Evaluating lung cancer care in the Netherlands: staging, treatment and surgical quality assurance

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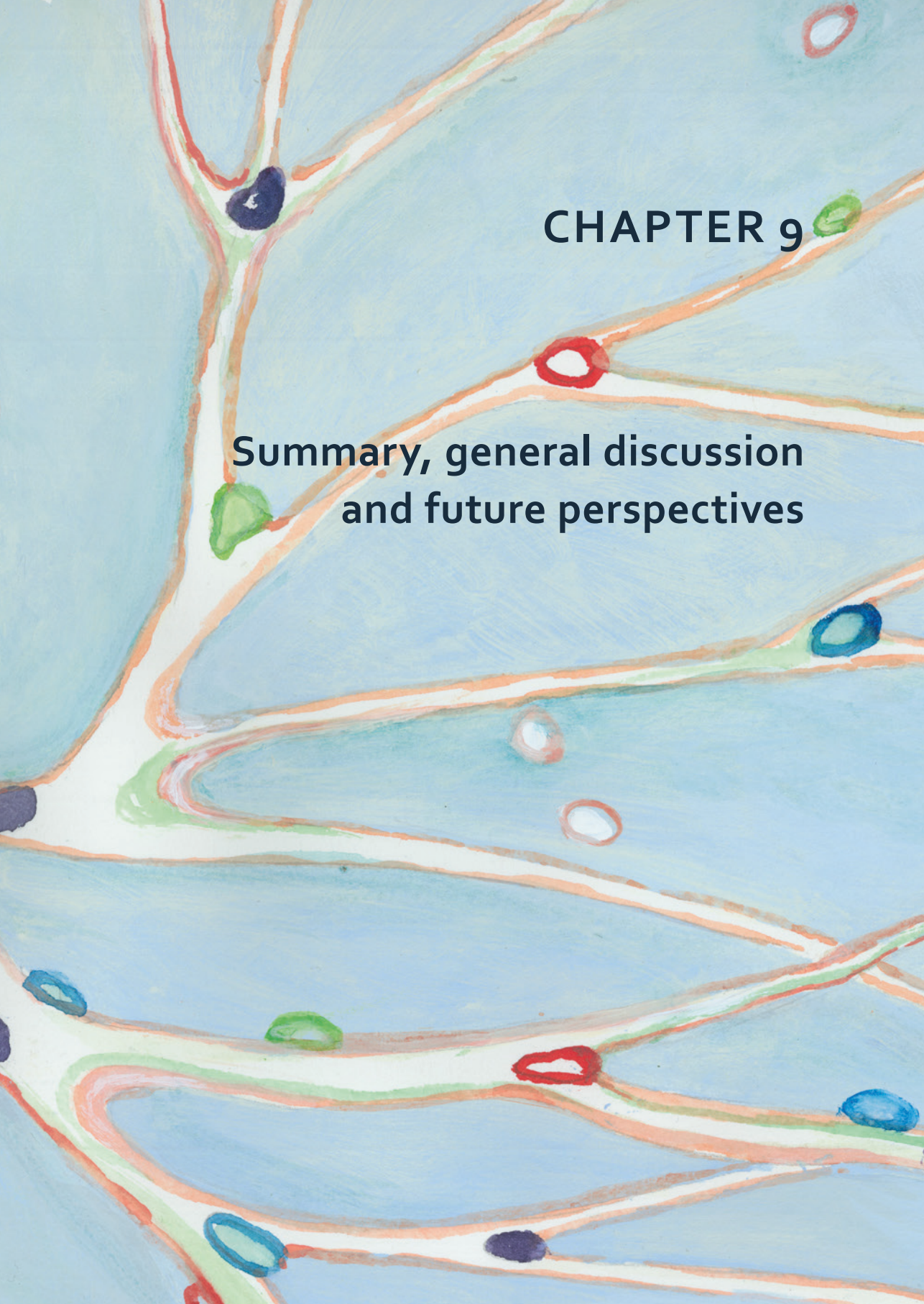

CHAPTER 9

Summary, general discussion and future perspectives

SUMMARY

In 2010 the Dutch Institute for Clinical Auditing (DICA) was founded in the Netherlands to facilitate clinical auditing. It provides benchmarked feedback to clinicians on one hand, and transparent outcome information for patients and stakeholders in healthcare on the other hand. (1) By measuring and comparing outcomes, (short-cycle) improvement initiatives are stimulated with the belief that this forms an essential part of the continuous improvement of health care.

