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Trine Stokstad

Timelines in lung cancer diagnostic workup

Doctoral thesis

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Thesis for the Degree of
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Department of Clinical and Molecular Medicine

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Trondheim, Januar 2019

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Ventetider for utredning og behandling av lungekreft

Lange ventetider for å starte kreftutredning eller -behandling fører til bekymring for at kreftsykdommen utvikler seg slik at det ikke lenger finnes effektiv behandling. Det er derfor innført pakkeforløp og målet er at flertallet av norske kreftpasienter skal være ferdig utredet og starte behandling innen gitte forløpstider. Det er underforstått at dette er et kvalitetsmål, men det finnes veldig lite datagrunnlag for at kvaliteten faktisk bedres eller at det å overholde de valgte forløpstidene gir bedre behandlingsresultat.

Vi har studert utredningstiden for lungekreft fordi det er en sykdom som rammer mange og er den kreftsykdommen som tar flest liv. I Norge er det et mål at minst 70% av lungekreftpasientene skal starte behandling innen 35 dager (cellegift) eller 42 dager (strålebehandling og kirurgi).

Utredningen av lungekreft er kompleks. Så langt vi vet er det ingen som har undersøkt hvor mange som realistisk sett kunne ha startet behandling innen anbefalt tid og med dagens ressurser. Det er heller ikke vist at raskere utredning er assosiert med økt overlevelse.

Vi fant at for få pasienter med lungekreft fikk behandling innen anbefalt tid. Spesielt kunne flere pasienter ha vært utredet uten å måtte repetere undersøkelser og følgelig ville man spare både tid, penger og ressurser. Pasienter som startet behandling innen anbefalt tid hadde totalt sett kortere overlevelse enn de som ventet lenger, og dette er i tråd med tidligere studier. Imidlertid var det ikke slik i alle behandlingsgrupper og det behøves mer forskning for å forstå sammenhengen mellom utredningstid og overlevelse.

Dataene ble innhentet ved en retrospektiv gjennomgang av pasientjournaler til alle pasienter som ble diagnostisert med lungekreft ved lungeavdelingen ved St. Olavs hospital i årene 2011-2013. Vi identifiserte viktige årsakene til forsinkelser og ut fra dette anbefaler vi endringer som kan føre til et bedre utredningsforløp. Framtidige studier kan vise om implementeringen lykkes, og om kortere utredningstid bedrer overlevelsen ved lungekreft.

Name of candidate:	Trine Stokstad
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Main supervisor:	Bjørn Henning Grønberg
Co-supervisor:	Sveinung Sørhaug
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for the degree of PhD in medicine and health sciences.
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Thursday 12th September 2019 at 12.15 p.m.

Norsk sammendrag

Lange ventetider for å starte kreftutredning eller -behandling fører til bekymring og oppfattes som en medisinsk risiko som kan påvirke mulighetene til å få effektiv behandling. Derfor er det innført krav til ventetider i mange land. Det er imidlertid ikke sikkert at raskere kreftutredning bedrer kvaliteten av kreftbehandlingen.

Lungekreft er en av de vanligste kreftformene, har dårlig prognose, og er den kreftformen som tar flest liv. Derfor mener vi at lungekreft er godt egnet som modellsykdom for å studere organiseringen av kreftutredningen. De norske retningslinjene anbefaler at tid fra sykehuset mottar en henvisning for mistenkt lungekreft til behandlingen starter skal være ≤35 dager for cellegift og ≤42 dager ved kirurgi eller strålebehandling.

St. Olavs hospital- Trondheim universitetssykehus, i Trondheim, valgte standardiserte pasientforløp som forbedringsmetode. Vi har gjennomført en retrospektiv gjennomgang av pasientjournaler til alle pasienter som ble diagnostisert med lungekreft ved lungeavdelingen på St. Olavs hospital i 2011-2013. Målsetningen var å undersøke om det er grunn til å tro at det er mulig å redusere utredningstiden slik at den anbefalte forløpstiden overholdes, og om det å overholde forløpstiden kan føre til bedre overlevelse.

Vi gjennomførte tre delstudier:

1. De eksisterende utredningstidene var ikke undersøkt, og klinisk erfaring tilsier at mange pasienter ikke kan starte behandling innenfor tidsrammene av medisinske årsaker. Totalt startet 49% behandling innen anbefalt tid. Til og med blant de minst kompliserte pasientene, definert som pasienter som gjennomgikk 0-1 vevsdiagnostiske undersøkelser og som ikke hadde utsettelser >3 dager som følge av komplikasjoner ved diagnostikken eller behandling for komorbide tilstander eller akutt sykdom, ble kravet møtt hos kun 66%.
2. Vi undersøkte årsakene til forsinkelser blant pasienter der de første CT-bildene indikerte stadium I-II og som fikk kurativ behandling. Vi fant at det ble gjort flere undersøkelser enn strengt tatt nødvendig, og at man ved bedre planlegging ville redusert antall diagnostiske prosedyrer samtidig som man ville spart tid, penger og

ressurser. Dersom alle var blitt optimalt utredet ville andelen som kunne startet behandling innenfor anbefalt tid økt fra 40% til 80%.

3. Totalt sett hadde pasienter som startet behandling innenfor anbefalt forløpstid kortere median overlevelse enn de som ventet lenger. Imidlertid var det ikke en slik sammenheng i alle behandlingsgruppene, hvilket tilsier at utredningstid alene ikke er en uavhengig prognostisk faktor eller en valid indikator for kvaliteten på helsetjenesten.

