the indicator; 'optimal treatment' should not be used because the optimal treatment for an individual patient highly depends on the characteristics of the patient and the tumour, and not only on the clinical stage of the tumour. Therefore, the word 'optimal' was finally discarded.

When there was disagreement on the result of the different sub-indicators (TRT-1 A-B-C), validation of the individual patient data proved that a deviation from the 'optimal' treatment for an individual patient could always be motivated based on all the characteristics of the patient and the tumour. So, replacing 'optimal' by 'guideline-concordant' treatment from the description of the indicator could lead to agreement with the indicator results.

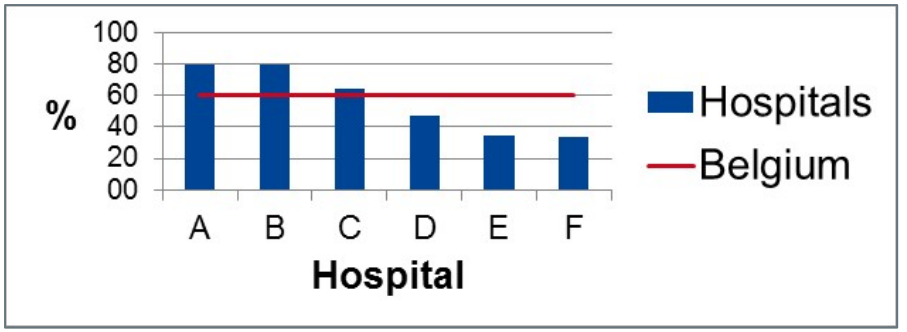
Quality Indicator TRT-1 (A):

Description: Proportion of NSCLC patients who received optimal *[guideline-concordant]* treatment: resection for stage I and II (Figure 16)

Numerator: Number of clinical stage I-II NSCLC patients with surgery with curative intent (within 9 months of incidence date)

Denominator: All NSCLC patients with clinical stage I-II

Figure 16 – Proportion of patients with NSCLC who received *guideline-concordant* treatment: resection for stage I and II: results of the validating hospitals



Comments of the validating hospitals: One of the hospitals considered its result as too high and another considered its result as too low.

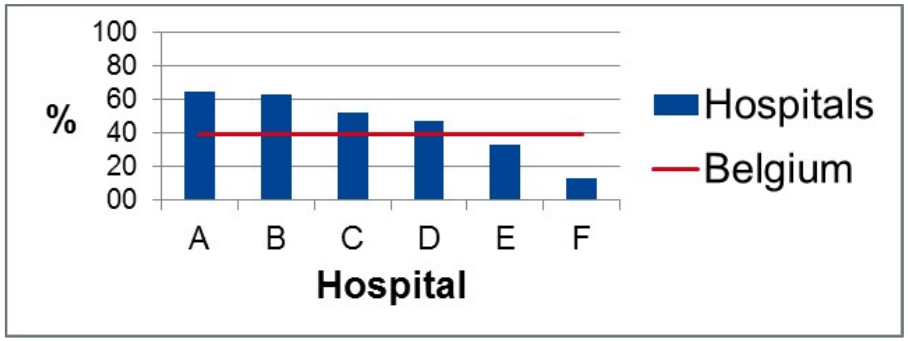
Quality Indicator TRT-1 (B):

Description: Proportion of patients with NSCLC who received optimal *[guideline-concordant] treatment*: chemoradiation for stage III (Figure 17)

Numerator: number of clinical stage III NSCLC patients with (concurrent or sequential) chemoradiation (followed or not by surgery) (within 9 months of incidence date)

Denominator: All NSCLC patients with clinical stage III

Figure 17 – Proportion of NSCLC patients who received *guideline-concordant* treatment: chemoradiation for stage III: results of the validating hospitals



Comments of the validating hospitals: One of the hospitals considered its result as too high and another considered its result as too low.

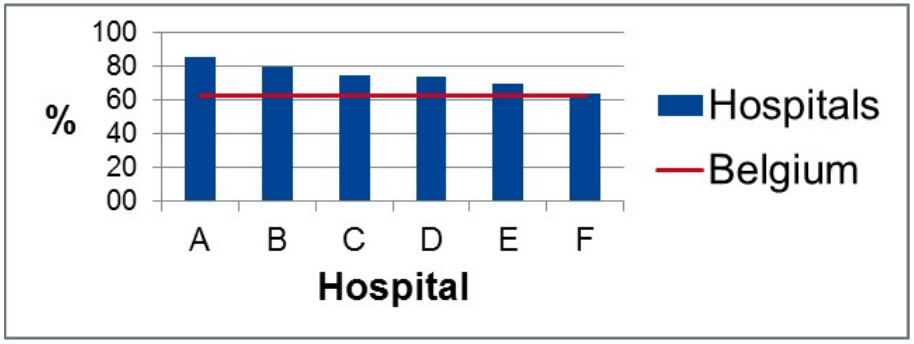
Quality Indicator TRT-1 (C):

Description: Proportion of patients with NSCLC who received optimal *[guideline-concordant]* treatment: chemotherapy or targeted treatment for stage IV (Figure 18)

Numerator: Number of clinical stage IV NSCLC patients with chemotherapy or targeted therapy (within 9 months of incidence date)

Denominator: All NSCLC patients with clinical stage IV

Figure 18 – Proportion of patients with NSCLC who received *guideline-concordant* treatment: chemotherapy for stage IV: results of the validating hospitals



Comments of the validating hospitals: One of the hospitals considered its result as too low.

Quality Indicator TRT-3: Adjuvant chemotherapy after resection

Description: Proportion of pT1-T3 pN1-2 M0 NSCLC patients who are treated with adjuvant chemotherapy (Table 11)

Numerator: Number of pT1-T3 pN1-2 M0 NSCLC patients who received chemotherapy within 3 months after surgery (and no neoadjuvant chemotherapy and no radiotherapy)

Denominator: Number of pT1-T3 pN1-2 M0 NSCLC patients who had surgery with curative intent within 9 months of incidence date and no neoadjuvant chemotherapy and/or radiotherapy

Table 11 – Proportion of pT1-T3 pN1-2 M0 NSCLC patients who are treated with adjuvant chemotherapy: Results of validating hospitals

Hospital	Numerator/Denominator
A	5/5
B	2/3
C	2/2
D	2/2
E	1/1
F	1/1

Comments of the validating hospitals: Two hospitals regarded their results as too high. However, the small number of patients involved were considered as the reason why the results were different than expected.

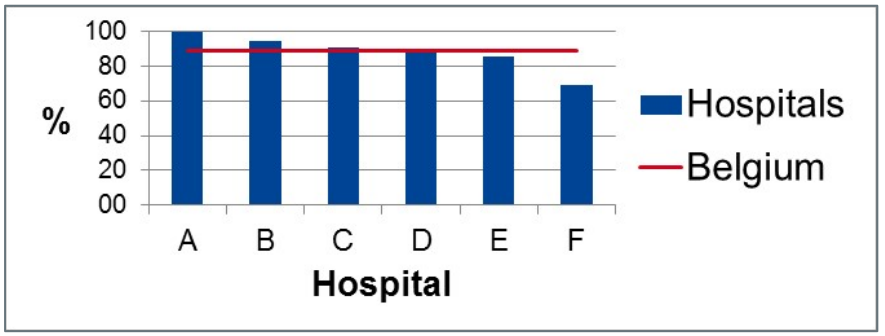
Quality Indicator DS-6: FEV1 and DLCO

Description: Proportion of NSCLC patients who have FEV1 and DLCO performed before curative surgery (Figure 19)

Numerator: Number of NSCLC patients who had FEV1 and DLCO performed within 3 months before curative surgery

Denominator: All NSCLC patients who had surgery with curative intent within 9 months of incidence date

Figure 19 – Proportion of NSCLC patients who have FEV1 and DLCO performed before curative surgery: results of the validating hospitals



Comments of the validating hospitals: Three hospitals evaluated their scores as too low. These lower scores can be explained because, according to the indicator, both tests should have been performed to be taken into account in the numerator

Quality Indicator TRT-2: Chemoradiotherapy for stage III NSCLC patients

Description: Proportion of stage cIII NSCLC patients receiving radiotherapy, who received concurrent or sequential chemotherapy (Table 12)

Numerator: number of stage cIII NSCLC patients who received concurrent or sequential chemoradiation

Denominator: all stage cIII NSCLC patients who received (at least) radiotherapy with curative intent within 9 months of incidence date

Table 12 – Proportion of stage cIII NSCLC patients receiving concurrent or sequential chemoradiotherapy, among all patients who received radiotherapy: results of the validating hospitals

Hospital	Numerator/Denominator
A	12/14
B	12/14
C	11/13
D	9/10
E	5/5
F	2/2

Comments of the validating hospitals: All hospitals participating in the validation phase agreed with their scores.

Quality Indicator DS-10: EGFR mutation analysis before EGFR treatment

Description: Proportion of NSCLC patients receiving anti-EGFR treatment who were previously tested for EGFR-mutation (Table 13)

Numerator: Number of NSCLC patients who received anti-EGFR treatment for whom a molecular test on the tumour was performed before the start of anti-EGFR treatment

Denominator: All NSCLC patients who received anti-EGFR treatment within one year after incidence date

Table 13 – Proportion of NSCLC patients receiving anti-EGFR treatment who were tested for EGFR-mutation: new results of the validating hospitals

Hospital	Numerator/Denominator
A	12/14
B	11/13
C	6/11
D	8/10
E	6/10
F	2/5

Comment of the research team: shortly after start of the second phase of the validation process, this quality indicator was withdrawn from the validation phase due to a programming error.

The quality indicator was recalculated and new results were shown to the hospitals participating in the validation phase at the evaluation meeting. No comments were formulated.

6.3.2.5 Quality indicators related to treatment of SCLC

Quality Indicator TRT-5: Guideline-concordant treatment SCLC

All hospitals' representatives reported to have a problem with the description of the indicator; 'optimal treatment' should not be used because the optimal treatment for an individual patient highly depends on the characteristics of the patient and the tumour, and not only on the clinical stage of the tumour. Therefore, the word 'optimal' was finally replaced by 'guideline-concordant'.

Quality Indicator TRT-5 (A):

Description: Proportion of patients with SCLC who received optimal *[guideline-concordant]* treatment: chemoradiation (concurrent or sequential) for cI-III patients (Table 14)

Denominator: All SCLC patients with clinical stage I-III

Numerator: number of c I-III SCLC patients who received chemoradiation (concurrent or sequential) within 9 months of incidence date

Table 14 – Proportion of patients with SCLC who received *guideline-concordant* treatment: chemoradiation (concurrent or sequential) for cI-III patients: results of the validating hospitals

Hospital	Numerator/Denominator
A	7/10
B	2/3
C	2/3
D	2/3
E	1/2
F	0/1

Comments of the validating hospitals: Two hospitals evaluated their scores as too low. Also for this indicator a problem might occur concerning the start date of radiotherapy (see DS-1). Therefore, a more advanced method to estimate the start date of radiotherapy was developed afterwards and the indicator could be recalculated.

Quality Indicator TRT-5 (B):

Description: Proportion of patients with SCLC who received optimal *[guideline-concordant]* treatment: platinum-etoposide combination first-line chemotherapy for cIV patients (Table 15)

Numerator: Number cIV SCLC patients who received platinum-etoposide combination first-line chemotherapy within 9 months of incidence date *Denominator*: All SCLC patients with clinical stage IV

Table 15 – Proportion of patients with SCLC who received *guideline-concordant* treatment: platinum-etoposide combination first-line chemotherapy for cIV patients: results of the validating hospitals

Hospital	Numerator/Denominator
A	9/14
B	7/9
C	7/7
D	4/5
E	3/3
F	3/3

Comments of the validating hospitals: One hospital evaluated its score as too high. However, the small numbers in the denominator of the indicator were considered as the reason why the results were different than expected.

6.3.2.6 *Quality indicators related to over-diagnosis and to over-treatment*

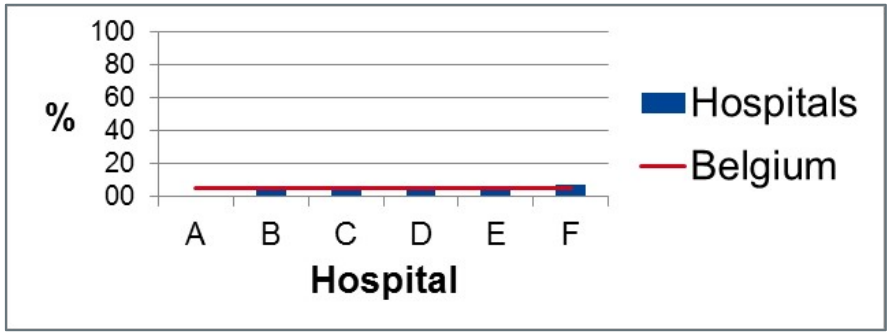
Quality Indicator DS-7: Bone scintigraphy performed after a PET-CT

Description: Proportion of NSCLC patients who had a bone scintigraphy performed after a PET-CT (Figure 20)

Numerator: Number of NSCLC patients who had a bone scintigraphy performed after a PET-CT

Denominator: Number of NSCLC patients who had a PET-CT performed 3 months before or after the incidence date

Figure 20 – Proportion of NSCLC patients who had a bone scintigraphy performed after a PET-CT: results of the validating hospitals



Comments of the validating hospitals: All hospitals agreed with their calculated indicator results. Though, they wanted to explain that a bone scintigraphy could eligibly be performed after PET-CT for a trauma or as a necessary test in case of suspicion of a new metastasis. One hospital reported that validation of individual patient information revealed an administrative error, because in reality there was no bone scintigraphy performed.

Quality Indicator TRT-4: Adjuvant chemotherapy stage IA

Description: Proportion of patients with stage pIA NSCLC who received adjuvant chemotherapy (Table 16)

Numerator: Number of stage pIA NSCLC patients who received adjuvant chemotherapy

Denominator: Number of stage pIA NSCLC patients who underwent surgery

Table 16 – Proportion of patients with stage pIA NSCLC who received adjuvant chemotherapy: results of the validating hospitals

Hospital	Numerator/Denominator
A	1/14
B	1/13
C	0/4
D	0/4
E	0/3
F	0/2

Comments of the validating hospitals: One hospital reported an error in the TNM classification of a patient. Because of this notification and a national result higher than expected, the BCR performed an additional check on the TNM stage of patients included in this indicator. This check revealed the same kind of error for other patients. After correction, the indicator could be recalculated, which leaded to acceptable result as expected by the hospitals' representatives during the meeting.

6.3.3 Conclusion

After taking into account the remarks given during the validation process, the calculation of the quality indicators based on BCR and IMA — AIM data closely resembles the true value as if they would have been calculated by the hospitals based on the medical files. Although small differences exist at hospital level, it seems that the national indicator result is calculable based on the BCR data and IMA — AIM data because biases occur in both directions and are not systematic.

Based on the results of this validation phase and expert opinion, it was decided to redefine and recalculate some of the indicators that raised questions. Therefore, the indicators as discussed in this report are not completely the same as those tested in the validation phase and described in this chapter.

7 CASE-MIX ADJUSTMENT

Outcomes but also results of process indicators are influenced by risk factors. It is thus particularly important to tend to capture as many confounders as possible in the analyses, in particular when measuring quality of care and benchmarking hospitals on this quality. Therefore indicator results were presented broken down by different risk factors such as age, sex, tumour characteristics, etc. Moreover, the regression models used to analyse patient survival and volume-outcome relationship were built taking a series of cofounders into account in order to minimize the risk of bias (case-mix adjustment).

Variables available for case-mix adjustment

The following patient characteristics and tumour characteristics were readily available in the BCR data:

- Age that was used as age groups of 10 years (<50 years, 50-59 years, 60-69 years, 70-79 years, 80+ years).
- Sex.
- WHO performance status, that evaluates the fitness of the patient (0: Asymptomatic, 1: Symptomatic but completely ambulatory, 2: Symptomatic, up and about more than 50% of waking hours, 3: Symptomatic, confined to bed or chair more than 50% of waking hours and 4: Completely disabled; totally confined to bed or chair).
- Clinical, pathological and combined TNM stages,
- Tumour localisation (C34.0 Main Bronchus, C34.1 Upper Lobe, C34.2 Middle Lobe, C34.3 Lower Lobe, C34.8 Overlapping lesion of lung, C34.9 Lung, not otherwise specified)
- Tumour histological type (NSCLC, SCLC, others) and NSCLC subtype (adenocarcinoma, squamous cell carcinoma, large cell carcinoma or other).

These variables were considered essential but not sufficient to apply a valuable case-mix adjustment. We also used a variable used in the literature that estimates the health status of the patient based on the **number of hospitalization days** spent by the patient in the 12 months before his/her lung cancer diagnosis.[42] The variable was categorized in 4 classes: no days, 1-5 days, 6-15 days and more than 15 days.

Furthermore, considering the RHM-MZG (hospital discharge data) was not available in the frame of the present project, we developed a methodology based on the pharmaceutical billing data available in the IMA — AIM data to identify major patient comorbidities that could have an impact on the treatment strategy. The methodology and the developed variables used in case-mix adjustment are presented in the section below.

8 IDENTIFICATION OF LUNG CANCER PATIENTS' COMORBID CONDITIONS BASED ON THEIR PHARMACEUTICAL BILLING DATA

8.1 Introduction

Comorbidities in a cancer patient can be defined as non-cancer-related physical and mental diseases that also affect the patient's tolerance to treatment and/or outcomes.[43,44] **By definition, the presence of comorbidities at baseline (i.e. at the time of cancer diagnosis) may have an impact on care for patients with cancer**[45] and may influence both therapeutic decisions and outcomes for lung cancer patients.[45-47] As comorbidities are mainly present in older people, lung cancer patients, who are around aged 69 years for males and 66 years for females[b] suffer often from one or more comorbid diseases.[48] Moreover, the high frequency of smokers in the lung cancer population increases the number of comorbid conditions at baseline (U.S. Department of Health and Human Services).

Measuring comorbidity in cancer populations is complex, and no gold standard approach exists.[49] Ideally, the presence of comorbid diseases at diagnosis should be assessed by a standardized clinical evaluation for each patient (e.g. Charlson comorbidity index, cumulative illness rating scale (CIRS), ACE-27…). However, this evaluation needs to be planned (prospective study) and is expensive in cost and human resources. An alternative solution to minimize cost and obtain accurate estimations about patients with comorbid conditions is to use administrative sickness funds reimbursement data of pharmaceutical consumption.[50-54]

This part of the study pursues three objectives: 1) to identify main comorbid conditions in lung cancer patients; 2) to identify comorbidities that might be retrieved within the pharmaceutical consumption data; 3) to elaborate and validate a disease case definition based on pharmaceutical consumption within a sample of Belgian hospitals.

b http://www.kankerregister.org/Incidence_Fact_Sheets_FR_version

8.2 Methods and Materials

8.2.1 Identification of comorbidities associated with lung cancer

A literature review was performed in PubMed to identify comorbidities often associated with lung cancer. The keywords used were: Lung Cancer; Comorbidity. The listing of the selected articles is reported in the Appendix 2.1.1 "***review literature***".

8.2.2 Measure of comorbidities based on pharmaceutical consumption

The Anatomical Therapeutic Chemical (ATC) classification from the World Health Organization (WHO, 2013) was used to classify drugs from the pharmaceutical database allowing national and international comparisons of pharmaceutical data. The active substances are categorized into 14 main groups according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties (www.whocc.no). For each ATC drug, a Defined Daily Dose (DDD) is given which is the assumed average maintenance dose per day for a drug used for its main indication in adults (WHO Collaboration Centre for Drug Statistics Methodology website – www.whocc.no). The DDD does not necessarily reflect the Prescribed Daily Dose. The DDD provides a unit of measurement independent of price and dosage form enabling researchers to assess the drug consumption.

For each comorbid condition selected in the literature review, the list of all ATC codes necessary to identify this condition was retrieved from the consulted articles (see Appendix 2.1.1 "***review literature***"). For each patient, the total consumption of specific drug categories during the period of 1-year prior to the diagnosis of lung cancer was computed, based on the sum of DDDs reimbursed during this period.

8.2.3 Selection, definition and validation of the presence of comorbid diseases

Databases

The databases used in the present study were the database of the Belgian Cancer Registry (BCR) linked to the national administrative database containing the claims data of all sickness funds (InterMutualistic Agency database, i.e. IMA-AIM) (see Chapter 5 for more details). Patients diagnosed with lung cancer can be identified in the BCR database, including their incidence date. The IMA-AIM database contains, for each individual patient, all details on reimbursed drugs prescribed to the patient, both in the ambulatory setting and during hospitalisation.

Study population

All patients included in the QI lung cancer project are included in this analysis (i.e. patients with a lung cancer diagnosed between January 1, 2010 and December 31, 2011, who have no multiple tumours). For the definition of the measure, a sample of patients from six selected hospitals was used for the validation phase (same patients as the ones selected for the QI validation phase done in the pilot study – see Chapter 6).

Methods

In order to capture the comorbidities using the pharmaceutical data, a disease case definition needs to be elaborated. A case definition is a set of rules to distinguish patients with or without the comorbid disease based on pharmaceutical consumption.

The validation phase was based on statistical comparison between identification of comorbidities via pharmaceutical data and the reporting of these comorbidities in the patient's hospital medical file (i.e. considered as the gold standard in this study). This validation phase with medical files of patients from 6 Belgian hospitals was performed to evaluate the reliability of the case definition rules. To collect the comorbid conditions recorded in the patient's medical file, an ACCESS database was built to identify comorbidities based on the ICD-10 classification. A user manual of the ACCESS database was developed and explained during a meeting with hospital data managers to reduce the intra-/inter-variability of hospital for retrieving the comorbidity from the medical files (the ACCESS database user

manual is available on request at info@kce.fgov.be). All comorbidities diagnosed prior to or at the same time of the lung cancer had to be recorded in the ACCESS database by the data managers under the supervision of the physicians responsible of the pilot study in each hospital.

There were five statistical validation measures used for this phase: Kappa statistic, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) (Table 17).

Table 17 – Calculation of statistical validation measures between pharmaceutical consumption and medical files

		Medical files	
Pharmaceutical data		**Comorbid Disease present**	**Comorbid Disease absent**
	Drug consumption positive	**A** (True positive)	**B** (False positive)
	Drug consumption Negative	**C** (False negative)	**D** (True negative)

*Sensitivity = A / (A+C) *100; Specificity = D / (D+ B)*100; PPV = A / (A+B)*100; NPV = D / (D+C)*100*

Kappa Statistic (*K*) - A measure of the degree of non-random agreement between observers or measurements of the same categorical variable. The kappa statistic corrects for the possibility of agreement due to chance.

The interpretation of the *K* used in this report is:[55]

<0 Less than chance agreement

0.01 – 0.20 Slight agreement

0.21 – 0.40 Fair agreement

0.41 – 0.60 Moderate agreement

0.61 – 0.80 Good agreement

0.81 – 0.99 Very good agreement

Sensitivity - The probability that a diseased person (case) in the population (medical files) will be identified as diseased by the case definition built on pharmaceutical data. Sensitivity is thus the probability of correctly diagnosing a case or the probability that any given case will be identified in the pharmaceutical database.

Specificity - The probability that a person without the disease (in the medical files) will be correctly identified as non-diseased by the case definition built on pharmaceutical data. It is thus the probability of correctly identifying a non-diseased person in the pharmaceutical database.

Positive predictive value (PPV) - The probability that a person with a positive test result is a true positive (e.g., does have the disease). Here, it is the probability that a case identified through the case definition in the pharmaceutical data is also identified as a case in the medical file.

Negative predictive value (NPV) - The probability that a person with a negative test result is a true negative (e.g., does not have the disease). Here, it is the probability that a non-case identified through the case definition in the pharmaceutical data is also identified as a non-case in the medical file.

The first step is to determine the optimal cut-off value for the total drug consumption. Patients with a total volume of DDDs above this cut-off value will be identified as patients with comorbid condition, other patients (with lower use or no use at all) as patients with no comorbid condition. Receiver Operating Characteristic (ROC) curves are used by maximising the Youden's index. The ROC curve is a graph of the Sensitivity versus (1 – Specificity) over all possible threshold values of the drug consumption. The Youden's index provides a criterion for choosing the "optimal" threshold

value for the total volume of DDDs, the value for which [(Sensitivity + Specificity)-1] is maximized. The objective of this technique is to minimize the number of false negatives and false positives.

Analyses were performed using the SAS software package version 9.3 (SAS institute, Cary, NC).

8.3 Results

Appendix 2.1.1 "***review literature"*** listed the selected articles reviewed in full along with the purpose of the selection.

8.3.1 Identification of main comorbidities associated with lung cancer based on the literature review

The literature review identified 17 comorbidities (see Table 18) but highlighted five major categories of comorbidities for patients diagnosed with lung cancer: respiratory diseases, cardiovascular diseases, renal diseases, previous history of cancer and diabetes. Table 18 reports the prevalence of comorbidities mentioned in several studies based mainly on medical records, patients questionnaires and prospective databases.

Table 18 – Prevalence of comorbidity in the literature for patients with a diagnosis of lung cancer

	Lopez-Encuentra et al. (2002) [56]	Tammemagi et al. (2003) [47]	Colinet et al. (2005) [43]	Blanco et al. (2008) [57]	Janssen-Heijnen et al. (1998) [58]	Janssen-Heijnen et al. (2004) [45]	Janssen-Heijnen et al. (2007) [59]
Type of Lung cancer considered	Operable lung cancer at initial stages	All	NSCLC	Advanced NSCLC	Newly diagnosed lung cancer	NSCLC	SCLC
Sample size	**2 992**	**1 155**	**735**	**294**	**3 864**	**4 076**	**1 661**
Comorbidities							
Respiratory diseases			**44%**				
- **COPD**	**50%**	**28.6%**		**33%**	**22%**	**23%**	**22.1%**
- **Asthma**		**4.4%**					
- Pulmonary fibrosis		0.5%					
Cardiovascular diseases (NOS)	**13.5%**		**36%**	**19%**	**23%**	**22.6%**	**24.4%**
• **Congestive heart failure**		**7.6%**					
• **Arterial hypertension**	**16.5%**				**12%**	**12.6%**	**14.2%**
Previous tumour	**15.5%**		**12%**	**7%**	**15%**	**13.7%**	**10.8%**
Previous metastatic tumour		1.2%					
Peripheral vascular disease	10%	10.2%			23%		
Diabetes	**9%**		**9%**	**11%**	**7%**	**7.8%**	**9.1%**
Liver disease		2.8%					
Tuberculosis		0.4%					
HIV/AIDS		0.7%					
Thyroid/Glandular		7.2%					
Anaemia		6.7%					
Dementia		2.0%					

	Lopez-Encuentra et al. (2002) [56]	Tammemagi et al. (2003) [47]	Colinet et al. (2005) [43]	Blanco et al. (2008) [57]	Janssen-Heijnen et al. (1998) [58]	Janssen-Heijnen et al. (2004) [45]	Janssen-Heijnen et al. (2007) [59]
Renal disease		**5.9%**					
Connective tissue disease		22.2%					

NOS: Not otherwise specified

8.3.2 Identification of comorbidities based on the ATC codes

The literature review (see Appendix 2.1.1 "**review literature**") identified methods to measure comorbidities from administrative drug consumption database via the Anatomical Therapeutic Chemical (ATC) classification. It appears that the possibility of an exact differentiation between specific diseases via ATC codes is challenging and even, in certain cases, unfeasible.[51] For example, beta-blockers are prescribed both for patients with hypertension and for patients with other cardiovascular diseases. A clear distinction between ATC codes for cardiac diseases and for hypertension cannot be done. Therefore, it was decided to include the hypertension in the group of cardiovascular diseases group.

Table 19 shows the ATC codes used in literature to identify the four main categories of comorbidities: diabetes, cardiovascular disease, respiratory disease and renal disease.[50-53, 60-64] Previous tumour was not retained in this study as the target population includes by definition only patients with one primary tumour.