The Dutch Lung Cancer Audit – Surgery (DLCA-S, formerly Dutch Lung Surgery Audit) started in 2012. Nowadays over 5000 lung surgical procedures are registered annually by all Dutch hospitals where lung surgery is performed. (2) The first analyses from the DLCA-S showed variation in practice between Dutch hospitals performing lung surgery and an overall low concordance between clinical and pathological staging of non-small cell lung cancer (NSCLC) in the Netherlands. (3-5) These outcomes led to the desire to research this variation more extensively.

The main goal of this thesis is to improve care for lung cancer patients by evaluating lung cancer care and providing insight into care processes. To achieve this, multiple strategies were used, ranging from international comparisons to in-depth analyses of DLCA-S data, adding process information on a hospital level to DLCA-S data, and analyzing multidisciplinary team (MDT) decision making by observing MDTs.

With outcome information available on a national level and the possibility to compare interhospital differences, the next step was to compare overall performance internationally. In **Chapter 2** we compared the Dutch and the Danish audit data. Lung surgery in Denmark is much more centralized than in The Netherlands and both countries have differences in funding and governance. Nevertheless, both countries had low mortality: 1.5% in Denmark vs. 1.9% in the Netherlands. Also, accuracy of clinical staging was very similar in both countries with 53%. Comparing complications after lung cancer surgery showed a difference: 24.4% of patients had a complicated course in Denmark vs. 34.8% in the Netherlands. Although analyzed in the same way by using the raw data available from both registries, it remained hard to compare this outcome between both countries due to differences in data definitions and data dictionaries.

DICA has a solid framework to secure data quality and in **Chapter 3** we described these processes for the DLCA-S. Build-in control mechanisms by which the data are already checked during registration, direct feedback about data quality by a 'completeness indicator', and data verification are important steps for data quality. The latter showed

a case ascertainment of 99.4% in the 15 selected hospitals over registration year 2014, with 0% under-registration of mortality and 3.3% wrongly registered complications. However, one must be aware that data extraction from hospital EPD systems comes with different challenges than registration by health professionals themselves or hospital data managers. This can lead (in addition to definition differences) to different errors and incomparable results.

The study described in **Chapter 4** was designed to perform an in-depth analysis of one of the possible causes of inaccuracy in clinical staging. Especially inaccurate staging of the mediastinal lymph nodes might have clinical consequences leading to suboptimal treatment. (Video)mediastinoscopy has been the gold standard in lymph node staging for years. However, esophageal ultrasound (EUS) and endobronchial ultrasound (EBUS) are nowadays the modality of first choice in lymph node staging. They are less invasive, leading to fewer complications, don't require general anesthesia, and after a period of learning curve, high sensitivity and specificity are reached. This made the added value of a (video)mediastinoscopy questionable, especially keeping in mind that it has also considerable morbidity and often causes a delay until definitive treatment. We analyzed performance of (video)mediastinoscopy in the Netherlands and showed that only 51% of all these procedures are performed according to the Dutch guideline, and 75.4% met the less strict ESTS guideline. Adherence to the stricter Dutch guideline led to less unforeseen N2 disease compared to non-adherence to this guideline (8.6% vs. 11.9%; $p<0.05$), which makes following of the Dutch guideline advisable.