Konklusjonen er at bedre organisering av lungekreftutredningen kan forbedre utredningstiden signifikant. Vi mener derfor at man bør implementere et mer optimalt pasientforløp i tråd med det vi foreslår. Framtidig forskning kan vise om implementeringen lykkes, og avklare om det er en assosiasjon mellom utredningstid og overlevelse.

Summary in English

Long waiting time for cancer diagnosis and treatment causes anxiety and is conceived as a medical risk that may reduce the chances for a successful treatment, target times from referral until start of treatment has therefore been set in many countries. However, it is not evident that speeding up diagnostic workup for suspected cancer improves the quality of cancer care.

Lung cancer is one of the most common types of cancer, the survival time is short, and it is the type that causes most cancer-related deaths. We therefore believe it is a highly relevant model disease for studying the organization of cancer care. In Norway, timely lung cancer treatment is defined as ≤35 days until chemotherapy and ≤42 days until surgery or radiotherapy from a referral letter for suspected lung cancer is received at public hospitals.

St. Olavs hospital- Trondheim University Hospital, in Trondheim, Norway, chose clinical pathways as the strategy for improvement. We performed a retrospective chart review of consecutive lung cancer patients diagnosed in 2011-2013 in the Department of Thoracic Medicine at St. Olavs hospital. We aimed to investigate whether there are reasons to believe that it is possible to reduce the time until start of treatment to comply with Norwegian recommendations, and whether such a reduction might improve survival.

We performed three sub-studies:

1. The actual timelines were unknown, and we hypothesized that delays had medical explanations. Among all patients, 49% started timely treatment. However, even among the least complex, defined as undergoing ≤1 tissue sampling procedure and having no delays of >3 days due to complications to a diagnostic procedure, or treatment for comorbid conditions or intercurrent disease, the timeframes were met in only 66%.
2. We identified reasons for delay among patients presenting with stage I-II on the base-line CT scan who were eligible for curative treatment. We found that the patients underwent more tissue sampling procedures than necessary, and that more optimal decision making would have reduced the number of tissue sampling

procedures and concurrently saved time, money and resources. If an optimal pathway for diagnostic workup had been applied in all patients, the numbers starting treatment within the recommended timeframes would have increased from 40% to 80%.

3. Overall, median survival was significantly shorter among patients who started treatment within the recommended timeframes compared to those waiting longer. However, the impact varied significantly between important subgroups treatment, indicating that time until treatment start alone is not an independent prognostic factor or a valid indicator of the quality of healthcare.

To conclude, better organization of lung cancer diagnostic workup may significantly improve the timelines. Our suggestions for a more optimal clinical pathway should therefore be implemented. Future research may show if the implementation succeeded and clarify if there is an association of time to treatment and survival.

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List of papers

I Stokstad T, Sørhaug S, et al. **Medical Complexity and Time to Lung Cancer Treatment - a three-year retrospective chart review.** *BMC Health Serv Res* 2017;**17**(1):45

II Stokstad T, Sørhaug S, et al. **Reasons for Prolonged Time for Diagnostic Workup for Stage I-II Lung Cancer and Estimated Effect of Applying an Optimized Pathway for Diagnostic Procedures.** *Under review.*

III Stokstad T, Sørhaug S, et al. **Timelines for Diagnostic Workup for Lung Cancer Patients and Survival.** *Ready for submission.*

Abbreviations

CCI	Charlsson Comorbidity Index
EBUS	Endobronchial UltraSound
TBNA	Transbronchial Needle Aspiration
FEV1%	Forced Expiratory Volume in Percent of expected value at 1 second
MDT	Multi-Disciplinary Team
NSCLC	Non-Small-Cell Lung Cancer
PET CT	Positron Emission Tomography Computer Tomography
SCLC	Small-Cell Lung Cancer
TTNB	Trans-Thoracic Needle Biopsy

1. Introduction

Long waiting time for cancer diagnostic workup and treatment causes anxiety and is conceived as a medical risk that may reduce the chances for a successful treatment. Long waiting time is a public and political concern, and consequently, target times from referral until start of treatment has been set in many countries.

It is, however, not evident that speeding up diagnostic workup for suspected cancer improves the quality of cancer care. We designed this project in order to investigate whether there are reasons to believe that it is possible to reduce the time until start of treatment to comply with Norwegian recommendations, and whether such a reduction might improve survival.

Lung cancer is one of the most common types of cancer, the survival time is short, it is the type that causes most cancer-related deaths, and thus, we believe it is a highly relevant model disease for such research. In Norway, timely lung cancer treatment is defined as ≤35 days until chemotherapy and ≤42 days until surgery or radiotherapy from a referral letter for suspected lung cancer is received at public hospitals. We retrospectively analyzed the courses of all patients who were diagnosed with lung cancer at St. Olavs hospital between 2011 and 2013 in order to:

- assess the actual timelines and the reasons for delays
- define an optimal pathway for lung cancer diagnostic workup and investigate whether implementing this pathway may increase the proportion starting timely treatment
- investigate if shorter intervals until treatment start was associated with improved survival

2. Background

The overall cancer incidence is increasing due to the growing and aging population, screening and improved methods for diagnosing cancer, and lifestyle factors.[1] Worldwide, it was estimated that 14.1 million new cases of cancer occurred and 8.2 million people died in 2012,[2] while corresponding numbers in 2018 were 18.1 and 9.6 million.[3] Consequently, a high and growing number of cancer patients needs to be cared for by the Norwegian healthcare system every year. In Norway the accumulated risk of cancer up to the age of 75 was 35.9% in men and 30.0% in women in 2013-2017, and in 2017 the incidence rates per 100 000 were 712.2 in men and 543.0 in women.[4]

Medical advances have made it possible to offer treatment to more cancer patients than just a few years ago. Advances include minimal invasive surgical techniques, stereotactic radiotherapy, numerous chemotherapeutics, and more recently the evolvement of targeted therapies and immunotherapies. The increasing number of treatment options requires more accurate staging and tumor classification including molecular characteristics and genetic profile. Consequently, more procedures for diagnosis and staging of cancer patients are needed before a treatment recommendation can be given. This requires involvement from more medical disciplines than a few years ago which represents an organizational challenge.