Table 19 – ATC codes selected to identify the comorbidity in pharmaceutical database

Comorbidity	ATC codes
Diabetes	A10 DRUGS USED IN DIABETES
Cardiovascular disease	C01 CARDIAC THERAPY
	C02 ANTIHYPERTENSIVES
	C03 DIURETICS
	C04 PERIPHERAL VASODILATORS
	C07 BETA BLOCKING AGENTS
	C08 CALCIUM CHANNEL BLOCKERS
	C09 AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM
	B01 ANTITHROMBOTIC AGENTS (Excl. B01AB (Heparin))
Respiratory disease	R03 DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
Renal Disease*	A11CC VITAMIN D AND ANALOGUES
	B03XA OTHER ANTIANEMIC PREPARATIONS
	V03AE DRUG FOR TREATMENT OF HYPERKALEMIA AND HYPERPHOSPHATEMIA
	Nomenclatures codes for dialyse (Appendix 2.1.2 nomenclature) available in the billing data from RIZIV/INAMI

**only reimbursed drugs or procedures for chronic renal failure can be identifiable in the IMA-AIM database.*

8.3.3 Validation phase in six pilot hospitals

A total of 603 patients with lung cancer diagnosed between 2010 and 2011 from six hospitals were included in this pilot study. The median age was 66 years [58-74], 84% of lung cancers were Non-Small Cell type and 42% of cases had stage IV disease. The number of patients by hospital ranged from 74 to 129 patients for this period. The prevalence of comorbid conditions and the estimates of agreement between data retrieved from the medical files and pharmaceutical consumption are summarized in Table 20.

As mentioned in the methodology, the ROC curve analysis allows to determine a cut-off for the number of drug consumption days for each comorbidity in order to minimize the number of false negatives and false positives.

The results showed a cut-off value of 30 DDDs within the year before cancer diagnosis for diabetes mellitus, 80 DDDs for chronic respiratory diseases, 186 DDDs for chronic cardiovascular diseases (rounded to 180 days (around 6 months)) and 0.42 DDDs for renal insufficiency (see the ROC curves under Appendix 2.1.3). For renal insufficiency, the Area Under the Curve (AUC) was very low and it was not possible to use the number of DDDs as it is. The decision was to define a case if at least one ATC drug from the selected ATC groups was delivered during the studied period.

In addition to the number of DDDs, another rule was taken into account to determine the presence of the disease. Patients having purchased a drug at more than six different dates in the year preceding the cancer diagnosis were also considered as a case for the disease.

Table 20 – Estimates of prevalence of comorbid conditions, and estimates of agreement between medical file and pharma consumption, all ages and all centres.

		Prevalence (%)			Estimates of agreement				
Comorbidity	**Cut-off**	**Medical files (A) (patient history)**	**Pharmaceutical database (drug consumption) (B)**	***Diff (=A-B)***	***K***	**Se**	**Sp**	**PPV**	**NPV**
Chronic respiratory diseases	>80 DDDs or 6 drug delivery dates	25.4	27.6	-2.2%	0.48 [0.41-0.56] Moderate	65	85	60	88
Chronic cardiovascular diseases (Incl. Hypertension)	>180 DDDs or 6 drug delivery dates (?)	55.1	57.1	-2.0%	0.64 [0.57-0.70] Good	85	78	83	81
Diabetes mellitus	>30 DDDs or 6 drug delivery dates (?)	13.8	14.1	-1.3%	0.83 [0.77-0.90] Very Good	87	97	85	98
Renal insufficiency	At least 1 drug delivery date or dialyse	5.0	5.3	-0.3%	0.22 [0.07-0.37] Fair	27	96	25	96

K Kappa Statistic; Se Sensibility; Sp Specificity; PPV Positive Predicted value; NPV Negative Predicted value

Table 20 shows the prevalence of each comorbid condition reported in the medical files and in the pharmaceutical database (according to the decision rules adopted based on the drug consumption days). The medical files identified 55.1% (vs 57.1% for pharmaceutical database) of patients with a chronic cardiovascular disease (incl. Hypertension), 25.4% (vs 27.6% for pharmaceutical database) of chronic respiratory diseases, 5% (vs 5.3% for pharmaceutical database) of renal insufficiency and 13.8% (vs 14.1% for pharmaceutical database) of diabetes mellitus.

The K statistic indicated a very good agreement between the case definition based on pharmaceutical consumption and based on medical files for the diabetes mellitus (k = 0.83) and good agreement for chronic cardiovascular diseases (k= 0.64); a moderate agreement for chronic respiratory disease (k=0.48) and a fair agreement for renal insufficiency (k = 0.22). The sub-analyses by hospital revealed a reliable estimation of comorbid conditions between hospitals (Figure 21 and Figure 22).

Figure 21 – Kappa statistics for Diabetes Mellitus and Chronic respiratory diseases, all ages and by hospital.

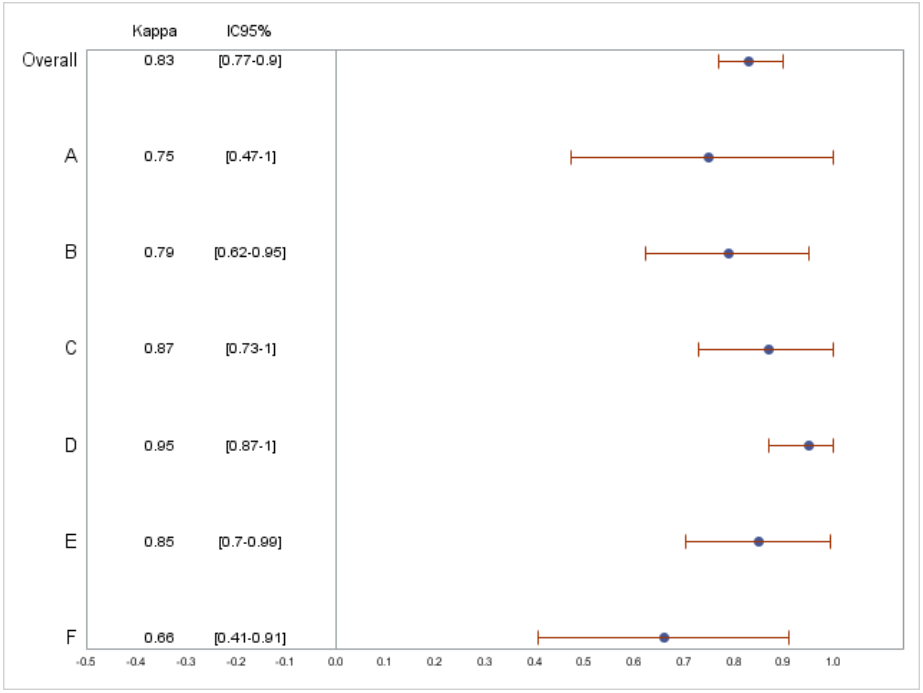


Fig 21a. Diabetes Mellitus

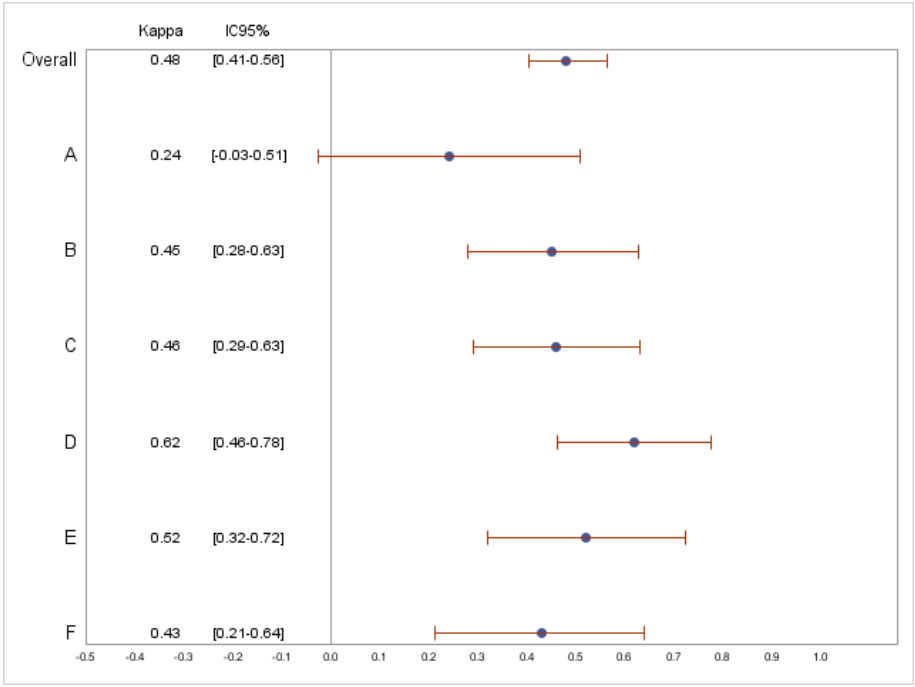


Fig 21b. Chronic respiratory diseases

Figure 22 – Kappa statistics for Chronic cardiovascular diseases and Renal insufficiency, all ages and by hospital.

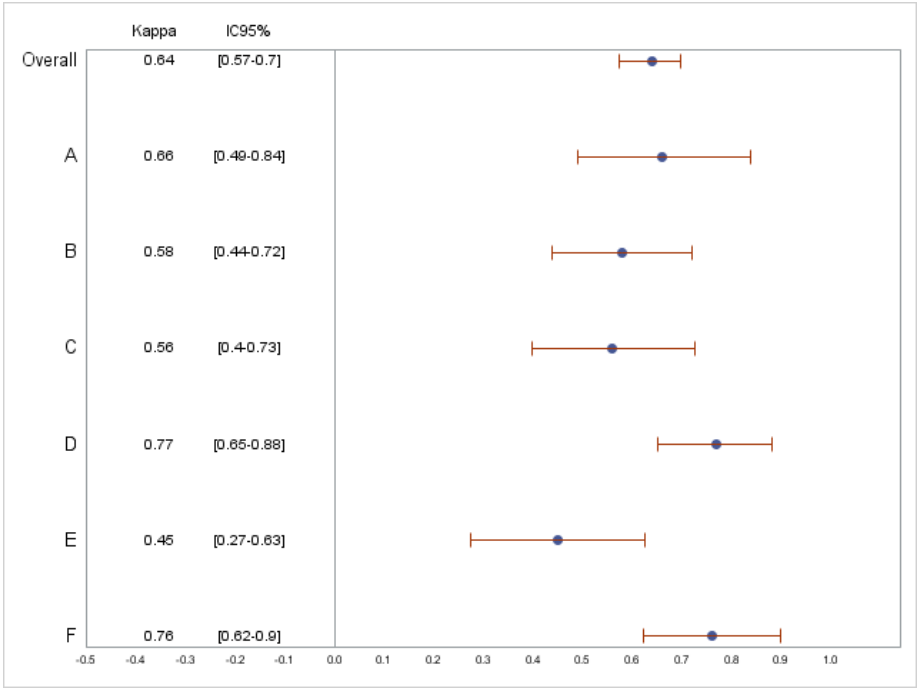


Fig 22a. Chronic cardiovascular diseases

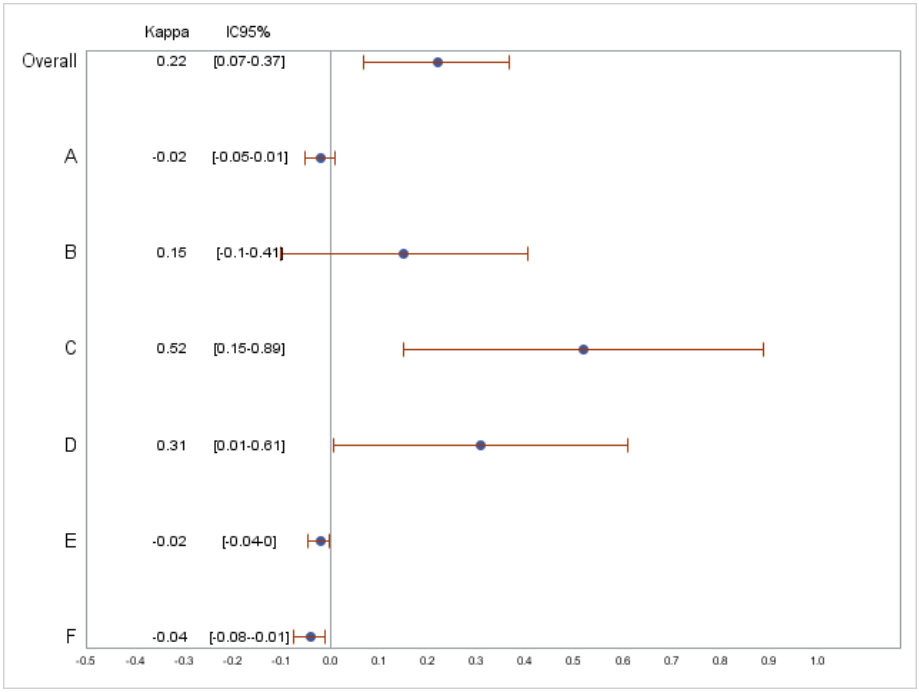


Fig 22b. Renal insufficiency

Sensitivity was highly variable, and ranged from 27% (renal disease) to 87% (diabetes) across the 4 comorbid conditions. Diabetes and cardiovascular diseases obtained the higher sensitivity, i.e. 87% and 85% respectively. A moderate sensitivity was found for chronic respiratory diseases (65%) and a low sensitivity for renal insufficiency (27%). The positive predictive values were relatively high for 2 comorbid conditions (diabetes and cardiovascular diseases). This means that the probability to have a comorbid condition recorded in the medical file when the comorbid condition is detected through the pharmaceutical database is relatively high. Specificity was consistently high for 3 groups of diseases (respiratory diseases, diabetes mellitus and renal insufficiency). It ranged from 85% to 97% (Table 20). Cardiovascular diseases had a lower specificity, i.e. 78%. The negative predictive values were high for the 4 comorbid conditions. This means that the probability to not have the disease when the patient was not identified through the pharmaceutical database is high. For example, the probability to not have a chronic respiratory disease when the pharmaceutical database definition is negative was 87%.

The Kappa statistic for renal insufficiency was fair but the capacity to detect cases was poor. Only 27% of patients having the comorbid condition recorded in the medical file were well-identified in the pharmaceutical database. Consequently, renal insufficiency was not retained as a comorbid condition for the project based on this validation phase.

8.3.4 *Measurement of comorbid conditions on the national cohort of patients with lung cancer using pharmaceutical data only*

Table 21 describes the patient and tumour characteristics according to the three selected comorbid conditions.

Among the 12 839 patients of the studied population, the proportions of comorbid conditions were similar to those obtained during the validation study. The proportion of chronic respiratory diseases was 23.5%, 57.5% for cardiovascular diseases and 14% for diabetes mellitus.

The proportion of comorbid conditions by age group was higher for cancer patients older than 60 years compared to patients younger than 60 years. In terms of combined stage, the proportion of chronic respiratory diseases was higher for stage I compared to other stages (34% vs 22%). This phenomenon was confirmed by the TNM category where chronic respiratory diseases were more often in the early category than in the other categories. The same trend was observed for chronic cardiovascular diseases, even if the difference was lower than for chronic respiratory disease (61% of stage I vs 57% of other stages). The proportion of diabetes mellitus was not different between stages.

Table 21 – Patient and tumour characteristics by comorbid condition (N= 12 839)

Characteristics (N (%))	Chronic respiratory diseases Yes	Diabetes mellitus Yes	Chronic cardiovascular diseases Yes
Overall	3 012 (23.46)	1 805 (14.06)	7 377 (57.46)
Sex			
Male	2 166 (23.93)	1 375 (15.19)	5 391 (59.55)
Female	846 (22.35)	430 (11.36)	1 986 (52.46)
Age group			
<50 years	69 (10.73)	21 (3.27)	83 (12.91)
50-59 years	399 (16.49)	181 (7.48)	856 (35.39)
60-69 years	920 (23.66)	595 (15.30)	2 129 (54.74)
70-79 years	1 077 (27.73)	683 (17.58)	2 743 (70.62)
≥80 years	547 (27.30)	325 (16.22)	1 566 (78.14)
WHO performance status			
0 – Fully active, able to carry on all pre-disease performance without restriction	306 (21.16)	177 (12.24)	815 (56.36)

Characteristics (N (%))	Chronic respiratory diseases Yes	Diabetes mellitus Yes	Chronic cardiovascular diseases Yes
1 – Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work	1 494 (22.18)	891 (13.23)	3 701 (54.95)
2 – Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours	350 (24.37)	237 (16.50)	866 (60.31)
3 – Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours	157 (27.40)	90 (15.71)	366 (63.87)
4 – Completely disabled; cannot carry on any selfcare; totally confined to bed or chair	64 (32.82)	28 (14.36)	112 (57.44)
Missing	641 (26.12)	382 (15.57)	1 517 (61.82)
Region			
Brussels-Capital Region	222 (22.16)	150 (14.97)	537 (53.59)
Flemish Region	1 661 (22.41)	981 (13.24)	4 232 (57.10)
Walloon Region	1 129 (25.51)	674 (15.23)	2 608 (58.92)
Histological subtype			
Non-Small Cell lung cancer	2 171 (22.11)	1 320 (13.45)	5 500 (56.03)
Small Cells lung cancer	468 (23.35)	318 (15.87)	1 175 (58.63)
Other specified lung cancer	373 (36.64)	167 (16.40)	702 (68.96)
Clinical tumour size (TNM)			
T1	572 (31.12)	243 (13.22)	1 099 (59.79)
T2	618 (21.54)	416 (14.50)	1 624 (56.61)
T3	412 (21.88)	255 (13.54)	1 053 (55.92)

Characteristics (N (%))	Chronic respiratory diseases Yes	Diabetes mellitus Yes	Chronic cardiovascular diseases Yes
T4	454 (20.69)	286 (13.04)	1 197 (54.56)
NS	735 (24.04)	476 (15.57)	1 857 (60.75)
X	221 (22.14)	129 (12.93)	547 (54.81)
Combined stage*			
I	584 (33.93)	256 (14.88)	1 055 (61.30)
II	236 (24.71)	123 (12.88)	537 (56.23)
III	652 (24.71)	360 (13.64)	1535 (58.17)
IV	994 (18.84)	717 (13.59)	2 840 (53.84)
X	540 (24.31)	343 (15.44)	1 393 (62.72)
NA	6 (21.43)	6 (21.43)	17 (60.71)

** Combined stage: compilation of pathological stage and clinical stage. Pathological stage prevails over clinical stage, except when clinical stage is IV.*

8.4 Discussion

This study has demonstrated that pharmaceutical data provide a valid approach to measure three major comorbidities among lung cancer patients (cardiovascular diseases, respiratory diseases and diabetes mellitus), and failed to do so for a fourth one (renal insufficiency). The measure of agreement was very good for diabetes mellitus and good to moderate for chronic cardiovascular diseases and chronic respiratory diseases. The positive and negative predictive values were relatively high for these 3 comorbid conditions and suggested a good ability to detect a lung cancer patient with comorbid conditions as to exclude patients without comorbid condition. Nevertheless, renal insufficiency showed poor agreement between medical files and administrative data (pharmaceutical and administrative billing database). The basic assumption to identify comorbidity from pharmaceutical data was not fulfilled for this comorbid condition, since patients with renal insufficiency were generally not treated with drugs and cannot be identified in the pharmaceutical database. In addition, the administrative billing database did not improve the validation score. The decision was thus to exclude the renal insufficiency of the subsequent analyses.

Some selected comorbidities (chronic respiratory diseases and cardiovascular diseases) are very common among people diagnosed with lung cancer. We identified 23.5% of patients using drugs for respiratory disease before or at the time of the diagnosis of lung cancer. These findings are in line with other studies estimating prevalence of chronic diseases (Table 18). A higher proportion of patients having cardiovascular disease was found. Not surprisingly and in line with several studies, the analysis

shows that respiratory diseases affected all ages, but with an increase in older age groups.[65,48] Another interesting fact in this validation study is that respiratory drugs users were more often identified in early stage of the disease than in more advanced stages. A possible explanation is that some lung cancers are diagnosed earlier because they are found fortuitously after diagnostic tests performed for other respiratory medical conditions (such as a chest x-ray or chest CT scan). In this case, survival analysis can be biased due to lead time. Lead time is the time gained in treating or controlling a disease when detection is earlier than usual (e.g. in the pre-symptomatic stage). This early detection of lung cancers will appear to artificially improve survival independently of treatment effectiveness.

The main strength of this approach, using pharmaceutical consumption data rather than medical files, is its independence from the hospitals where patients are treated for lung cancer. In fact, the drugs were generally prescribed by general practitioners before the diagnosis of lung cancer. In contrast to hospitalisation database where comorbidities are coded by hospital data managers. The quality and validity of this information depend on the coding practice of the data manager. These approaches have been tested with success in several studies but are time and cost consuming for population-based studies.[43, 48, 66-69]

Our study has also several limitations, some of which are specific to our design, and others are related to the nature of pharmaceutical data, as already described by other authors. First, the registration of comorbidities from medical files was considered as the 'gold standard'. Nevertheless, a variability in case definition between hospitals and observers cannot be excluded. The user manual was developed to reduce this bias. A double blind review should be the best way to improve the accuracy of the medical file registration but the cost in time and the burden of registration was too high for this validation phase. A part of the variability between hospitals for the K statistic could be explained by this limitation. The second limitation is, as already described in the literature, that some diseases cannot be differentiated because the same drugs are used for these diseases.[51] For example, it appeared very difficult to distinguish asthma and COPD, or hypertension from some other cardiovascular diseases. Using pharmaceutical data to identify a specific disease implies that those drugs are used exclusively for the treatment of that disease. Furthermore, the drugs identified must be used at any stage of the disease in order to be able to identify the disease whatever its stage. For example, moderate renal diseases are not treated and cannot be identified in pharmaceutical database although they have an influence on the management of lung cancer patients as confirmed by the experts accompanying the present study. A difficulty regarding the respiratory disease is to differentiate treatment for chronic respiratory disease and treatment for symptoms of lung cancer around the diagnosis date as the same organ is impacted.

In conclusion, this study showed that pharmaceutical data may be a valuable source for identifying and measuring three main comorbidities for lung cancer population-based study, when these data are not otherwise available at a population level. These comorbid conditions may contribute to risk adjustment modelling of quality indicators.

9 LUNG CANCER PATIENTS IN 2010-2011: DESCRIPTIVE STATISTICS

9.1 Baseline demographics and tumour characteristics

9.1.1 Patient characteristics

Lung cancer occurs more frequently in men (70.5%) and in older patients. The mean age at diagnosis is 67.7 years old (median 68 years), with 46% of patients who were at least 70 years old at diagnosis. The majority of patients (64.7%) was symptomatic but completely ambulatory (WHO definition). More details on patient characteristics can be found in Table 22.

9.1.2 Tumour characteristics

Table 23 summarizes the tumour characteristics (tumour localisation, laterality, clinical, pathological and combined stage) of the population included in the analysis. For more than half of the patients (with known stage), the tumour had already metastasized at the time of diagnosis (cIV, 52%). The distribution of clinical stage by tumour type is shown in Figure 23.

Because the c-stage (clinical stage) and/or p-stage (pathological stage) is lacking for many patients, a combined stage is calculated for each patient. To determine this combined stage, known p-stage prevails over known c-stage, except when there is clinical proof of distant metastasis. When only c-stage is known, this is considered as the combined stage. Otherwise, when p-stage and c-stage are unknown, the combined stage also remains unknown, which is the case for 17% of the patients.

Further details on lymph node status for each stage can be found in Table 24 and Table 25.

Table 22 – Descriptive patient characteristics at diagnosis (lung cancer incidence 2010-2011)

	All patients (N = 12 839)		NSCLC (N = 9 817)		SCLC (N = 2 004)	
	n	%	n	%	n	%
Sex						
Male	9 053	70.5	6 904	70.3	1 413	70.5
Female	3 786	29.5	2 913	29.7	591	29.5
Age group						
Mean, SD (years)	67.7	SD 11.1	67.0	10.9	67.0	10.3
<50 years	643	5.0	547	5.6	73	3.6
50-59 years	2 419	18.8	1 931	19.7	420	21.0
60-69 years	3 889	30.3	3 058	31.2	669	33.4
70-79 years	3 884	30.3	2 981	30.4	600	29.9
80+ years	2 004	15.6	1 300	13.2	242	12.1
WHO performance status						
0 – Asymptomatic	1 436	11.2	1 163	11.8	144	7.2
1 – Symptomatic but completely ambulatory	6 685	52.1	5 232	53.3	1 016	50.7
2 – Symptomatic, up and about more than 50% of waking hours	1 429	11.1	986	10.0	275	13.7
3 – Symptomatic, confined to bed or chair more than 50% of waking hours	570	4.4	359	3.7	89	4.4
4 – Completely disabled; totally confined to bed or chair	194	1.5	113	1.2	34	1.7
Missing	2 525	19.7	1 964	20.0	446	22.3

Table 23 – Descriptive tumour characteristics (lung cancer incidence 2010-2011)

	All patients (N = 12 839)		NSCLC (N = 9 817)		SCLC (N = 2 004)	
	n	%	n	%	n	%
Tumour localisation						
C34.0 Main Bronchus	773	6.0	501	5.1	231	11.5
C34.1 Upper Lobe, lung	4 699	36.6	3 669	37.4	619	30.9
C34.2 Middle Lobe, lung	448	3.5	344	3.5	65	3.2
C34.3 Lower Lobe, lung	2 399	18.7	1 930	19.7	295	14.7
C34.8 Overlapping lesion of lung	34	0.3	22	0.2	5	0.2
C34.9 Lung, NOS	4 486	34.9	3 351	34.1	789	39.4
Tumour laterality						
Left	4 847	37.8	3 662	37.3	778	38.8
Right	6 553	51.0	5 083	51.8	948	47.3
Unknown	1 439	11.2	1 072	10.9	278	13.9
Clinical stage*						
X*	3 002	23.4	2 229	22.7	583	29.1
Non missing:						
I	1 412	14.4	1 107	14.6	48	3.4
II	748	7.6	619	8.2	69	4.9
III	2 535	25.8	1 987	26.2	378	26.6
IV	5 142	52.3	3 875	51.1	926	65.2
Pathological stage[$]						

	All patients (N = 12 839)		NSCLC (N = 9 817)		SCLC (N = 2 004)	
X*	441	20.3	384	18.4	17	36.2
Non missing:						
I	972	56.2	952	56.0	20	66.7
II	481	27.8	475	27.9	6	20.0
III	234	13.5	230	13.5	3	10.0
IV	44	2.5	43	2.5	1	3.3
Combined stage*, **						
X*	2 249	17.5	1 516	15.4	544	27.1
Non missing:						
I	1 721	16.3	1 415	17.0	50	3.4
II	955	9.0	826	10.0	69	4.7
III	2 639	24.9	2 073	25.0	394	27.0
IV	5 275	49.8	3 987	48.0	947	64.9

**X (missing) category includes 28 tumours with staging not applicable (NA). The % for stages I, II, III and IV are computed excluding the X category.*
*** Combined stage combines information from the clinical and pathological stage. The pathological stage prevails over the clinical stage except when the clinical stage is stage IV.*
$ For 2 172 operated patients only. X (missing) category includes 10 tumours with staging not applicable (NA).