After interpretation of all imaging, invasive staging procedures and pathological results, the MDT decides on the clinical stage of the patient's disease. Especially for higher staged patients this is not always 'adding up numbers' but requires considering uncertainties. Based on this clinical stage a treatment proposal is made, using the best available oncological evidence, but patient-tailored, considering patient factors and preferences. It is ultimately a multidisciplinary process. An evaluation of potential factors influencing MDT decision making is reported in **Chapter 5**. Eleven MDTs each evaluated the same 10 challenging stage IIIA cases of NSCLC patients in their weekly MDT meeting. Using Randolph's free-marginal multirater kappa, we showed considerable variation among MDT's in both staging and treatment recommendations. Suspicion of invasion of surrounding structures and distinction between N1 and N2 disease were an important source of discordance. According to additional diagnostics and treatment proposal, it emerged that where guidelines and evidence were unambiguous there was more uniformity, and in the case where evidence was lacking and guidelines were outdated more variation was seen. These findings underline the importance of evaluation of

NSCLC patients with locally advanced disease in an experienced MDT setting to minimize variation in treatment and outcomes.

Both the low level of concordance in staging and the variation found between MDT's in clinical staging show that the TNM staging system has its shortcomings in clinical practice. Merely focusing on the TNM for treatment decisions is not enough. **Chapter 6** is an opiniated discussion in which we are questioning whether the heavy focus on the TNM stage in making treatment decisions for NSCLC patients is still justified. With the increasing complexity of NSCLC treatment with new treatment options often based on tumor biology, histopathology and molecular staging quickly become more important. In this chapter we conclude that "In the newest era, the MDTs make treatment decisions combining morphologic and biological features, patient factors, and shared decision making, to optimize patient-tailored treatments. Ideally, a new system should be developed that takes all these factors into account."

High-quality surgery is important but at least as important is the quality of perioperative care, which is aimed at rapid recovery, without complications or readmissions. (6)

In **Chapter 7** we used length of stay (LOS) as a quality measure of perioperative care. Because LOS has its shortcomings and is also depended on other factors such as age, comorbidity, extent of treatment and complications, we first analyzed whether LOS was an adequate measure for perioperative care by assessing whether it was a hospital characteristic. Analyzing LOS on a hospital level for both uncomplicated and complicated patients showed clear between-hospital variation and showed that hospitals with shorter LOS in uncomplicated cases also have shorter LOS in complicated cases. This persisted after casemix correction: 4 hospitals managed to discharge significantly more uncomplicated patients in <4 days than expected, and 8 hospitals significantly less patients than expected, based on their casemix. After casemix correction short LOS in uncomplicated patients was statistically significantly correlated with shorter LOS in complicated patients, proving that LOS could be used as a hospital characteristic.

Median LOS after minimally invasive lung surgery between 2012 and 2017 was 6 days in the Netherlands. Between-hospital variation in median LOS of uncomplicated patients varied from 3 to 8 days. Both the long LOS and the wide range between hospitals suggest that substantial improvements can be made by implementing uniform guidelines for perioperative care as described in the Enhanced Recovery After Thoracic Surgery (ERATS) protocol.

An important item of perioperative care after pulmonary resection is chest tube management. Persistent air leak (PAL; in the Netherlands defined as air leak >5 days after surgery) is the most common complication after pulmonary resection. It leads to increased morbidity and prolonged LOS. Incidence rates of PAL range between 8 and 26% according to the literature. In **Chapter 8** we found a Dutch national incidence of 9% with a wide range between hospitals from 2.6 to 19.3%. In an online survey, national practice was investigated, leading to a response of 68 thoracic surgeons (49% response rate). Almost all hospitals (97%) had protocols for chest drain management but only 61% of them described what to do in case of PAL. There was a lot of variation in the use of sealants, digital vs. analogue drain systems, and the use of suction versus water seal. On a hospital level using water seal instead of suction to a chest tube was associated with significantly less incidence of PAL [-2.92% (-5.42 to -0.43)]. Improvements can be achieved by increased awareness of these results and applying water seal to chest tubes in the hospitals that weren't already doing so. With this research we show that using national data to measure and analyze outcomes and to compare hospitals can lead to insights and specific actions to improve outcomes.