Cancer is associated with suffering, loss of functions and unpredictable prognosis, and a main fear is to miss opportunities for effective treatment. The media frequently present stories of shortcomings of cancer care and the quality of cancer care is therefore a public and political concern.

The understanding of "healthcare quality" has evolved over the past fifty years, but healthcare quality assessment and improvement while maintaining cost control still causes controversies among policy-makers, healthcare managers and healthcare professionals.[5,6]

2.1 What is healthcare quality?

Healthcare quality may be defined as the "degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge".[7]

The assessment of healthcare quality has been debated for many years. In 1966, The Milbank Memorial Fund Quarterly published an article by Avedis Donabedian that reviewed the methods that were used back then to assess healthcare quality. He categorized the approaches of assessment as "structure": how healthcare is delivered and by whom; "process": the components of care; and "outcome of medical care": "in terms of recovery, restoration of functions, and survival".[8] This conceptual framework is still the leading approach in healthcare quality assessment.

In 2001 the former Institute of Medicine in the US (now The National Academies of Science, Engineering and Medicine, Health and Medicine Division) published the report "Crossing the Quality Chasm: A New Health System for the 21st Century". They presented perspectives of healthcare aims and principles for redesigning care processes that is now the main healthcare organization philosophy worldwide.[9]

The Institute of Medicine stated that the overarching aims for healthcare delivery are safety, effectiveness, patient-centeredness, timeliness, efficiency and equitability. These six dimensions of healthcare quality have been adopted by a range of healthcare organizations including the public Norwegian healthcare system.

The basic principles for redesigning the healthcare system were defined as continuity, customization, patient control, information flow, evidence-based decision-making, safety as a system property, transparency, anticipation of needs, continuous decrease in waste, and cooperation among clinicians.

2.2 Healthcare quality assessment

2.2.1 Reporting of severe events

Historically, quality assurance was done as a response to severe events.[10] Hospitals have systems for the reporting of accidents, events of harm, and situations that could have caused harm. Risk management includes retrospective analyses of the clinical care

related to such severe events. A high number of reported severe events indicate sub-optimal performance, but the definition and reporting of adverse events vary.

2.2.2 Quality metrics

Performance indicators are developed by many health organizations for governance and as a means of improvement. Typical **outcome indicators** are short- and long-term survival, length of hospital stay, reoperation rate[11]; **process indicators** are measures of adherence to guidelines, time intervals[12-14]; and **structure-indicators** are waiting times, IT-systems, volume, competence.[15,16] **Indicators of care coordination** have been suggested, such as time from hospital discharge until the discharge letter is written, time from initiating a treatment in the hospital until primary care follow-up, and structure and completeness of referral forms and hospital reports.[17] **Patient experience-indicators** have been introduced as a means to drive and inform service improvement,[13,14,18] and in the UK, they systematically conduct surveys of the cancer patients experiences with, e.g. the quality of information and the coordination of care.[19] Other indicators include reporting to registers, research funding, and clinical study recruitment.[15] However, validity and reliability of these indicators have been questioned.[20-25]

2.3 Quality improvement strategies

2.3.1 Organizational trends

The past decades there has been an increasing political focus on healthcare quality and cost control and consequently, public healthcare systems are subject to increased political steering and monitoring.[26,27] National programs to improve healthcare performance has been introduced,[28-30] and more marked-oriented organizational models have been applied.[31,32] The methods for quality improvement are inspired by practices that dispersed from the product industries. The most widespread concept is that of **Lean**, founded on the philosophy of the Toyota Production System.[33] The main philosophy of Lean is to "improve the value for the customer" by "eliminating waste". Examples of "waste" in healthcare are waiting, repetition of procedures, complications, cancellations, overtreatment. The principles of Lean are 1) specify value for the

customer, 2) identify the value stream, 3) create flow, 4) create pull, 5) perfection through continuous improvement. Finally, Lean is a way of practicing, and a set of tools that may be classified under the headings: “standardization”, “flow”, “visibility” and “continuous improvement”.[33]

2.3.2 Clinical guidelines

Practice guidelines aim to guide decisions concerning diagnostic workup, treatment, management, follow-up of specified conditions. They refer to the current evidence and make suggestions for best practice.[34] The content, scope and methodological quality of guidelines has been shown to vary considerably.[35-37] In addition, the adherence to guidelines vary, partly for organizational reasons[38] and partly due to a gap between “ideal” study patients and “real life” patients.[39] For these reasons it has been difficult to prove the efficacy of guidelines.