Figure 23 – Distribution of clinical stage by lung cancer type (incidence 2010-2011)

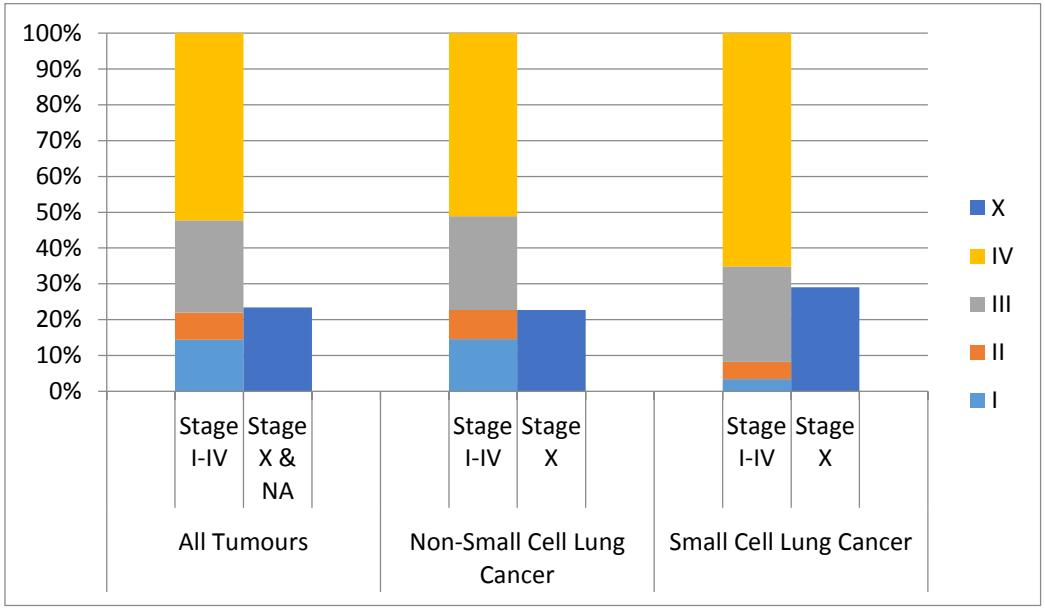


Table 24 – Lymph node status by clinical stage

Clinical stage	cN0	cN1	cN2	cN3	cNX	Total
I	1 233				179	1 412
II	367	282			99	748
III	188	183	1 393	679	92	2 535
IV	470	385	1 729	1 419	1 139	5 142
X					2 974	2 974
TNM not applicable						28
Total	**2 258**	**850**	**3 122**	**2 098**	**4 483**	**12 839**

Table 25 – Lymph node status by pathological stage, for operated patients

Pathological stage	pN0	pN1	pN2	pN3	pNx	Total
I	908				64	972
II	222	247			12	481
III	28	77	122	4	3	234
IV	23	9	5		7	44
X					441	441
Total	**1 181**	**333**	**127**	**4**	**527**	**2 172**

For 1 945 patients, both clinical and pathological stage were known at BCR. Pathological stage was identical to clinical stage for 1 326 patients (68.1%) (Table 26).

Following the TNM classification, a pTNM is only assigned after the tumour has been surgically resected. However, in daily practice, pN category is also often assigned based on cytology/histology of lymph nodes only.

Table 26 – Consistency between clinical and pathological staging for NSCLC patients diagnosed 2010-2011

Clinical stage				Pathological stage							
		p-stage missing	**p-stage reported**	pI		pII		pIII		pIV	
	N	N	N	n	%	n	%	n	%	n	%
cI	1 107	421	686 (100%)	**508**	**74.1%**	117	17.1%	53	7.7%	8	1.2%
cII	619	336	283 (100%)	63	22.3%	**154**	**54.4%**	58	20.5%	8	2.8%
cIII	1 987	1 610	377 (100%)	62	16.4%	66	17.5%	**229**	**60.7%**	20	5.3%
cIV	3 875	3 276	599 (100%)	36	6.0%	22	3.7%	106	17.7%	**435**	**72.6%**
Total known c-stage	7 588	5 643 (74.3%)	1 945								
cX	2 229	1516	713 (100%)	361	50.6%	153	21.5%	123	17.3%	76	10.7%
Total	9 817	7159									

Note: % of cases where clinical and pathological are consistent are indicated in bold.

9.1.3 Histopathology

Lung cancer is typically divided into two types: small cell lung cancer (SCLC, 15.6%) and non-small cell lung cancer (NSCLC, 76.5%). For this last type, different subtypes are further identified, with the two most common being adenocarcinoma (40.1% of the whole cohort) and squamous cell carcinoma (24.5%).

As shown in Table 27, 7.7% of the patients are classified as 'unspecified malignant neoplasms' because one of the following reasons:

- Clinical diagnosis only (thus no microscopic confirmation of the diagnosis)
- Malignancy confirmed by cytology but no further specification of histological type
- Pathology report and MDT report confirm malignant disease but give no further indication on histology

In all analyses, the "all patient" group includes NSCLC, SCLC, other histology (e.g. sarcoma) and unspecified malignant neoplasms.

Table 27 – Histopathological diagnosis of included tumours*

	Total (N = 12 839)	
	n	%
Small cell lung cancer	**2004**	**15.6**
Non-small cell lung cancer	**9817**	**76.5**
Squamous cell carcinoma	3144	24.5
Adenocarcinoma	5152	40.1
Large cell carcinoma	550	4.3
Other specified carcinoma	387	3.0
Unspecified non-small cell lung cancer	584	4.5
Other types of lung cancer	**28**	**0.2**
Sarcoma	16	0.1
Other specified malignant neoplasm	12	0.1
Unspecified malignant neoplasm	**990**	**7.7**

**For the list of ICD-O-3 morphology codes, we refer to appendix*

9.2 Diagnostic and staging procedures

An overview of the most common diagnostic and staging procedures in the diagnostic work up of lung cancer, within 3 months before and 3 months after the incidence date, is reported in Table 28.

Imaging is an important technique to diagnose lung cancer, and is an important element in treatment decisions. While local imaging (RX thorax) is usually the first diagnostic exam where the tumour is discovered, global imaging techniques allow the search for possible metastases of the tumour. The most frequent imaging exams performed were CT (98.5%), RX thorax (93.9%), imaging of the brain (77.0%), and PET-CT (60.2%).

The most commonly performed endoscopic procedures were bronchoscopy (77.7%), gastrointestinal endoscopy (19.8%) and EBUS (15.0%). Mediastinoscopy was performed in 8.2% of the patients.

9.3 Main therapeutic procedures

Most frequently used therapeutic interventions were chemotherapy or targeted therapy (34.8%), radiotherapy with or without chemotherapy (24.0%) and surgery (16.9%) with or without (neo)-adjuvant therapy (Table 29).

Approximately 24% of patients received no surgery, no radiotherapy with curative intent and no systemic therapy (Table 30).

An overview of the chemotherapy and targeted therapy used can be found in Table 31 and Table 32 respectively.

Table 28 – Descriptive statistics of diagnostic and staging procedures performed within 3 months around the incidence date*$

Category	All patients (N = 12 839)		NSCLC (N = 9 817)		SCLC (N = 2 004)	
	n	%	n	%	n	%
Multidisciplinary Team Meeting	10 256	79.9	7 881	80.3	1 566	78.1
Imaging						
RX thorax	12 056	93.9	9 254	94.3	1 886	94.1
CT	12 642	98.5	9 676	98.6	1 973	98.5
MRI	501	3.9	402	4.1	77	3.8
Brain imaging (CT and/or MRI)	9 886	77.0	7 603	77.4	1 717	85.7
CT Brain	7 999	62.3	6 117	62.3	1 389	69.3
MRI Brain	3 752	29.2	2932	29.9	677	33.8
PET-CT	7 730	60.2	6 355	64.7	916	45.7
Bone scan	4831	37.6	3 651	37.2	916	45.7
Other scintigraphy	1 577	12.3	1 303	13.3	184	9.2
Pulmonary function test	9 442	73.5	7 469	76.1	1 381	68.9
Punction biopsy pulmonary lesion or pleura biopsy	3 390	26.4	2 964	30.2	309	15.4
Endoscopy						
Bronchoscopy	9 977	77.7	7 817	79.6	1 641	81.9
Tracheoscopy	1 169	9.1	954	9.7	164	8.2
EBUS and/or EUS	2 300	17.9	1 891	19.3	328	16.4
EBUS	1 930	15.0	1 596	16.3	267	13.3
EUS	470	3.7	385	3.9	69	3.4

Category	All patients (N = 12 839)		NSCLC (N = 9 817)		SCLC (N = 2 004)	
Mediastinoscopy	1 058	8.2	939	9.6	87	4.3
Gastro-Intestinal endoscopy	2 541	19.8	1 927	19.6	436	21.8
Exploratory surgery						
Exploratory thoracotomy	296	2.3	267	2.7	22	1.1
Histopathology						
Histological diagnosis	11 171	87.0	8 924	90.9	1 826	91.1
Cytology	10 620	82.7	8 398	85.5	1 695	84.6
Predictive test anti-EGFR therapy						
IHC EGFR (RIZIV/INAMI code 588976- 588980)	3 313	25.8	3 236	33.0	61	3.0
Molecular test (any)	2 205	17.2	2 171	22.1	22	1.1
article 33	1 298	10.1	1 270	12.9	18	0.9
article 33bis	992	7.7	986	10.0	4	0.2

** For included RIZIV – INAMI nomenclature codes, we refer to the appendices of the supplementary document (available on our website).*
$ From 3 months before to 3 months after incidence date

Table 29 – Descriptive statistics of main therapeutic procedures (primary treatment) for patients diagnosed in 2010-2011*§

Category	All patients (N = 12 839)		NSCLC (N = 9 817)		SCLC (N = 2 004)	
	n	%	n	%	n	%
Primary treatment						
Major Surgery with curative intent	2 172	16.9	2 084	21.2	47	2.3
Total or partial lung excision with lymphadenectomy (227216/-20)	1 677	13.1	1 618	16.5	34	1.7
Total or partial lung excision (227253/-64)	404	3.1	367	3.7	17	0.8
Resection with anastomosis of bronchus or trachea (227275/-86)	139	1.1	135	1.4	2	0.1
Neo-adjuvant or adjuvant treatment						
None	1 270	9.9	1 225	12.5	11	0.6
Neo-adjuvant chemotherapy	216	1.7	211	2.1	5	0.2
Adjuvant chemoradiotherapy	92	0.7	80	0.8	11	0.5
Adjuvant chemotherapy	600	4.7	574	5.8	20	1.0
Adjuvant radiotherapy	68	0.5	67	0.7	1	0.0
Primary (chemo)radiotherapy (no major surgery)	2 634	20.5	2 001	20.4	449	22.4
Category 2 (2D)	277	2.2	208	2.1	50	2.5
Category 3 (3D)	1 781	13.9	1 335	13.6	341	17.0
Category 4 (IMRT)	576	4.5	458	4.7	58	2.9
Chemoradiotherapy	1 828	14.2	1 379	14.0	430	21.5
Radiotherapy alone	806	6.3	622	6.3	19	0.9

Category	All patients (N = 12 839)		NSCLC (N = 9 817)		SCLC (N = 2 004)	
Primary chemotherapy or targeted treatment (no major surgery, no (chemo)radiotherapy)	4 919	38.3	3 692	37.6	1 184	59.1
Other treatment						
Other treatments						
Thoracotomy with attempt of excision	26	0.2	25	0.3	1	0.0
Other codes for surgery£	133	1.0	122	1.2	6	0.3
Radiotherapy (no timeframe)) (category 1) (Palliative)	2 576	20.1	1 851	19.2	604	30.1
Only patients died before 1/01/2013	*2 230*	*24.5*	*1 665*	*24.7*	*485*	*29.2*
No treatment						
No surgery with curative intent, no radiotherapy with curative intent, no chemotherapy or targeted treatment received	3 114	24.3	2 040	20.8	324	16.2
No surgery with curative intent, no radiotherapy with curative or palliative intent, no chemotherapy or targeted treatment received	2 706	21.1	1 723	17.6	301	15.0

** For included RIZIV – INAMI nomenclature codes, we refer to the appendices of the supplementary document (available on our website). §This table presents procedures performed within 9 months after incidence date unless stated otherwise*
£nomenclature codes 227194/-205, 227334/-45, 227570/-81, 228115/-26, 259033/-44

Table 30 – Characteristics of lung cancer patients who received no surgery, no radiotherapy with curative intent and no chemotherapy or targeted treatment (incidence 2010-2011)

	All patients (N = 3 114)		NSCLC (N = 2 040)		SCLC (N = 324)	
	n	%	n	%	n	%
Sex						
Male	2 238	71.9	1 469	72.0	233	71.9
Female	876	28.1	571	28.0	91	28.1
Age group						
Mean, SD (years)	74.0	SD 10.9	72.8	11.0	73.3	10.4
<50 years	69	2.2	50	2.5	4	1.2
50-59 years	297	9.5	230	11.3	36	11.1
60-69 years	571	18.3	416	20.4	67	20.7
70-79 years	1 025	32.9	701	34.4	109	33.6
80+ years	1 152	37.0	643	31.5	108	33.3
WHO performance status						
0 – Asymptomatic	183	5.9	106	5.2	10	3.1
1 – Symptomatic but completely ambulatory	1 115	35.8	743	36.4	78	24.1
2 – Symptomatic, up and about more than 50% of waking hours	542	15.8	346	17.0	56	17.3
3 – Symptomatic, confined to bed or chair more than 50% of waking hours	370	11.9	220	10.8	36	11.1
4 – Completely disabled; totally confined to bed or chair	147	4.7	77	3.8	23	7.1
Missing	757	24.3	548	26.9	121	37.3
Vital status (at 31/12/2014)						
Alive	191	6.1	92	4.5	6	1.9

	All patients (N = 3 114)		NSCLC (N = 2 040)		SCLC (N = 324)	
Dead	2 920	93.8	1947	95.4	316	97.5
Lost to follow-up	3	0.1	1	0.0	2	0.6
Survival length in days: Median and P25-P75 (Follow-up until 31/12/2014)	50	19-157.5	50	21-145	22.5	9-61.5

Table 31 – Overview of chemotherapy products (-1m<inc<+9m) for NSCLC patients

		Combined stage			Total
Product ATC-code	**Product name**	**I-III (N = 4 314)**	**IV (N = 2 073)**	**X (N = 1 516)**	**Total (N = 9 817)**
Chemotherapy					
L01AA01	Cyclophosphamide	6	7	2	15
L01AA02	Chlorambucil	2	1	0	3
L01AA03	Mephalan	0	2	0	2
L01AA06	Ifosfamide	52	18	4	74
L01BA04	Pemetrexed	412	1 243	273	1 928
L01BB02	Mercaptopurine	1	0	1	2
L01BB03	Tioguanine	0	1	0	1
L01BC01	Cytarabine	1	1	0	2
L01BC02	Fluorouracil	9	12	4	25
L01BC05	Gemcitabine	758	949	273	1 980
L01CA01	Vinblastine	1	2	0	3
L01CA02	Vincristine	0	4	1	5
L01CA03	Vindestine	0	0	1	1
L01CA04	Vinorelbine	932	730	206	1 868

		Combined stage			Total
L01CB01	Etoposide	216	97	65	378
L01CD01	Paclitaxel	0	5	1	6
L01CD02	Docetaxel	305	554	144	1 003
L01DB01	Doxorubicin	4	8	4	16
L01DB03	Epirubicin	3	5	2	10
L01DB07	Mitoxantrone	0	2	0	2
L01DC01	Bleomycin	0	12	2	14
L01DC03	Mitomycin	12	6	0	18
L01XA01	Cisplatin	1 779	1 887	523	4 189
L01XA02	Carboplatin	553	893	237	1 683
L01XA03	Oxaliplatin	0	1	1	2
L01XD03	Methyl aminolevulinate	1	0	0	1
L01XD04	Aminolevulinic acid	0	2	1	3
L01XX05	Hydroxycarbamide	5	5	3	13
L01XX11	Estramustine	1	0	0	1
L01XX17	Topotecan	1	7	0	8
Targeted therapy					
L01XC02	Rituximab	1	1	1	3
L01XC03	Trastuzumab	0	1	1	2
L01XC06	Cetuximab	0	1	0	1
L01XC07	Bevacizumab	0	0	1	1
L01XE01	Imatinib	0	1	0	1

		Combined stage			Total
L01XE02	Gefitinib	18	110	23	151
L01XE03	Erlotinib	227	607	137	971
All patients receiving chemotherapy or targeted therapy		2 254	2 762	784	5 800

Table 32 – Overview of chemotherapy products (-1m<inc<+9m) for SCLC patients

		Combined stage			
product ATC-code	product name	I-III (N = 513)	IV (N = 947)	X (N = 544)	Total (N = 2 004)
Chemotherapy					
L01AA01	Cyclophosphamide	11	49	25	85
L01AA02	Chlorambucil	1	0	0	1
L01AA06	Ifosfamide	1	8	2	11
L01BA04	Pemetrexed	0	3	3	6
L01BC02	Fluorouracil	1	4	1	6
L01BC05	Gemcitabine	5	8	3	16
L01CA02	Vincristine	17	48	22	87
L01CA03	Vindestine	2	7	3	12
L01CA04	Vinorelbine	5	6	2	13
L01CB01	Etoposide	444	785	393	1.622
L01CD01	Paclitaxel	0	0	1	1
L01CD02	Docetaxel	1	3	4	8
L01DB01	Doxorubicin	8	38	19	65
L01DB03	Epirubicin	6	23	11	40
L01DC01	Bleomycin	0	0	1	1

		Combined stage			
L01DC03	Mitomycin	1	1	0	2
L01XA01	Cisplatin	276	269	186	731
L01XA02	Carboplatin	228	564	241	1 033
L01XA03	Oxaliplatin	0	1	0	1
L01XX05	Hydroxycarbamide	3	0	0	3
L01XX11	Estramustine	0	1	0	1
L01XX17	Topotecan	33	176	54	263
L01XX19	Irinotecan	0	3	0	3
Targeted therapy					
L01XC02	Rituximab	0	1	0	1
L01XC06	Cetuximab	0	1	0	1
L01XE02	Gefitinib	0	1	0	1
L01XE03	Erlotinib	1	2	0	3
L01XX32	Bortezomib	0	1	0	1
All patients receiving chemotherapy or targeted therapy		456	798	398	1 652

10 IMPACT OF HOSPITAL VOLUME ON PATIENTS TREATMENT AND OUTCOME

This chapter aims to answers the following questions:

1. Do NSCLC patients operated in hospitals which perform more often lung cancer surgery (high-volume centres, or specialized centres) have better outcomes? (section 10.1)
2. Do lung cancer patients treated with radiotherapy in high-volume radiotherapy centres have better outcomes? (section 10.2)
3. Are there differences in survival and treatments given between low- and high-volume centres, based on the number of patients diagnosed per year (diagnostic volume)? (sections 10.3 and 10.4)

10.1 Impact of surgical volume on outcomes

10.1.1 Introduction

The question whether there is a relationship between the hospital's surgical volume and outcomes for operated lung cancer patients was raised by the guideline development group (GDG) when developing the KCE guideline (KCE report 206, 2013).[3] In the guideline, it was recommended that lung cancer surgery should be performed in surgical high-volume centres specialised in thoracic surgery, which is a weak recommendation based on low level of evidence, according to the GRADE system.

10.1.2 Methods

Patients included in the analyses

Only NSCLC patients with unique tumours who underwent thoracic surgery with curative intent were included in the cohort and the analyses below.

Definition of hospital surgical volume

To determine the surgical volume of each hospital, patients with multiple tumours were also counted; the hospital's surgical volume was thus based on the number of unique patients diagnosed with lung cancer between 2009-2011 undergoing surgery with curative intent within 9 months after incidence during the years 2010-2011. The annual surgical volume of each hospital was then calculated dividing this result in two.

Centres were categorised, based on expert opinion and the need to have a balanced repartition of centres and patients over the categories, as follows:

- Very low-volume centres: less than 10 patients per year
- Low-volume centres: between 10 and 19 patients per year
- Medium-volume centres: between 20 and 39 patients per year
- High-volume centres: at least 40 patients per year

Of note, the definition of these categories is based on the Belgian data and differs from definitions used in other countries. For example, in a UK study, low-volume hospitals performed less than 70 interventions per year.[18]

Statistical models

Statistical modelling was used to assess the relation between volume and outcomes, adjusted for potential confounders.

Surgical volume was treated as primary exposure, all potential confounders identified beforehand were included in the model. Potential confounders were: sex, age group, histological subtype, sub-localization, combined stage, number of days of hospitalization prior to lung cancer diagnosis, WHO performance status and comorbidities (chronic respiratory disease, cardiovascular disease and diabetes mellitus).

While it is more usual to speak about short-term and medium-term survival, all results were reported as probability to die 60 days after the main treatment (surgical resection or radiotherapy), or 1 year or 3 years after diagnosis.

Type of modelling differed per outcome:

- For 60-day mortality, logistic regression on odds ratios was performed. Univariate and multivariate logistic regression models (with 95% confidence intervals) were fitted to determine the relation between hospital volume and 60-day mortality after thoracic surgery (or radiotherapy), adjusted for potential confounders.
- For 1-year and 3-year survival, multivariate analyses using Cox proportional hazard models for overall (observed) survival were performed. Schoenfeld residuals were used to detect departures from the proportional hazards assumption. The Efron approximation was used in case of tied survival times. In case of missing data in some covariates of the multivariate analysis, a categorical value was created (e.g. Stage 'X' for missing value of combined stage).

In the primary analysis, surgical volume was treated as a categorical variable in 4 categories (see above). Sensitivity analyses were performed by dichotomising the volume into low volume (<20/year) versus medium/high volume (at least 20 per year). Additional post hoc analyses were performed on the request of the expert group, where the volume variable was modelled continuously, with a knot at 10 interventions per year.

Interaction effects
Interaction was not assessed and no interaction terms were included in the models. The Wald test was used for type3 tests and for the confidence intervals in the models. Presence of confounding was assessed by comparing the crude and adjusted effect measures, odds ratios or hazard ratios depending on the type of outcome measured.

Intra hospitals correlations
To study whether intra-hospital correlations have an influence on the volume-outcome effect, models were performed taking into account these correlations; a GEE model for 60 day mortality and frailty models for survival. However, intra-hospital correlation was very low. Exchangeable Working Correlation of 0.000964 for the GEE model on 60-day post-operative mortality and covariance parameters close to zero in the frailty models for 1 year (REML estimate 0.03200, standard error 0.05504) and 3-year survival (REML estimate 0.000651, standard error 0.01726). However, multiple problems arose with these models (converging of the models, complexity). Additionally, parameters were close to the estimations provided by the logistic and cox regressions without adjutment for intra-hospital correlation. Therefore, the additional complexity of these models taking intra-hospital correlations into account was not justified and the models without this correlation are presented.

General remark on confounders:
Note that the models are constructed to assess the relationship between volume and outcome, adjusted for confounders. The models are not developed to assess in depth the relationship between the outcome and the confounders. The estimated effects for these confounders are therefore not discussed in this chapter.

10.1.3 Results

Surgical Volume

During the period 2010-2011, 89 hospitals performed surgery for lung cancer. The annual surgical volume per centre is illustrated in Figure 24. The majority of hospitals are low-volume centres, with half of the centres being very low-volume centres (< 10 operations per year) and only 9 centres being high-volume (i.e. ≥40 operations per year).

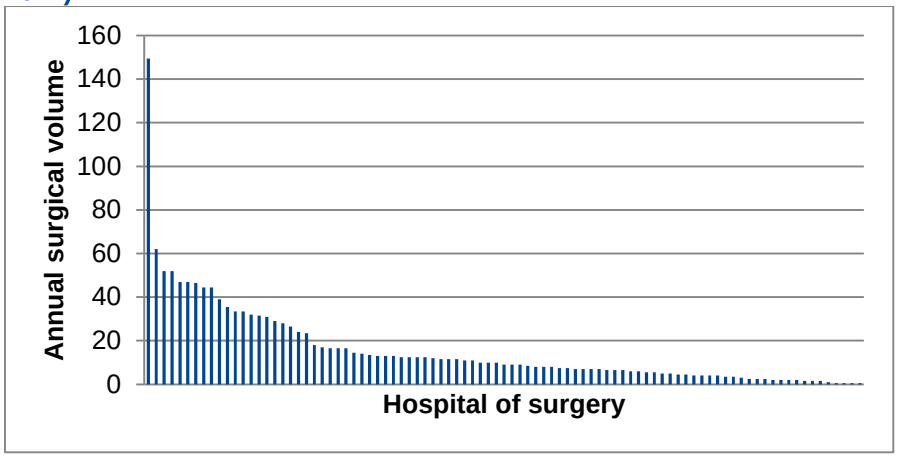
Sex, age, histology, comorbidities, WHO score and days of hospitalisation one year before the lung cancer diagnosis are similar whatever the surgical volume of the centres. High volume centres have a worse stage mix compared to very-low volume centres (less combined stage I, more stage II and III), they had less unknown stage than lowest volume centres but higher than the middle category. We find some differences in type of surgery performed (e.g. total or partial lung resection with/without retroperitoneal gland dissection) but there is no clear pattern (Table 33). In general, statistical models confirmed the presence of a negative confounding factor: taking into account the case-mix increased the differences observed in outcomes between low and high-volume centres (see below).

Outcomes

Overall survival at 1, 2 and 3-year of NSCLC patients operated is respectively 88.3%, 77.5% and 68.9%. Those results stratified by patients and tumour characteristics are presented in Appendix 3.1.1.

Table 34 presents the mortality and survival results at three time points, by hospitals' annual surgical volume.

Figure 24 – Annual surgical volume for lung cancer patients* (2010-2011)



** All lung cancer patients (including patients with multiple tumours) diagnosed in 2009-2011 with surgery in 2010-2011 within timeframe (-1m≤incidence≤+9m)*
Source: BCR-IMA-AIM

Table 33 – Differences in case mix of NSCLC patients who underwent surgical intervention, by surgical volume category

	Annual surgical volume of centres (2010-2011)				
	Very low (<10 per year)	Low (10-19 per year)	Medium (20-39 per year)	High (≥40 per year)	Total
N of hospitals	44	24	12	9	**89**
N of patients (100%)	306	474	534	770	**2 084**
Sex (%)					
Males	69.3	67.9	65.0	67.9	**67.4**
Females	30.7	32.1	35.0	32.1	**32.6**
Age (mean)	64.2	64.2	63.9	64.5	**64.2**
<50 years (%)	7.8	6.5	5.8	6.4	**6.5**

50-59 years (%)	22.5	25.5	24.5	21.8	**23.5**
60-69 years (%)	35.9	35.4	38.4	39.0	**37.6**
70-79 years (%)	28.4	28.7	28.3	28.8	**28.6**
80+ years (%)	5.2	3.8	3.0	4.0	**3.9**
Histological subtype					
Adenocarcinoma	47.4	54.4	56.0	51.0	**52.5**
Squamous cell carcinoma	38.9	31.2	33.7	36.8	**35.0**
Large cell carcinoma	3.6	3.0	1.9	3.2	**2.9**
Other*	10.1	11.4	8.4	9.0	**9.5**
Clinical stage (%)**					
I	59.6	53.2	58.1	45.9	**52.4**
II	16.3	23.7	21.5	25.4	**22.9**
III	18.0	16.9	15.0	21.6	**18.4**
IV	6.2	6.2	5.4	7.1	**6.3**
Unknown	41.8	31.4	33.9	29.0	**32.7**
Pathological stage (%)**					
I	64.2	56.4	54.4	53.9	**56.0**
II	25.4	29.7	29.1	26.9	**27.9**
III	8.2	12.2	13.4	16.5	**13.5**
IV	2.2	1.8	3.1	2.7	**2.5**
Unknown	24.2	15.4	16.3	19.5	**18.4**
Combined stage (%)**					
I	61.4	53.2	53.0	48.3	**52.5**

II	23.8	27.6	27.7	25.9	**26.5**
III	10.1	13.6	13.8	19.4	**15.3**
IV	4.7	5.6	5.6	6.4	**5.8**
Unknown	9.5	2.1	6.0	4.3	**5.0**
Comorbidities					
Chronic respiratory disease (% Yes)	33.3	30.4	26.8	27.5	**28.8**
Cardiovascular disease (% Yes)	54.9	55.5	54.9	54.2	**54.8**
Diabetes mellitus (% Yes)	12.4	11.8	15.0	10.8	**12.3**
Days of hospitalization one year before incidence date lung cancer (%)					
None	66.0	68.6	70.0	68.4	**68.5**
1-5 days	18.6	19.0	20.4	21.4	**20.2**
6-15 days	10.8	7.4	5.4	6.5	**7.1**
More than 15 days	4.6	5.1	4.1	3.6	**4.2**
WHO performance status (%)					
0 – Asymptomatic	25.2	24.9	27.0	23.9	**25.1**
1 – Symptomatic but completely ambulatory	47.4	58.9	45.7	56.2	**52.8**
2 – Symptomatic, <50% in bed during the day	2.3	1.9	2.6	2.2	**2.3**
3 – Symptomatic, confined to bed or chair more than 50% of waking hours	0.7	0.2	0.4	0.3	**0.3**

4 – Completely disabled; totally confined to bed or chair	0.3	0.0	0.4	0.3	**0.2**
Missing	24.2	14.1	24.0	17.1	**19.2**
Type of surgery					
227220	73.9	82.3	71.5	77.5	**76.5**
227264	20.9	14.1	26.0	11.2	**17.1**
227286	5.2	3.6	2.4	11.3	**6.4**

**include Large cell carcinoma, other specified carcinoma, Unspecified Non-Small Cell Lung Cancer*
***Unknown stage (X) is excluded to calculate the percentages for stage I, II, III, IV.*
Billing codes:

227220 = Total or partial lung resection with retroperitoneal gland dissection
227264 = Total or partial lung resection
227286 = Resection of major bronchus or trachea with anastomosis (bronchus-bronchus or trachea-bronchus) with thoracotomy

Table 34 – Observed survival of operated Non-Small Cell Lung Cancer patients by annual surgical volume (N=2 084)

	60-day mortality		1-year observed survival (%)		3-year observed survival (%)	
Annual Surgical volume	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**
Very low (<10 patients)	6.2	6.4	85.29	84.19	67.31	64.55
Low (10-19 patients)	3.0	3.1	87.95	86.95	68.48	68.16
Medium (20-39 patients)	3.7	4.0	89.14	89.03	70.40	69.41
High (≥40 patients)	3.6	3.3	89.22	89.91	68.95	70.41

Short-term (60 day) post-operative mortality and volume

Table 35 shows the results of the logistic regression on 60-day mortality, the adjusted odds ratio (95%CI) and the type 3 test results for the volume variable. All results are presented in Appendix 3.1.2 - Additional results on impact of surgical volume on outcome. Additionally, the unadjusted odds ratios for surgical volume are presented.