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

Variation in medical practice dates back to the origins of medicine itself. For a very long time, no scientific evidence was available for medical treatment by doctors. In the 19th century, anesthetics and antisepsis made surgery possible, and together with the development of antibiotics in the 20th century, this was a starting point for an exploding increase in medical-scientific knowledge. Trust in doctors and the possibilities of medical practice became unlimited. (7)

Currently, high expectations of health care, an aging population, rapid innovations, growing health care costs, and limited available resources are challenging the healthcare system and require critical appraisal of current medical practice and evidence. Not surprisingly, in the last decades, multiple initiatives have appeared worldwide in which health care data and outcomes are collected and compared, to increase value for patients and to manage costs.

Importance of reliable and complete data

Real world data (RWD) in health care have been used for a long time, but its use has expanded substantially the last decades. Technical advancements made data collection, storage, and analysis much easier. The importance of quality assessment in health care

is nowadays widely supported and for this use, reliability and completeness of data are of utmost importance.

For the Dutch Lung Cancer Audit (DLCA) data are collected by the Dutch Institute of Clinical Auditing (DICA). In Chapter 3 we describe this process for the DLCA-Surgery (-S) and report high validity of these data. Nevertheless, challenges in collection, extraction and uniform data definitions remain.

Lung cancer is a high-volume disease, with multiple treatment modalities. Therefore, multidisciplinary evaluation of health care is essential. The Dutch Lung Cancer Audit (DLCA) covers all Dutch lung cancer patients in the sub-registries Surgery (-S), Radiotherapy (-R), and Lung Oncology (-L). There is a strong desire to integrate these audits to follow the full patient journey and to compare outcomes of different treatments. However, this has been a persistent struggle for many years. The strict Dutch privacy legislation is a complicating factor in achieving this comprehensive and integrated lung cancer registry. In the meanwhile, the difficulty lies in registering all relevant variables without creating a substantial registration burden and keeping all participating professionals involved. An integrated audit would make this easier.

In addition to national health care evaluation, RWD can be used for international comparisons of processes and outcomes. In **Chapter 2** we performed the first international comparison for outcomes of lung surgery, between the DLCA-S and the Danish Lung Cancer Registry (DLCR). Thirty-day mortality and stage concordance are solid end-points, which could easily be compared and which turned out very similar between both countries. However, in Denmark 24.4% of patients had a complicated course after surgical treatment vs. 34.8% in the Netherlands ($p < 0.05$). This seems an important difference, which requires in-depth analysis to reveal opportunities for improvement. Unfortunately, this isn't possible with the existing data. Differences in data definitions, registration, and collection made one-to-one comparison and drawing solid conclusions impossible.

The problems encountered regarding comparability of complications, substantiate the importance of transparent and unambiguous data definitions. The importance of data quality is an internationally recognized item. Already in 2015, the Society of Thoracic Surgeons (STS) and The European Society of Thoracic Surgeons (ESTS) standardized their variable definitions and terminology. (8) Also, the International Consortium for Health Outcomes Measurement (ICHOM) strives for uniform data definitions and published a structured outcome set for lung cancer in 2016. (9) Despite these efforts and multiple other initiatives, further action to internationally harmonize and standardize relevant data sets remains imperative.

Using variation in health care to learn and improve

As one would expect at the start of any clinical audit, variation in processes and outcomes exist between hospitals. Analyzing DLCA-S data, we have identified variation in daily clinical practice for lung cancer patients, offering valuable insights for improving clinical care.

We analyzed Length of hospital stay (LOS), a valuable outcome measure that can serve as an indicator of perioperative care quality, as it tends to increase in cases where practices and outcomes are not optimal. Significant variation in median LOS was found, which suggests room for improvement and underscores the importance of uniform perioperative care protocols. (**Chapter 7**) Currently the 'Enhanced Recovery after Thoracic Surgery (ERATS) protocol' is implemented in a study in multiple Dutch hospitals, aiming at faster recovery and fewer complications. (10) We expect that with less invasive surgery, better postoperative pain management and optimized chest drain protocols, as well as more attention to early mobilization, LOS can be further reduced, without an increase in readmissions or complications. Not only may this contribute to the wellbeing and recovery of patients, but it also may reduce costs. Recently, the randomized controlled Optimal postoperative Pain management After Lung surgery (OPtriAL) included the last patient. Results are eagerly awaited to optimize post-operative pain strategies further. (11)

