Lung Cancer in Belgium

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Introduction: Health Care System

The kingdom of Belgium with its capital Brussels is located in Western Europe (Fig. 1) and has a population of 11,492,641 inhabitants (January 2020) for a surface of 30,689 km^2. The country is a member of the European Union (EU) and federally organized with a Dutch-speaking majority in the northern Flemish region, a French-speaking region (Wallonia) in the south, and the Brussels capital region. Its population is mainly of White, with 10% immigrants from different non-EU countries, mostly Africa and Middle East.

The organization of its "Bismarck type" health care is based on principles of therapeutic freedom for physicians, freedom of choice for patients, and fee for service payment.[1] All disease-oriented care is of federal competence, whereas prevention, screening, teaching, and health care organization are of regional competence. Health care is financed through a compulsory social insurance covering almost the whole population and administrated by a National Institute for Health and Disability, representing the following different stakeholders: sickness funds, (para)medical health care workers, pharmaceutical industry, and the federal ministry of Social Affairs, the latter covering the—yearly increasing—deficits in annual budget. In 2019, the share of health care spending represented 14.6% of all taxes and contributions and 10.3% of the gross domestic product.[2] It is estimated that an additional 1% is spent on out-of-pocket contributions and is—partially—reimbursed by private insurances, proposed by various sickness funds and private companies.

The density of health care resources is high: Belgium has 34,962 "acute care" beds in 128 hospitals, seven of which linked to a university medical faculty.[3] All hospitals were recently grouped in 25 locoregional networks, each covering approximately 500,000 citizens. A National Electronic Health Database (e-Health) for physicians makes institutional medical data available on a single platform and largely facilitates cross-referrals and second opinions. This platform is linked to Social Security's data warehouse, which allows for checking the patient's vital status. The publication of two royal decrees introduced multidisciplinary tumor boards (MDTBs) and oncological care programs in 2002 and 2003, respectively. Because the endorsement of the National Cancer Plan (NCP) of 2008,

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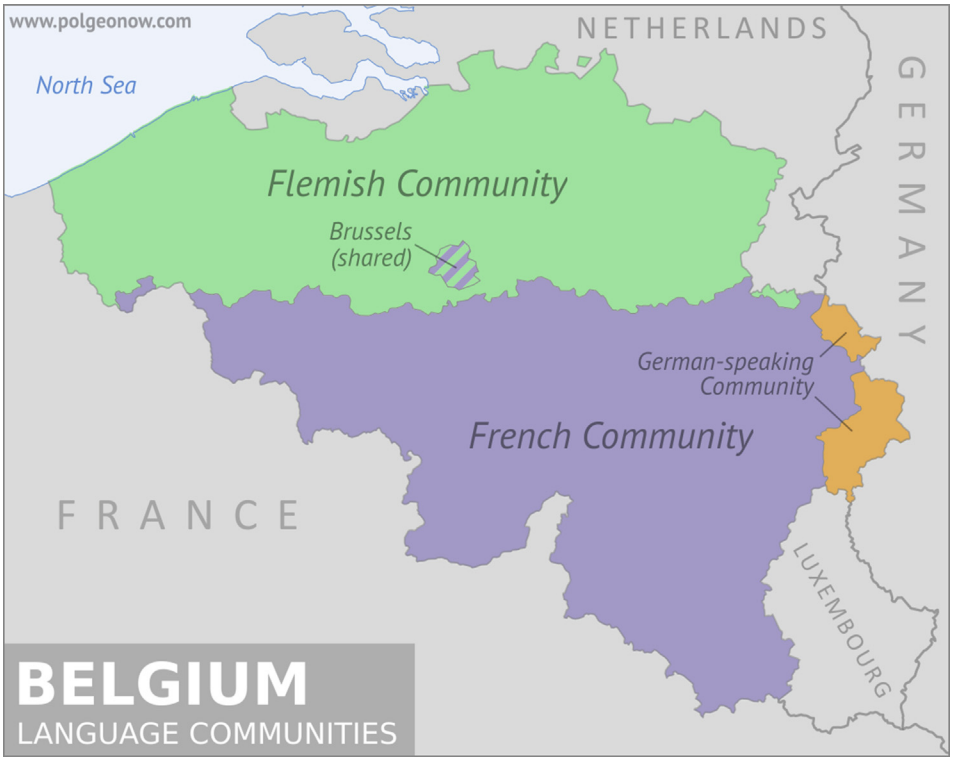

Figure 1. Belgium map. GER., Germany; LUX., Luxembourg.

cancer care is compulsory organized in multidisciplinary care programs, governed by structure and volume indicators.[4] Lung cancer MDTBs are attended by pulmonologists, thoracic surgeons, radiation oncologists, radiologists, nuclear physicians, pathologists, and oncology nurses. At these MDTBs, incidental cases and treatments, which are reported, are discussed and allocated, respectively. Presence of general practitioners (GPs) at MDTBs is possible, although seldom obtained. MTDB reports serve as the basis for local and national cancer registry databases and, for the Flemish region, publicly available quality indicators.[5] The provision of a reimbursement fee has largely contributed to the successful implementation of these MDTBs and the creation of integrated multidisciplinary oncology care programs. Other achievements of NCP are the inclusive availability of psychologists, dieticians, and oncology nurses for hospitalized and ambulatory oncology patients and their relatives.

The acquisition and exploitation of expensive medical equipment such as linear accelerators (LINACs), magnetic resonance imaging (MRI), and integrated positron emission tomography (PET)-computed tomography (CT) scanners are subject to central planning and restricted to hospital sites. In 2021, patients have access to 11.6 MRI and 2.62 PET-CT scanners per million inhabitants, which is lower than that in similar Organisation for Economic Co-operation and Development countries.[6] The equally low number of CT scanners (29 per million inhabitants) could hamper the future implementation of CT scanner screening for lung cancer.