Multivariate analysis with volume as a categorical variable (four categories) showed no significant effect, although a trend towards lower mortality rates in centres with higher surgical volumes can be noted (p=0.097). Dichotomized modelling (as a sensitivity analysis), (very) low versus medium/high volume, was performed with no significant result (OR=0.80, 95%CI (0.50,1.28), p value= 0.35).

A model with the volume variable treated as a continuous variable with a knot at 10 interventions per year (additional analysis) showed an improved survival with a HR of 0.9386 (95%CI (0.8847, 0.9959)) before the knot and no effect with a HR of 0.9986 (95%CI (0.9953, 1.0019)) after the knot. This shows that treating more patients has a beneficial effect until about 10 patients per year, but after this number, no additional benefit can be observed.

Comparison of the crude and adjusted odds ratios shows that there was negative confounding, meaning that the unadjusted association was an underestimation. The data did not allow to distinguish on the type of resection, which is a major limitation as pneumectomies have a 5 times higher mortality than other types of surgeries (P. De Leyn, personal communication).

Table 35 – Effect of surgical volume on 60-day mortality: results from logistic regression (n=2 083)

Characteristics	Odds ratios (95%CI)				Type 3 test
	Unadjusted OR	Adjusted OR	Lower Limit	Upper limit	P value
Annual surgical volume (ref=Very low (<10 patients))					0.0972
Low (10-19 patients)	0.46	0.45	0.216	0.939	
Medium (20-39 patients)	0.59	0.60	0.307	1.173	
High (≥40 patients)	0.57	0.49	0.260	0.910	

Factors included in the model are: sex, age, stage, subtype, performance status, 3 comorbidities (chronic respiratory disease, cardiovascular disease and diabetes) and hospital admission days the year before diagnosis.All results available in Appendix 3.1.2.

1-year survival and volume

Table 36 shows the results from a Cox proportional hazard regression model on 1-year mortality including unadjusted and crude hazard ratio, 95%CI and results from the type 3 tests for the volume variable. All results are presented in Appendix 3.1.2- Additional results on impact of surgical volume on outcome.

The data show a statistically significant relationship between surgical volume and survival at one year (p=0.026); 1-year survival is worse for patients surgically treated in a hospital with surgical volume less than 10, compared with higher volume centres (Table 36).

Dichotomising the volume outcome in the categories 'less than 20' and '20 or more' surgical patients results in a statistical significant hazard ratio of 0.74, with a 95% CI of (0.568, 0.959) (p value= 0.0232).

A model with volume continuously modelled with a knot at 10 interventions per year (additional analysis) showed an improved survival with a HR of 0.9536 (95%CI (0.9218, 0.9865)) before the knot and no effect with a HR of 0.9985 (95%CI (0.9967, 1.0004)) after the knot.

Comparison of the unadjusted and adjusted hazard ratios shows that there was negative confounding, meaning that the unadjusted association was an underestimation.

Table 36 – Effect of surgical volume on 1-year survival: results from Cox PH regression (n=2 083)

Characteristics	Hazard ratios (95%CI)				Type 3 test
	Unadjusted HR	Adjusted HR	Lower Limit	Upper limit	P value
Annual surgical volume (ref= Very low (<10 patients))					0.0259
Low (10-19 patients)	0.79	0.71	0.474	1.054	
Medium (20-39 patients)	0.72	0.66	0.445	0.984	
High (>=40 patients)	0.71	0.56	0.387	0.816	

Factors included in the model are: sex, age, stage, subtype, performance status, 3 comorbidities (chronic respiratory disease, cardiovascular disease and diabetes) and hospital admission days the year before diagnosis. All results available in Appendix 3.1.2.

3-year survival and volume

Table 37 shows the results from a Cox proportional hazard regression model on 3-year mortality: unadjusted and adjusted hazard ratios, 95%CI and results from the type 3 tests for the volume variable. All results are presented in Appendix 3.1.2- Additional results on impact of surgical volume on outcome.

For volume outcome, type 3 test is not statistically significant, implying that survival was not statistically different across the different volume categories for patients treated in a centre with surgical volume less than 10 compared to centres with a larger volume.

Dichotomising the volume outcome in the categories (very low/low versus medium/high) did also not reveal a statistically significant result (HR 0.87, 95% CI (0.743; 1.030), p value = 0.108).

As an additional analysis, a model with volume as a continuous variable with a knot at 10 intervention per year showed an improved survival with a HR of 0.9739 (95%CI=0.9507; 0.9977) before the knot and no effect with a HR of 0.9996 (95%CI=0.9986; 1.0007) after the knot.

Comparison of the crude and adjusted hazard ratios shows that there was some negative confounding, meaning that the unadjusted association was somewhat underestimated.

Table 37 – Effect of surgical volume on 3-year survival: results from Cox PH regression (n=2 083)

Characteristics	Hazard ratios (95%CI)				Type 3 test
	Unadjusted HR	Adjusted HR	Lower Limit	Upper limit	P value
Annual surgical volume (ref= Very low (<10 patients))					0.2583
Low (10-19 patients)	0.95	0.87	0.669	1.120	
Medium (20-39 patients)	0.87	0.82	0.636	1.060	
High (>=40 patients)	0.93	0.79	0.618	1.000	

Factors included in the model are: sex, age, stage, subtype, performance status, 3 comorbidities (chronic respiratory disease, cardiovascular disease and diabetes) and hospital admission days the year before diagnosis.All results available in Appendix 3.1.2.

10.1.4 Discussion

There is some evidence that centres treating more than 20 patients a year have better survival at 1 year than centres with lower surgical volumes. Results also show a trend towards a better survival at 3 years but this effect is no longer statistically significant. For short term postoperative mortality (60 days) evidence is mitigated, except for very low-volume centres (<10) which consistently display worse results than other centres. In absolute terms, for 1- and 3-year survival, the differences are modest, 5% between the lowest and the highest category.

To further study the volume-outcome effect, models in which the volume variable was entered continuously with a knot at 10 interventions per year, revealed for the three time intervals an effect for hospitals with a surgical volume lower than 10 per year. Below this cut-off, the more patients a hospitals treats, the better the survival for these patients. Beyond this cut-off of 10 interventions per year, no additional benefit was found for treating more patients.

Comparison of the crude and adjusted odds/hazard ratios reveals a negative confounding for all three outcomes (mortality at 60 days after surgery and 1-year and 3-year survival), to a varying degree, meaning that the unadjusted association was underestimated for the three outcomes. There may still be considerable residual confounding. For example, comorbidity is difficult to measure and we are not sure we were able to measure all relevant comorbidities. Additionally, socio-economic status was not assessed and it

is shown to be strongly associated with mortality[70]. However, it is not clear what the effect of a more extensive control for confounding would be.

The hazard ratio seen at one year is not statistically significant at three years but difference in survival remains constant at 5% in absolute terms. The fact that the hazard ratio at one year differs considerably from the hazard ratio over 3 years also implies that the proportional hazard assumption is not fulfilled in the 3-year model. The proportional hazard assumption implies the assumption that the hazard ratio is constant over the examined period.

Our findings are similar to what is reported in the international literature. A systematic review on the relation between surgical volume and outcome was performed and discussed in our guideline,[3] which identified 19 studies on the effect of procedural volume or surgeon specialty on outcomes.[71] For hospitals' surgical volume there was a variation across studies in cut-off values of the highest hospital volume strata (between 20 and 129.4 procedures annually) and the lowest volume strata (between 3.6 and 60 procedures annually). The systematic review concludes that there is a significant relationship in favour of high-volume hospitals for postoperative mortality (OR (95%CI): 0.7; [0.62-0.81]) determined by a pooled estimated effect size. The effect for survival (OR (95%CI): 0.93 [0.84-1.03]) was not statistically significant.[71]

A KCE report of 2009 on volume outcome, using a combination of MCD, BCR and IMA data, showed a statistically significant inverse relationship between hospital volume and 2-year mortality. However, the relationship was modest: respectively 27.3% (in very low volume centres, 1-4/year), 29.5% (5-10/year), 26.3% (11-20/year), 29.1% (21-40/year) and 21.4% in four very high volume hospitals (> 40/year). Only the highest volume category, more than 40 patients a year, showed a clear benefit, however, number of centres in this category was too low and the findings should be interpreted with caution. These differences were reinforced when case mix was taken into account, as low volume hospitals treated more patients with stage I than high volume centres.

There may be several explanations for this lack of clear relationship, especially at the longer term. First, the effect may genuinely be seen only at the short term, and the benefits of larger centres is only present in the first year, it gets diluted at the longer term when looking at the hazard ratio but remains 5% in absolute terms. Second, some of the high volume centres are recently merged small centres. These new structures may be still superficial or exists only on paper; merged centres may still work as individual entities without centralizing specific procedures in 1 campus. Patients operated in this kind of centres may not have the same benefit as patients in other (real) high volume centres. Third, it is also possible that the threshold of 10 interventions per year is too low, our report from 2009 showed only a lower mortality from 40 interventions on, although the number of centres was low in this study. The fact that the models with the continuous parameter on surgical volume show an increase up to 10 and not beyond that point, pleads against this. Fourth, although there is a statistically significant volume-outcome effect at one year, the size of the effect seems modest in the light of the fact that there may be many potential biases that were not taken into account in the adjustments we did. However, from a clinical point of view and for individual patients a 5%-difference in survival is meaningful.

Conclusion: 1-year and 3-year survival rates are higher in high-volume centres, but the results at three years are less pronounced. The effect of surgical volume on post-operative mortality is not demonstrated, except for very low-volume centres (<10) which display worse results than other centres.

The three main limitations of these analyses are:

- Case-mix was not fully taken into account: potentially important confounders such as socioeconomic status or respiratory function were lacking. Some major comorbidities having an impact on treatment strategy (e.g. renal insufficiency) could not be captured. Missing data on stage are more frequent in low-volume centres.
- Some "high-volume" hospitals are in reality a cluster of low-volume sites, each performing a small number of operations yearly, which may have attenuated the differences between low and high-volume hospitals.
- Administrative data hamper to differentiate the types of surgery, lobectomy from pneumonectomy (the latter having higher mortality rates, and probably performed more often in high-volume centres).

A correction of these shortcomings may alter the observed volume-outcome relationship.

10.2 Impact of radiotherapy volume on outcomes

10.2.1 Introduction

Whereas the relationship between volume and outcome has been examined in a lot of studies about lung cancer surgery, little is known about the volume-outcome for lung cancer patients who were treated with radiotherapy.

No recommendations concerning the minimal volume of centres to obtain optimal results were put forward in our guideline. The analysis was done at the demand of stakeholders and experts.

10.2.2 Methods

Patients

All lung cancer patients who received radiotherapy with curative intent (category 2, 3 or 4) were included in the analysis.

We excluded combined stage IV because it is likely that most treatments with radiotherapy are palliative treatments. To enhance the chance that no palliative series were taken into account, we also excluded tumours with an unknown combined stage.

It should be noted that the population defined for the 60 day mortality is not the same as for the 1-year and 3-year survival. Patient selection for the 60 day mortality is the same as described in the technical fiche concerning 60 day mortality after radiotherapy (QI SAF-2 in the technical fiches), whereas patient selection for the 1-year and the 3-year survival models is the same as described in the technical fiche concerning survival (QI S-1 in the technical fiches). This implies that for the 60-day mortality, stage I-III of both SCLC patients as NSCLC patients were included, whereas for the models on 1-year and 3-year survival only stage I-III NSCLC patients were included.

Radiotherapy volume

To determine a radiotherapy volume, all patients included in the study (i.e. patients with unique tumours) who underwent radiotherapy were included in the analyses. Only the first RT series was taken into account per patient.

Radiotherapy volume was divided in the categories low volume (<50 patients/year), medium volume (between 50 and 99 patients per year) and high volume (at least 100 patients per year).

Statistical models

Same methods to model the relationship between volume and outcome were used as for surgical volume outcome.

10.2.3 Results

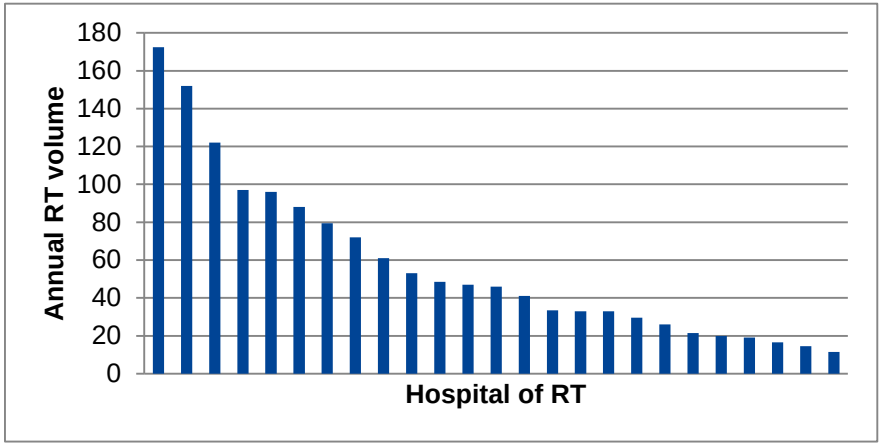
Description of the cohort

Table 38 shows the differences in case mix for the NSCLC cancer patients, combined stage I-III. Age-groups are similar over the RT volume categories of the centres. High-volume centres have slightly more adenocarcinomas and female patients.

Volume of radiotherapy

Figure 25 presents the radiotherapy volume for the 25 centres.

Figure 25 – Annual RT volume for lung cancer patients



Note: 1 patient could not be assigned to a RT centre Source: BCR-IMA – AIM

Table 38 – Differences in case mix of NSCLC patients who underwent RT in low-, medium- and high-volume RT centres

	Annual RT volume of centres (2010-2011)			
	Low (<50 per year)	Medium (50-99 per year)	High (≥100 per year)	Total
N of RT centres	15	7	3	25
N of patients	382	465	323	1 170
Sex (%)				
Males	79.1	75.9	70.0	75.3
Females	20.9	24.1	30.0	24.7
Age (mean)	67.2	68.8	68.6	68.2
<50 years (%)	4.5	4.9	4.3	4.6
50-59 years (%)	19.6	16.3	15.8	17.3
60-69 years (%)	33.0	29.0	30.7	30.8
70-79 years (%)	29.3	31.4	32.2	30.9
80+ years (%)	13.6	18.3	17.0	16.4
Histology				
Adenocarcinoma	33.5	38.1	41.5	37.5
Squamous cell carcinoma	53.1	50.3	45.8	50.0
Large cell carcinoma	2.6	5.6	5.3	4.5
Other*	10.7	6.0	7.4	7.9
Clinical stage (%)				
I**	15.7 (16.1*)	21.3 (21.4*)	18.0 (18.2*)	18.5 (18.8*)
II**	11.8 (12.1*)	12.5 (12.5*)	12.1 (12.2*)	12.1 (12.3*)

III**	70.2 (71.9*)	65.8 (66.1*)	68.7 (69.6*)	68.0 (68.9*)
X	2.4	0.4	1.2	1.3
Pathological stage (%)				
I**	1.6 (13.0*)	2.8 (22.4*)	0.9 (7.3*)	1.9 (15.2*)
II**	1.3 (10.9*)	0.6 (5.2*)	0.0 (0.0*)	0.7 (5.5*)
III**	9.2 (76.1*)	9.0 (72.4*)	11.8 (92.7*)	9.8 (79.3*)
X	88.0	87.5	87.3	87.6
Combined stage (%)				
I**	16.5	21.7	16.7	18.6
II**	11.5	12.3	11.5	11.8
III**	72.0	66.0	71.8	69.6

Note: 1 patient could not be assigned to a RT centre

**includes other specified carcinoma and unspecified non-small cell lung cancer*

**Unknown stage (X) is excluded to calculate the percentages.*

Table 39 – Observed survival of NSCLC patients who underwent RT, in low-, medium- and high-volume RT centres

	1-year observed survival (%)		3-year observed survival (%)	
Annual RT volume	Observed	Adjusted	Observed	Adjusted
Low (<50 patients)	70.16	69.11	30.37	30.98
Medium (50-99 patients)	64.66	65.30	26.73	26.50
High (≥100 patients)	65.33	64.79	26.63	25.70

Impact of radiotherapy volume on short term (60 days) mortality after radiotherapy with curative intent

Table 40 shows the results from logistic regression evaluating impact of hospital' RT volume on 60-day mortality, the adjusted odds ratio and 95% CI + results from type 3 test for the volume variable. All results are presented in Appendix 3.1.3 - Additional results on impact of radiotherapy volume on outcome.

The conclusion of the analysis is that there is no statistically significant association between radiotherapy volume and mortality within 60 days after end of treatment (type 3 p-value= 0.5711, Table 40)

Table 40 – Effect of radiotherapy volume on 60-day post radiotherapy mortality: results from logistic regression (n=1 412).

Characteristics		Odds ratios (95%CI)			Type 3 test
		Adjusted OR	Lower Limit	Upper limit	P value
Annual radiotherapy volume (ref= Low (<50 patients)	**Unadjusted OR**				0.5711
Medium (50-99 patients)	1.080	1.03	0.649	1.629	
High (≥100 patients)	1.280	1.26	0.785	2.021	

Factors included in the model are: sex, age, stage, subtype, performance status, 3 comorbidities (chronic respiratory disease, cardiovascular disease and diabetes) and hospital admission days the year before diagnosis.All results available in Appendix 3.1.3

Impact of radiotherapy volume on 1 year survival

Table 41 shows the results from a Cox proportional hazard regression model on 1-year survival: adjusted hazard ratio and 95% CI and results from the type 3 tests for the volume variable. All results are presented in Appendix 3.1.3. For the volume outcome relationship, confidence limits for the category 50-99 patients per year compared to <50 patients per year excludes 1, but the overall type 3 test is not statistically significant.

Table 41 – Effect of radiotherapy volume on 1-year survival: results from Cox proportional hazard regression model (n=1 170).

Characteristics	Unadjusted HR	Hazard ratios (95%CI) Adjusted HR	Lower Limit	Upper limit	Type 3 test P value
Annual radiotherapy volume (ref= Low (<50 patients)					0.0960
Medium (50-99 patients)	1.253	1.31	1.025	1.672	
High (≥100 patients)	1.205	1.19	0.913	1.554	

Factors included in the model are: sex, age, stage, subtype, performance status, 3 comorbidities (chronic respiratory disease, cardiovascular disease and diabetes) and hospital admission days the year before diagnosis.All results available in Appendix 3.1.3

Impact of radiotherapy volume on 3-year survival

Table 42 shows the results from a Cox proportional hazard regression model on 3-year survival: adjusted hazard ratio and 95% CI and results from the type 3 tests for the volume variable. All results are presented in Appendix 3.1.3 - Additional results on impact of radiotherapy volume on outcome.

The p-values for age group, combined stage, days of hospitalisation one year before diagnosis and WHO performance status show an association that after adjustment is statistically significant. For radiotherapy volume, no significant effect is found.

Table 42 – Effect of radiotherapy volume on 3-year survival: results from Cox PH regression (n=1 170)

Characteristics		Hazard ratios (95%CI) Adjusted HR	Lower Limit	Upper limit	Type 3 test P value
Annual radiotherapy volume (ref= Low (<50 patients))	Unadjusted HR				0.1354
Medium (50-99 patients)	1.111	1.15	0.976	1.354	
High (≥100 patients)	1.144	1.18	0.986	1.411	

Factors included in the model are: sex, age, stage, subtype, performance status, 3 comorbidities (chronic respiratory disease, cardiovascular disease and diabetes) and hospital admission days the year before diagnosis.All results available in Appendix 3.1.3

10.2.4 Discussion

There is no proof that there is a radiotherapy volume effect on 60 day mortality after radiotherapy with curative intent and for 1 and 3 year survival; overall type 3 test is not significant. Absolute difference is only 5 %.

To the best of our knowledge no information exists on volume-outcome relationship for radiotherapy on lung cancer patients. There are some data for other cancer types. A Taiwanese study conducted in Taiwan confirmed a positive volume-outcome relationship for nasopharyngeal cancer. In this study, patients receiving either chemoradiotherapy or radiotherapy were included and their 10-year survival was analysed.[72] It is difficult to judge if these data are relevant for our context.

10.3 Impact of diagnostic volume on outcomes

10.3.1 Introduction

This section aims the following question:

1. Are there differences in survival between low- and high-volume centres, based on the number of patients diagnosed per year (diagnostic volume)?

In the following section, patterns of treatments are compared between low and high volume diagnostics centres.

10.3.2 Methods

Patients included

All NSCLC patients.

Diagnostic Volume

Centres were divided in 4 diagnostic volume categories, taking for each centre into account all lung cancer patients who had most of their diagnostics in that centre (see section 6.2 - Validation of the algorithm to assign patients to a diagnostic centre)

Patients referred for treatment are counted in the centre of diagnosis.

Statistical Models

Same methods to model the relationship between volume and outcome were used as for surgical volume outcome.

Because the relationship showed to be very different for stage IV patients, a separate model was used to assess the relationship.

10.3.3 Results

Table 43 shows observed and adjusted 1-year and 3-year survival, by diagnostic volume for stage I-III and for stage IV separately. Results from models are presented in the following tables. Table 44 to Table 47 present results from a Cox PH model on 1-year survival and 3-year survival, for stage I-III and stage IV separately. In those tables, only the effect of diagnostic volume are presented. The detailed tables are available in Appendix 3.1.4 - Additional results on impact of diagnostic volume on outcome.

Survival 1-year after diagnosis

No effect of diagnostic volume was observed for combined I-III stages (Table 44, p volume = 0.8174)

On the contrary, for stage IV, there is a statistically significant effect of diagnostic volume (Table 45 p volume =0.0041), but in an unexpected direction: survival is lower for centres that have 50 or more patients a year than for centres that have less patients.

Survival 3-year after diagnosis

At three years, both models do not show an effect of diagnostic volume on survival three years after diagnostic (Table 46 for combined stage I-III, Table 47 for combined stage IV).

Table 43 – Unadjusted and adjusted 1-year and 3-year survival for stage I-III and for stage IV patients, by diagnostic volume

Annual diagnostic volume		1-year Observed survival (%)		3-year Observed survival (%)	
		Unadjusted	Adjusted	Unadjusted	Adjusted
stage I-III					
Annual diagnostic volume	1- Low (<50 patients)	65.99	68.23	37.93	41.42
	2- Medium (50-99 patients)	68.75	68.42	41.60	41.54
	3- High (100-149 patients)	71.51	69.25	44.42	40.96
	4- Very high (≥150 patients)	68.28	68.01	42.55	41.58
stage IV					
Annual diagnostic volume	1- Low (<50 patients)	28.81	31.28	4.42	6.66
	2- Medium (50-99 patients)	26.94	26.72	5.34	5.26
	3- High (100-149 patients)	27.64	26.85	5.62	5.56
	4- Very high (≥150 patients)	29.10	26.57	5.58	5.15

Table 44 – Effect of diagnostic volume on 1-year survival for combined stage I-III patients: results from Cox PH regression (n=4 281)

Characteristics		Hazard ratios (95%CI)			Type 3 test
		Adjusted HR	Lower Limit	Upper limit	P value
Annual diagnostic volume (ref= Low (<50 patients))	**Unadj. HR**				0.8174
Medium (50-99 patients)	0.897	1.01	0.881	1.156	
High (100-149 patients)	0.796	0.98	0.836	1.151	
Very high (≥150 patients)	0.910	1.07	0.902	1.266	

Factors included in the model are: sex, age, stage, subtype, performance status, 3 comorbidities (chronic respiratory disease, cardiovascular disease and diabetes) and hospital admission days the year before diagnosis.All results available in Appendix 3.1.4.

Table 45 – Effect of diagnostic volume on 1-year survival for combined stage IV patients: results from Cox PH regression (N=3 955)

Characteristics		Hazard ratios (95%CI)			Type 3 test
		Adjusted HR	Lower Limit	Upper limit	P value
Annual diagnostic volume (ref= Low (<50 patients))	**Unadjusted HR**				0.0041
Medium (50-99 patients)	1.080	1.17	1.066	1.293	
High (100-149 patients)	1.064	1.17	1.050	1.308	
Very high (≥150 patients)	1.042	1.19	1.048	1.344	

Factors included in the model are: sex, age, stage, subtype, performance status, 3 comorbidities (chronic respiratory disease, cardiovascular disease and diabetes) and hospital admission days the year before diagnosis.All results available in Appendix 3.1.4.

Table 46 – Effect of diagnostic volume on 3-year survival for combined stage I-III patients: results from Cox PH regression (n=4 281)

Characteristics		Hazard ratios (95%CI)			Type 3 test
		Adjusted HR	Lower Limit	Upper limit	P value
Annual diagnostic volume (ref= Low (< 50 patients))	**Unadjusted HR**				0.9838
Medium (50-99 patients)	0.901	1.00	0.901	1.100	
High (100-149 patients)	0.825	1.02	0.905	1.142	
Very high (≥150 patients)	0.879	0.99	0.877	1.128	

Factors included in the model are: sex, age, stage, subtype, performance status, 3 comorbidities (chronic respiratory disease, cardiovascular disease and diabetes) and hospital admission days the year before diagnosis.All results available in Appendix 3.1.4.

Table 47 – Effect of diagnostic volume on 3-year survival for combined stage IV patients: results from Cox PH regression (N=3 955)

Characteristics		Hazard ratios (95%CI)			Type 3 test
		Adjusted HR	Lower Limit	Upper limit	P value
Annual diagnostic volume (ref= Low (<50 patients)/year)	**Unadjusted HR**				0.1296
Medium (50-99 patients)	1.020	1.10	1.010	1.195	
High (100-149 patients)	0.998	1.08	0.977	1.183	

Characteristics		Hazard ratios (95%CI)			Type 3 test
		Adjusted HR	Lower Limit	Upper limit	P value
Very high (≥150 patients)	0.985	1.11	0.994	1.233	

Factors included in the model are: sex, age, stage, subtype, performance status, 3 comorbidities (chronic respiratory disease, cardiovascular disease and diabetes) and hospital admission days the year before diagnosis.All results available in Appendix 3.1.4.

10.3.4 Discussion

There is no evidence for a diagnostic volume-outcome relationship in general for patients with combined stage I to III.

For patients with stage IV, patients in centres with less than 50 patients a year have a somewhat better survival after 1 year, although in absolute terms this difference is small (<5%) at 1 year and extremely small at 3 year 0.6% (note that survival for stage IV at 3 years is extremely low). One reason for this small difference for stage IV patients may be that in larger centres end of life treatment is less aggressive, or that treatment is stopped earlier, as care is mainly palliative for stage IV patients. As will be shown below, there is also a small volume effect on the proportion of patients that receive chemotherapy in stage IV patients. It is unclear if there is a causal relationship between the 2 or if they are both the result of selection bias and residual confounding by the confounders put in the statistical model.