2.3.3 Multidisciplinary teams

The definition of a multidisciplinary team (MDT) is “a group of people of different healthcare disciplines, which meets together at a given time (whether physically in one place, or by video or tele-conferencing) to discuss a given patient and who are each able to contribute independently to the diagnostic and treatment decisions about the patient”.[40] They are implemented to ensure timely care delivered by professionals with the appropriate competence, to improve coordination and continuity of care, and to ensure that patients are adequately supported and informed. MDTs are associated with improved clinical decision making and adherence to evidence-based medicine and guidelines for best practice,[41] and are therefore considered to be the gold standard for cancer care organization. However, the effect on clinical outcomes are less clear,[40 ,42-44] and their roles and scope are still debated.[45]

2.3.4 Clinical pathways

A clinical pathway is defined by the European Pathway Association as “a complex intervention for the mutual decision making and organization of care processes for a well-defined group of patients during a well-defined period”.[46] The criteria for clinical pathways were revised in 2016 by consensus: “1) the intervention is a structured

multidisciplinary plan of care; 2) the intervention is used to translate guidelines or evidence into local structures; 3) the intervention details the steps in a course of treatment or care in a plan, pathway, algorithm, guideline, protocol or other 'inventory of actions' (i.e. the intervention has time-frames or criteria-based progression); and 4) the intervention aim to standardize care for a specific population".[47] The concept is also referred to as "care pathways", "integrated care pathways", "critical pathways" and more than ten other terms of which "clinical pathways" is among the commonest.

Characteristics of clinical pathways include that they describe the components, sequence and timing of the care, define the roles of the members of the multidisciplinary team, function as tools for analyzing variation and outcome, and identify resource deficits and help to control costs.[48] In a review published in 2010 the authors concluded that "clinical pathways are associated with reduced in-hospital complications and improved documentation without negatively impacting on length of stay and hospital costs".[49] However, relatively few studies met the inclusion criteria on the definition of a clinical pathway.

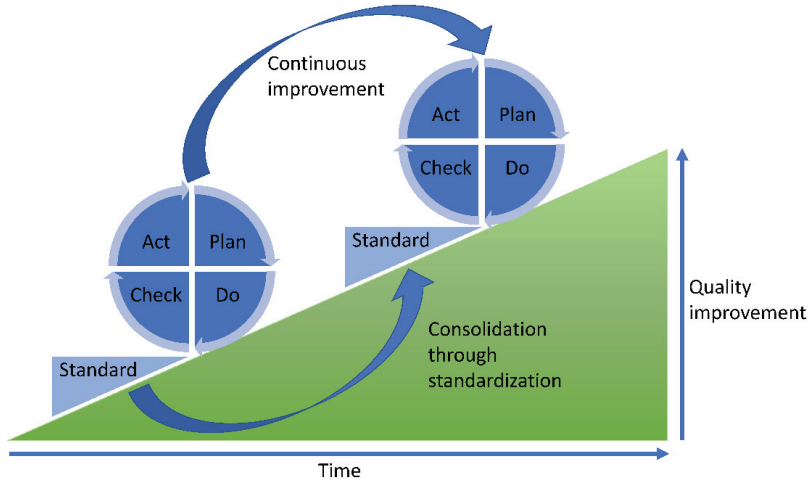
There are several studies of clinical pathway development and implementation, but their mode of action, in particular in the long-time run, is still debated.[50-52] Successful implementation of clinical pathways is facilitated by bottom-up initiatives, clear goals, teamwork, leadership involvement, small units, and patient coordinators. Barriers are time constraints, IT-systems and technical support, lack of ownership, resistance to change, and skepticism to the concept and jargon. Some attributes of healthcare organizations amplify the difficulties of implementation. Examples include professional identity and hierarchical organization, functional and professional silos, people involved in improvement are those who are willing and not necessarily those who should, changing strategies, and weak links between strategy and improvement programs.[53,54]

2.3.5 Continuous improvement

Areas for improvement may be found by studying the existing practice, structures and outcomes. Consequently, changes of the structure or practice may be tested, evaluated,

and finally implemented into a new standard. Standardization imply such an iterative process of **plan – do – check – act** (Figure 1).[55]

Figure 1 Plan-do-check-act cycle and continuous improvement



Tools for analyzing practice include process mapping and value stream analysis. **Process maps** are flow diagrams showing how components impact each other, and they may be used to define a more optimal flow and to identify measurable outputs.[56] **Value stream analyses** are performed in order to distinguish between components that add value and those which can be defined as "waste" by patients.[57]

Statistical process control is a set of methods for monitoring processes or outcomes, founded un the understanding of normal and special variance. The approach is learning through data, using graphical methods. It is conceived to be useful in quality improvement, but important barriers are that data collection may be laborious and that healthcare workers lack experience and methodological support.[58] Furthermore, a perfectly organized care process includes addressing capacity needs.[29,30,59]

2.4 Time indicators

2.4.1 Timeframes

Data from the European Cancer Registry for the periods 1990-1994 and 1995-1999 showed that cancer survival was poorer in the UK and Denmark than in comparable European countries.[60,61] There was a conception that the poorer outcomes had organizational explanations, in particular that cancer patients had to wait too long to start treatment. Consequently, in 1998 the British Thoracic Society published practice guidelines that included a maximum of 62 days interval from referral for suspected cancer until start of treatment,[62] and in 2000, the National Health Services UK introduced the "two-week wait" rule which entitles patients to see a hospital specialist within two weeks after their general practitioner sends a referral letter for suspected cancer. Between 2001 until 2005, they implemented a maximum interval of 62 days from receiving an urgent referral letter for suspected cancer until start of cancer treatment.[30]

In Denmark, the National Indicator Project was established in 2000,[28] and National Cancer Pathways were implemented in 2009. The latter defined a target of 42 days from referral to a cancer pathway until start of treatment,[29] and included referral criteria for each patient group.