Figures from 2009 estimate the direct and indirect costs of lung cancer care to amount to €88,000,000 and €467,000,000, respectively, representing a cost of €8 per person.[7] There is a large increase in drug expenditures owing to immunotherapy's reimbursement.[8] Whereas yearly total drug expenditures for stage IV NSCLC were less than €20 million before 2010, this amount more than tripled in 2017 to more than €75 million (Fig. 2). This increase is due not only to a higher number of patients with stage IV NSCLC receiving oncology drugs (1242 in 2004 and 2151 in 2017) but also to a price effect with nivolumab and pembrolizumab's reimbursement. The mean cost per patient with stage IV NSCLC increased from less than €5000 before 2006 to more than €35,000 in 2017.

Presumed patients with lung cancer are typically referred by their GPs for workup and staging to one of the approximately 650 pulmonologists, although the chameleon-like presentation of the disease results in referrals by means of diverse other medical specialties. Once diagnosed, staged, and discussed in MDTBs, patients can be either referred for surgery or radiotherapy (RT) to the appropriate network hospital or treated locally by a certified thoracic oncologist. The latter has access to the reimbursed prescription of expensive drugs, for example, targeted agents and immune

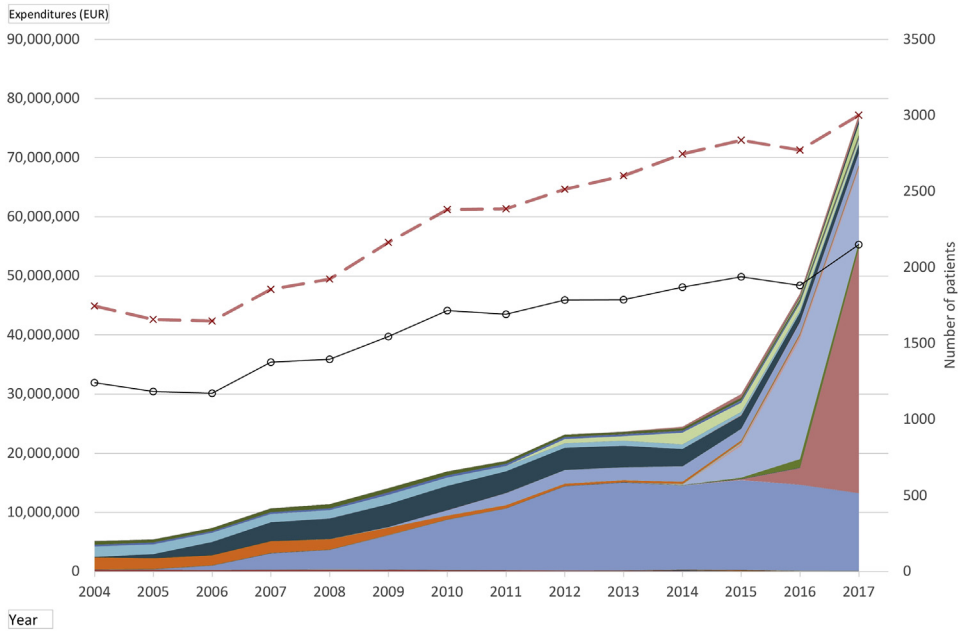

Figure 2. Drug expenses for the treatment of stage IV NSCLC in the first 2 years after incidence, per incidence year.[8] Reprinted with permission from KCE. KCE, Belgian Health Care Knowledge Centre.

checkpoint inhibitors (ICIs). Hence, since 2013, most patients with advanced-stage lung cancer are managed from diagnosis to death by one of the 183 thoracic oncologists, which is thought to improve patient's confidence and treatment compliance and reflects care continuity.

Epidemiology

The Belgian Cancer Registry (BCR) is a population-based registry with a national coverage from the incidence year 2004 onward. The Belgian Health Law of December 2006 provides a legal basis for its activities and objectives and makes BCR participation mandatory for oncological care programs and pathology laboratories. This law also authorizes the national Social Security number use as the patient's unique identifier and the linkage with other administrative databases to perform, for example, active follow-up on vital status.

In 2018, a total of 8815 new lung cancers were diagnosed: 5726 (65%) in males and 3089 (35%) in females.[9] This accounts for 12% of all new cancer diagnoses and makes lung cancer the second and third most incident cancer in males and females, respectively. The world-standardized incidence rate corresponds to 49 per 100,000 person years in males and 26 per 100,000 person years in females, resulting in a male-female ratio of 1.88. Lung cancer incidence rates (LCIRs) for males are among the highest in Europe according to the European Cancer Information System national estimates for 2020 and comparable to Eastern European countries, France, and Spain.[10] LCIRs for females are in the upper quarter of European rates and similar to neighboring countries Germany and France. Between 2004 and 2018, LCIRs in males decreased from 61 per 100,000 to 48 per 100,000, corresponding to an average annual percentage change (AAPC) of −1.6%. In contrary, as in many other European countries, LCIRs in females increased (AAPC +3.3%) from 16 per 100,000 in 2004 to 26 per 100,000 in 2018 (Fig. 3*A*).[11]

A total of 5803 deaths by lung cancer in 2017 makes it the most important cause of cancer-related death in males (n = 3969) and the second in females (n = 1834) after breast cancer. The world-standardized mortality rates for 2017 were 32 per 100,000 for males and 14 per 100,000 for females. Between 2004 and 2018, lung cancer mortality rates decreased in males (AAPC −3.2%) more sharply than LCIR. Nevertheless, in females, lung cancer mortality rates slowly increased (AAPC +1.7%) but to a lesser extent than LCIR (AAPC +3.3%) (Fig. 3*A*).[9]

NSCLC accounts for 71% of lung cancers, SCLC for 15%, and other types (including cases without histologic confirmation) for 14%. From 2007, adenocarcinoma (ADC) replaced squamous cell carcinoma (SCC) as the dominant NSCLC histologic subtype in male. Notwithstanding that, lung cancer incidence has an overall decreasing trend in men, whereas ADC incidence gradually increases (AAPC for 2004–2018: +1.4%). Since the start of BCR reporting in 2004, ADC has always been the predominant histological subtype in female.