10.4 Impact of diagnostic volume on guideline-concordant treatment

10.4.1 Introduction

The proportion of patients receiving guideline-concordant treatment may be one of the factors that contribute to a better outcome for patients. We looked at the relationship between the received treatment and the diagnostic volume of the hospital.

10.4.2 Methods

Patients included

NSCLC and SCLC patients are included in the analysis

Diagnostic volume

Centres were divided in 4 diagnostic volume categories, taking for each centre into account all lung cancer patients who had most of their diagnostics in that centre (see section 6.2 - Validation of the algorithm to assign patients to a diagnostic centre) Patients referred for treatment are counted in the centre of diagnosis.

Statistical Models

Logistic modelling was used to test for the relationship between diagnostic volume of the centres and the type of treatment received by the patients. Results are presented for small cell and non-small cell lung cancer separately, and separate models were used for clinical stages I-II, III, and IV (non-small cell lung cancer) and clinical stages I-III and IV (small cell lung cancer) as the guidelines describe a different kind of treatment for these stages .

10.4.3 Results

Non-small-cell lung cancer patients

The percentage of NSCLC patients receiving guideline concordant treatment was 58.3%, and differed by stage: 59.9% for cI-II patients, 33.8% for cIII patients and 70.2% for cIV patients. These results are presented descriptively in Table 48, and the results from statistical models for the diagnostic volume category are then presented in Table 49 (stage I-II) Table 50 (stage III) and Table 51 (stage IV). All results for these tables are

available in Appendix 3.1.5 - Additional results on impact of diagnostic volume on guideline concordant treatment for NSCLC patients.

For both stages I-II the model shows a trend towards a higher use of guideline-concordant treatment in centres with a higher diagnostic volume, but the relationship is not statistically significant. Comparison of the adjusted and unadjusted OR indicate that there is limited positive confounding in the model. Note that there is no such thing as a statistical test for confounding.

For stage III, data do not show indications of a volume effect and no indications that there is confounding.

For stage IV, data show that there is lower use of chemotherapy in centres with a higher diagnostic volume and the relationship is statistically significant. Comparison of the adjusted and unadjusted OR indicate that there is important negative confounding in the model.

Table 48 – NSCLC patients receiving guideline-concordant treatment, according to the diagnostic volume of the hospital, all patients and by stage

	All Patients cI-IV			cI-II			cIII			cIV		
Annual Diagnostic volume	N	n	**%**	N	n	**%**	N	n	%	N	n	**%**
Low (<50 patients)	1 857	1 070	**57.6**	374	200	**53.5**	563	185	**32.9**	920	685	**74.5**
Medium (50-99 patients)	2 776	1 629	**58.7**	594	349	**58.8**	697	228	**32.7**	1 485	1 052	**70.8**
High (100-149 patients)	1 687	1 014	**60.1**	442	279	**63.1**	388	148	**38.1**	857	587	**68.5**
Very high (≥150 patients)	1 211	708	**58.5**	306	205	**67.0**	322	110	**34.2**	583	393	**67.4**
Centre unknown	57	3	**5.3**	10	1	**10.0**	17	0	**0.0**	30	2	**6.7**
Total	7 588	4 424	**58.3**	1 726	1 034	**59.9**	1 987	671	**33.8**	3 875	2 719	**70.2**

Note: Guideline concordant treatment for NSCLC patients is defined as surgical resection for stage cI-II, chemoradiation for stage cIII and chemotherapy for stage cIV.

Table 49 – Effect of diagnostic volume on probability to receive guideline-concordant treatment (surgery) for cI-II NSCLC patients: results from logistic regression (n=1 716)

Characteristics		Odds ratios (95%CI)			Type 3 test
		Adjusted OR	Lower Limit	Upper limit	P value
Annual diagnostic volume (ref= Low (<50 patients))	**Unadjusted OR**				0.0980
Medium (50-99 patients)	1.24	1.25	0.928	1.678	
High (100-149 patients)	1.49	1.23	0.890	1.691	
Very high (≥100 patients)	1.77	1.58	1.103	2.253	

Factors included in the model are: sex, age, stage, subtype, performance status, 3 comorbidities (chronic respiratory disease, cardiovascular disease and diabetes) and hospital admission days the year before diagnosis.All results available in Appendix 3.1.5.

Table 50 – Effect of diagnostic volume on probability to receive guideline-concordant treatment (chemoradiation) for cIII NSCLC patients: results from logistic regression (n=1 970)

Characteristics		Odds ratios (95%CI)			Type 3 test
		Adjusted OR	Lower Limit	Upper limit	P value
Annual diagnostic volume (ref= Low (<50 patients))	**Unadjusted OR**				0.5102
Medium (50-99 patients)	0.99	0.94	0.730	1.209	
High (100-149 patients)	1.26	1.15	0.856	1.531	
Very high (≥100 patients)	1.06	0.93	0.679	1.261	

Factors included in the model are: sex, age, stage, subtype, performance status, 3 comorbidities (chronic respiratory disease, cardiovascular disease and diabetes) and hospital admission days the year before diagnosis.All results available in Appendix 3.1.5.

Table 51 – Effect of diagnostic volume on probability to receive guideline-concordant treatment (chemotherapy) for cIV NSCLC patients: results from logistic regression (n=3 845)

Characteristics		Odds ratios (95%CI)			Type 3 test
		Adjusted OR	Lower Limit	Upper limit	P value
Annual diagnostic volume (ref= Low (<50 patients))	**Unadjusted OR**				<.0001
Medium (50-99 patients)	0,83	0.73	0.608	0.884	
High (100-149 patients)	0,75	0.59	0.479	0.728	
Very high (≥100 patients)	0,71	0.50	0.396	0.629	

Factors included in the model are: sex, age, stage, subtype, performance status, 3 comorbidities (chronic respiratory disease, cardiovascular disease and diabetes) and hospital admission days the year before diagnosis.All results available in Appendix 3.1.5.

Small-cell lung cancer patients

The percentage of SCLC patients receiving guideline concordant treatment was 70.2%, and differed by stage: 50.7% for cI-III patients and 80.7% for cIV patients. These results are presented descriptively in Table 52, and the results from statistical models for the diagnostic volume category are then presented in Table 53 (stage I-III) and in Table 54 (stage IV). All results for these tables are available in Appendix 3.1.6 - Additional results on impact of diagnostic volume on guideline concordant treatment for SCLC patients.

For both groups, stages I-III and stage IV, models show a tendency to a higher use of guideline-concordant treatment in centres with a higher diagnostic volume, but the relationship is statistically not significant.

Comparison of the adjusted and unadjusted OR indicate that there is limited negative confounding in the model for stage I-III and some limited positive confounding for stage IV.

Table 52 – SCLC patients receiving guideline-concordant treatment, according to the diagnostic volume of the hospital, all patients and by stage

	All Patients cI-IV (N = 1 421)			cI-III (N = 495)			cIV (N = 926)		
Annual diagnostic volume*	**N**	**n**	**%**	**N**	**n**	**%**		**n**	**%**
Low (<50 per year)	364	237	**65.1**	130	58	**44.6**	234	179	**76.5**
Medium (50-99 per year)	484	340	**70.2**	160	83	**51.9**	324	257	**79.3**
High (100-149 per year)	339	246	**72.6**	115	58	**50.4**	224	188	**83.9**
Very high (≥150 per year)	225	175	**77.8**	87	52	**59.8**	138	123	**89.1**
Centre unknown	9	0	**0.0**	3	0	**0.0**	6	0	**0.0**
Total	1 421	998	**70.2**	495	251	**50.7**	926	747	**80.7**

**Diagnostic volume refers to all patients (NSCLC, SCLC or other) diagnosed during one year (as the average of incidence dates 2010 and 2011) in the centre. Patients who are referred for treatment remain assigned to the referring centre.*
Note: Guideline concordant treatment for SCLC patients is defined as chemoradiation (concurrent or sequential) for stage cI-III and platinum-etoposide combination first-line chemotherapy for cIV patients

Table 53 – Effect of diagnostic volume on probability to receive guideline-concordant treatment (chemoradiation) for cI-III SCLC patients: results from logistic regression (n=492).

Characteristics	Odds ratios (95%CI) Unadjusted OR	Adjusted OR	Lower Limit	Upper limit	Type 3 test P value
Annual diagnostic volume (ref= Low (<50 patients))					0.0722
Medium (50-99 patients)	1.34	1.39	0.820	2.358	
High (100-149 patients)	1.26	1.35	0.743	2.441	
Very high (≥150 patients)	1.84	2.43	1.257	4.692	

Factors included in the model are: sex, age, stage, subtype, performance status, 3 comorbidities (chronic respiratory disease, cardiovascular disease and diabetes) and hospital admission days the year before diagnosis.All results available in Appendix 3.1.6.

Table 54 – Effect of diagnostic volume on probability to receive guideline-concordant treatment (platinum-etoposide combination first-line chemotherapy) for cIV SCLC patients: results from logistic regression (n=920)

Characteristics	Odds ratios (95%CI)				Type 3 test
	Unadjusted OR	Adjusted OR	Lower Limit	Upper limit	P value
Annual diagnostic volume (ref= Low (<50 patients))					0.3320
Medium (50-99 patients)	1.18	0.98	0.609	1.560	
High (100-149 patients)	1.60	1.40	0.816	2.390	
Very high (≥150 patients)	2.52	1.54	0.774	3.074	

Factors included in the model are: sex, age, stage, subtype, performance status, 3 comorbidities (chronic respiratory disease, cardiovascular disease and diabetes) and hospital admission days the year before diagnosis.All results available in Appendix 3.1.6.

10.4.4 Discussion

There is no evidence that there is a relation between diagnostic volume and proportion of patients that receive optimal treatment for stage I-II and stage III NSCLC and stage I-III SCLC; overall type 3 tests are not statistically significant.

The trend in resection rates (however non-significant) is congruent with Wouters et al.[41] who assessed volume outcome in 43 544 patients who were diagnosed with NSCLC. The resection rates for stage I/II NSCLC patients increased during the study period, but they varied by region and were higher in teaching hospitals for thoracic surgeons (OR 1.5; 95%CI1.2-1.9, p < 0.001) and in hospitals with a diagnostic volume of more than 50/year (OR 1.3; 95%CI 1.1-1.5, p < 0.001). He also found that chemoradiation rates for stage III patients were not higher in high volume hospitals (>100 diagnoses a year).

For stage IV NSCLC, small centres give more chemotherapy. Reasons for this are unclear. Though, in the expert group some put forward that larger centres tend to discuss more with the patient whether treatment is wanted; a lot of patients decide not to undergo chemotherapy. This is difficult to verify though.

11 CONCLUSION, DISCUSSION AND RECOMMENDATIONS

See the "Synthesis" document which is available on our website.

12 APPENDICES

APPENDIX 1. APPENDICES FROM CHAPTER 4: SELECTING QUALITY INDICATORS: PROCESS AND RESULTS

Appendix 1.1.1. Search strategy Medline

Datebase	**Medline (OVID)**		
Date	**2014-06-30**		
Search Strategy	**#**	***Query***	***Results***
	1	exp Lung Neoplasms/	**172939**
	2	(lung? adj (neoplasm$ or cancer$ or carcinoma$ or adenocarcinoma$ or angiosarcoma$ or chrondosarcoma$ or sarcoma$ or teratoma$ or lymphoma$ or blastoma$ or microcytic$ or carcinogenesis or tumour$ or tumor$ or metast$ or malign$)).ti,ab.	**123071**
	3	(NSCL or SCLC).ti,ab.	**5333**
	4	1 or 2 or 3	**206181**
	5	"Quality of Health Care"/	**57180**
	6	Patient Care Management/	**2341**
	7	"Organization and administration"/	**14247**
	8	og.fs.	**377911**
	9	Quality Assurance, Health Care/	**49013**
	10	Quality Indicators, Health Care/	**10204**
	11	(quality adj5 (healthcare or (health adj5 care))).tw.	**17324**
	12	(administrative adj3 (technics or technique?)).tw.	**45**
	13	logistics.tw.	**2867**

	14	supervision.tw.	**18616**
	15	(quality adj3 indicator?).tw.	**7226**
	16	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	**504334**
	17	4 and 16	**810**
	18	limit 17 to yr="1980 -Current"	**795**

Note

Appendix 1.1.2. Relevant quality indicators excluded due to measurability issues

Category	Quality indicator	Reference	Reason not measurable
Timeliness of diagnosis and treatment	Time from first imaging (X-Ray/CT) to start of treatment or refusal of treatment documented	Gould 2008[24]	No data on protocol of imaging
	Time from first visit in pneumology or oncology to first treatment, by treatment modality		No data on reasons for visit to pneumologist or oncologist
Diagnosis & Staging (including Pathology)	Percentage of mediastinoscopies with at least five lymph node stations explored and at least three sampled, included one ipsilateral, one contralateral station and lymph node station number 7 (subcarinal)	Ouwens 2007[33], Hermens 2006[25], Ryoo 2014[38]	No data on outcome of mediastinoscopy available
	Percentage of lung cancer patients who undergo EBUS-TBNA or EUS-FNA for whom sample of all enlarged lymph nodes and mapping of ipsilateral and contralateral paratracheal stations and the subcarinal station is performed	KCE guidelines	No data on outcome of EBUS/EUS available
	Percentage of pathology reports that contain the following essential data: tumour location, tumour size, pleura visceral involvement, histological tumour type, histological grading, surgical margin status, lymph node status, UIVV-classification, Angio-invasion, atelectasis or obstructive pneumonitis	Auman 2013[13], Gephardt 1996[23]	No data on content of pathology reports available

Category	Quality indicator	Reference	Reason not measurable
	Percentage of stage IV lung cancer patients without EGFR mutation who had ALK rearrangement test performed	KCE guidelines	No data on results of EGFR mutation analysis available, ALK rearrangement test not available in 2010-2011
Treatment of early stage NSCLC	Percentage of patients with NSCLC undergoing surgery who have at least lobe-specific systematic nodal dissection performed	SIGN, Conron 2007[19], Chien 2008[18], Brunelli 2009[14], Allen 2001[12], Ryoo 2014[38]	No details of performed surgery available, no specific RIZIV/INAMI reimbursement codes
	Percentage of NSCLC patients with borderline pulmonary function who had their residual lung function estimated before surgery	KCE guidelines	No data on results of pulmonary function tests
	Percentage of positive resection margins in patients who underwent surgery	Santeon, Allen 2011[12], Conron 2007[19]	No results from pathology reports
	Percentage of stage I-II NSCLC patients with positive surgical margins who receive postoperative radiotherapy	Chien 2008[18]	No results from pathology reports
	Percentage of patients with NSCLC undergoing surgery who underwent lobectomy or greater	Allen 2001[12], Jakobsen 2009[26], Caldarella 2012[15]	No specific RIZIV/INAMI reimbursement codes
Treatment of stage cIII NSCLC	Percentage of stage III NSCLC lung cancer patients receiving concurrent chemoradiotherapy	DLRA, Evans 2013[20], Komaki 2013[27], Ryoo 2014[38], Tanvetyanon 2011[40], IKNL, Hermens 2006[25]	Insufficient data to determine starting date of radiotherapy. Will be calculated as a proxy in sensitivity analysis for other indicator on multimodality treatment
Treatment of parietal pleura	Percentage of operated NSCLC patients with a sulcus superior tumour who received neoadjuvant chemoradiation	KCE guidelines	Sulcus superior tumours cannot be defined in the databases

Category	Quality indicator	Reference	Reason not measurable
Treatment of stage cIV NSCLC	Percentage of patients with advanced NSCLC and EGFR mutation treated with TKI during course of disease	KCE guidelines	No result of EGFR mutation analysis available
	Percentage of cIV NSCLC ALK mutation-positive patients who received crizotinib as second-line therapy	KCE guidelines	ALK mutation analysis not performed in 2010-2011; no result of test available
Treatment of limited-stage disease SCLC	Percentage of limited disease SCLC patients receiving concurrent radiotherapy who start radiotherapy during the first or second cycle of chemotherapy	KCE guidelines	Insufficient data to determine starting date of radiotherapy
	Percentage of patients with limited disease SCLC who are treated with prophylactic brain radiotherapy (after chemoradiation)	IKNL	No specific reimbursement codes for radiotherapy
Overdiagnosis and Overtreatment	Percentage of cIV NSCLC patients with wild-type EGFR status tumour who received TKI treatment	KCE guidelines	No results of EGFR mutation test available

Appendix 1.1.3. Initial selection of quality indicators

Category	ID QI new	Quality Indicator	S/O/P*
Diagnosis & staging	1	Percentage of lung cancer patients who have their TNM stage recorded (cTNM and/or pTNM)	P
	2	Percentage of lung cancer patients who receive PET-CT prior start of curative treatment	P
	3	Percentage of lung cancer patients who are discussed at MDT meeting before any treatment	P
	4	Percentage of CM0 patients who had (minimally) invasive mediastinal staging (EBUS or EUS or mediastinoscopy)	P
	5	Percentage of CM0 patients who had mediastinoscopy preceded by EBUS or EUS	P
	6	Percentage of lung cancer patients cI-III who had brain imaging (CT or MRI) before treatment	P
	7	Percentage of lung cancer patients who have a tumour type and subtype identified	P
	8	Percentage of patients with stage IV non squamous cell of the lung for whom no mutation analysis was performed	P
	9	Time from pathological diagnosis to first treatment, by treatment modality	O

Generic indicators	10	Survival (1-2-5 year) overall, by stage and by treatment received (no treatment, surgical resection, chemotherapy, radiotherapy, chemoradiation)	O
	11	Number of lung cancer patients treated by surgery per centre yearly	S
	12	Number of lung cancer patients treated by chemotherapy per centre yearly	S
	14	Number of lung cancer patients treated by radiotherapy per centre yearly	S
	13	Percentage of patients with NSCLC who received "optimal" treatment (resection for stage I and II, chemoradiation for stage III, chemotherapy for stage IV)	P
Treatment of early stage NSCLC	15	Percentage of pT1-T3 pN1-2 M0 NSCLC patients who are treated with adjuvant chemotherapy before or after resection	P
	16	Percentage of patients considered for surgery who have FEV1 and DLCO performed	P
	17	Percentage of patients who underwent lung cancer surgery in high volume centre specialized in thoracic surgery	S
	18	Percentage of patients with a TI-II N0 tumour not eligible for lobectomy who are treated with radiotherapy who received SBRT (only measurable since October 2013)	P
Treatment of stage cIII NSCLC	19	Percentage of stage III NSCLC lung cancer patients receiving concurrent or sequential chemoradiotherapy	P
	20	Percentage of stage IIIA N2 NSCLC operated patients who were discussed in MDT preoperatively	P
Treatment of stage cIV NSCLC	21	Percentage of patients receiving anti EGFR treatment who were not tested for (as a proxy who were not tested for EGFR mutation)	P
	22	Percentage of cIV NSCLC patients for whom performance status was assessed (WHO performance status)	P
Treatment of limited-stage disease SCLC	23	Percentage of stage I-III SCLC patients who receive chemo/radiochemotherapy	P
Treatment of extensive stage disease	24	Percentage of patients with extensive stage disease SCLC who receive first line chemotherapy	P
	25	Percentage of patients with extensive stage disease SCLC receiving first line chemotherapy who received platinum-etoposide combination	P
End of Life	26	Percentage of patients (stage IV) who received an active medical treatment within 2 weeks/ 30 days of death, by treatment modality (*to be discussed again in function of results descriptive stats*)	P
Safety and Complications	27	Percentage of patients with toxicity grade 3 or more during the first 30 days after surgery (early NSCLC) (Clavien grading)	O
	28	Percentage of patients with lung cancer(stage I-III) who die within 30/60/90 days of active treatment, by treatment modality (surgery, radiotherapy, chemotherapy)	O

Over-diagnosis and over-treatment	29	Percentage of NSCLC patients who had a bone scintigraphy performed after a PET-CT	P
	30	Percentage of patients with stage IA NSCLC who received adjuvant chemotherapy	P
	31	Number of PET scan after treatment with curative intent during 2 years follow-up period	P
	32	Total cost per patient for diagnostic procedures	O

**S=Structure; P=Process; O=Outcome*

APPENDIX 2. APPENDICES FROM CHAPTER 8: IDENTIFICATION OF LUNG CANCER PATIENTS' COMORBID CONDITIONS BASED ON THEIR PHARMACEUTICAL BILLING DATA

Appendix 2.1.1. Review of literature - list of articles reviewed in depth

Authors	Year	Title	Lung cancer comorbidities identification	ATC codes identification	Validation tool	General information on Indices	Prevalence comorbidity
Battafarano et al. [46]	2002	Impact of comorbidity on survival after surgical resection in patients with stage I NSCL cancer				x	
Ceratti et al. [46]	2008	Health data quality improvement by comparing administrative medical data and billing data		x			
Chini et al. [52]	2011	Can we use the pharmacy data to estimate the prevalence of chronic conditions? A comparison of multiple data sources		x			
Colinet et al. [43]	2005	A new simplified comorbidity score as prognostic factor in NSCL cancer patients: description and comparison with the Charlson's index	x		x		x
Dominick et al. [73]	2005	Comparison of three comorbidity measures for predicting health service use in patients with osteoarthritis			x	x	

Authors	Year	Title	Lung cancer comorbidities identification	ATC codes identification	Validation tool	General information on Indices	Prevalence comorbidity
Firat et al. [43]	2002	Comorbidity and Karnofsky performance score are independent prognostic factors in stage III NSCL cancer: An institutional analysis of patients treated on four RTOG studies				x	
Firat et al. [68]	2002	Comorbidity and KPS are independent prognostic factors in stage I NSCL cancer				x	
Goldsbury et al.[74]	2012	Using administrative health data to describe colorectal and lung cancer care in New South Wales, Australia: a validation study	x		x		
Halfon et al. [53]	2013	Disease identification based on ambulatory drugs dispensation and in-hospital ICD-10 diagnosis: a comparison		x	x		
Huber et al. [51]	2013	Identifying patients with chronic conditions using pharmacy data in Switzerland: an updated mapping approach to the classification of medications		x			
INAMI	2004	Rapport du groupe d'expertise morbidité		x			
Janssen-Heijnen et al. [59]	2007	Negligible influence of comorbidity on prognosis of patients with small cell lung cancer: A population based study in the Netherlands	x				x
Janssen-Heijnen et al. [45]	2004	Effect of comorbidity on the treatment and prognosis of elderly patients with non-small cell lung cancer	x				x
Janssen-Heijnen et al. [58]	1998	Prevalence of co-morbidity in lung cancer patients and its relationship with treatment: a population-based study	x				

Authors	Year	Title	Lung cancer comorbidities identification	ATC codes identification	Validation tool	General information on Indices	Prevalence comorbidity
Kuo et al. [61]	2011	Predicting healthcare utilization using pharmacy-based metric with the WHO's anatomical therapeutic chemical algorithm		x			
Lopez-Encuentra et al. [56]	2002	Comorbidity in operable lung cancer. A multicenter descriptive study on 2992 patients	x				x
Overbeek et al. [63]	2012	Cardiovascular comorbidities among patients with metastatic colorectal cancer		x			
Sarfati [49]	2012	Review of methods used to measure comorbidity in cancer population: No gold standard			x		
Sarfati et al. [75]	2014	Cancer-specific administrative data-based comorbidity indices provided valid alternative to Charlson and National Cancer Institute Indices				x	
Sarfati et al. [50]	2014	Development of a Pharmacy based comorbidity index for patients with cancer		x	x		
Sloan et al. [64]	2003	Construction and Characteristics of the RxRisk-V		x	x		
Tammemagi et al. [47]	2003	Impact of comorbidity on lung cancer survival					x
Von Korff et al [62]	1992	A chronic disease score from automated pharmacy data		x			
	2014	National Lung Cancer Audit report	x				

Appendix 2.1.2. Nomenclature codes for identification of renal insufficiency

Code	Label_NL	Label_FR	Date_start	Date_end
107096	Forfaitair honorarium betaalbaar aan de huisarts voor het eerste jaar van een zorgtraject-contract gesloten met een rechthebbende met een chronische nierinsufficiëntie	Honoraires forfaitaires payables au médecin généraliste pour la première année d'un trajet de soins conclu avec un bénéficiaire atteint d'une insuffisance rénale chronique	20090601	29991231
107111	Forfaitair honorarium betaalbaar aan de geneesheer-specialist voor het eerste jaar van een zorgtraject-contract gesloten met een rechthebbende met een chronische nierinsufficiëntie	Honoraires forfaitaires payables au médecin spécialiste pour la première année d'un trajet de soins conclu avec un bénéficiaire atteint d'une insuffisance rénale chronique	20090601	29991231
107133	Forfaitair honorarium betaalbaar aan de huisarts voor het tweede, derde en vierde jaar van een zorgtraject-contract gesloten met een rechthebbende met een chronische nierinsufficiëntie	Honoraires forfaitaires payables au médecin généraliste pour les deuxième, troisième et quatrième années d'un trajet de soins conclu avec un bénéficiaire atteint d'une insuffisance rénale chronique	20090601	29991231
107155	Forfaitair honorarium betaalbaar aan de geneesheer-specialist voor het tweede, derde en vierde jaar van een zorgtraject-contract gesloten met een rechthebbende met een chronische nierinsufficiëntie	Honoraires forfaitaires payables au médecin spécialiste pour les deuxième, troisième et quatrième années d'un trajet de soins conclu avec un bénéficiaire atteint d'une insuffisance rénale chronique	20090601	29991231
235174	Aanleggen van een rechtstreekse arterioveneuze fistel of van een onrechtstreekse arterioveneuze fistel (shunt type Scribner) met het oog op hemodialyse	Création de fistule artérioveineuse directe ou d'une fistule artérioveineuse indirecte (shunt type Scribner) en vue d'une hémodialyse	19850401	29991231
235185	Aanleggen van een rechtstreekse arterioveneuze fistel of van een onrechtstreekse arterioveneuze fistel (shunt type Scribner) met het oog op hemodialyse	Création de fistule artérioveineuse directe ou d'une fistule artérioveineuse indirecte (shunt type Scribner) en vue d'une hémodialyse	19850401	29991231
470470	Extrarenale zuivering, verricht voor de behandeling van een chronische nierinsufficiëntie in een ziekenhuis volgens de techniek van de hemodialyse of de intermitterende hemofiltratie	Epuration extra-rénale réalisée pour le traitement d'une insuffisance rénale chronique en centre hospitalier par la technique d'hémodialyse ou d'hémofiltration intermittente	19910101	29991231

Code	Label_NL	Label_FR	Date_start	Date_end
470481	Extrarenale zuivering, verricht voor de behandeling van een chronische nierinsufficiëntie in een ziekenhuis volgens de techniek van de hemodialyse of de intermitterende hemofiltratie	Epuration extra-rénale réalisée pour le traitement d'une insuffisance rénale chronique en centre hospitalier par la technique d'hémodialyse ou d'hémofiltration intermittente	19910601	29991231
470735	Kwalitatieve en audiovelocimetrische evaluatie van (arteriële en/of veneuze) circulatieverschijnselen door Dopplereffect, in arterioveneuze fistels voor hemodialyse, buiten de heelkundige verstrekkingen, met protocol en besluit op basis van gestandaardiseerde Dopplerogrammen	Evaluation qualitative et audiovélocimétrique de phénomènes circulatoires (artériels et/ou veineux) par l'effet Doppler, au niveau du shunt artério-veineux d'une hémodialyse, en dehors des prestations chirurgicales, avec protocole et conclusion sur base de Dopplerogrammes standardisés	20081201	29991231
470746	Kwalitatieve en audiovelocimetrische evaluatie van (arteriële en/of veneuze) circulatieverschijnselen door Dopplereffect, in arterioveneuze fistels voor hemodialyse, buiten de heelkundige verstrekkingen, met protocol en besluit op basis van gestandaardiseerde Dopplerogrammen	Evaluation qualitative et audiovélocimétrique de phénomènes circulatoires (artériels et/ou veineux) par l'effet Doppler, au niveau du shunt artério-veineux d'une hémodialyse, en dehors des prestations chirurgicales, avec protocole et conclusion sur base de Dopplerogrammes standardisés	20081201	29991231
589374	Percutane endovasculaire plastiek van de ader bij veneuze stenose ten gevolge van chronische hemodialysebehandeling of bij compressie van de vena cava superior of inferior, van de vena supclavia of van de vena iliaca door een expansief proces, inclusief de manipulaties en controles tijdens de behandeling en/of het gebruikte materiaal, met uitsluiting van de dilatatiecatheter, de farmaca en de contrastmiddelen en de eventuele stent	Plastie endovasculaire percutanée de la veine pour sténose veineuse à la suite d'un traitement chronique par hémodialyse ou pour compression de la veine cave supérieure ou inférieure de la veine sous-clavière ou de la veine iliaque par processus expansif, y compris les manipulations et les contrôles au cours du traitement et/ou le matériel utilisé, à l'exclusion du cathéter de dilatation, des produits pharmaceutiques et de contraste et du tuteur éventuel	19951001	29991231

Code	Label_NL	Label_FR	Date_start	Date_end
589385	Percutane endovasculaire plastiek van de ader bij veneuze stenose ten gevolge van chronische hemodialysebehandeling of bij compressie van de vena cava superior of inferior, van de vena supclavia of van de vena iliaca door een expansief proces, inclusief de manipulaties en controles tijdens de behandeling en/of het gebruikte materiaal, met uitsluiting van de dilatatiecatheter, de farmaca en de contrastmiddelen en de eventuele stent	Plastie endovasculaire percutanée de la veine pour sténose veineuse à la suite d'un traitement chronique par hémodialyse ou pour compression de la veine cave supérieure ou inférieure de la veine sous-clavière ou de la veine iliaque par processus expansif, y compris les manipulations et les contrôles au cours du traitement et/ou le matériel utilisé, à l'exclusion du cathéter de dilatation, des produits pharmaceutiques et de contraste et du tuteur éventuel	19951001	29991231
754294	zorgtraject chronische nierinsufficiëntie – bloeddrukmeter – publieke officina	trajet de soins insuffisance rénale chronique – tensiomètre – officine publique	20090601	29991231
757433	zorgtraject chronische nierinsufficiëntie – bloeddrukmeter – ziekenhuisofficina	trajet de soins insuffisance rénale chronique – tensiomètre – officine hospitalière	20090601	29991231
761272	Vast bedrag voor verpleegdag : Forfait nierdialyse	Forfait pour journée d'entretien : Forfait dialyse rénale	19870101	29991231
761283	Vast bedrag voor verpleegdag : Forfait nierdialyse	Forfait pour journée d'entretien : Forfait dialyse rénale	19870101	29991231
761456	Hemodialyse thuis - hemodialyse thuis met verpleegkundige assistentie aan huis	Hémodialyse à domicile - hémodialyse à domicile avec assistance d'un praticien de l'art infirmier à domicile	20010701	29991231
761493	Dialyse thuis of in een centrum : Hemodialyse thuis	Dialyse à domicile ou dans un centre : Hémodialyse à domicile	19850401	29991231
761515	Dialyse thuis of in een centrum : Dialyse in een collectief auto-dialysecentrum	Dialyse à domicile ou dans un centre : Dialyse dans un centre collectif d'autodialyse	19850401	29991231
761526	Dialyse thuis of in een centrum : Dialyse in een collectief auto-dialysecentrum	Dialyse à domicile ou dans un centre : Dialyse dans un centre collectif d'autodialyse	20051001	29991231

Appendix 2.1.3. ROC curves for each comorbid conditions, all ages and all centres.