Timeframes for cancer diagnostic workup and treatment are now widely used, but the specifications vary among the healthcare systems. For example, the RAND Corporation (Santa Monica, California) suggested in 2000 that diagnostic workup for lung cancer should start within two months after a pathological chest radiogram, and treatment should start within six weeks of diagnosis.[63]

2.5 The Norwegian healthcare system

2.5.1 Organization

The Norwegian health care is mainly public, and the national health insurance system cover expenses exceeding € 236 per year[64]. Norwegian health care is provided by the Government, regional health enterprises, hospitals, municipalities and healthcare workers. The municipalities are responsible for the primary healthcare, while general

practitioners run single or group enterprises with public operating subsidies. All inhabitants are entitled a public general practitioner. In 2002 the responsibilities for the public hospitals were transferred from the counties to the government; regional health enterprises were established, and hospitals were organized as local enterprises. The minister of health appoints the executive boards of the regional health enterprises that appoint the directors of the regional health enterprises, and the hospital boards. The Directory of Health functions are counselling, implementation of policies, managing laws and regulations, and maintenance of the general Norwegian healthcare preparedness.

2.5.2 National cancer strategies and organization of cancer care in Norway

The need of a national cancer strategy was passed by the Norwegian Parliament in 1995.[65] The National Cancer Plan (1999-2003) included cancer prevention through anti-smoking campaigns, dietary improvement, increased physical activity and radio-protection; a national mammography screening program (a national cervical screening program was implemented in 1995); increasing the radiotherapy capacity; increasing the number of key personnel including physician specialists and oncology nurses; and improving the competence within palliative care. The work-up for the plan also addressed the need for national quality standards and cost control.[66,67] The strategy was evaluated, revised and presented as the National Cancer Strategy (2006-2009, prolonged until 2011). Among the most important additions was a strategy for further development and implementation of national standards and guidelines, improving logistics and timeliness of care, improving the competence within primary care, and an emphasize on rehabilitation.[68,69]

Initial cancer diagnostic workup of cancer is mainly carried out in local hospitals. Cancer surgery is to a large extent centralized to regional centers, radiation therapy is performed at ten departments and most of the systemic therapy/chemotherapy is administered at local hospitals according to national guidelines or as recommended by the regional oncology department. Follow-up is performed at all hospital levels and by the primary healthcare.

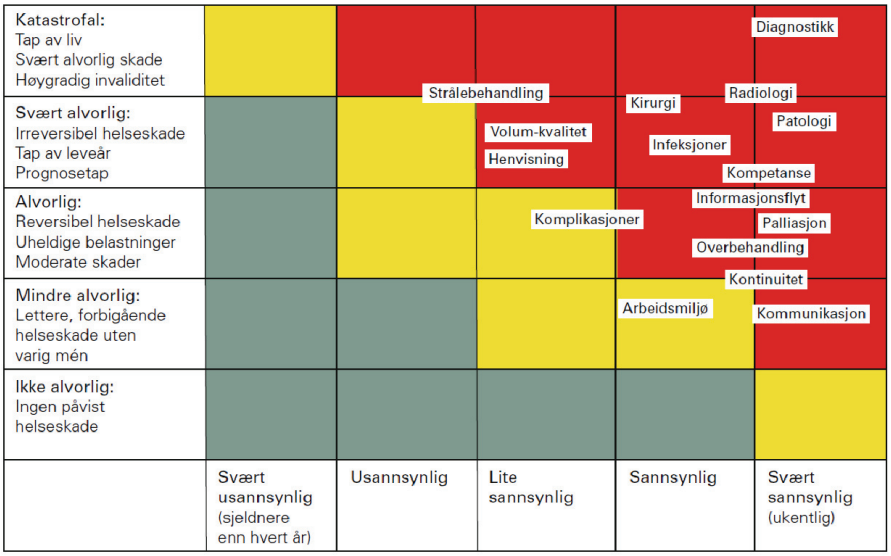
2.6 Improving the quality of cancer care in Norway

2.6.1 A National evaluation

The Norwegian Board of Health Supervision supervise the specialized health services. In 2010, they decided to carry out national risk analyses for specific diagnostic groups and medical specialties and they chose cancer care as a pilot project. The workup for the analysis included the identification of types of adverse events that were reported through public systems, patient compensation claims, and the media. They then arranged a seminar to discuss the data, inviting in total 23 professionals from the health trusts, municipal health services, and regional health authorities. Risks were summarized in a risk matrix according to consensus within the group. They concluded that the risk level of cancer treatment was too high. Insufficient capacity within radiology, pathology and colonoscopy were highlighted as bottlenecks causing delays to start treatment, and inefficient investigation logistics, inadequate information flow, lack of continuity and varying competence were identified as other risk factors (Figure 2).[70]

Figure 2 Risk matrix for cancer treatment in Norway

Source: Report from the Norwegian Board of Health Supervision 4/2010



2.6.2 Introduction of normative timeframes for cancer care

In June 2011 the Norwegian Health Minister pledged that unless there are good medical reasons, no patients should wait more than twenty working days from the day they were referred for suspected cancer until start of cancer treatment. Consequently, the twenty-days normative timeframe was implemented in all national guidelines for cancer care, provided by the Norwegian Directorate of Health, in December 2011.