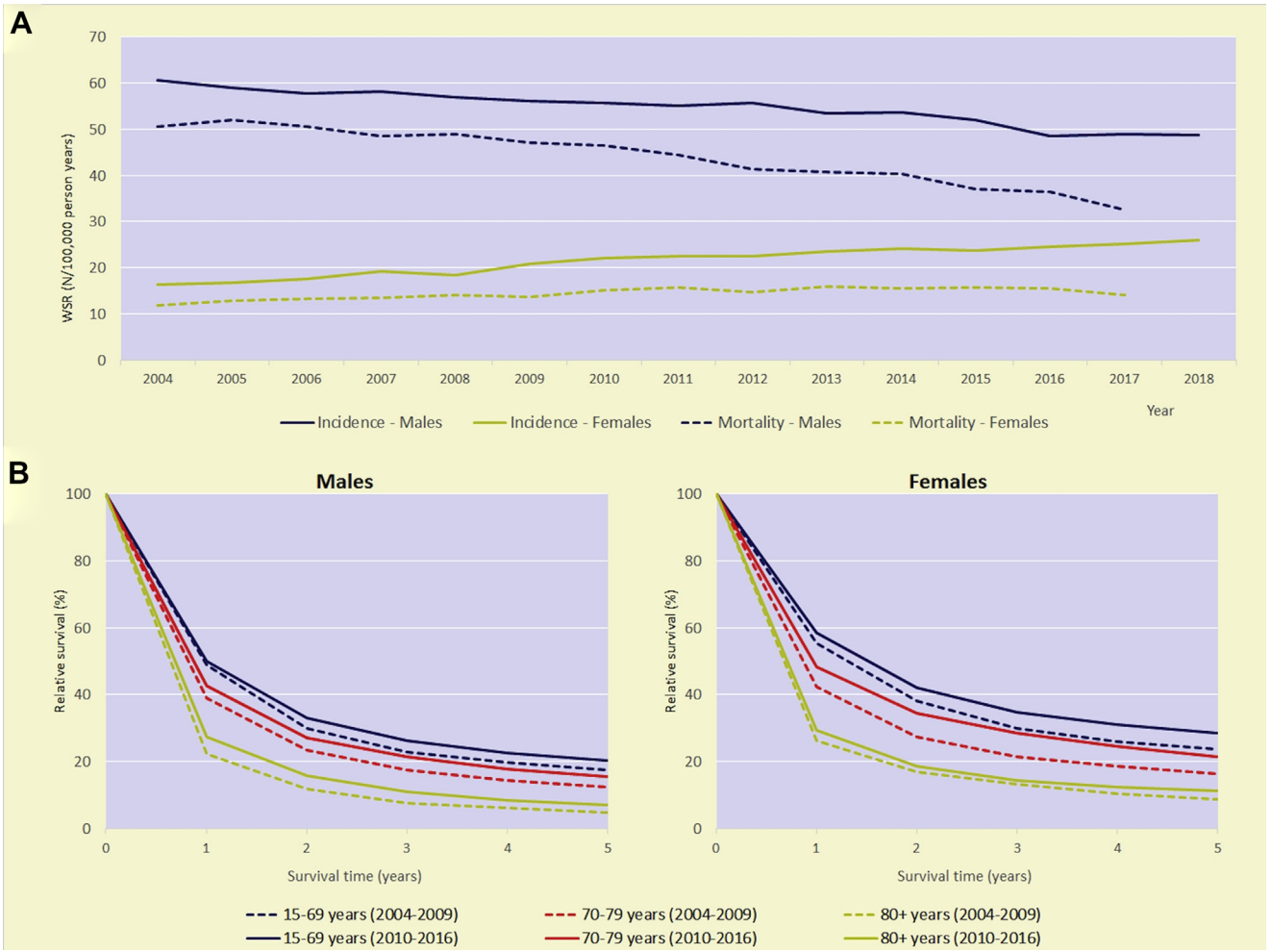

Figure 3. Evolution of lung cancer incidence and mortality in Belgium over time.[9] (*A*) Evolution of the age-standardized incidence rate (2004–2018) and age-standardized mortality rate (2004–2017) by sex (using the world standard population). (*B*) Relative survival by sex and age group in Belgium in 2004 to 2009 versus 2010 to 2016. Reprinted with permission from BCR. BCR, Belgian Cancer Registry; N, number; WSR, world-standardized incidence rate.

Stage distribution by sex is fairly equal (Table 1). Stage IV NSCLC accounts for 44.4% of the cases in the incidence period 2014 to 2017. The 5-year relative survival for the lung cancer 2012 to 2016 cohort is 18% in males versus 27% in females, and the female benefit persists throughout all age groups (Fig. 3*B*). Survival is inversely related to age, with a 5-year relative survival of 9% and 16% in males and females aged 80 years or more, respectively. BCR data reveal that the 3-year survival for lung cancer increased from 19% in 2004 to

Table 1. Stage Distribution of Lung Cancer by Sex and Histologic Type in Belgium in 2018[9]

	Males		Females	
	NSCLC	SCLC	NSCLC	SCLC
Stages	n (%)	n (%)	n (%)	n (%)
I	811 (18)	59 (8)	554 (24)	29 (6)
II	367 (8)		170 (7)	
III	978 (22)	166 (21)	424 (18)	127 (27)
IV	2009 (46)	495 (63)	1091 (47)	288 (61)
Unknown	219 (5)	62 (8)	101 (4)	26 (6)

BCR, Belgian Cancer Registry.
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24% in 2013 and 29% in 2016. The 3-year survival in stage IV NSCLC was 5.6% in 2004 and 15.5% in 2017.[12] Nevertheless, the median survival for this group remained quite the same for the years 2004 and 2017, at 0.5 to 0.6 years, respectively. This improvement is probably related to more accurate staging and gradual uptake of more efficient treatments, such as targeted and immunotherapies, and innovative irradiation techniques.