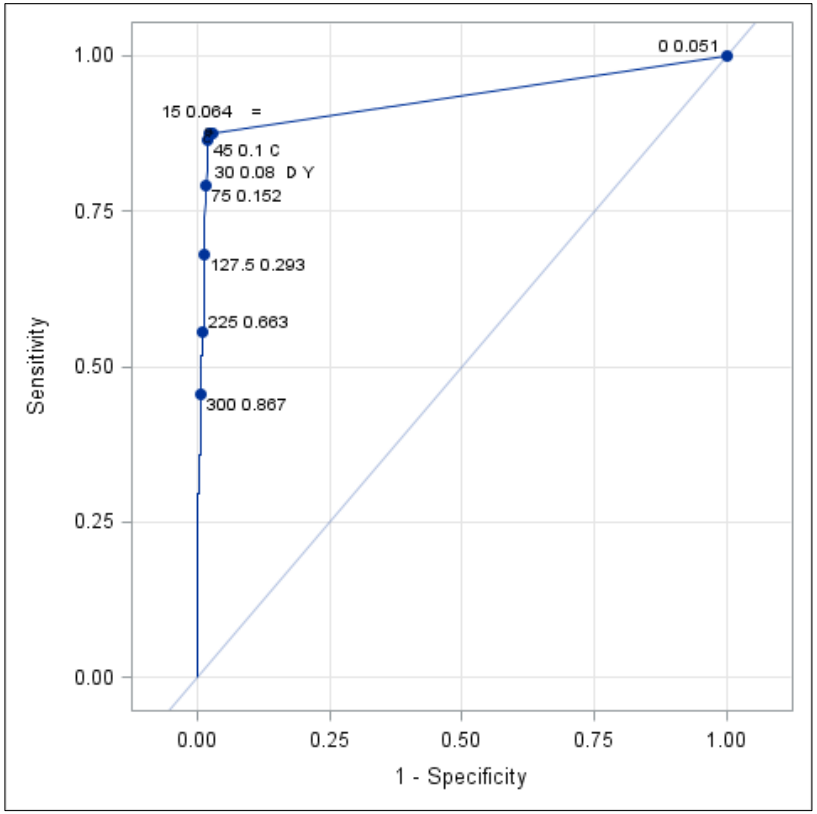


Fig 1a. Diabetes Mellitus

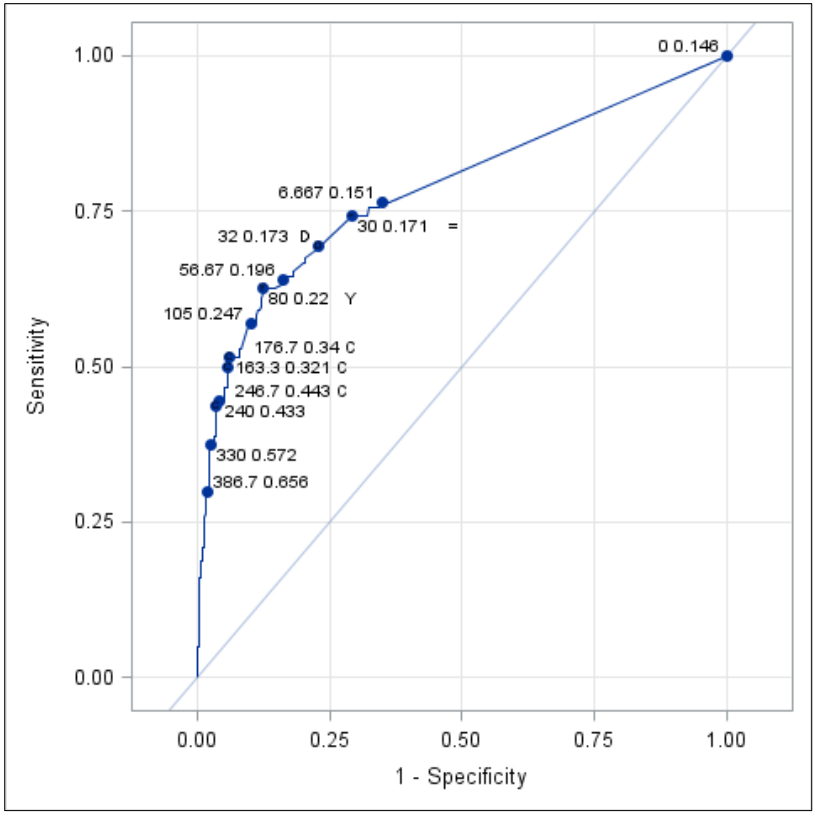


Fig 1b. Chronic respiratory diseases

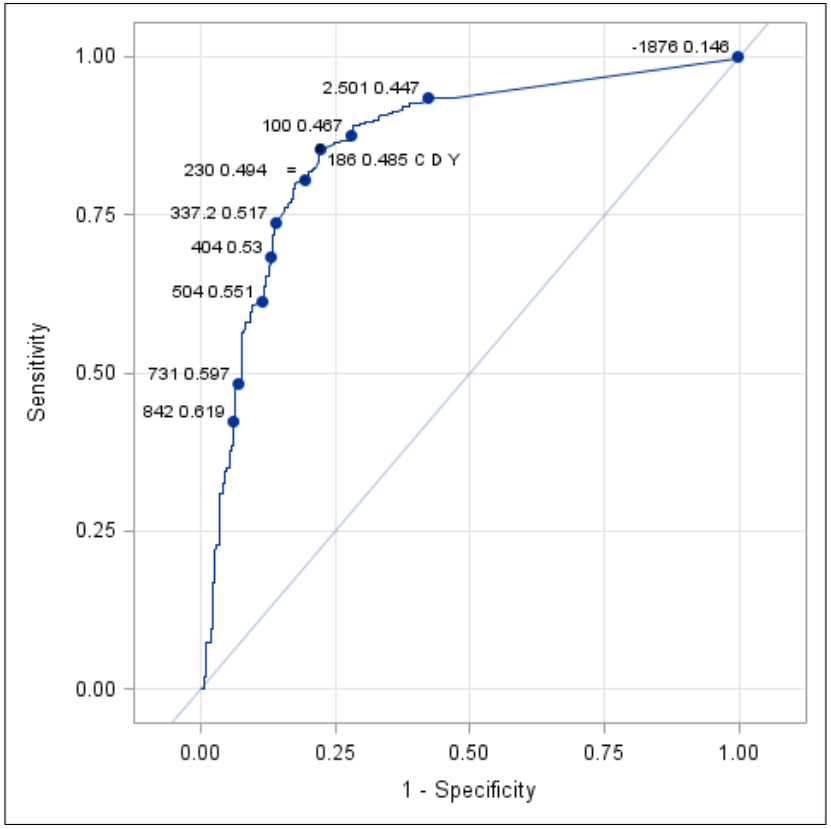


Fig1c. Chronic cardiovascular diseases

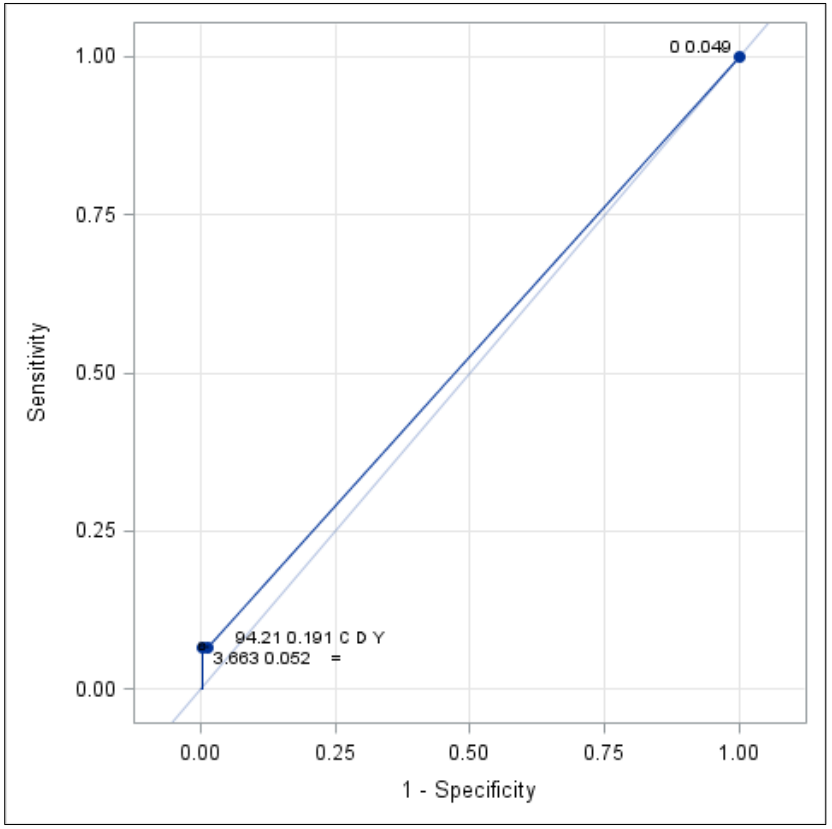


Fig1d. Renal insufficiency

APPENDIX 3. APPENDICES FROM CHAPTER 11: IMPACT OF HOSPITAL VOLUME ON PATIENTS TREATMENT AND OUTCOME

Appendix 3.1.1. Observed survival of operated Non-Small Cell Lung Cancer patients by patient and tumour characteristics

Table 1 – Observed survival of operated NSCLC patients by patient and tumour characteristics (N=2 084)

Characteristics	Observed survival (%)					
	N at risk	1-year	2-year	3-year (95%CI)		Median survival (months)
Overall	**2 084**	88.3	77.5	68.9	*(66.8-70.8)*	
Sex						
Male	1 404	85.9	73.3	64.1	*(61.5-66.5)*	58.2
Female	680	93.4	86.2	78.8	*(75.5-81.7)*	
Age group						
<50 years	135	92.6	85.2	82.2	*(74.6-87.7)*	
50-59 years	489	89.6	78.1	69.9	*(65.6-73.8)*	
60-69 years	783	90.2	78.1	69.9	*(66.6-73.0)*	
70-79 years	596	84.7	75.2	65.4	*(61.5-69.1)*	59.1
80+ years	81	82.7	71.6	55.6	*(44.1-65.6)*	44.1
Histological subtype						
Adenocarcinoma	1 095	89.9	79.3	71.2	*(68.4-73.8)*	

Characteristics	Observed survival (%)					
	N at risk	1-year	2-year		3-year (95%CI)	Median survival (months)
Large Cell Carcinoma	60	73.3	60.0	56.7	*(43.2-68.1)*	45.8
Other specified Carcinoma	165	93.9	83.6	75.7	*(68.4-81.6)*	
Squamous Cell Carcinoma	730	86.6	75.3	65.3	*(61.8-68.7)*	59.1
Unspecified Non-Small Cell Lung Cancer	34	76.5	64.7	58.8	*(40.6-73.2)*	51.0
Sublocalisation						
C34.0 Main bronchus	29	89.7	72.4	62.1	*(42.1-76.9)*	
C34.1 Upper lobe, bronchus or lung	994	88.7	78.5	69.5	*(66.6-72.3)*	
C34.2 Middle lobe, bronchus or lung	89	88.8	78.7	70.8	*(60.1-79.1)*	
C34.3 Lower lobe, bronchus or lung	557	87.3	78.1	70.3	*(66.4-74.0)*	
C34.9 Bronchus or lung, unspecified	415	88.6	74.4	65.5	*(60.7-69.8)*	59.1
Clinical stage						
I	735	92.5	83.5	76.7	*(73.5-79.6)*	
II	321	84.4	71.3	62.0	*(56.4-67.0)*	57.8
III	258	83.7	69.8	60.4	*(54.2-66.1)*	54.9
IV	89	68.5	47.2	38.2	*(28.2-48.1)*	23.0

Characteristics	Observed survival (%)					Median survival (months)
	N at risk	1-year	2-year		3-year (95%CI)	
X	681	90.0	80.8	70.9	*(67.3-74.2)*	
Pathological stage						
I	952	93.3	86.6	77.9	*(75.2-80.4)*	
II	475	86.3	71.8	62.9	*(58.4-67.1)*	59.1
III	230	78.7	57.4	46.0	*(39.5-52.3)*	31.7
IV	43	69.8	62.8	51.2	*(35.5-64.8)*	41.2
X	384	86.4	75.7	69.4	*(64.6-73.8)*	
Combined stage						
I	1,039	93.6	86.8	78.6	*(76.0-81.0)*	
II	524	87.0	73.9	65.1	*(60.8-69.0)*	59.1
III	303	80.2	62.0	51.8	*(46.0-57.2)*	39.2
IV	114	67.5	50.0	40.4	*(31.3-49.2)*	24.6
X	104	88.5	77.9	72.1	*(62.4-79.7)*	
Chronic respiratory disease						
No	1 483	88.6	78.5	70.5	*(68.1-72.8)*	

Characteristics	Observed survival (%)					
	N at risk	1-year	2-year	3-year (95%CI)		Median survival (months)
Yes	601	87.7	74.9	64.9	*(60.9-68.6)*	59.1
Cardiovascular disease						
No	943	88.7	77.7	70.4	*(67.4-73.2)*	
Yes	1 141	88.1	77.3	67.6	*(64.8-70.3)*	
Diabetes mellitus						
No	1 827	88.6	78.4	70.1	*(68.0-72.2)*	
Yes	257	86.8	71.2	59.9	*(53.7-65.6)*	
Days of hospitalisation one year before incidence date lung cancer						
None	1 428	89.2	78.1	69.6	*(67.2-72.0)*	
1-5 days	421	86.2	76.0	67.9	*(63.2-72.2)*	
6-15 days	147	89.8	78.9	69.4	*(61.2-76.2)*	
More than 15 days	88	81.8	72.7	60.2	*(49.2-69.6)*	43.0
WHO - performance status						
0 – Asymptomatic	523	90.6	82.8	75.1	*(71.2-78.6)*	
1 – Symptomatic but completely ambulatory	1 101	87.2	74.8	65.7	*(62.8-68.4)*	

Characteristics	Observed survival (%)					
	N at risk	1-year	2-year		3-year (95%CI)	Median survival (months)
2 – Symptomatic, <50% in bed during the day	47	78.7	61.7	51.1	*(36.1-64.2)*	36.6
3 – Symptomatic, confined to bed or chair more than 50% of waking hours	7	42.9	42.9	42.9	*(9.8-73.4)*	7.6
4 – Completely disabled; totally confined to bed or chair	5	100.0	100.0	60.0	*(12.6-88.2)*	
Missing	*401*	90.3	80.0	72.0	*(67.4-76.2)*	59.1

Appendix 3.1.2. Additional results on impact of surgical volume on outcome

Table 1 – Effect of surgical volume on 60-day mortality: results from logistic regression (n=2 083)

Characteristics	Odds ratios (95%CI)				Type 3 test
	Unadjusted OR	Adjusted OR	Lower Limit	Upper limit	P value
Annual surgical volume (ref=Very low (<10 patients))					0.0972
Low (10-19 patients)	0.46	0.45	0.216	0.939	
Medium (20-39 patients)	0.59	0.60	0.307	1.173	
High (≥40 patients)	0.57	0.49	0.260	0.910	
Sex (ref=Male)					0.0035
Female		0.35	0.177	0.712	
Age group (ref= <60)					0.0002
60-69 years		2.15	0.990	4.692	
70-79 years		4.60	2.128	9.964	
80+ years		5.82	1.999	16.929	
Combined stage (ref=I)					0.0016
II		1.48	0.807	2.726	
III		3.32	1.786	6.155	
IV		3.30	1.339	8.129	
X		1.27	0.401	4.002	
WHO performance status (ref=0 – Asymptomatic)					0.0748
1 – Symptomatic but completely ambulatory		1.21	0.646	2.284	
2 – Symptomatic, <50% in bed during the day		1.85	0.483	7.073	
3 & 4– Symptomatic, confined to bed or chair more than 50% of waking hours		11.68	2.142	63.659	

Characteristics	Unadjusted OR	Odds ratios (95%CI)			Type 3 test
		Adjusted OR	Lower Limit	Upper limit	P value
Missing		1.26	0.578	2.727	
Histological subtype (ref=Adenocarcinoma)					0.0162
Other subtypes		2.69	1.348	5.356	
Squamous Cell		1.59	0.939	2.710	
Respiratory disease (ref=No)					0.6674
Yes		0.89	0.528	1.506	
Cardiovascular disease (ref=No)					0.9565
Yes		0.99	0.591	1.644	
Diabetes (ref=No)					0.9709
Yes		0.99	0.510	1.915	
Days of hospitalization one year before incidence date lung cancer (ref=0)					0.8833
1-5 days		1.24	0.708	2.168	
6-15 days		0.97	0.367	2.550	
More than 15 days		1.20	0.398	3.617	

Table 2 – Effect of surgical volume on 1-year survival: results from Cox proportional hazard regression model (n=2 083)

Characteristics	Unadjusted HR	Hazard ratios (95%CI) Adjusted HR	Lower Limit	Upper limit	Type 3 test P value
Annual surgical volume (ref= Very low (<10 patients))					0.0259
Low (10-19 patients)	0.79	0.71	0.474	1.054	
Medium (20-39 patients)	0.72	0.66	0.445	0.984	
High (>=40 patients)	0.71	0.56	0.387	0.816	
Sex (ref=Male)					<.0001
Female	0.45	0.51	0.367	0.716	
Age group 1 (ref= <60)					0.0005
60-69 years	1.02	1.04	0.738	1.478	
70-79 years	1.63	1.80	1.259	2.567	
80+ years	1.90	2.14	1.169	3.929	
Combined stage (ref=I)					<.0001
II	2.10	2.10	1.486	2.981	
III	3.35	3.74	2.600	5.371	
IV	5.91	6.67	4.392	10.118	
X	1.88	1.98	1.025	3.810	
Sublocalisation (ref=C34.0 Main bronchus)					0.6607
C34.1 Upper lobe, bronchus or lung	1.12	1.41	0.440	4.514	
C34.2 Middle lobe, bronchus or lung	1.10	1.21	0.325	4.496	
C34.3 Lower lobe, bronchus or lung	1.27	1.63	0.505	5.257	
C34.9 Bronchus or lung, unspecified	1.13	1.28	0.392	4.158	
WHO performance status (ref=0 – Asymptomatic)					0.0267

Characteristics	Unadjusted HR	Hazard ratios (95%CI)			Type 3 test
		Adjusted HR	Lower Limit	Upper limit	P value
1 – Symptomatic but completely ambulatory	1.40	1.09	0.785	1.526	
2 – Symptomatic, <50% in bed during the day	2.42	1.82	0.914	3.633	
3 & 4 – Symptomatic, confined to bed or chair more than 50% of waking hours	4.28	3.91	1.387	11.002	
Missing	1.05	0.88	0.564	1.360	
Histological subtype (ref=Adenocarcinoma)					0.1367
Other subtypes	1.32	1.49	1.007	2.200	
Squamous Cell	1.35	1.09	0.819	1.462	
Respiratory disease (ref=No)					0.6142
Yes	1.08	1.08	0.810	1.428	
Cardiovascular disease (ref=No)					0.3437
Yes	1.06	0.87	0.660	1.156	
Diabetes (ref=No)					0.5861
Yes	1.17	1.11	0.762	1.618	
Days of hospitalization one year before incidence date lung cancer (ref=0)					0.0438
1-5 days	1.30	1.46	1.071	1.989	
6-15 days	0.94	1.13	0.656	1.941	
More than 15 days	1.74	1.70	0.994	2.901	

Table 3 – Effect of surgical volume on 3-year survival: results from Cox proportional hazard regression model (n=2 083)

Characteristics	Unadjusted HR	Hazard ratios (95%CI) Adjusted HR	Lower Limit	Upper limit	Type 3 test P value
Annual surgical volume (ref= Very low (<10 patients))					0.2583
Low (10-19 patients)	0.95	0.87	0.669	1.120	
Medium (20-39 patients)	0.87	0.82	0.636	1.060	
High (≥40 patients)	0.93	0.79	0.618	1.000	
Sex (ref=Male)					<.0001
Female	0.53	0.58	0.478	0.704	
Age group (ref= <60)					0.0019
60-69 years	1.11	1.07	0.875	1.317	
70-79 years	1.33	1.35	1.082	1.682	
80 years+	1.81	1.82	1.254	2.650	
Combined stage (ref=I)					<.0001
II	1.80	1.76	1.437	2.151	
III	2.81	2.92	2.351	3.629	
IV	3.99	4.11	3.110	5.438	
X	1.42	1.43	0.949	2.161	
Sub-localisation (ref=C34.0 Main bronchus)					0.8137
C34.1 Upper lobe, bronchus or lung	0.77	0.97	0.525	1.795	
C34.2 Middle lobe, bronchus or lung	0.75	0.87	0.424	1.788	
C34.3 Lower lobe, bronchus or lung	0.76	0.98	0.528	1.835	
C34.9 Bronchus or lung, unspecified	0.90	1.08	0.581	2.019	
WHO performance status 1 (ref=0 – Asymptomatic)					0.0039

Characteristics	Unadjusted HR	Hazard ratios (95%CI)			Type 3 test
		Adjusted HR	Lower Limit	Upper limit	P value
1 – Symptomatic but completely ambulatory	1.47	1.21	0.988	1.485	
2 – Symptomatic, <50% in bed during the day	2.38	1.94	1.241	3.043	
3 & 4 Symptomatic, confined to bed or chair more than 50% of waking hours	2.58	2.36	1.032	5.391	
Missing	1.16	0.97	0.748	1.267	
subtype (ref=Adenocarcinoma)					0.2244
Other subtypes	1.11	1.23	0.955	1.574	
Squamous Cell	1.25	0.98	0.822	1.174	
Respiratory disease (ref=No)					
Yes	1.23	1.24	1.048	1.469	0.0122
Cardiovascular disease (ref=No)					
Yes	1.11	0.96	0.810	1.143	0.6642
Diabetes (ref=No)					0.0094
Yes	1.41	1.34	1.074	1.672	
Days of hospitalization one year before incidence date lung cancer (ref=0)					0.2434
1-5 days	1.08	1.15	0.942	1.398	
6-15 days	1.00	1.11	0.811	1.522	
More than 15 days	1.39	1.35	0.950	1.928	

Appendix 3.1.3. Additional results on impact of radiotherapy volume on outcome

Table 1 – Results from logistic regression on 60-day mortality: adjusted odds ratio and 95% CI + results from type 3 tests, unadjusted odds ratio for RT volume (n=1 412).

Characteristics		Odds ratios (95%CI)			Type 3 test
		Adjusted OR	Lower Limit	Upper limit	P value
Annual radiotherapy volume (ref= Low (<50 patients))	**Unadjusted OR**				0.5711
Medium (50-99 patients)	1.080	1.03	0.649	1.629	
High (≥100 patients)	1.280	1.26	0.785	2.021	
Sex (ref=Male)		1.04	0.667	1.630	0.8541
Female					
Age group (ref= <60)					0.0013
60-69 years		1.70	0.925	3.142	
70-79 years		2.48	1.342	4.584	
80 years+ years		3.73	1.866	7.446	
Combined stage (ref=I)					0.0207
II		1.88	0.862	4.098	
III		2.43	1.291	4.570	
WHO performance status 1 (ref=0 – Asymptomatic)					0.0466
1 – Symptomatic but completely ambulatory		1.49	0.802	2.751	
2 – Symptomatic, <50% in bed during the day		2.47	1.101	5.533	
3 & 4 – Symptomatic, confined to bed or chair more than 50% of waking hours		4.41	1.229	15.807	
Missing		2.40	1.016	5.645	
Histological subtype (ref=Adenocarcinoma)					0.9834

Characteristics	Odds ratios (95%CI)			Type 3 test
	Adjusted OR	Lower Limit	Upper limit	P value
Other subtypes	1.02	0.623	1.681	
Squamous Cell	0.98	0.621	1.546	
Respiratory disease (ref=No)				0.0297
Yes	0.62	0.404	0.954	
Cardiovascular disease (ref=No)				0.2550
Yes	1.28	0.838	1.950	
Diabetes (ref=No)				0.2337
Yes	1.35	0.825	2.201	
Days of hospitalization one year before incidence date lung cancer (ref=0)				0.2427
1-5 days	1.32	0.802	2.181	
6-15 days	0.92	0.423	2.015	
More than 15 days	2.06	0.930	4.561	

Table 2 – Effect of radiotherapy volume on 1-year survival: results from Cox proportional hazard regression (n=1 170).