2.6.3 National cancer pathways

The National Cancer Strategy (2013-2017) understated the target that 80% of cancer patients should start treatment within 20 working days after being referred for suspected cancer.[71] The strategy further addresses the patients' needs of well-coordinated care, to participate in decision making, and to be offered supportive care.[72] Recommendations included to increase the number of indicators, and to develop national cancer pathways.

In 2015, national pathways for 28 types of cancer were introduced. The pathways provide evidence-based clinical guidelines, organizational requirements such as treatment levels and the composition and meeting frequency of multidisciplinary teams,

and organizational targets including timeframes. The timeframes for cancer diagnosis and treatment vary between the cancer types, and in general they are longer than the 20 working days previously recommended.

2.7 St. Olavs hospital

St. Olavs hospital, Trondheim University Hospital, in Trondheim, Norway, is the primary hospital for 320 000 people, and the regional cancer center for the Central Norwegian Health Region with a population of approximately 725 000 people. There are seven hospitals in the region.

2.7.1 Clinical pathways at St. Olavs hospital

In 2006, the Central Norwegian Regional Enterprise decided that a model and methodology for clinical pathways should be developed.[73] At St. Olavs hospital, a healthcare worker was educated and appointed as "clinical pathway supervisor", whose tasks were to develop a template for clinical pathways and assist the professional teams developing them. A written manual including a short introduction of the Lean philosophy, a description of value stream analysis and the principles of plan-do-check-act cycles and statistical process control was made. The first clinical pathways at St. Olavs hospital were presented in 2008. However, their impact on clinical practice has not been evaluated, partly because relevant and measurable process indicators had not been identified, partly due to insufficient systems for collection and storage of relevant data.

2.7.2 The project to improve the timelines for lung cancer diagnosis and treatment at St. Olavs hospital

Data published by the Norwegian Patient Registry in 2012 indicated that time until start of cancer treatment took longer than required at St. Olavs hospital. In June 2012, St. Olavs hospital launched a project to improve the timelines for most common groups of cancer patients: breast-, lung- and colorectal cancer.

2.7.3 Lung cancer organization at St. Olavs hospital

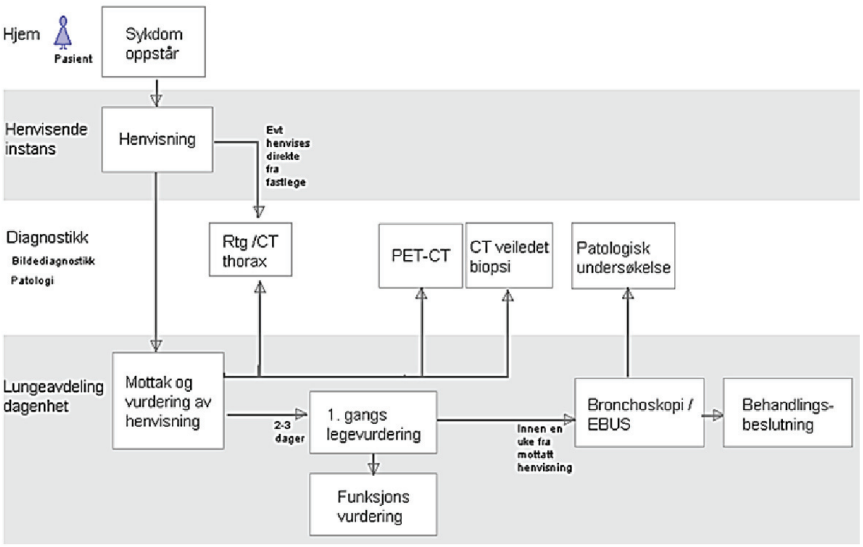
The Department of Thoracic Medicine is responsible for diagnostic workup of lung cancer, and also offer systemic therapy to patients with advanced disease. All facilities for appropriate diagnostic work-up are available, though a PET CT scanner was not installed until October 2013. The Cancer Department provide radiotherapy, and surgery is performed in the Department of Cardio-Thoracic Surgery.

Diagnostic workup for lung cancer is mainly done on an outpatient basis. A weekly, regional, multidisciplinary tumor board meeting is held between pulmonary physicians, thoracic surgeons, an oncologist specializing in lung cancer medical treatment and radiotherapy, a thoracic radiologist, a specialist in nuclear medicine, a pathologist and a nurse coordinator. In addition, there is a local, weekly multidisciplinary team meeting at St. Olavs hospital.

2.7.4 Development of the clinical pathway for lung cancer diagnostic workup and treatment

Between September 1, 2012 and January 31, 2013, the multidisciplinary team revised the routines and procedures for lung cancer diagnostic workup and a clinical pathway was developed that included the national recommendations for timelines. They assigned a pulmonologist specializing in lung cancer diagnosis and treatment as the leader of the multidisciplinary team (MDT), who in addition to leading the lung cancer MDT carries out general pulmonology consultant work and duty shifts. The MDT leader is responsible for overseeing that the pathway is followed and is expected to alert leaders at all involved clinics about potential organizational barriers. The clinical pathway for lung cancer diagnostic workup and treatment was published at the official St. Olavs hospital website on February 1, 2013, and thereby its implementation was stated. However, the exact sequence of the diagnostic workup procedures was not specified in the pathway (Figure 3)

Figure 3 Clinical pathway for lung cancer diagnostic workup



2.7.5 Timeframes for lung cancer diagnostic workup until start of treatment

The current national target timeframes, in calendar days from receiving a referral letter for suspected lung cancer, are 7 days until start of diagnostic workup, 28 days until treatment decision, 35 days until first day of systemic treatment, and 42 days until surgery or start of radiotherapy.[74] The targets are that 70% of new lung cancer patients are referred to a lung cancer pathway and that 70% of those referred start treatment within these timeframes.

