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Lung Cancer in the Netherlands



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Introduction

The Netherlands is a small European country with a population of 17.45 million (September 2020) distributed over 41,543 km².¹ There are 79 hospitals (in total, 109 locations), of which seven are university medical centers, one cancer center, and 28 large teaching hospitals. On average, the hospitals are within easy reach, as

99% of the Dutch inhabitants can reach a hospital by car within 30 minutes (Fig. 1).²

Health Care System

General practitioners (GPs) are the “gatekeepers” in the Dutch health care system: in general, a referral by a GP is mandatory for access to nonemergency-based

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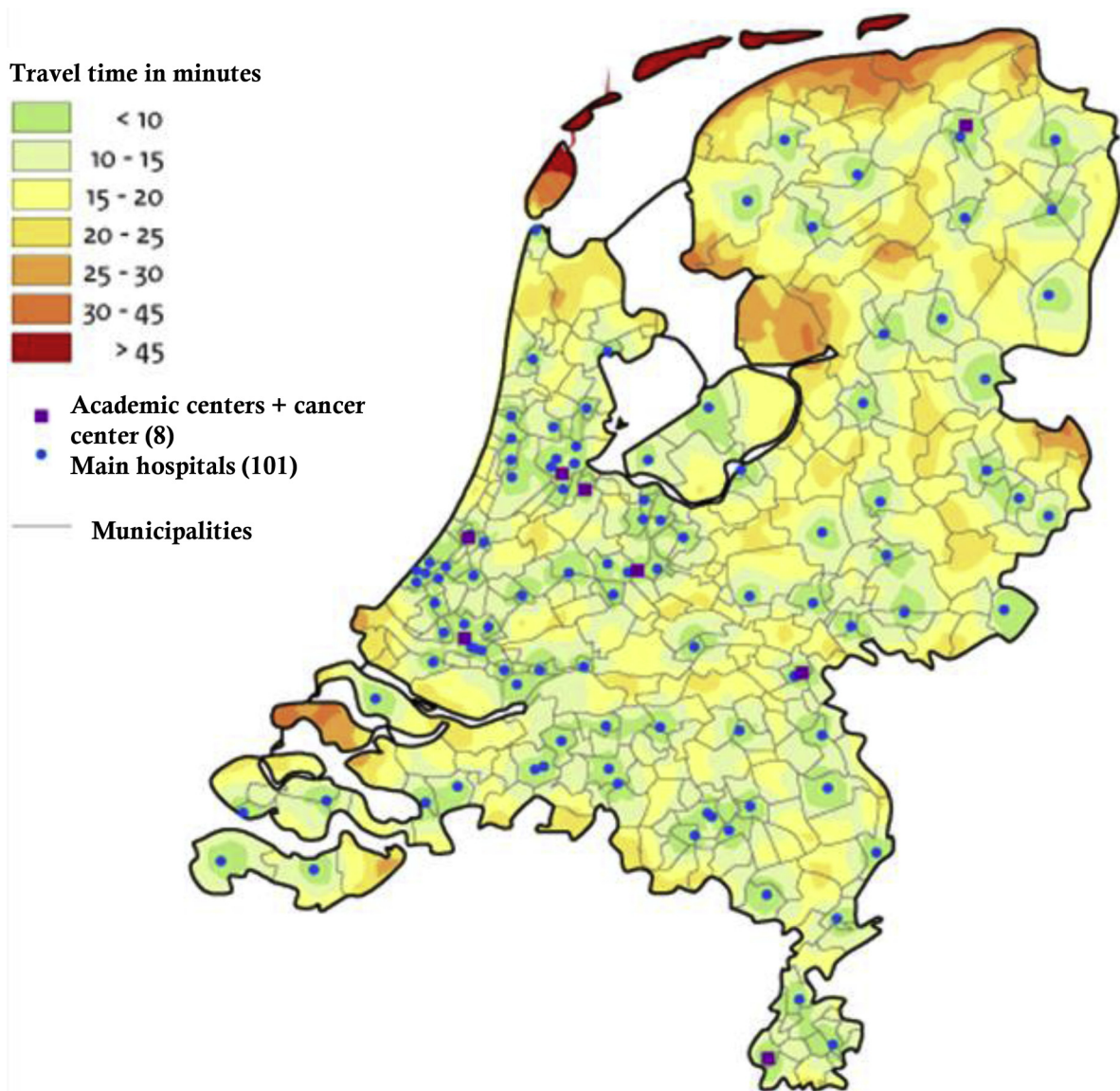