Characteristics	Hazard ratios (95%CI)				Type 3 test
	Unadjusted HR	Adjusted HR	Lower Limit	Upper limit	P value
Annual radiotherapy volume (ref= Low (<50 patients))					0.0960
Medium (50-99 patients)	1.253	1.31	1.025	1.672	
High (≥100 patients)	1.205	1.19	0.913	1.554	
Sex (ref= Male)					0.1750
Female		0.84	0.646	1.083	
Age group 1 (ref= <60)					<.0001
60-69 years		1.14	0.830	1.563	
70-79 years		1.48	1.073	2.049	
80+ years		2.42	1.702	3.450	
Combined stage (ref=I)					<.0001
II		2.54	1.648	3.930	
III		3.34	2.331	4.781	
Sublocalisation (ref=C34.0 Main bronchus)					
C34.1 Upper lobe, bronchus or lung		0.88	0.575	1.334	0.8410
C34.2 Middle lobe, bronchus or lung		0.96	0.488	1.898	
C34.3 Lower lobe, bronchus or lung		0.88	0.560	1.379	
C34.9 Bronchus or lung, unspecified		0.79	0.508	1.236	
WHO performance status 1 (ref=0 – Asymptomatic)					0.0012
1 – Symptomatic but completely ambulatory		1.52	1.078	2.135	
2 – Symptomatic, <50% in bed during the day		2.42	1.562	3.760	

Characteristics	Unadjusted HR	Hazard ratios (95%CI)			Type 3 test
		Adjusted HR	Lower Limit	Upper limit	P value
3 & 4 – Symptomatic, confined to bed or chair more than 50% of waking hours		2.60	1.190	5.663	
Missing		1.71	1.060	2.768	
Histological subtype (ref=Adenocarcinoma)					0.6568
Other subtypes		1.16	0.837	1.611	
Squamous Cell		1.07	0.848	1.345	
Respiratory disease (ref=No)					0.2398
Yes		0.87	0.698	1.094	
Cardiovascular disease (ref=No)					0.2864
Yes		1.13	0.901	1.425	
Diabetes (ref=No)					0.2143
Yes		1.19	0.905	1.559	
Days of hospitalization one year before incidence date lung cancer (ref=0)					0.0004
1-5 days		0.88	0.651	1.189	
6-15 days		1.20	0.816	1.772	
More than 15 days		2.40	1.571	3.659	

Table 3 – Effect of radiotherapy volume on 3-year survival: results from Cox proportional hazard regression model (n=1170)

Characteristics		Hazard ratios (95%CI)			Type 3 test
		Adjusted HR	Lower Limit	Upper limit	P value
Annual radiotherapy volume (ref= Low (<50 patients))	Unadjusted HR				0.1354
Medium (50-99 patients)	1.111	1.15	0.976	1.354	
High (≥100 patients)	1.144	1.18	0.986	1.411	
Sex (ref=Male)					0.0444
Female		0.84	0.705	0.996	
Age group (ref= <60)					<.0001
60-69 years		1.04	0.845	1.269	
70-79 years		1.28	1.038	1.588	
80+ years		2.13	1.677	2.716	
Combined stage (ref=I)					<.0001
II		1.70	1.306	2.216	
III		2.01	1.631	2.483	
Sub-localisation (ref=C34.0 Main bronchus)					0.4537
C34.1 Upper lobe, bronchus or lung		0.84	0.626	1.133	
C34.2 Middle lobe, bronchus or lung		1.11	0.706	1.738	
C34.3 Lower lobe, bronchus or lung		0.84	0.612	1.152	
C34.9 Bronchus or lung, unspecified		0.83	0.607	1.123	
WHO performance status 1 (ref=0 – Asymptomatic)					<.0001
1 – Symptomatic but completely ambulatory		1.47	1.187	1.817	
2 – Symptomatic, <50% in bed during the day		2.08	1.540	2.805	

Characteristics	Hazard ratios (95%CI)			Type 3 test
	Adjusted HR	Lower Limit	Upper limit	P value
3 & 4 – Symptomatic, confined to bed or chair more than 50% of waking hours	1.83	0.997	3.372	
Missing	1.59	1.159	2.188	
Histological subtype (ref=Adenocarcinoma)				0.5369
Other subtypes	1.04	0.830	1.308	
Squamous Cell	1.09	0.934	1.279	
Respiratory disease (ref=No)				0.6973
Yes	1.03	0.886	1.199	
Cardiovascular disease (ref=No)				0.0609
Yes	1.16	0.993	1.353	
Diabetes (ref=No)				0.2551
Yes	1.12	0.922	1.356	
Days of hospitalization one year before incidence date lung cancer (ref=0)				0.0265
1-5 days	0.86	0.708	1.055	
6-15 days	1.14	0.870	1.490	
More than 15 days	1.50	1.074	2.096	

Appendix 3.1.4. Additional results on impact of diagnostic volume on outcome

Table 1 – Effect of diagnostic volume on 1-year survival for combined stage I-III patients: results from Cox proportional hazard regression model (n=4 281)

Characteristics		Hazard ratios (95%CI)			Type 3 test
		Adjusted HR	Lower Limit	Upper limit	P value
Annual diagnostic volume (ref= Low (<50 patients))	**Unadj. HR**				0.8174
Medium (50-99 patients)	0.897	1.01	0.881	1.156	
High (100-149 patients)	0.796	0.98	0.836	1.151	
Very high (≥150 patients)	0.910	1.07	0.902	1.266	
Sex (ref=Male)					0.4225
Female		0.95	0.832	1.080	
Age group 1 (ref= <60)					<.0001
60-69 years		1.16	0.977	1.374	
70-79 years		1.73	1.469	2.044	
80+ years		2.72	2.254	3.292	
Sub-localisation (ref=C34.0 Main bronchus)					0.0008
C34.1 Upper lobe, bronchus or lung		0.68	0.542	0.861	
C34.2 Middle lobe, bronchus or lung		0.66	0.453	0.969	
C34.3 Lower lobe, bronchus or lung		0.72	0.564	0.922	
C34.9 Bronchus or lung, unspecified		0.85	0.676	1.082	
WHO performance status 1 (ref=0 – Asymptomatic)					<.0001
1 – Symptomatic but completely ambulatory		1.32	1.106	1.575	
2 – Symptomatic, <50% in bed during the day		2.56	2.047	3.195	

Characteristics	Hazard ratios (95%CI)			Type 3 test
	Adjusted HR	Lower Limit	Upper limit	P value
3 & 4 – Symptomatic, confined to bed or chair more than 50% of waking hours	5.22	4.022	6.772	
Missing	1.20	0.938	1.540	
Combined stage (ref=I)				<.0001
II	2.36	1.920	2.895	
III	4.63	3.904	5.484	
Histological subtype (ref=Adenocarcinoma)				0.0007
Other subtypes	1.37	1.166	1.617	
Squamous Cell	1.12	0.990	1.267	
Respiratory disease (ref=No)				0.1140
Yes	1.10	0.978	1.235	
Cardiovascular disease (ref=No)				0.3292
Yes	0.94	0.834	1.063	
Diabetes (ref=No)				0.1193
Yes	1.13	0.969	1.314	
Days of hospitalization one year before incidence date lung cancer (ref=0)				0.0515
1-5 days	0.96	0.824	1.123	
6-15 days	1.10	0.890	1.360	
More than 15 days	1.35	1.075	1.705	

Table 2 – Effect of diagnostic volume on 1-year survival for combined stage IV patients: results from Cox proportional hazard regression model (N=3 955)

Characteristics		Hazard ratios (95%CI)			Type 3 test
		Adjusted HR	Lower Limit	Upper limit	P value
Annual diagnostic volume (ref= Low (<50 patients))	**Unadjusted HR**				0.0041
Medium (50-99 patients)	1.080	1.17	1.066	1.293	
High (100-149 patients)	1.064	1.17	1.050	1.308	
Very high (≥150 patients)	1.042	1.19	1.048	1.344	
Sex (ref=Male)					<.0001
Female		0.79	0.725	0.858	
Age group 1 (ref= <60)					<.0001
60-69 years		1.05	0.947	1.162	
70-79 years		1.22	1.095	1.352	
80+ years		1.64	1.438	1.860	
Sub-localisation (ref=C34.0 Main bronchus)					0.5434
C34.1 Upper lobe, bronchus or lung		0.91	0.775	1.068	
C34.2 Middle lobe, bronchus or lung		0.85	0.675	1.081	
C34.3 Lower lobe, bronchus or lung		0.93	0.784	1.104	
C34.9 Bronchus or lung, unspecified		0.96	0.817	1.125	
WHO performance status 1 (ref=0 – Asymptomatic)					<.0001
1 – Symptomatic but completely ambulatory		1.30	1.111	1.512	
2 – Symptomatic, <50% in bed during the day		2.26	1.902	2.675	
3 & 4 – Symptomatic, confined to bed or chair more than 50% of waking hours		3.97	3.285	4.797	
Missing		1.42	1.167	1.739	

Characteristics	Hazard ratios (95%CI)			Type 3 test
	Adjusted HR	Lower Limit	Upper limit	P value
Histological subtype (ref=Adenocarcinoma)				<.0001
Other subtypes	1.36	1.234	1.508	
Squamous Cell	1.05	0.953	1.150	
Respiratory disease (ref=No)				0.3178
Yes	1.05	0.957	1.144	
Cardiovascular disease (ref=No)				0.0906
Yes	1.07	0.989	1.165	
Diabetes mellitus (ref=No)				0.1127
Yes	1.09	0.979	1.223	
Days of hospitalization one year before incidence date lung cancer (ref=0)				0.0084
1-5 days	1.02	0.913	1.134	
6-15 days	1.02	0.866	1.199	
More than 15 days	1.39	1.151	1.676	

Table 3 – Effect of diagnostic volume on 3-year survival for combined stage I-III patients: results from Cox proportional hazard regression model (n=4 281)

Characteristics		Hazard ratios (95%CI)			Type 3 test
		Adjusted HR	Lower Limit	Upper limit	P value
Annual diagnostic volume (ref= Low (<50 patients))	**Unadjusted HR**				0.0041
Medium (50-99 patients)	1.080	1.17	1.066	1.293	
High (100-149 patients)	1.064	1.17	1.050	1.308	
Very high (≥150 patients)	1.042	1.19	1.048	1.344	
Sex (ref=Male)					
Female		0.87	0.790	0.957	0.0044
Age group 1 (ref= <60)					
60-69 years		1.14	1.013	1.282	<.0001
70-79 years		1.55	1.379	1.746	
80+ years		2.71	2.361	3.121	
Sub-localisation (ref=C34.0 Main bronchus)					<.0001
C34.1 Upper lobe, bronchus or lung		0.72	0.602	0.859	
C34.2 Middle lobe, bronchus or lung		0.67	0.510	0.889	
C34.3 Lower lobe, bronchus or lung		0.72	0.600	0.874	
C34.9 Bronchus or lung, unspecified		0.86	0.721	1.036	
WHO performance status 1 (ref=0 – Asymptomatic)					<.0001
1 – Symptomatic but completely ambulatory		1.41	1.251	1.594	
2 – Symptomatic, <50% in bed during the day		2.44	2.060	2.879	
3 & 4 – Symptomatic, confined to bed or chair more than 50% of waking hours		4.66	3.755	5.773	
Missing		1.19	1.000	1.409	

Characteristics	Hazard ratios (95%CI)			Type 3 test
	Adjusted HR	Lower Limit	Upper limit	P value
Combined stage (ref=I)				<.0001
II	1.82	1.596	2.081	
III	3.68	3.307	4.097	
Histological subtype (ref=Adenocarcinoma)				0.0071
Other subtypes	1.20	1.058	1.357	
Squamous Cell	1.11	1.016	1.215	
Respiratory disease (ref=No)				0.0008
Yes	1.16	1.062	1.259	
Cardiovascular disease (ref=No)				0.7807
Yes	0.99	0.904	1.079	
Diabetes mellitus (ref=No)				0.0025
Yes	1.19	1.062	1.327	
Days of hospitalization one year before incidence date lung cancer (ref=0)				0.0210
1-5 days	0.92	0.822	1.028	
6-15 days	1.05	0.895	1.226	
More than 15 days	1.26	1.051	1.502	

Table 4 – Effect of diagnostic volume on 3-year survival for combined stage IV patients: results from Cox proportional hazard regression model (N=3 955)

Characteristics		Hazard ratios (95%CI)			Type 3 test
		Adjusted HR	Lower Limit	Upper limit	P value
Annual diagnostic volume (ref= Low (<50 patients)/year)	**Unadjusted HR**				0.1296
Medium (50-99 patients)	1.020	1.10	1.010	1.195	
High (100-149 patients)	0.998	1.08	0.977	1.183	
Very high (≥150 patients)	0.985	1.11	0.994	1.233	
Sex (ref=Male)					<.0001
Female		0.83	0.770	0.889	
Age group 1 (ref= <60)					<.0001
60-69 years		1.04	0.953	1.135	
70-79 years		1.20	1.092	1.309	
80+ years		1.50	1.333	1.680	
Sub-localisation (ref=C34.0 Main bronchus)					0.1084
C34.1 Upper lobe, bronchus or lung		0.86	0.752	0.994	
C34.2 Middle lobe, bronchus or lung		0.79	0.646	0.975	
C34.3 Lower lobe, bronchus or lung		0.90	0.775	1.043	
C34.9 Bronchus or lung, unspecified		0.92	0.801	1.058	
WHO performance status 1 (ref=0 – Asymptomatic)					<.0001
1 – Symptomatic but completely ambulatory		1.24	1.097	1.410	
2 – Symptomatic, <50% in bed during the day		1.98	1.717	2.289	
3 & 4– Symptomatic, confined to bed or chair more than 50% of waking hours		3.42	2.895	4.035	

Characteristics	Hazard ratios (95%CI)			Type 3 test
	Adjusted HR	Lower Limit	Upper limit	P value
Missing	1.21	1.018	1.428	
Histological subtype (ref=Adenocarcinoma)				<.0001
Other subtypes	1.31	1.192	1.429	
Squamous Cell	1.07	0.987	1.164	
Respiratory disease (ref=No)				0.5260
Yes	1.03	0.948	1.110	
Cardiovascular disease (ref=No)				0.0258
Yes	1.08	1.010	1.164	
Diabetes mellitus (ref=No)				0.4048
Yes	1.04	0.944	1.153	
Days of hospitalization one year before incidence date lung cancer (ref=0)				0.2012
1-5 days	0.97	0.885	1.072	
6-15 days	0.97	0.838	1.117	
More than 15 days	1.19	1.000	1.419	

Appendix 3.1.5. Additional results on impact of diagnostic volume on guideline concordant treatment for NSCLC patients

Table 1 – Effect of diagnostic volume on probability to receive guideline-concordant treatment (surgery) for cI-II NSCLC patients: results from logistic regression (n=1 716)

Characteristics		Odds ratios (95%CI)			Type 3 test
		Adjusted OR	Lower Limit	Upper limit	P value
Annual diagnostic volume (ref= Low (<50 patients))	**Unadjusted OR**				0.0980
Medium (50-99 patients)	1.24	1.25	0.928	1.678	
High (100-149 patients)	1.49	1.23	0.890	1.691	
Very high (≥100 patients)	1.77	1.58	1.103	2.253	
Sex (ref=Male)					0.8733
Female		1.02	0.793	1.314	
Age group 1 (ref= <60)					<.0001
60-69 years		0.60	0.436	0.840	
70-79 years		0.39	0.280	0.549	
80+ years		0.09	0.056	0.138	
Sub-localisation (ref=C34.0 Main bronchus)					<.0001
C34.1 Upper lobe, bronchus or lung		3.06	1.577	5.923	
C34.2 Middle lobe, bronchus or lung		4.28	1.830	10.010	
C34.3 Lower lobe, bronchus or lung		3.41	1.730	6.707	
C34.9 Bronchus or lung, unspecified		1.57	0.796	3.085	
WHO performance status 1 (ref=0 – Asymptomatic)					<.0001
1 – Symptomatic but completely ambulatory		0.58	0.436	0.765	
2 – Symptomatic, <50% in bed during the day		0.15	0.084	0.254	
3 & 4 – Symptomatic, confined to bed or chair more than 50% of waking hours		0.08	0.033	0.181	

Characteristics	Odds ratios (95%CI)			Type 3 test
	Adjusted OR	Lower Limit	Upper limit	P value
Missing	0.65	0.397	1.051	
Histological subtype (ref=Adenocarcinoma)				0.0015
Other subtypes	0.57	0.400	0.809	
Squamous Cell	0.71	0.554	0.908	
Respiratory disease (ref=No)				<.0001
Yes	0.57	0.455	0.720	
Cardiovascular disease (ref=No)				0.3980
Yes	1.11	0.868	1.430	
Diabetes mellitus (ref=No)				0.9029
Yes				
Days of hospitalization one year before incidence date lung cancer (ref=0)				0.0123
1-5 days	1.28	0.948	1.723	
6-15 days	0.88	0.580	1.327	
More than 15 days	0.56	0.354	0.874	

Table 2 – Effect of diagnostic volume on probability to receive guideline-concordant treatment (chemoradiation) for cIII NSCLC patients: results from logistic regression (n=1 970)

Characteristics		Odds ratios (95%CI)			Type 3 test
		Adjusted OR	Lower Limit	Upper limit	P value
Annual diagnostic volume (ref= Low (<50 patients))	**Unadjusted OR**				0.5102
Medium (50-99 patients)	0.99	0.94	0.730	1.209	
High (100-149 patients)	1.26	1.15	0.856	1.531	
Very high (≥100 patients)	1.06	0.93	0.679	1.261	
Sex (ref=Male)		0.95	0.753	1.201	0.6734
Female					
Age group 1 (ref= <60)					<.0001
60-69 years		0.87	0.672	1.117	
70-79 years		0.48	0.369	0.637	
80+ years		0.10	0.059	0.165	
Sub-localisation (ref=C34.0 Main bronchus)					0.0381
C34.1 Upper lobe, bronchus or lung		1.18	0.777	1.807	
C34.2 Middle lobe, bronchus or lung		0.96	0.475	1.933	
C34.3 Lower lobe, bronchus or lung		0.96	0.606	1.504	
C34.9 Bronchus or lung, unspecified		0.80	0.518	1.245	
WHO performance status 1 (ref=0 – Asymptomatic)					<.0001
1 – Symptomatic but completely ambulatory		0.85	0.635	1.150	
2 – Symptomatic, <50% in bed during the day		0.44	0.276	0.696	
3 & 4 – Symptomatic, confined to bed or chair more than 50% of waking hours		0.12	0.047	0.319	
Missing		0.72	0.446	1.158	

Characteristics	Odds ratios (95%CI)			Type 3 test
	Adjusted OR	Lower Limit	Upper limit	P value
Histological subtype (ref=Adenocarcinoma)				0.9653
Other subtypes	1.04	0.761	1.427	
Squamous Cell	1.02	0.815	1.272	
Respiratory disease (ref=No)				0.2295
Yes	0.87	0.691	1.093	
Cardiovascular disease (ref=No)				0.5675
Yes	0.94	0.754	1.167	
Diabetes mellitus (ref=No)				0.7646
Yes	1.05	0.770	1.427	
Days of hospitalization one year before incidence date lung cancer (ref=0)				0.1312
1-5 days	0.87	0.653	1.159	
6-15 days	0.76	0.488	1.180	
More than 15 days	0.52	0.271	0.993	

Table 3 – Effect of diagnostic volume on probability to receive guideline-concordant treatment (chemotherapy) for cIV NSCLC patients: results from logistic regression (n=3 845)

Characteristics		Odds ratios (95%CI)			Type 3 test
		Adjusted OR	Lower Limit	Upper limit	P value
Annual diagnostic volume (ref= Low (<50 patients))	**Unadjusted OR**				<.0001
Medium (50-99 patients)	0,83	0.73	0.608	0.884	
High (100-149 patients)	0,75	0.59	0.479	0.728	
Very high (≥100 patients)	0,71	0.50	0.396	0.629	
Sex (ref=Male)					0.6840
Female		0.97	0.829	1.131	
Age group 1 (ref= <60)					<.0001
60-69 years		1.02	0.840	1.233	
70-79 years		0.64	0.523	0.775	
80+ years		0.24	0.183	0.303	
Sub-localisation (ref=C34.0 Main bronchus)					0.8454
C34.1 Upper lobe, bronchus or lung		1.00	0.739	1.359	
C34.2 Middle lobe, bronchus or lung		1.02	0.654	1.578	
C34.3 Lower lobe, bronchus or lung		1.12	0.809	1.553	
C34.9 Bronchus or lung, unspecified		1.01	0.744	1.372	
WHO performance status 1 (ref=0 – Asymptomatic)					<.0001
1 – Symptomatic but completely ambulatory		0.97	0.741	1.269	
2 – Symptomatic, <50% in bed during the day		0.49	0.364	0.667	
3 & 4 – Symptomatic, confined to bed or chair more than 50% of waking hours		0.22	0.157	0.320	
Missing		0.82	0.569	1.174	

Characteristics	Odds ratios (95%CI)			Type 3 test
	Adjusted OR	Lower Limit	Upper limit	P value
Histological subtype (ref=Adenocarcinoma)				<.0001
Other subtypes	0.62	0.514	0.754	
Squamous Cell	0.89	0.742	1.057	
Respiratory disease (ref=No)				0.9732
Yes	1.00	0.846	1.189	
Cardiovascular disease (ref=No)				0.0818
Yes	1.15	0.983	1.342	
Diabetes mellitus (ref=No)				0.5488
Yes	0.94	0.753	1.163	
Days of hospitalization one year before incidence date lung cancer (ref=0)				<.0001
1-5 days	1.21	0.980	1.496	
6-15 days	0.91	0.670	1.240	
More than 15 days	0.43	0.295	0.618	

Appendix 3.1.6. Additional results on impact of diagnostic volume on guideline concordant treatment for SCLC patients

Table 1 – Effect of diagnostic volume on probability to receive guideline-concordant treatment (chemoradiation) for cI-III SCLC patients: results from logistic regression (n=492).

Characteristics		Odds ratios (95%CI)			Type 3 test
		Adjusted OR	Lower Limit	Upper limit	P value
Annual diagnostic volume (ref= Low (<50 patients))	**Unadjusted OR**				0.0722
Medium (50-99 patients)	1.34	1.39	0.820	2.358	
High (100-149 patients)	1.26	1.35	0.743	2.441	
Very high (≥150 patients)	1.84	2.43	1.257	4.692	
Sex (ref=Male)					0.0874
Female		1.48	0.944	2.324	
Age group 1 (ref= <60)					<0.0001
60-69 years		0.85	0.507	1.436	
70-79 years		0.37	0.214	0.641	
80+ years		0.06	0.022	0.182	
Sublocalisation (ref= C34.0 Main bronchus)					0.2924
C34.1 Upper lobe, bronchus or lung		1.20	0.615	2.322	
C34.2 Middle lobe, bronchus or lung		0.95	0.283	3.210	
C34.3 Lower lobe, bronchus or lung		2.11	0.967	4.625	
C34.9 Bronchus or lung, unspecified		1.15	0.579	2.303	
WHO performance status 1 (ref=0 – Asymptomatic)					0.0014
1 – Symptomatic but completely ambulatory		0.81	0.435	1.507	
2 – Symptomatic, <50% in bed during the day		0.29	0.119	0.724	

Characteristics	Odds ratios (95%CI)			Type 3 test
	Adjusted OR	Lower Limit	Upper limit	P value
3 – Symptomatic, confined to bed or chair more than 50% of waking hours	0.10	0.025	0.420	
Missing	0.52	0.177	1.512	
Clinical stage(ref=I)				0.0210
II	2.44	1.013	5.852	
III	2.86	1.363	5.998	
Respiratory disease (ref=No)				0.7796
Yes	0.94	0.598	1.471	
Cardiovascular disease (ref=No)				0.3105
Yes	0.80	0.513	1.236	
Diabetes mellitus (ref=No)				0.0866
Yes	0.57	0.294	1.086	
Days of hospitalization one year before incidence date lung cancer (ref=0)				0.1878
1-5 days	1.22	0.661	2.260	
6-15 days	0.45	0.187	1.068	
More than 15 days	0.58	0.193	1.750	

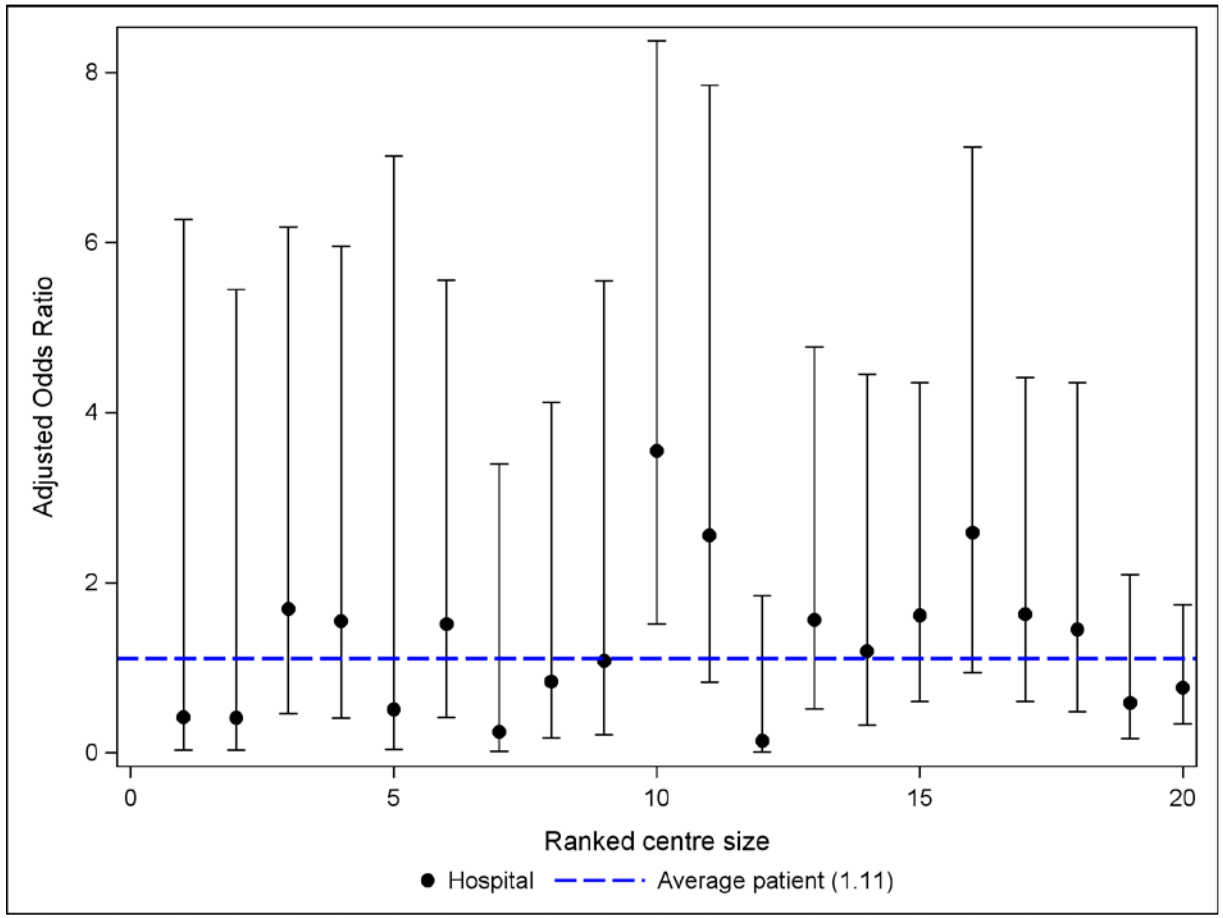
Table 2 – Effect of diagnostic volume on probability to receive guideline-concordant treatment (platinum-etoposide combination first-line chemotherapy) for cIV SCLC patients: results from logistic regression (n=920)