Guidelines and Quality Management

In 2013, within the framework of an integrated quality system in oncology, the Belgian Health Care Knowledge Centre (KCE) and the Belgian College of Oncology published evidence-based guidelines on diagnosis, treatment, and follow-up of patients with lung cancer,[13] but not prevention, screening, shared decision making, or palliative care (PC). These guidelines scored therefore three on six in an international comparison of guidelines across European countries.[14]

After this, KCE with BCR and a panel of national experts developed a set of evidence-based process and outcome indicators to evaluate care quality and variability between hospitals.[15,16] This retrospective study was based on linked data from BCR, insurance claims, and vital status for 12,839 patients diagnosed with having lung cancer between 2010 and 2011. A total of 20 indicators were measured (Table 2). Good results were achieved for histopathological diagnosis confirmation (Fig. 4*A*), PET-CT use before curative-intent treatment, and 60-day postsurgical mortality (3.9%). Areas for improvement included staging information reported to BCR (80%), brain imaging use for patients with stage III eligible for curative-intent treatment (79%) (Fig. 4*B*), and time between diagnosis and start of active treatment (median of 20 d). The relationship between patient characteristics, institutional diagnostic volume, treatment type, and survival was also investigated. Overall, 20.8% of the patients did not receive an oncological treatment. Among patients with stage I to II diseases, 59% had surgery and 22.1% (chemo)radiation. Of patients with stage III disease, 34% received chemoradiation, and 17% of those with stage IIIA disease had surgery. Of patients with stage IV disease, 70% received chemotherapy or targeted therapy. Moderate variability between centers was observed. Although not all patients with NSCLC received treatment according to guidelines, this does not necessarily represent poor quality care as patient characteristics and preferences need to be taken into account.[17] The KCE report also contained a detailed volume-outcome analysis of patients undergoing surgery for NSCLC. It revealed, as in other countries, that a higher hospital surgical volume was associated with improved outcome after resection.[18] Minimally 10 surgical interventions per year were deemed required to achieve optimal performance, and KCE issued a policy recommendation to centralize lung cancer surgery. After that report's release, all health insurers in Belgium published openly the number of annual lung cancer resections performed by each hospital, in an unprecedented attempt to improve information to patients and general public. A recent KCE report on benefits and costs of innovative oncology drugs in general and in NSCLC is critical on their benefits and cost-effectiveness.[8]

Prevention and Screening

In the 2018 National Health Interview Survey, 19% of citizens aged 15 years or more were active smokers, 15% daily smokers, and 4% occasional smokers. In addition, 19% of males were daily smokers versus 12% of females. The proportion of daily smokers decreased by 25% compared with that in 2008 (20.5%), whereas the average amount of daily smoked cigarettes decreased from 17 in 2004 to 15 in 2018. Still, 4.7% of the smokers are categorized as heavy smokers (at least 20 cigarettes per day).[19] Electronic cigarette use is most prevalent in 15- to 54-year-old cohorts.[20] The percentage of never-smoking citizens increased from 45% in 1997 to 57% in 2018. Behavioral smoking cessation support is partially reimbursed, as are varenicline and bupropion, but not nicotine replacement therapies, and is provided by different health workers, certified as smoking cessation practitioners or tobaccologists.[21] Nevertheless, in 2018, 65% of active smokers and 84.5% of ex-smokers did not mention using smoking cessation aid or counseling for their quit attempts. Tobacco regulation needs further strengthening because Belgium was classified at the tenth place (obtaining 58% of total points) in the 2019 EU Tobacco Control Scale.[22] As of January 2021, further progress has been made by adopting plain packaging legislation and banning smoking in cars in presence of minors.

Currently, no official lung cancer screening program for high-risk (ex)smokers is installed. Because lung cancer screening is organized at the regional level, the request for a future lung cancer screening program needs to be accepted separately by either the Flemish, Walloon, or Brussels' minister of health.[23] Efforts are currently underway to obtain its implementation in the Flemish region. KCE is performing a study on the cost-effectiveness of lung cancer screening. In the 2020 Smoking Survey of the Belgian Foundation against Cancer, 81% of the respondents expressed interest in lung cancer screening, and two of three future screening participants in simultaneous smoking cessation counseling.[24]

Diagnosis and Staging

Histopathologic confirmation of lung cancer is obtained in 93% of incidental cases.[15] As in most countries,

Table 2. Selected Process and Outcome QPIs for Diagnosis and Management of Patients With Lung Cancer: Results at National Level and Indication of Variability Between Centers[16]