Figure 1. Distribution of hospitals across the Netherlands and travel time by care to a hospital (used with permission from RIVM). RIVM, National Institute for Health and Environment.

hospital care (as insurance does not cover the costs otherwise). Common medical care is covered by basic insurance, which is mandatory by law for all Dutch inhabitants. In lieu of this, health insurance companies cannot refuse a person for this basic insurance. Standard work-up and treatments as defined by a so-called diagnosis-treatment combination (DBC) for cancer are reimbursed by basic insurance. This includes all costs incurred by the European Medicines Agency (EMA)-registered and national health authorities-approved medical interventions and treatments.

Epidemiology

The population-based Netherlands cancer registry records data on all patients newly diagnosed to have

cancer in the Netherlands.³ Trained registry personnel actively collects data on demographics, diagnosis, staging, and treatment from medical records, on the basis of notification by the national automated pathologic archive and on hospital discharge diagnoses. Pathology confirmation is secured by means of a link with the Netherlands Pathology Registry, and survival status update is through a link with the centralized civil registry.⁴ In 2019, in the Netherlands, 14,500 lung tumors were diagnosed in 14,300 patients.³ In 2018, a total of 10,400 patients died from lung cancer.⁵ These numbers make lung cancer the fourth most common cancer but with the highest number of cancer-related deaths. In the past decades, incidence rates among male individuals have been decreasing (from 72.62 per 100,000 person years

[world standardized rate] in 1989 to 38.6 in 2019), whereas these rates have been increasing in female individuals in this period (from 12.0 to 33.1 per 100,000 person years [world standardized rate], respectively). Incidence rates among female patients younger than 60 years seem to flatten or even slightly decrease during the past years. The trends in incidence mostly reflect the high tobacco consumption decades ago, which also explains the relatively high incidence and mortality rates compared with other (European) countries.⁶ NSCLC accounts for 70% of lung cancers, SCLC for 11%, carcinoids for 1%, and the remaining 17% is clinically diagnosed (usually suspicion of early-stage NSCLC referred for stereotactic radiotherapy without pathologic diagnosis). In 2018, a total of 49% of the patients were diagnosed to have stage IV (19% IVA, 30% IVB); percentages for stages I, II, and III were 21%, 8%, and 21%, respectively; and for 1% of the patients, the stage was unknown. For patients diagnosed between 2012 and 2018, the 1-year overall survival (OS) rate was 46%, and 5-year OS rate was 19% (median 10 mo). More specifically, for patients diagnosed in 2018, the 1-year survival rates for stages I, II, III, and IV NSCLC were 90%, 82%, 62%, and 31%, respectively. For SCLC, these percentages were 75%, 60%, 61%, and 23%, respectively.^{3,5}

Lung Cancer Prevention and Screening

The Dutch government is committed to the “smoke – free generation” initiative.⁷ The goal is that in 2040, nobody will start smoking. To meet this goal, several interventions have been implemented. First, an increase in the value-added tax for a 20-cigarette package, with a target price of 10 euros per package by 2023. Second, in 2020, smoking bans on all school yards, plain packaging, and reduction of selling points for tobacco products.⁷ In addition, most hospitals have forbidden the use of tobacco products on their grounds. In 2019, 21.7% of the adults were active smokers, which is a 4% reduction compared with that in 2014.⁸ With the interventions mentioned previously, the goal for 2040 is to reduce the percentage of active smokers to 5% or less.

Currently, lung cancer screening is not implemented as a standard of care in the Netherlands. However, after the positive results of the randomized Dutch-Belgian NELSON trial, revealing a cumulative rate ratio of 0.76 (95% confidence interval: 0.61–0.94) for lung cancer deaths at 10 years with volume-based, low-dose computed tomography (CT) screening compared with no screening in patients at high risk for lung cancer,⁹ implementation of screening is being considered. In general, screening for cancer and screening with the use of ionizing radiation is forbidden by law in the Netherlands. Therefore, alteration of legislation is mandatory for each cancer for which screening is

considered. A multidisciplinary steering committee consisting of pulmonologists, epidemiologists, radiologists, and patient advocacy groups, among others, is preparing a request for approval that will be submitted to the political institutions. It is expected that this process will last for an extended period, and it is unsure whether approval will be obtained.

Simultaneously, several implementation studies are being initiated in the Netherlands, also in collaboration with other European countries, that investigate further refinement of screening (e.g., personalized interval, population selection, blood, and exhaled breath biomarkers).