In **Chapter 8** we showed variation in persistent air leak (PAL). In most hospitals with a high incidence of PAL, treating physicians were unaware of this. Lack of evidence about postoperative chest drain device settings led to a wide practice variation with a suction vs. water seal ratio of almost 50:50 between hospitals. In our study, hospitals using water seal directly after surgery reported a lower incidence of PAL. Throughout the timeframe of the questionnaire administration, the randomized controlled trial conducted by Holbeck et al. offered further clarification and found that a pressure of -2cmH_2O reduces air leak duration, drainage duration, and fluid output compared to a postoperative pressure of -10cmH_2O. (12) The recently published Dutch guideline, subsequently recommends low suction or water seal (≤ -8 cmH_2O) postoperatively after anatomical lung resection. The specific pressure is, however, still open to debate. (13) The ERATS study protocol uses a pressure of -2cmH_2O, which is in line with Holbek's trial. (10, 12)

By using RWD for outcome research, as exemplified by the aforementioned studies, parameters can be evaluated and selected as quality indicators. Moreover, it can provide tools to improve these outcomes, for example by changing the settings of the chest drain devices. Feedback on LOS and PAL on a hospital level as quality indicators or on a real-time dashboard (Codman as used by DICA), provides healthcare professionals with the opportunity to monitor their performance. They can benchmark their outcomes

with other hospitals, preferably the best-performing ones (best 20%), as is currently facilitated by DICA. (1) Furthermore, insight into these outcomes provides the healthcare professional with the opportunity to use this information in the consultation room, to inform the patient on the expected peri-operative course and the comparative benefits and risks associated with their treatment, compared to a group of similar patients. Additionally, artificial intelligence can be applied to these RWD, to make even better predictions or to reveal improvement potential.

Clinical staging

Clinical staging for NSCLC can be challenging, reflected by a concordance between clinical and pathological TNM-stage of 55% (TNM 7 era). (5) In **Chapter 4** we found that mediastinoscopy, the gold standard in mediastinal lymph node staging for years, was performed according to the Dutch guideline in only 51% of the Dutch patients. However, guideline adherence reduced the number of unforeseen N2 by 3.3% (8.6% vs. 11.9%; p 0.043). For mediastinoscopy to be of additional value, strict guideline adherence is therefore advisable. Recently the MEDIASTRIAL demonstrated noninferiority in unforeseen N2 disease for immediate resection vs. confirmatory mediastinoscopy after E(B)US. Based on these results the authors state that in patients with resectable NSCLC with an indication for mediastinal staging, confirmatory mediastinoscopy after negative E(B)US can be omitted. Nowadays, mediastinoscopy should be reserved for specific cases. (14)

Another development in staging of NSCLC is the upcoming 9th edition of the TNM classification system. New in this version is the subdivision of the N2 stage in N2a (single N2 station involvement) and N2b (multiple N2 station involvement) and the subdivision of M1c in M1c1 and M1c2 (extra-thoracic metastases respectively in one or more organ systems). (15, 16) Since the first edition of the TNM, with almost every update new categories for T, N, or M were added, leading to a better prediction of prognosis. The question is whether this improves the usability of the system in clinical practice, or if it does the opposite. The system is getting more complex but on the other hand still only involves anatomical features, despite the increasingly important role of tumor biology in the treatment of NSCLC.

Another problem with the TNM system is its retrospective nature. The 9th edition is based on patients included from 2010 till 2019, who have never been treated with the treatment regimens that are currently evaluated in clinical trials in which patients are included based on these 'outdated' TNM categories. The tumor biology of these included patients can be very different. For example, stage III comprises patients with large tumors but also patients with mediastinal lymph node metastases, resulting in subgroups who will more or less benefit from immunotherapy and or targeted therapies. Therefore, trials

are recruiting patients with tumors with different biological behavior but with similar prognosis in older treatment regimens, making a trustworthy conclusion difficult for the modern treatment regimens that are being investigated. Often, trials are not sufficiently powered to perform relevant subgroup analyses to solve this. In an era where patient-tailored treatment is increasingly important, the TNM system alone may no longer provide sufficient information to guide treatment decisions. Combining morphologic and biological features, patient factors, and shared decision-making, is necessary to optimize patient-tailored treatments, which we proclaim in **Chapter 6**.