Category and QPI Description	N	Result at National Level	Variability Between Centers
Timeliness to start treatment			
Median time from incidence date to first active treatment	10,100	20 d	Very large
Multidisciplinary team meetings			
Proportion of patients discussed in MDTB within 6 weeks after incidence date	12,839	72.8%	Large, with many low outliers
Proportion of patients with cIII NSCLC treated by surgery and discussed in MDTB before start of treatment	258	66.3%	Could not be assessed owing to small sample size
Pathology			
Proportion of patients with histopathologically confirmed diagnosis (*Fig. 4A*)	12,839	92.7%	Moderate, with some low outliers
Proportion of patients with NSCLC for whom the histologic subtype has been identified	9817	94.1%	Moderate, with some low outliers
EGFR testing			
Proportion of patients with cIV nonsquamous NSCLC for whom EGFR mutation analysis was performed in 2011	1535	52.7%	Moderate, with some low outliers
Medical imaging			
Proportion of patients with cI-III NSCLC who had a PET-CT before treatment with curative intent	2471	94.4%	Limited
Proportion of patients with cIII who had brain imaging (CT or MRI) before treatment with curative intent (*Fig. 4B*)	1295	78.7%	Moderate, with some low outliers
Proportion of patients with cI-III NSCLC who had a bone scintigraphy performed after a PET-CT	3477	5.2%	Moderate, with some high outliers
Mediastinal staging			
Proportion of patients with cII-III NSCLC who had minimally invasive mediastinal staging (EBUS or EUS or mediastinoscopy) before treatment with curative intent (*Fig. 4C*)	1518	46.0%	Moderate, with some low outliers
Proportion of patients with cII-III NSCLC who had mediastinoscopy before treatment with curative intent, for whom mediastinoscopy was preceded by EBUS or EUS	312	30.1%	Could not be assessed owing to small sample size
Safety of care (60-d mortality after treatment)			
Proportion of patients with NSCLC who died within 60 d after primary surgery	2083	3.9%	Limited, with a few high outliers
Proportion of patients with cI-II-III who died within 60 d after end of primary (chemo)RT with curative intent	1414	9.3%	Very limited, with no outliers
Aggressiveness of care at the end of life			
Proportion of patients who received chemotherapy or targeted therapy within two weeks of death	9114	12.9%	Could not be assessed because center not known for all patients
Quality of data reporting to Belgian Cancer Registry			
Proportion of patients with clinical TNM stage reported to the BCR	12,811	76.8%	Large, with many low outliers
Proportion of patients treated by surgery with pathologic TNM stage reported to the BCR	2162	80.1%	Large, with many low outliers

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BCR, Belgian Cancer Registry; c, clinical stage; CT, computed tomography; EBUS, endobronchial ultrasound; EUS, endoscopic ultrasound; KCE, Belgian Health Care Knowledge Centre; MDTB, multidisciplinary tumor board; MRI, magnetic resonance imaging; PET, positron emission tomography; QPI, Quality Performance Indicator; RT, radiotherapy.

patients are often diagnosed in advanced stage, with limited diagnostic material available.[25] Immunohistochemical subtyping is done in a tissue-sparing way, allowing molecular testing in most cases, either on request or as reflex testing.[26] The Belgian health authorities recently issued guidelines on pharmacodiagnostic molecular testing for different tumor types and its reimbursement.[27,28] For lung cancer, an algorithm is proposed with updates every 6 months. A taskforce of the Belgian Society of Pathology also regularly publishes recommendations to handle scarce material.[29,30] In all solid tumors, testing for *NTRK* fusion, microsatellite instability, and tumor mutational burden is proposed, although there is little evidence that microsatellite instability and tumor mutational burden have any predictive value in lung cancer. In samples from smokers with SCC, the only tests performed are programmed death-ligand 1 tumor proportion score and NTRK expression evaluation by immunohistochemistry (IHC), with the last one followed by fluorescence in situ