Lung Cancer Diagnosis and Staging

GPs refer patients with symptoms or signs suggestive of lung cancer to the pulmonologist, who establishes a diagnosis and stages the lung cancer.

Time from referral of the GP to the first appointment with the pulmonologist compares favorably with other countries such as Sweden or the United Kingdom. CT and magnetic resonance imaging facilities are available in all hospitals. All patients have access to positron emission tomography, sometimes in another nearby hospital. Depending on the location(s) of the suspicious lesions, tissue is obtained by (a combination of) bronchoscopy, endobronchial ultrasound, endoscopic ultrasound, ultrasound, or CT-guided biopsies. Imaging-guided biopsies are usually performed by interventional radiologists, although in some centers, this is also done by the pulmonologists. Furthermore, most centers have pulmonologists trained in endobronchial ultrasound or endoscopic ultrasound, and if not, agreements have been made with centers nearby for easy referral.

According to Dutch guidelines, it is mandatory to discuss all newly diagnosed lung cancer patients in multidisciplinary tumor boards for staging and treatment recommendations. Adherence is good, as for example, before start of curative treatment, almost all patients (98.9%) are discussed.¹⁰

In general, the pulmonologist remains the physician coordinating all lung cancer care throughout the patient journey, and in contrast to several other countries, the pulmonologist also initiates and prescribes the systemic therapy.¹¹

Molecular and Programmed Death-Ligand 1 Testing

In a consensus meeting in 2018, the challenges of harmonization of molecular testing and the clinical use of predictive markers in the Netherlands were discussed.¹² In 2020, the Dutch guideline on NSCLC was updated.¹³ One of the most important molecular-related items was the recommendation to test every patient with

stage IV NSCLC adenocarcinoma, or patients with squamous histology but without a significant smoking history, at least for molecular aberrations in the following predictive markers: KRAS, EGFR, BRAF, HER2, ALK, MET, ROS1, RET, NTRK1-3, and NRG1, and for programmed death-ligand 1 expression (the latter is also advised for squamous cell carcinoma). Many pathology laboratories perform molecular analyses using next-generation sequencing with panels covering greater than 30 predictive markers for treatment decision making at primary diagnosis and at progression owing to treatment resistance.¹⁴ For the detection of predictive gene fusions, most laboratories use fluorescent in situ hybridization. As an increasing number of different gene fusions needs to be evaluated (ALK, ROS1, RET, NTRK1-3, and NRG1), some larger laboratories now use more cost-effective RNA-based platforms, such as Nanostring and Archer. The current discussion is whether centralization of complex molecular testing is required to give every patient access to complete molecular testing. Centralization is also preferred because of the increasing complexity of molecular testing, appropriate tissue management of the mostly rather small tissue biopsies, and cost-efficiency by sufficient test volume.

Molecular Tumor Board

As the interpretation of molecular results becomes increasingly complex, the Dutch guideline also recommends to discuss treatment recommendations of patients with NSCLC with rare (incidence < 1%) and unknown mutations in one of the seven molecular tumor boards (MTBs) in the Netherlands.^{13,15} These MTBs minimally consist of a pulmonologist with extensive experience with targeted therapy working in one of the designated centers for patients with NSCLC and rare mutations (described in the Systemic Therapy section), a pathologist with expertise in lung cancer, and a clinical scientist in molecular pathology with expertise in testing such as next-generation sequencing, fluorescent in situ hybridization, and RNA-based testing. Targeted therapy recommendations resulting from the MTB workflow for complex molecular profiles were highly adhered to and resulted in a positive clinical response in most patients with metastatic NSCLC.¹⁶

Surgery

Thoracic surgery in the Netherlands is done by both general thoracic surgeons (mainly in community hospitals) and cardiothoracic surgeons (mainly in university hospitals).

In 2019, a total of 2384 NSCLC resections were performed: 83.6% (bi)lobectomies, 6.2% segmental resections, 5.5% wedge resections, and 4.5%

pneumonectomies (unpublished data, courtesy of the Dutch Lung Cancer Audit [DLCA]-Surgery, as part of the Dutch Institute of Clinical Auditing). Video-assisted thoracic surgery (VATS) was introduced in 2006 and was soon distributed throughout the Netherlands with 78.0% of resections being done by VATS in 2019.¹⁷ Robotic-assisted thoracic surgery, in 2019, is centralized in six Dutch hospitals and accounts for 3.8% of all NSCLC resections. The number of robotic-assisted thoracic surgery operations is not increasing, which might, at least partly, be accounted for by associated financial costs per procedure and limited evidence of superiority compared with VATS.