Current developments in lung cancer treatment

Many new treatment strategies are currently under investigation. All patients with early-stage NSCLC undergo radical local treatment if their physical status permits this. Upfront surgery has long been the standard for both stage I and II, but neo-adjuvant chemo-immunotherapy is rapidly introduced for tumors =>4cm or node-positive disease. For stage I NSCLC stereotactic ablative radiotherapy (SABR; also SBRT) can be an alternative, depending on the patient's condition and/or preferences. Combination of SABR and immunotherapy is stretching the indication of SABR to larger tumors (stage II).

Until recently, lobectomy was the standard surgical treatment. However, in 2022 the randomized JCOG 0802 trial showed significantly improved overall survival when comparing segmentectomy with lobectomy in patients with cNo disease and a peripheral tumor smaller than 2 cm. Surprisingly, in this study, a significantly higher rate of locoregional recurrences in the segmentectomy group did not lead to a worse overall survival. (17) Recently, the CALGB 140503, multicenter phase III trial also published long-term follow-up after lobar versus sublobar resection for tumors <=2cm and found that sublobar resection was not inferior concerning disease-free survival and had similar overall survival to lobectomy. In this study almost 60% of sublobar resections consisted of wedge resection. (18) Both studies recommend performing a frozen section of at least the hilar lymph nodes, and if tumor positive, to perform a lobectomy for better oncological outcome since there is a stage migration from stage I to stage II. (19) If lung cancer screening is to be implemented in the Netherlands, sublobar resections become even more relevant, given the anticipation of detecting a higher number of small tumors and abnormalities. Future research should focus on the question whether sublobar resection is still non-inferior in case of potentially unfavorable characteristics, for example pleural or visceral invasion or central tumors.

For locally advanced NSCLC the challenge was to carefully select patients that would benefit from (upfront) surgery, and neo-adjuvant strategies comprising chemotherapy and/or radiotherapy. Targeted therapy and immunotherapy, however, are changing the

approach to locally advanced disease. In 2020, the first approved targeted therapy for adjuvant use in patients with resected stage IB to IIIA NSCLC and EGFR mutations was Osimertinib. (20, 21) The first neoadjuvant regimen for patients with locally advanced NSCLC was chemotherapy combined with nivolumab, which showed a significantly longer event-free interval and a higher rate of pathologic complete response in the CheckMate 816 trial. (22)

Recently, perioperative regimens with durvalumab, pembrolizumab, toripalimab and nivolumab and were added to the options for stage II to IIIB resectable NSCLC and all showed significantly greater event-free survival and pathological complete response as compared with neoadjuvant chemotherapy alone in phase III trials. (23-26) The INCREASE trial added radiotherapy to their dual neo-adjuvant regimen with ipilimumab and nivolumab, which led to a complete pathologic response of 60%, a nearly twofold increase compared with chemoradiotherapy alone. (27, 28) The KEYNOTE-671's regimen incorporating pembrolizumab recently became the first perioperative regimen including immunotherapy with FDA approval, EMA approval is pending. In this light, invasive mediastinal staging by systematic EBUS and/or EUS will be of additional use to carefully select patients for neo-adjuvant treatment before surgery.