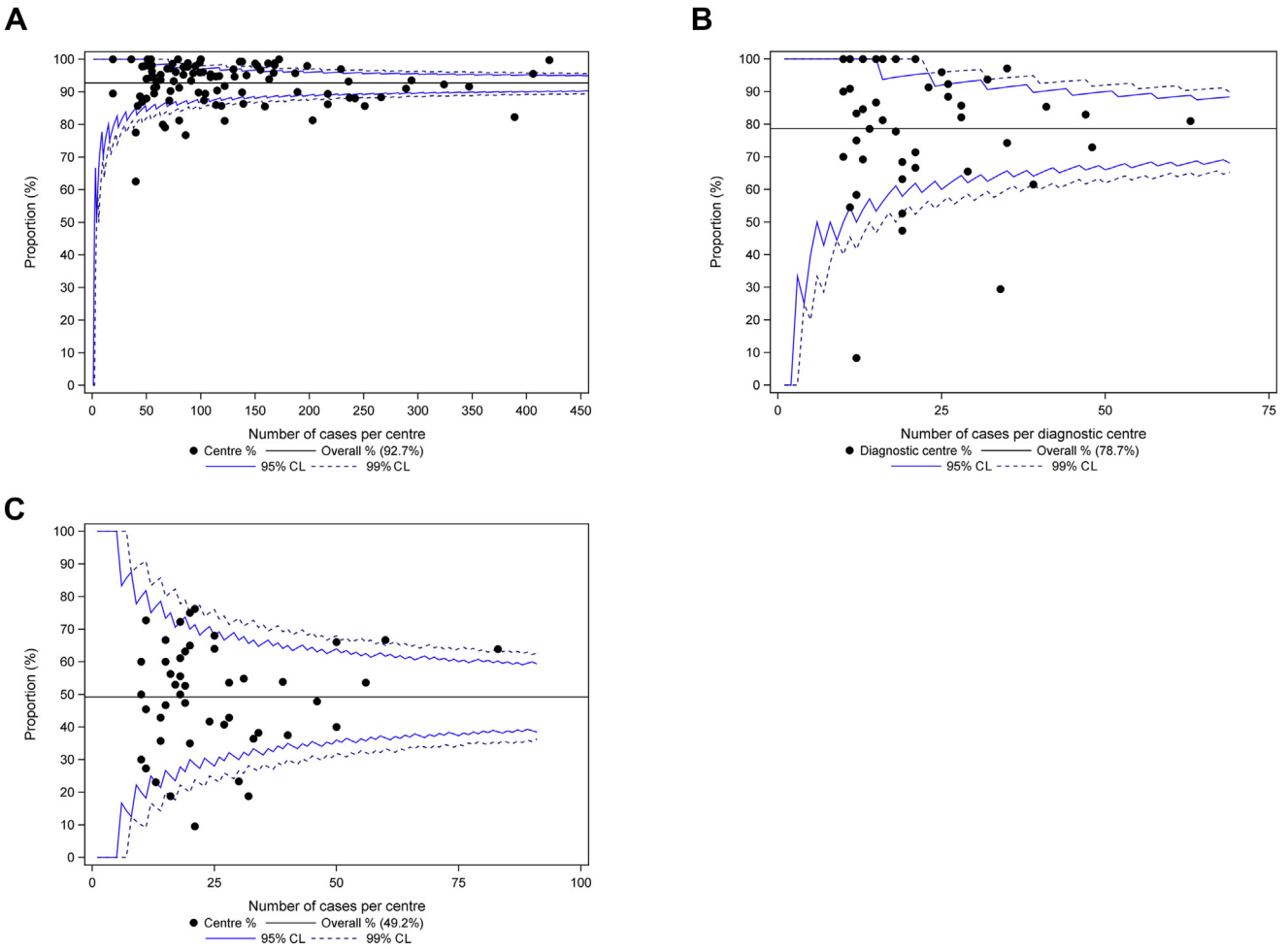

Figure 4. Funnel plots for three selected indicators to evaluate quality of care for patients with lung cancer. (*A*) Proportion of patients with histopathologically confirmed diagnosis, by center. (*B*) Proportion of patients with clinical stage III disease who had brain imaging (CT or MRI) before treatment with curative intent, by center. (*C*) Proportion of patients with clinical stage II to III NSCLC who had minimally invasive mediastinal staging (EBUS or EUS or mediastinoscopy) before treatment with curative intent, by center. Reprinted with permission from KCE. CL, confidence limits; CT, computed tomography; EBUS, endobronchial ultrasound; EUS, endoscopic ultrasound; KCE, Belgian Health Care Knowledge Centre; MRI, magnetic resonance imaging.

hybridization (FISH) or RNA sequencing in case of IHC positivity. In samples from nonsmokers with SCC or from unselected non-SCC, a series of tests is proposed, which can be run sequentially or in parallel: programmed death-ligand 1 (PD-L1) tumor proportion score, ALK, ROS1, and NTRK expression by IHC, the latter three followed by FISH or RNA sequencing in case of IHC positivity and assessment of mutations in *EGFR*, *KRAS*, *BRAF*, *MET*, and *HER2* genes, usually with DNA-based next-generation sequencing. Since April 2021, all IHC and FISH tests are reimbursed by means of a convention between genetic, clinical, and pathology laboratories organized in networks and the National Institute for Health and Disability. Registration in a central database and quality control of molecular tests are mandatory. Therefore, all pathology laboratories participate in (inter)national ring trials.[31–33] Lastly, the algorithm includes guidelines on retesting in case of NSCLC progression on targeted therapy and optional testing for targets such as *RET* fusion or *MET* copy number analysis. In the next few months, a fast and cheap single RNA sequencing will replace most of the separate fusion protein analyses, but ALK, which will continue to be reflex tested by IHC, and in case of IHC positivity, will not require to be validated by FISH or RNA sequencing.

Staging is done according to published international and Belgian guidelines.[13,34,35] Although imaging facilities are readily available, patients sometimes need to be referred for PET-CT scan or brain MRI. A complete workup within 3 weeks is feasible in most institutions.[15] A total of 30% of patients with lung cancer and 94% of those proceeding to resection undergo a PET-CT scan. Since 2005, implementation of endobronchial ultrasound (EBUS)-guided transbronchial needle aspiration and