Thoracic surgery care in the Netherlands is increasingly centralized; 80 hospitals offered lung cancer surgery in 2007 and 41 did so in 2019. This centralization occurred as all hospitals are required to meet several quality conditions laid down in the nationwide SONCOS document (the SONCOS is a platform for all Dutch societies involved in cancer care, initiated by the Dutch societies of medical, radiation, and surgical oncology [www.soncos.org]). Since 2012, all thoracic surgery procedures (i.e., lung, thoracic wall, diaphragm, mediastinal tumors) are registered in the DLCA-Surgery as part of the Dutch Institute of Clinical Auditing database for quality control and benchmarking of hospital treatment outcomes. This centralization and quality control resulted in a decline in complications and postoperative mortality.^{18,19}

Radiotherapy

There are 19 radiation oncology centers in the Netherlands, including three operational proton therapy facilities. The centers are distributed across the country to ensure easy access for all patients.

Radiation oncology departments have standard state-of-the-art linear accelerators with at least intensity-modulated radiation therapy and stereotactic radiotherapy of brain and extracranial tumors capabilities. Some centers also have MR-linacs, tomotherapy, Cyberknife, Gamma Knife, and hyperthermia and proton therapy. CT, magnetic resonance imaging, and positron emission tomography-CT integration are standard in all departments.

Radiation oncology is organized into platforms, which represent different subspecialties, including a Platform for Lung Cancer. In each platform, all institutions are represented by a radiation oncologist and a medical physicist. The platform is in connection with the Dutch Society of Radiation Oncology (NVRO) and with other professional organizations such as the Dutch Society for Pulmonary Medicine and Tuberculosis (NVALT), the Dutch Cancer Registry, and the patient advocacy group. The platform is also a place to discuss research and

organize multicentric studies. There is a separate Platform for Proton Therapy, which is reimbursed in The Netherlands for lung cancer according to the model-based approach.²⁰ Proton therapy research is coordinated in a separate group (DUPROTON).

Quality assessment is obligatory and consists of a variety of clinical and technical parameters and a minimum set of standardized items for follow-up, including toxicity and survival. Patients treated with proton therapy are followed up more extensively. It is obligatory to upload all items in a central national database that is used for quality assessment and research. Adherence to the guidelines and completeness of the uploaded data is monitored. The results of the quality audit are discussed yearly in the different platforms, and plans are made for improvements if needed in a continuous improvement/assessment cycle. Physical audits are done regularly and include all aspects of radiation oncology.

Systemic Therapy

The treatment algorithms for the first- and second-line systemic therapy options for advanced NSCLC are provided in [Figure 2A](#) and [B](#). Systemic (targeted) treatments of NSCLC characterized by oncogenic drivers with an incidence of greater than 5% in NSCLC are offered in all Dutch hospitals (i.e., *EGFR* exon 19 deletions/exon 21 L858R). On the basis of the FLAURA study data,²¹ the preferred first-line therapy for patients with NSCLC with a classical activating *EGFR* mutation is osimertinib.

To ensure quality and to expand knowledge, hospitals collaborate in regional networks, together with academic centers (comprehensive cancer networks [CCNs]). Treatment for rare oncogenic drivers (occurring in $\leq 5\%$ of lung cancers, including the *EGFR* T790M resistance mutation) is concentrated in six centers across the Netherlands. Criteria for expert center designation have been developed by the Dutch Society of Physicians for Lung Diseases and Tuberculosis.²² Agreements have been made that insurance companies will reimburse targeted therapies for rare oncogenic drivers only when provided by an expert center.

Using this system of expert centers, experience in treating patients with oncogenic drivers is high. One of the goals of these six centers is to give patients with rare oncogenic drivers access to (early) clinical trials. TKIs available within regular care are summarized in [Table 1](#).

Regional networks are also effective to introduce new and expensive therapies like immune checkpoint inhibitors (ICIs) safely.²³ ICI is allowed in hospitals that have met all the predefined required criteria (in summary): more than 20 new patients with lung cancer need to be treated with ICI, by at least one experienced pulmonologist; the hospital has a MDT specific for ICI treatment and its related toxicities; and

the hospital has at least, besides the pulmonologist, an ICI dedicated dermatologist, gastroenterologist, and endocrinologist.²⁴

On the basis of the reimbursement policy in the Netherlands (discussed subsequently), ICI combined with platinum-doublet chemotherapy is not reimbursed for the first-line treatment of metastatic SCLC, as the additive clinical value is judged low.