2.8 Evidence for defining timelines for lung cancer diagnostic workup

Lung cancer is one of the most prevalent malignant diseases and the most frequent cause of cancer related deaths worldwide.[3,4,75-77] Approximately 3200 people are diagnosed with lung cancer annually in Norway. The disease is often diagnosed at a late stage and data from the Norwegian Cancer Registry in 2018 showed that five-year survival was 17.8 among men and 24.4% among women.[4]

The main aim of implementing timeframes, in UK and Denmark, was to improve lung cancer survival. The process in Norway started somewhat later and was strongly influenced by the Danish National Cancer Pathway model, but the rationale for implementing timeframes in Norway were mainly a) to shorten the workup time, and b) to ensure that diagnostic workup is done efficiently.

2.8.1 Reasons for delay

Several studies and registry reports show that the timeframes for lung cancer care may be difficult to meet.[16 ,78-80] The most commonly reported reasons for delay are that tissue samples may be difficult to obtain, and that more time is needed in order to collect an appropriate sample and to perform necessary tissue analyses.[81-83] Other reasons are intercurrent diseases or comorbidities that puts cancer management on hold.[84 ,85] Consequently, it is accepted that the timeframes may not be met in more than 80%-70% of the patients, but there are no standard definitions of which patients who cannot comply with timelines.

2.8.2 Associations between timelines and clinical practice

Some successful quality improvement projects targeting timeliness of lung cancer care have been described. For example, in a Norwegian project they analyzed waiting- and processing times, implemented new standards, and reduced diagnostic work-up time from a median of 64 days to 16 days.[86] In another study from the US, the establishment of a multidisciplinary team meeting to discuss all new images suspicious of lung cancer was part of the successful intervention, which also included the appointment of a nurse coordinator and a thoracic surgeon.[87] Several studies demonstrate that patients receive more timely care in multidisciplinary lung cancer clinics.[88 ,89] However, we found no studies reporting that a program to improve timelines included alterations of medical practice, or that the best clinical practice was defined and found to be associated with more timely care.

2.8.3 Associations between timelines and survival

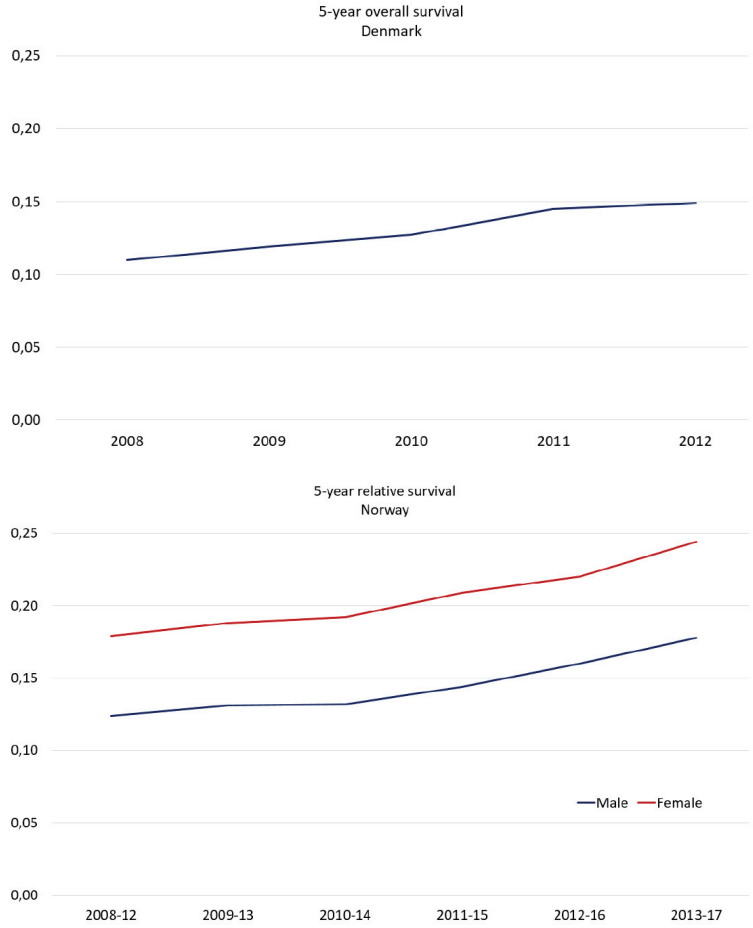
Recommended “time to lung cancer treatment” range from 35-62 days to 3 months in different countries.[36 ,90 ,91] However, the impact of diagnostic delay is uncertain. Some

studies show associations between increased mortality and long diagnostic workup intervals[92-94] or until start of treatment,[95-98] but not until the timeframes are as long as three to four months.[99 ,100] Paradoxically, other studies have shown that long intervals are associated with improved survival,[101-104] probably due to the differences in number and types of investigations for different stages of disease.[105-107] Others find no such associations.[108-110]

The effect on survival of shorter diagnostic workup intervals is unknown and the implementation of more accurate diagnosis and staging, and new treatments, is probably more important than the timelines. For example, lung cancer survival improved from 2008 until 2013 in both Norway and Denmark (Figure 4).[80 ,111] Denmark implemented the cancer pathways in 2009, while Norway implemented them in 2015. The results are not necessarily directly comparable due to different methods for estimation of survival, but it seems that the extent of improvement is similar in the two countries, and that survival is higher in Norway.