Advantages of neo-adjuvant therapies in localized NSCLC are the early targeting of micrometastases; the possibility to identify cohorts of patients most likely to benefit from surgery and guidance of adjuvant therapy (in vivo assessment of response). Selection of patients who might benefit from neo-adjuvant immunotherapy should be done carefully, because this strategy also causes a delay in surgery, with the risk of disease progression, it could potentially increase surgical complications and because of side effects it may lead to delay or cancellation of surgery. Overtreatment of subgroups is therefore not desirable. Another factor to address is the definition shift of what is considered 'resectable NSCLC': even multi-level N2 disease is not always deemed unresectable anymore. (29)

Optimization of lung cancer care for each patient

The growing palette of treatment options and the rapid innovations increase the complexity of NSCLC care. The considerable variation in staging and MDT treatment proposals that we found for stage IIIA lung cancer patients in **Chapter 5** underscores that variation is still an important problem in the pursuit of more uniform, but patient-tailored treatment. Analysis of the Netherlands Cancer Registry (NCR) data by de Ruiter et al showed higher resection rates for stage I NSCLC patients diagnosed in hospitals with in-house lung cancer surgery. Hospitals without in-house surgery had higher rates of curative intent radiotherapy, but no effect on overall survival was seen. (30) Close multidisciplinary and regional collaboration may help overcome these differences. The question is whether

this needs further centralization, which is intended in the Integrated Care Agreement (Integraal Zorg Akkoord; IZA). (31) For surgery, it seems reasonable to centralize care. Resections are becoming more complex on both ends of the spectrum, with minimally invasive segmentectomies on the one end, and surgery after different combinations of chemo-, immuno- and radiotherapy on the other end. Centralization of lung cancer surgery may also contribute to reduce variation LOS, and to faster implementation of policies such as ERATS and prehabilitation programs. In Denmark centralization of lung cancer care, coextensive with increased use of VATS and the introduction of an ERAS program, has led to fewer complications, shorter LOS and, improved resection rates and survival. (32, 33) On the other hand, we compared our national audit data with Denmark after centralization took place over there, and found comparable accuracy of staging and mortality rates for both countries. Only rates of patients with a complicated course were significantly lower for Denmark, although different definitions of endpoints in the databases preclude firm conclusions.

Conclusion and future perspectives

When we look ahead, the landscape of NSCLC appears promising, marked by advancements in diagnostics and treatment modalities.

As we have shown in this thesis, considerable variation exists in diagnosis, perioperative protocols and treatment, and even in the interpretation of diagnostics and subsequent treatment proposals by MDTs. This variation should be reduced to keep health care effective, efficient, and future proof.

On the other hand, treatment becomes more patient specific and tailored. Increased knowledge of tumor biology, molecular diagnostics such as liquid biopsy and whole genome sequencing (WGS), and advancements in immuno- and targeted therapies are developments that increase complexity of NSCLC treatment. On top of that, an aging, and more comorbid population requires patient specific treatment choices.

To make well-founded treatment choices for each patient, RWD that evaluate and compare treatment outcomes are imperative. RWD, whether or not combined with artificial intelligence, will allow evaluation of treatments in patients subgroups that are not represented in clinical trials. They provide also valuable information for shared decision-making. Efforts are necessary to improve data collection. There is a strong need for data connections, and solutions to collect more data in a smarter way than registration by doctors, nurses or data managers.

The future of NSCLC management hinges on a multifaceted approach, integrating innovative diagnostic techniques, personalized treatment strategies, and use of data. With the increasing complexity, multidisciplinary collaboration becomes even more important. Providing adequate care for individual patients within a rapidly evolving field necessitates a collective effort to reorganize our approach. Care should increasingly be provided in regional networks in which MDT's work together and specific treatment elements are provided in an efficient way for both patients and health care providers: decentralized and close to home when possible, centralized when needed.

Additional to national developments we need to intensify international collaboration, especially regarding data collection and innovation. We need to establish standardized data collection techniques, utilize consistent definitions, and create methodologies for data linkage. These measures will enhance our ability to answer key research questions and to progress personalized medicine.

Given our well-organized healthcare system, our commitment to self-evaluation and a proven history of conducting and coordinating large clinical trials, Dutch healthcare professionals would be well equipped to take a leading role in the set-up of an international network focusing on care, research and education, ultimately benefiting every patient worldwide with NSCLC and the healthcare professionals involved in their treatment.

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