Clinical Value of New Drugs: The Palliative, Adjuvant, Specific Toxicity, Quality of Life, Impact of Treatment, Level of Evidence Criteria

The Committee for judgment of oncological treatments (cieBOM) started in 1999 with the aim to evaluate the clinical value of new approved drugs and to harmonize the introduction of these drugs across the country. It is an initiative from the society of medical oncologists (NVMO) and supported by the NVALT. The cieBOM consists of medical oncologists, a pulmonologist, and three advisors (a medical statistician, a pharmacist, and a health technologist assessment advisor) and evaluates the clinical value of all newly EMA approved drugs, treatment methods, and treatment indications in the field of medical oncology. The goal is to come to a national agreement with the professional societies regarding the use of new, and often expensive, therapies. The evaluation is done after the completion of a randomized phase 2/3 trial (published in a peer-reviewed publication) and after EMA approval and is based on self-developed Palliative, Adjuvant, Specific Toxicity, Quality of Life, Impact of treatment, Level of Evidence criteria ([Table 2](#))²⁵ and aligned with the separate and independent evaluation of the Institute of Healthcare in the Netherlands (Zorginstuut Nederland).²⁵ In contrary to the ESMO magnitude of clinical benefit scale,²⁶ the Palliative, Adjuvant, Specific Toxicity, Quality of Life, Impact of Treatment, Level of Evidence criteria do not allow a gradual assessment. The conclusion will be a positive or negative advice for introduction of the treatment in the Netherlands. The consequence of a negative advice (e.g., IMPOWER 133) is that a drug/treatment will not be introduced in the Netherlands. Unfortunately, a positive advice of cieBOM does not automatically lead to reimbursement.

For drugs that are EMA approved on the basis of a single-arm phase II study (e.g., for rare oncogenic drivers), the “state of the art for medical science” is used.

Palliative Care

End-of-life care is more home-centered than hospital-centered.²⁷ Therefore, palliative care is mainly provided by generalists such as GPs. However, if needed, access to