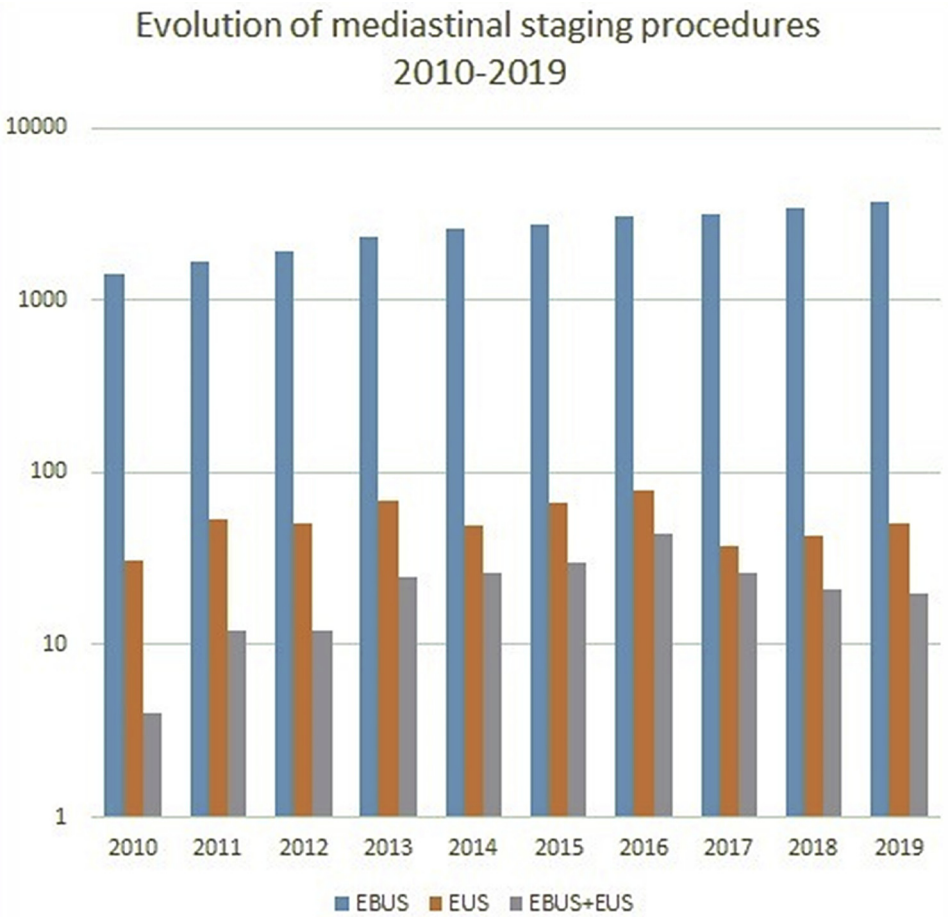

Figure 5. Evolution of mediastinal staging procedures from 2010 to 2019. Reprinted with permission from RIZIV-INAMI, 2021. EBUS, endobronchial ultrasound; EUS, endoscopic ultrasound; RIZIV-INAMI: National Institute for Health and Disability Insurance.

transesophageal endoscopic ultrasound (EUS)-guided fine-needle aspiration techniques plus or minus radial miniprobe-guided biopsies has made the diagnostic and mediastinal staging process less invasive, more precise, and cheaper as compared with when it was based on mediastinoscopy.[36,37] The number of endosonographic procedures continues to increase in time (Fig. 5). It is remarkable to note that a "one step" transesophageal and endobronchial approach is performed in only 1% to 3% of endosonography procedures, reflecting a suboptimal implementation of these new techniques.[38]

Although there is no formal dedicated national training program in interventional pulmonology, pulmonologists can follow certified courses organized by the European Respiratory Society for training in diverse techniques. Before 2005, pulmonologists mainly performed bronchoscopic techniques for tracheobronchial mechanical debridement and stenting, transthoracic needle aspirations, and medical thoracoscopies. After 2005, these last two procedures were taken over by radiologists and thoracic surgeons, respectively, whereas pulmonologists specialized in more sophisticated endobronchial techniques. Currently, there are 60 endosonography suites, providing at least linear EBUS-guided transbronchial needle aspirations, variably supplemented with radial EBUS and EUS-guided fine-needle aspirations. Autofluorescence, electromagnetic navigation, tracheobronchial stenting, and medical thoracoscopies are conducted in several centers, although exact figures are not available.

Surgery

Lung cancer surgery is performed by general, vascular, cardiac, or "pure" thoracic surgeons, as there is no specific certification in thoracic surgery. The first cases of video-assisted thoracic surgery (VATS) for lung cancer were reported in the early nineties and, in the past 15 years, minimally invasive techniques for anatomical lung resections (by VATS or robotic surgery) have spread.[39] As there is no specific nationwide database for thoracic surgery, no accurate national figures on the proportion of open, VATS, and robotic procedures performed for lung cancer are currently available.

Similarly, precise data regarding resection extent and lymphadenectomy completeness are lacking. Nevertheless, several large surgical centers participate to the registry of the European Society of Thoracic Surgeons.[40]

Between 2012 and 2016, KCE-audit 5656 resections for lung cancer were performed, corresponding to 17.7% of all diagnosed lung cancers. The proportion of patients with resected stage I to II NSCLC was 63.7%, and the 30-day after surgery mortality rate was 2.3% (stages I–IIIA: 2.0%, stages IIIB–IV: 3.9%). The median time from incidence date to surgery was 26 days, comparing favorably to other countries.[15,40–42] This short delay can be explained by the high density of surgical centers, which is however not a quality guarantee. Indeed, between 2010 and 2011, a total of 89 hospitals performed lung cancer surgery, but most were low-volume centers, half of them performing less than 10 and only nine performing at least 40 annual procedures. The 60-day mortality was more than 6% in centers with a surgical volume lower than 10 annual cases, whereas it was less than 3% in those with more than 10 annual cases.

A future challenge for oncologic thoracic surgery will be to deal with an expected increase in surgical activity after the implementation of screening programs, leading to more early stage lung cancer detections.[43] Although time intervals between diagnosis and surgery are currently acceptable, this could lengthen in the future because no nationwide policy has been established to assign more operating room capacity.[44]

Radiotherapy

With 24 RT centers and 13 satellite facilities, Belgium has the highest worldwide RT equipment density.[45] Although their access is easy, they are not efficiently spread across the country to ensure a homogeneous coverage,[46] and many treat less than 1000 patients per year, some barely reaching the 500 patients mandatory threshold.

All RT centers have modern equipment with state-of-the-art LINACs with at least intensity-modulated RT, static or rotational and stereotactic radiosurgery of the brain, and stereotactic body RT for extracranial tumors.[47] Some centers have niche machines, such as CyberKnife or Gamma Knife or magnetic resonance LINAC. Two proton-therapy centers will be available, one recently opened in the Flemish region and another is being built in Wallonia. RT centers have dedicated CT simulators or easy access to CT scan. PET-CT scan is routinely integrated in target selection and delineation in most centers. Some centers also perform dosimetric MRI. Many different image-guidance devices are used during treatment, including cone-beam CT scan and surface scanning.

Although most patients with lung cancer are discussed in local MDTBs, the actual RT use remains significantly lower than the evidence-based optimal recommendations.[48] Nevertheless, delivered treatments are well in line with advised MDTB reports.

Since 1995, the College of Radiotherapists advises health authorities on promoting RT quality by performing quality assurance monitoring, audits, and multicentric training. In that context, a public health program named Project on Cancer of the Lung centrally reviews target selection and volume delineation of mediastinal lymph nodes in stage III lung cancers.[49] The Project on Cancer of the Lung is also a national registry collecting RT parameters.