Characteristics		Odds ratios (95%CI)			Type 3 test
		Adjusted OR	Lower Limit	Upper limit	P value
Annual diagnostic volume (ref= Low (<50 patients))	**Unadjusted OR**				0.3320
Medium (50-99 patients)	1.18	0.98	0.609	1.560	
High (100-149 patients)	1.60	1.40	0.816	2.390	
Very high (≥150 patients)	2.52	1.54	0.774	3.074	
Sex (ref=Male)					0.0780
Female		0.67	0.435	1.045	
Age group 1 (ref= <60)					<.0001
60-69 years		0.56	0.306	1.028	
70-79 years		0.37	0.200	0.677	
80+ years		0.09	0.046	0.183	
Sublocalisation (ref= C34.0 Main bronchus)					0.0462
C34.1 Upper lobe, bronchus or lung		0.95	0.483	1.855	
C34.2 Middle lobe, bronchus or lung		1.15	0.355	3.699	
C34.3 Lower lobe, bronchus or lung		1.04	0.491	2.209	
C34.9 Bronchus or lung, unspecified		0.54	0.288	1.019	
WHO score 1 (ref=0 – Asymptomatic)					<0.0001
1 – Symptomatic but completely ambulatory		1.51	0.665	3.450	
2 – Symptomatic, <50% in bed during the day		0.59	0.254	1.386	
3 – Symptomatic, confined to bed or chair more than 50% of waking hours		0.11	0.044	0.277	
Missing		0.63	0.231	1.690	

Characteristics	Odds ratios (95%CI)			Type 3 test
	Adjusted OR	Lower Limit	Upper limit	P value
Respiratory disease (ref=No)				0.6520
Yes	1.10	0.724	1.674	
Cardiovascular disease (ref=No)				0.5245
Yes	0.87	0.571	1.331	
Diabetes mellitus (ref=No)				0.6269
Yes	0.89	0.546	1.440	
Days of hospitalization one year before incidence date lung cancer (ref=0)				0.7021
1-5 days	0.89	0.530	1.481	
6-15 days	0.67	0.335	1.326	
More than 15 days	0.95	0.355	2.536	

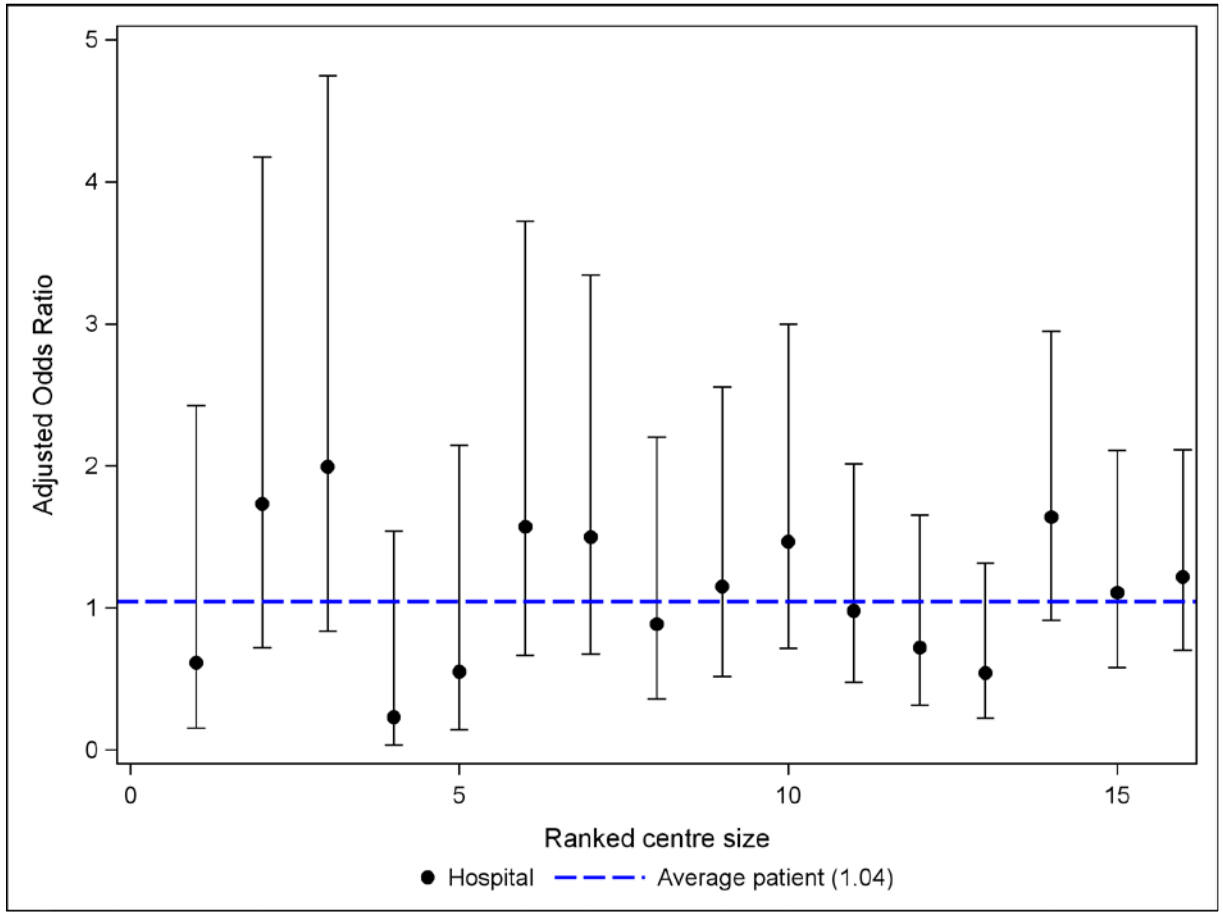
Appendix 3.1.7. Caterpillar plots of 60-day mortality, 1-3 year survival, per centre, adjusted for case mix

Figure 1 – Forest plot with adjusted odds ratios for 60 day mortality per surgical centre versus ranked centre size (NSCLC – surgically treated patients)



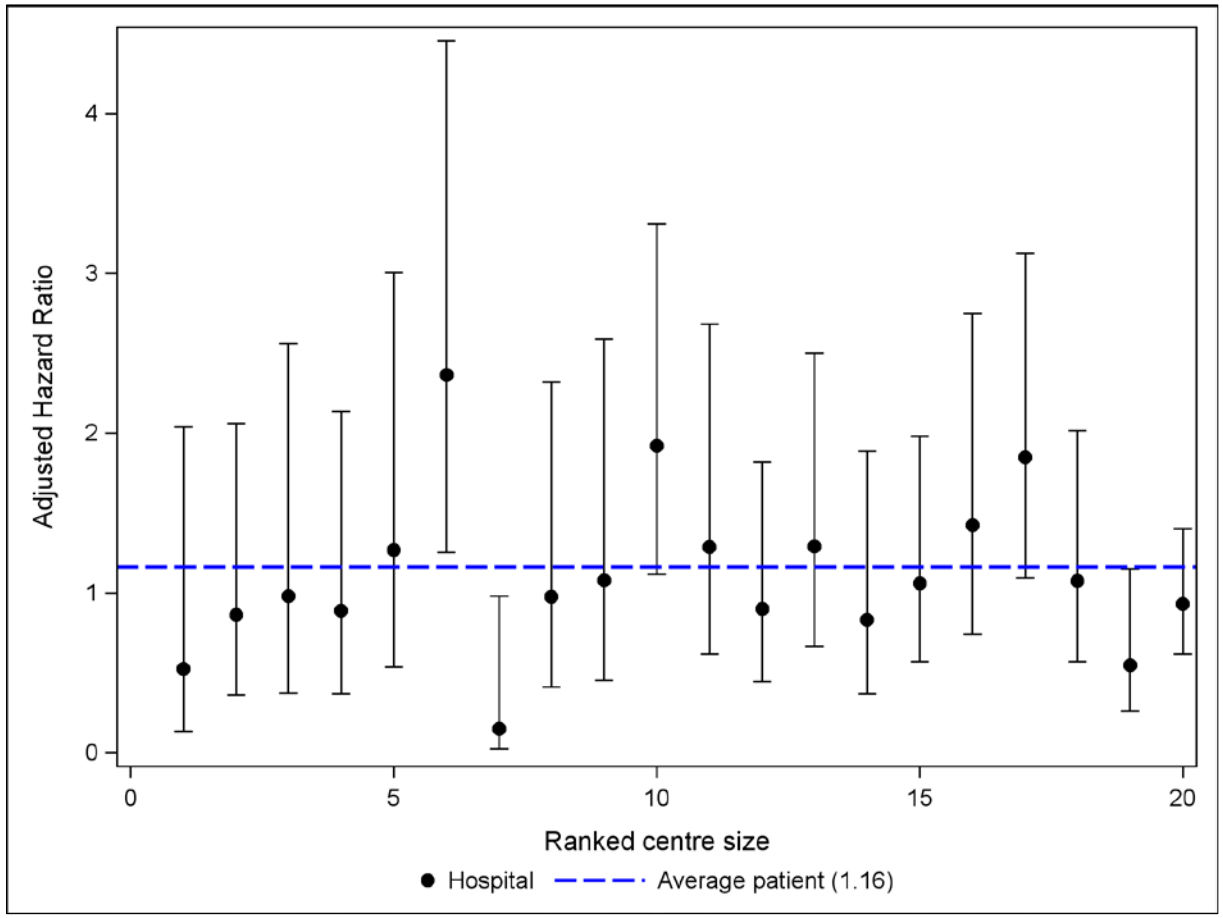
Note: Only centres with at least 35 patients treated with curative surgery were shown in the figure.

Figure 2 – Forest plot with adjusted odds ratios for 60 day mortality per RT centre versus ranked centre size (NSCLC)



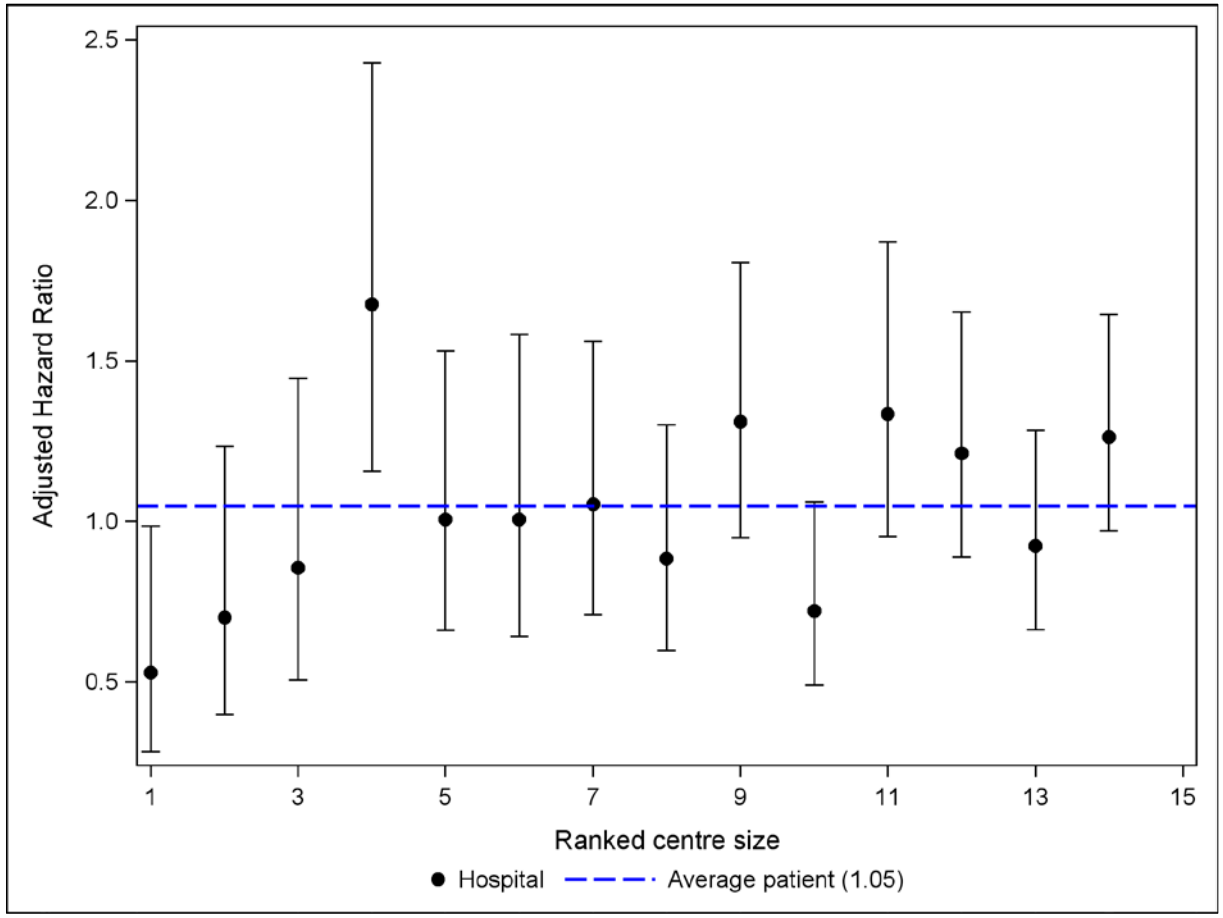
Note: Only centres with at least 35 patients treated with RT were shown in the figure.

Figure 3 – Forest plot with adjusted hazard ratios for observed survival at 1 year per surgical centre versus ranked centre size (NSCLC – surgically treated patients)



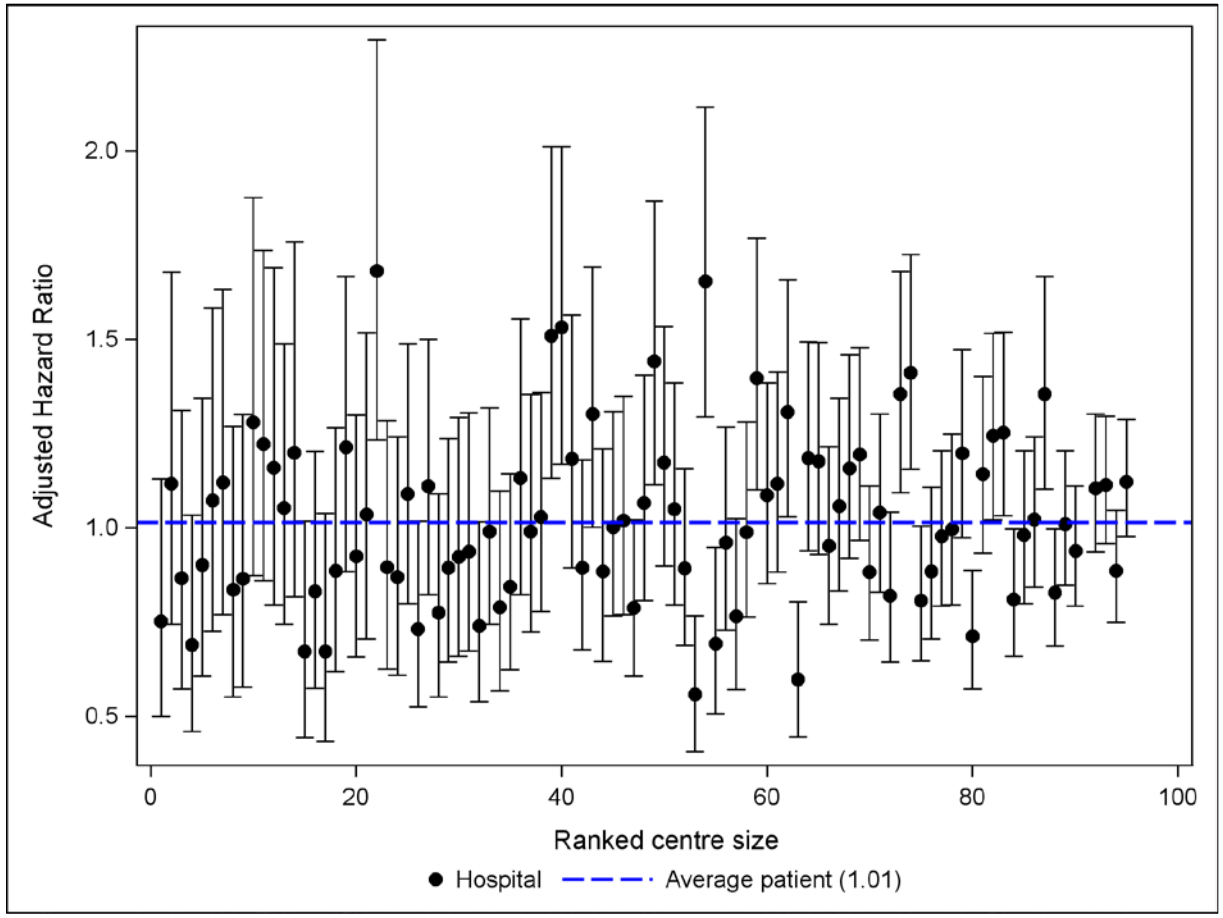
Note: Only centres with at least 35 patients treated with curative surgery were shown in the figure.

Figure 4 – Forest plot with adjusted hazard ratios for observed survival at 1 year per RT centre versus ranked centre size (NSCLC patients)



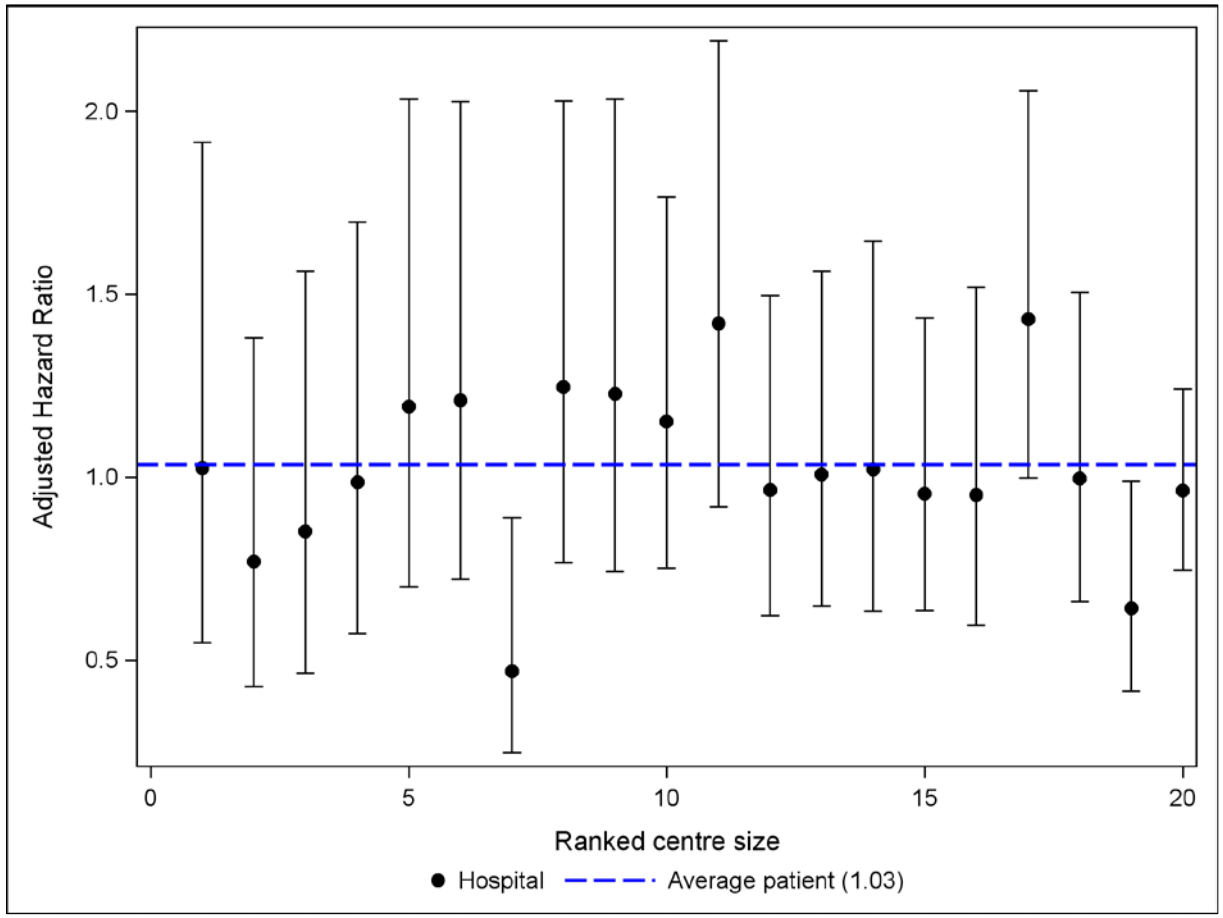
Note: Only centres with at least 35 patients treated with curative surgery were shown in the figure.

Figure 5 – Forest plot with adjusted hazard ratios for observed survival at 1 year per diagnostic centre (NSCLC patients)



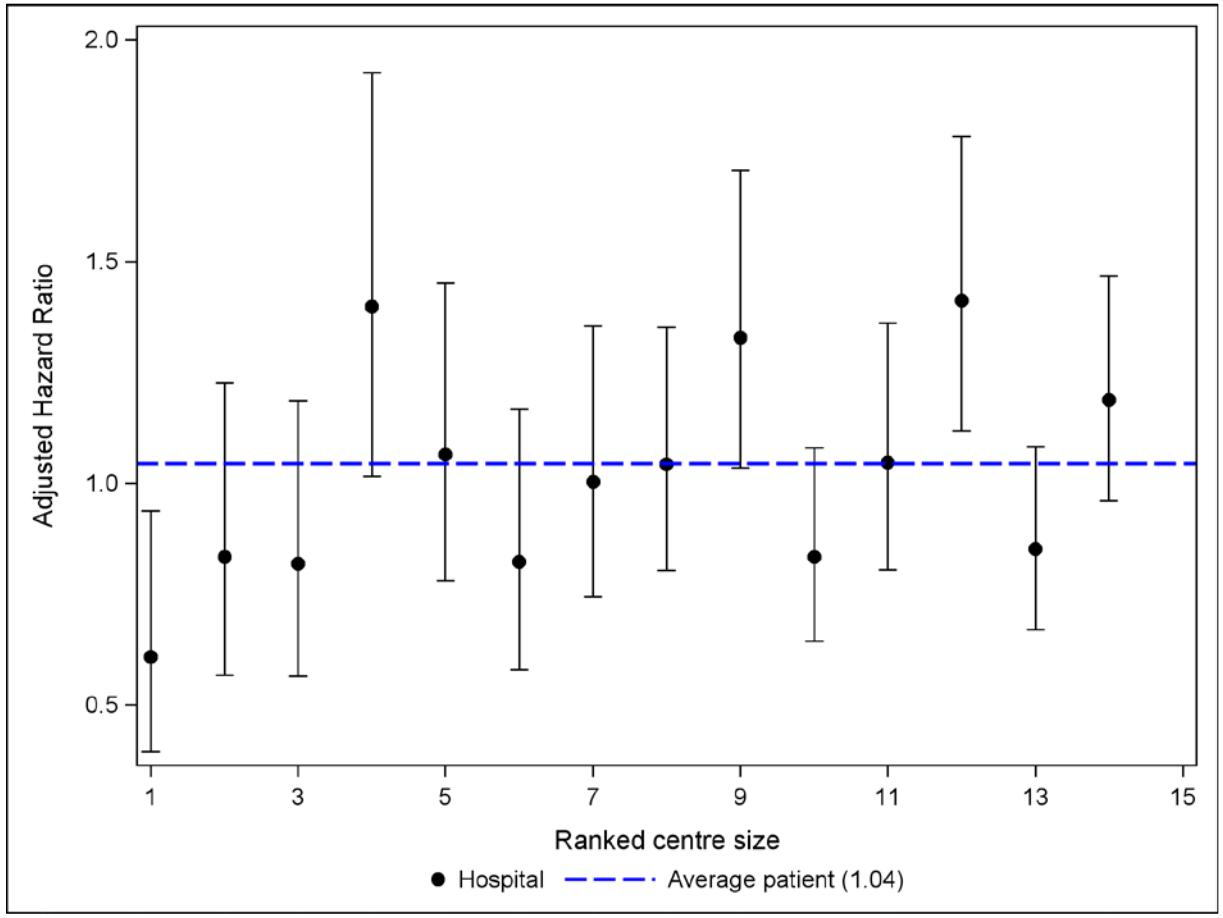
Note: Only centres with at least 35 patients diagnosed were shown in the figure.

Figure 6 – Forest plot with adjusted hazard ratios for observed survival at 3 year per surgical centre versus ranked centre size (NSCLC – surgically treated patients)



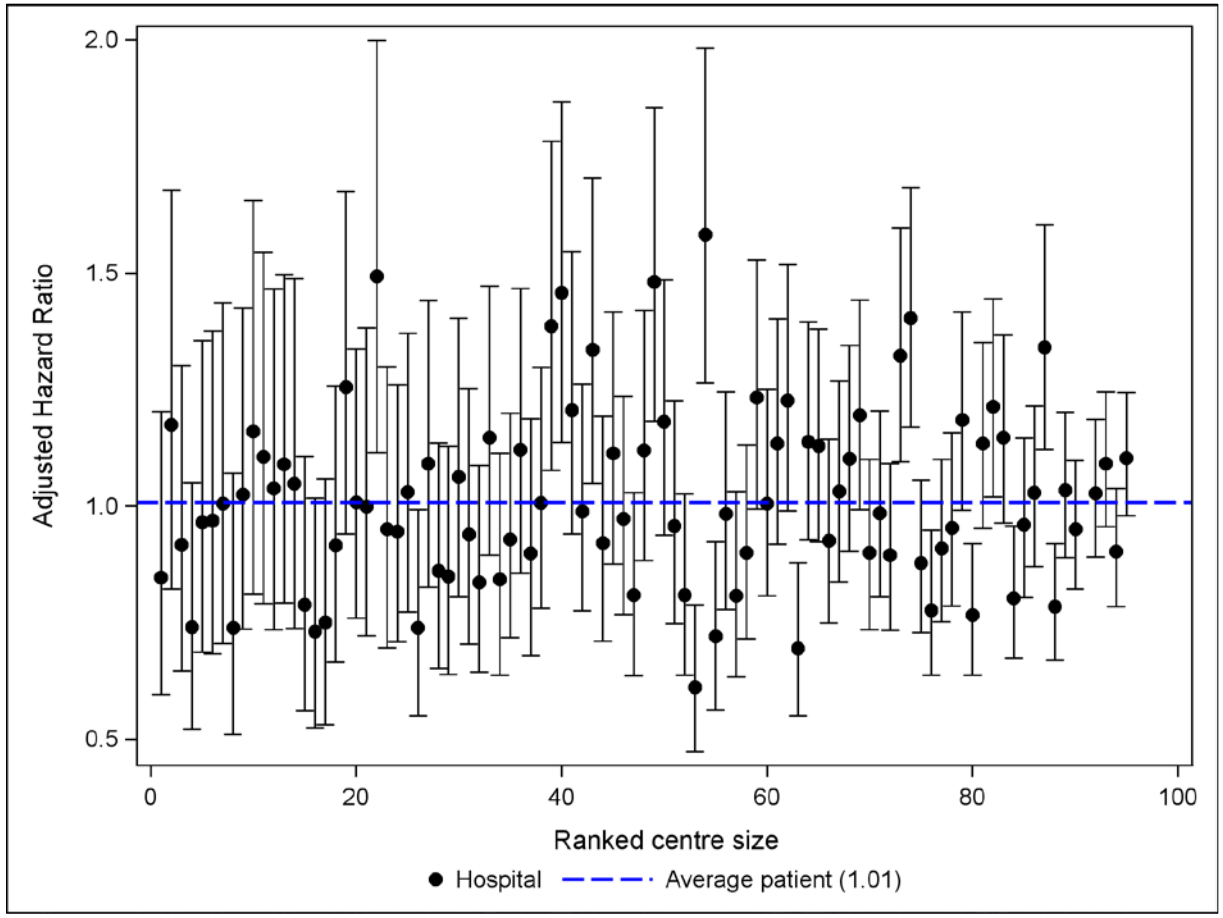
Note: Only centres with at least 35 patients treated with curative surgery were shown in the figure.

Figure 7 – Forest plot with adjusted hazard ratios for observed survival at 3 year per RT centre versus ranked centre size (NSCLC patients)



Note: Only centres with at least 35 patients treated with RT were shown in the figure.

Figure 8 – Forest plot with adjusted hazard ratios for observed survival at 3 year per diagnostic centre versus ranked centre size (NSCLC patients)



Note: Only centres with at least 35 patients diagnosed were shown in the figure.

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