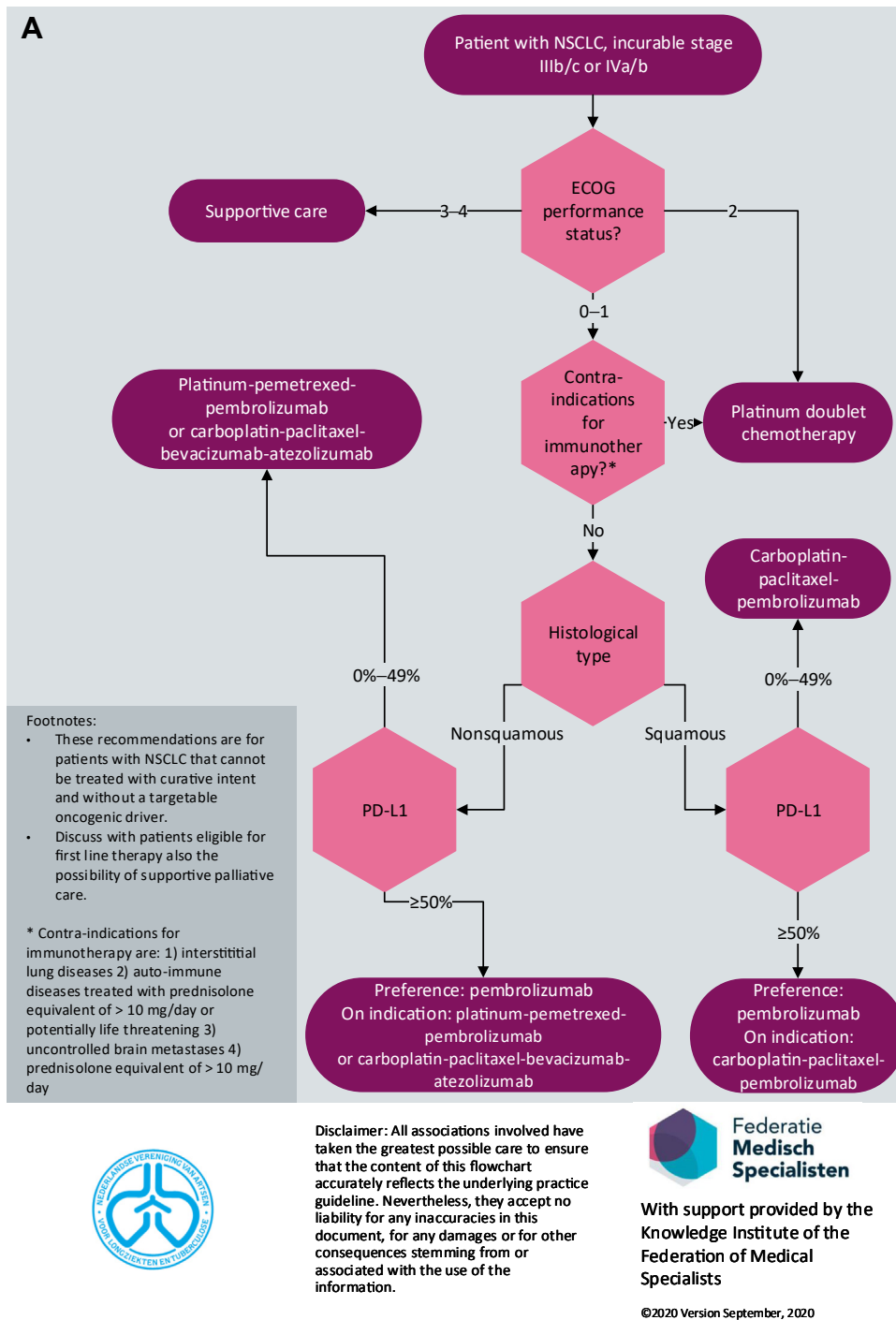
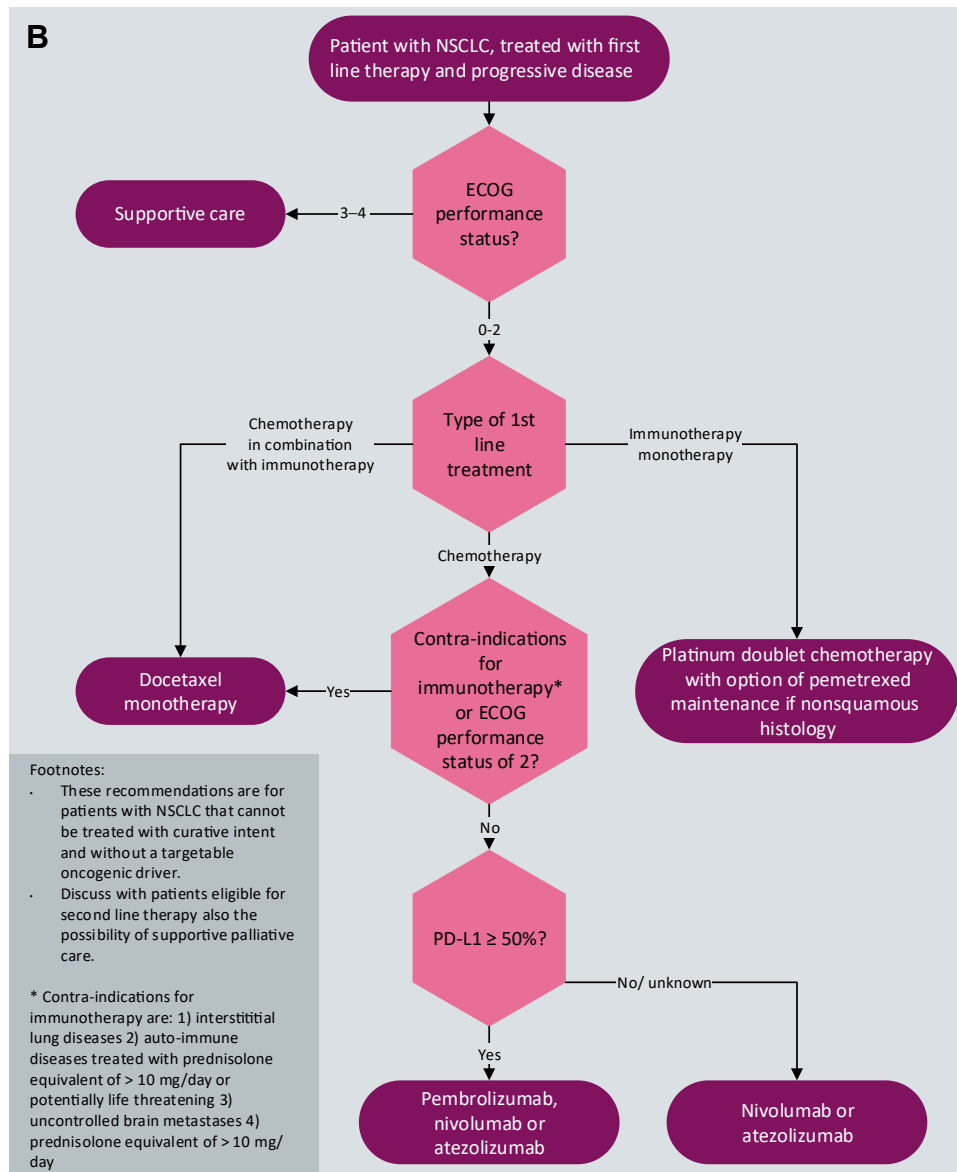