In the past years, more patients with early stage lung cancer are treated with stereotactic body RT. Four-dimensional planning CT scans are routinely used in all centers, and center-specific planning strategies are applied, including deep inspiration or midventilation breath-hold and midposition techniques. Likewise, institutions have their preferred motion management strategy during RT delivery. Treatment protocols are however not standardized across different centers.

Systemic Therapy

Access to novel systemic anticancer therapies is rather laborious in Belgium. After marketing authorization by the European Medicines Agency (EMA), the Belgian drug authorization process includes the submission of an application to the Commission for Reimbursement of Medicinal Products, simultaneously with a pricing application. The Minister of Social Affairs and Public Health takes the reimbursement decision on advice from the Commission for Reimbursement of Medicinal Products, and the Minister of Economic Affairs sets the maximum price of a drug.[50] This standard procedure should not take more than 180 calendar days. Nevertheless, on the basis of the European Federation of Pharmaceutical Industries and Associations Patients Waiting to Access Innovative Therapies survey, which analyzed 34 European countries between 2015 and 2018, 67% of EMA-approved anticancer treatments were fully publicly available (13th position of 34) and the mean time to access after EMA approval was 449 days (12th position of 34, range: 2.5 mo–2.5 y).[51] Nevertheless, while waiting for marketing authorization, access is possible through early access programs (EAPs) set up by pharmaceutical companies. Targeted and immunotherapies currently available are listed in Supplementary Table 1, with their indications and approval and reimbursement dates, giving an idea of the speed of the procedures. The average delay between EMA approval and reimbursement was 19.9 months for

targeted therapies and 4.1 months for ICIs. EAPs were available for 13 of 26 targeted therapy and 6 of 12 ICI indications. The average time between EMA approval and EAP start was −1.4 months for targeted therapies and −1.7 months for ICIs, as EAPs were often accessible before EMA approval.

To speed up the introduction of innovative medicines in Belgium, decisions on reimbursement increasingly turn to managed entry agreements (MEAs) whenever uncertainties persist over their added value. This temporary reimbursement mechanism allows for time to provide the necessary additional evidence. Nevertheless, MEAs do not stimulate the delivery of this evidence by the pharmaceutical industry. Besides, in these MEAs, the agreed drug prices remain confidential, which harms the transparency of the system and does not allow for an independent cost-effectiveness estimation.[8]

Lung cancer systemic treatment is mainly provided by certified thoracic oncologists and, less often, by medical oncologists. All of them are authorized to treat all lung cancer types, independently of their frequency, with no reference centers for rare oncogenic drivers or cancers. Most thoracic oncologists do however not have sufficient expertise in treating rare entities, such as malignant pleural mesothelioma and neuroendocrine and thymic cancers. This will change with the further implementation of reference centers for orphan and low-prevalent diseases.[52]

Thoracic oncologists mainly follow the European Society of Medical Oncology[34,53–56] or the American Society of Clinical Oncology guidelines[57,58] and, to a lesser extent, KCE recommendations.[59] Most systemic therapies and indications proposed in the European Society of Medical Oncology guidelines are available in Belgium, with a few exceptions (Supplementary Table 2).

PC and End-of-Life Care

PC and euthanasia developed synergistically in Belgium. This unique model of integral end-of-life care stands for PC, in which euthanasia is an available option at the end of a PC pathway.[60] In 2020, a total of 1569 patients with cancer underwent euthanasia, of which 20% had lung cancer.[61] A prospective Flemish study of advanced-stage lung cancer revealed that euthanasia was performed on eight of 105 consecutive patients.[62]

All interested physicians (GPs and specialists) can provide PC and end-of-life care at home, hospitals, PC units, and hospices. The inclusive availability of psychologists and oncology nurses by NCP helped to lower the threshold for access. PC service use is high but still occurs late in the disease trajectory. For patients with lung cancer, the median hospice stay is only 19 days despite the well-known benefits of early PC (EPC).[63] EPC remains a challenge in daily practice. In 2018, the PC Indicators Tool was published, which was a translation of the Supportive and Palliative Care Indicators Tool, aiming to identify palliative patients early and facilitate EPC. Nevertheless, one of the reimbursement and eligibility criteria to become a “palliative” patient remains a three months’ life expectancy, which is not adapted to this PC Indicators Tool scale. This is one of the reasons why EPC remains challenging although initiatives are taken to fulfill this unmet need.[64]

Conclusions

Lung cancer epidemiology, diagnosis, staging, and treatment in Belgium correspond to similar international reports of the disease and follow guidelines that reflect the state-of-the-art and the available evidence. Despite obvious shortcomings and lateness in some processes, lung cancer survival in Belgium is comparable with other affluent countries, suggesting a volume-driven health care with acceptable quality despite overconsumption and lack of structured referrals.

The lung cancer epidemic is reaching its peak and expected to abate in the following decades, thanks to better prevention and new treatments. Nevertheless, the prognosis remains grim and further improvements are likely not to be expected solely by better or more new drugs, as patients’ comorbidity and age are important drivers of treatment-related mortality.

Challenges for the near future include lung cancer screening implementation, reinforced primary (smoking) prevention, implementation of patient reported outcomes and better transmural integration of oncology care pathways. These challenges represent the ultimate litmus test for the affordability and resilience of its management. In the search for sustainability and waste reduction, efficiency and budget gains can surely be obtained by making the complex and multilayered Belgian health care system more lean.

CRediT Authorship Contribution Statement

Jan P. van Meerbeeck: Conceptualization; Writing—original draft for the sections Introduction: Belgium and Its (Cancer) Health Care System, Patient Advocacy, and Conclusion; Reviewing; and Editing.

Sebahat Ocak: Writing—original draft for the section Systemic Therapy; Reviewing; and Editing.

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Weynand: Writing different parts of the manuscript; Reviewing.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org/ and at https://doi.org/10.1016/j.jtho.2021.07.022.

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