Figure 2. (A) First- and (B) second-line systemic treatment options for patients with advanced NSCLC without a targetable oncogenic driver. ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed death-ligand 1.

palliative care specialists is good, as there are 14 ESMO designed centers of integrated oncology and palliative care (with this number, the Netherlands ranks fourth in Europe). Patients receiving palliative care from the GP are regularly discussed in palliative care teams including a palliative care consultant. There are 65 regional collaborative networks, with seven overarching

palliative care consortia. The aim is to incorporate palliative care early in the care for patients with advanced cancer, and in contrast to southern European countries, discussions on palliative care and end-of-life decision making are indeed more frequent in the Netherlands.²⁸⁻³⁰ As a result, the percentage of intensive care admittance in the past months of life is low (3%-



Disclaimer: All associations involved have taken the greatest possible care to ensure that the content of this flowchart accurately reflects the underlying practice guideline. Nevertheless, they accept no liability for any inaccuracies in this document, for any damages or for other consequences stemming from or associated with the use of the information.



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Figure 2. (continued).

5%), and only 18% of the patients with lung cancer die in the hospital.^{31,32} However, there is still room for improvement as relatives indicate that, although they were satisfied with the choice to start a treatment, treatment goals such as quality of life were often not achieved.³³ Furthermore, a substantial part of patients with lung cancer (52%) received chemotherapy in the past month of their life, which can be considered as aggressive end-of-life care.³⁴

Quality Control

In the Netherlands, several quality control systems exist to improve quality and equality of (lung) cancer care. The most important are the SONCOS and the DLCA.

To reduce waiting times, the SONCOS, has defined maximum through-put times for diagnosis and start of treatment of cancer [GP to first consultation specialist: 1 wk], diagnosis [specialist to diagnosis: 3 wk], and

Table 1. Overview of Possible Current TKI/Targeted Therapy Treatment Options in the Netherlands for Different Targets in NSCLC (September 2020)

Mutation and/or Fusion in NSCLC	Available Drugs (Alphabetical Order)
KRAS	Only within clinical trial
EGFR	Afatinib, dacomitinib, erlotinib, erlotinib-bevacizumab, erlotinib-ramucirumab, gefitinib, osimertinib
BRAF	Dabrafenib-trametinib
ALK	Alectinib, brigatinib, ceritinib, crizotinib, lorlatinib
ROS1	Crizotinib
MET exon 14 skipping or amplification	Only within clinical trial/early access program
HER2 mutation or amplification	Only within clinical trial
RET	Only within clinical trial/early access program
NTRK1-3	Only within clinical trial/early access program
NRG1	Only within clinical trial

TKI, tyrosine kinase inhibitor.

treatment [specialist to start of treatment: 6 wk]). Quality checks are performed, and at least 80% of the patients should be found and treated within these timelines.³⁵ This has resulted in a reduction of the waiting times; median time from diagnosis to start of treatment in 2016 was 28 days, and 90% of the patients start treatment within 58 days.³⁶

The DLCA gathers quality data from all health care institutes concerning lung cancer diagnosis and treatment. Quality is measured through indicators adopted from the International Consortium of Health Outcome Measurements with input from representatives of the NVALT, radiation oncologists, and surgeons together with the government, patient representatives, and insurance companies.¹⁹ As there is an annual cycle of internal and external indicator publications, quality of the lung cancer care can be monitored and improved on a national level. Since 2016, all relevant specialties (pulmonologists, radiation oncologists, and surgeons) have joined this registry. Internal indicators are found to be the strongest drivers of quality improvement (data not publicly available).

NVALT Studies

To foster innovation and to improve the quality of lung cancer care and collaboration between centers, the NVALT oncology section started with the development of investigator-initiated clinical trials in 2000. To formalize the organization for clinical studies, the NVALT study foundation was set up in 2007. Members of the NVALT oncology section propose and initiate multicenter clinical trials; the NVALT study foundation is the sponsor

Table 2. PASKWIL Criteria

Criteria	Description
Criteria for adjuvant therapy	
Primary end point	OS is the most relevant end point
Gain in DFS	Evaluation based on DFS is possible; this results in a preliminary advice that needs to be reevaluated after the OS results become available. A positive advice can be retracted if OS results are negative. DFS HR should be <0.7
Gain in OS	Minimum of 3 years of follow-up >5% >3% and HR < 0.7
Criteria for therapy with palliative intent	
Efficacy	
Gain in OS	>12 wk or HR < 0.7
Gain in PFS	>12 wk or HR < 0.7
ESMO-MCBS grading	Added when available
Toxicity (difference)	
Lethal (absolute)	<5%
Acute, severe	<25%
Chronic invalidating	Not specified
Impact of treatment	Treatment burden should be acceptable
Costs of treatment	Given for a median duration of treatment Given for 28 days Cost difference compared with standard of care

DFS, disease-free survival; ESMO-MCBS, European Society for Medical Oncology Magnitude of Clinical Benefit Scale; HR, hazard ratio; OS, overall survival; PASKWIL, Palliative, Adjuvant, Specific Toxicity, Quality of Life, Impact of Treatment, Level of Evidence; PFS, progression-free survival.

and facilitates the adherence to all applicable guidelines and regulations. Since 2010, a total of 27 phase 2 or phase 3 studies have been initiated, sometimes in collaboration with other international scientific societies. The NVALT studies significantly contributed to the lung cancer research field as is shown by multiple publications in (high-impact) medical journals.³⁷⁻⁴⁹

Patient Organization

There is an active Dutch lung cancer patient organization: Longkanker Nederland (www.longkankernederland.nl). This organization is committed to saving lives and accelerating lung cancer research and policy while empowering people living with, or at risk for, lung cancer. Longkanker Nederland conducts awareness campaigns, attacks the stigma of the disease, and advocates for more urgency and more funds for lung cancer research. It furthermore gives information to and organizes information days for patients and their relatives. It is funded

through a national cancer fund, the Ministry of Health, and donors and sponsors.

Longkanker Nederland works together with pulmonologists and patients who act as patient advocates. Currently, the most important goals of Longkanker Nederland are (1) to start with population-based screening of individuals at high risk of lung cancer, (2) to improve molecular testing in patients with NSCLC, (3) to improve shared decision making, (4) to have for all patients a designed person (nurse) to contact, and (5) to focus on centralization and expert referral for lung cancer.

For patients and their relatives, there is a dedicated website. There is also the possibility to ask questions online to a pulmonologist, radiotherapist, radiologist, pulmonary/thoracic surgeon, or pathologist, all specialized in lung cancer care. The website provides blogs and personal stories of patients with lung cancer. To further provide support, Longkanker Nederland has 11 private Facebook groups for different types of lung cancer (e.g., [very] young patients, *EGFR*, rare drivers, ICI, thymoma, family members).

Conclusions and Future Directions

As described in the Lung Cancer Europe position article, the health care quality in the Netherlands is at a good level.⁵⁰ Recent improvements include the organization of oncologic care in CCNs, centralization of specialist care, multidisciplinary tumor boards, and MTBs and the initiation of proton radiotherapy. Hospitals and CCNs can learn from each other on how to optimize care. National guidelines are in place for most tumor types and are frequently updated. As the treatment of lung cancer is becoming increasingly complex, discussions are also ongoing on how to optimize the training of physicians to deliver optimal lung cancer care. Nationwide studies in thoracic oncology, also with multidisciplinary collaboration, have been well-accruing for most indications. Initiatives (mobile applications) are also ongoing or already in place to provide easy access for health care providers and patients to rapidly identify ongoing trials throughout the Netherlands. Importantly, numerous challenges lie ahead, including the increasing demand to justify reimbursement of novel treatments and diagnostic tests, the continuing smoke prevention policy, and the necessity to acquire legislation for the initiation of lung cancer screening.

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