Figure 4 Lung cancer survival in Denmark and Norway 2008-2012

Source: the Danish Lung Cancer Registry and the Norwegian Cancer Registry



3. Rationale for the PhD project

Timeframes have been implemented worldwide to improve the quality of cancer care. However, relatively little has been done to evaluate whether timeframes are relevant quality indicators or to evaluate the effect of implementing timeframes.

Registry-data indicated that time until start of lung cancer treatment took longer than recommended at St. Olavs hospital when this project was initiated, and implementation of clinical pathways was selected as the method for improvement at our hospital. The current timelines were, however, not known, the medically most appropriate and most efficient diagnostic pathways were not defined, and significant bottlenecks were not identified. Furthermore, shortening the time until treatment start may not be feasible for both medical and economic reasons, but we are currently unable to assure the patients that waiting does not cause harm.

The aims of this project were to:

- Investigate the current timelines for diagnostic work-up and start of treatment for lung cancer at St. Olav's Hospital
- To investigate whether the clinical pathway for diagnostic work-up for lung cancer might be improved
- To investigate the feasibility of, or need for resources, for implementing a more optimal clinical pathway
- To estimate the potential for reducing the timelines if a more optimal clinical pathway was implemented
- To investigate whether there were reasons to believe that implementing such an optimal pathway might improve survival

Lung cancer patients comprise a large and important group of cancer patients with a large proportion of elderly and comorbid patients and was considered a highly relevant cohort for this project.

4. Aims and research questions

4.1 Paper I

A natural start was to estimate the actual timelines. Based on clinical experience, we knew that there are sometimes good medical reasons why diagnostic workup take longer than the recommended 35 or 42 days in some patients. We hypothesized that long intervals were caused by medical complexity. The aim of this study was to provide baseline data and assess whether time until start of lung cancer treatment did take longer than necessary. Main research questions were:

- What were the proportions of complex and non-complex lung cancer patients at St. Olavs hospital?
- What proportions started lung cancer treatment within the timeframes recommended in Norway?

4.2 Paper II

Treatment may be delayed if the correct decisions are not made throughout the diagnostic workup. There is, however, no international consensus on the optimal diagnostic pathway for lung cancer. Due to the heterogeneity and complexity of lung cancer patients in general, we limited the study to patients presenting with stage I-II on the base-line CT scan who were eligible for curative treatment. We aimed to assess how long lung cancer diagnostic workup ideally should take at St. Olavs hospital. Main research questions were:

- What were the reasons for delay?
- What is the optimal diagnostic pathway for these patients?
- How many patients could ideally start treatment within 42 days if the optimal diagnostic pathway had been applied?

4.3 Paper III

Treatment may be delayed if the correct decisions are not made throughout the diagnostic workup. There is, however, no international consensus on the optimal diagnostic pathway for lung cancer. Due to the heterogeneity and complexity of lung cancer patients in general, we limited the study to patients presenting with stage I-II on the base-line CT scan who were eligible for curative treatment. We aimed to assess how long lung cancer diagnostic workup ideally should take at St. Olavs hospital. Main research questions were:

- What were the reasons for delay?
- What is the optimal diagnostic pathway for these patients?
- How many patients could ideally start treatment within 42 days if the optimal diagnostic pathway had been applied?

5. Materials and methods

5.1 Study design, patients and data collection

Most previous studies of this topic are registry based. To answer our research questions, we found a more detailed data collection appropriate and performed a retrospective chart review to map the patient's courses, collect data about their clinical appearance, and to retrieve details about the clinical considerations and decisions that were made. Due to the large number of eligible patients at our institution and to avoid confounding inter-institutional variations, we decided to perform a single-institution study.

Patients registered with ICD 10 codes C34.0-9 ("lung cancer") were identified from the hospital's patient administrative system. Patient data were collected from the hospital electronic medical records. We collected data on all cases that started diagnostic work-up and who were diagnosed with lung cancer between January 1, 2011 until December 31, 2013, at the Department of Thoracic Medicine at St. Olavs hospital – Trondheim University Hospital, Trondheim, Norway. This time period comprised of a number of patients that we considered appropriate and manageable, while it allowed for a follow-up period considered relevant.

5.2 Definitions and classification

5.2.1 Baseline characteristics

Stage of disease was assessed according to the 7th edition of the TNM classification of lung cancer.[112] Patients were classified as having non-small-cell lung cancer (NSCLC); small-cell lung cancer (SCLC); other primary lung cancers; or no tissue diagnosis.

We used the forced expiratory volume at one second in percent of expected value (FEV1%) as a measure of pulmonary function, and the Charlsson Comorbidity Index score (CCI) without age-adjustment as a measure of comorbidity.

"Severe cancer symptoms" were defined as neurologic symptoms, symptoms due to infiltration of mediastinal structures (e.g. airway obstruction, hoarseness, dysphagia, superior vena cava syndrome), bone pain, pain due to other metastases, and weight-loss ≥5% the last three months prior to diagnosis.

Treatment was classified as curative treatment (surgery, stereotactic radiotherapy, radical radiotherapy or radio-chemotherapy of stage I-III disease); palliative treatment; or no cancer treatment including death before start of treatment. For the subgroup analyses in Paper III, we defined five treatment groups: 1) "Surgery": patients who underwent surgery for stage I-III disease; 2) "Other standard curative": radical radiotherapy for stage III NSCLC, or chemo-radiotherapy for stage I-III (limited disease) SCLC; 3) "Inoperable stage I-II": stereotactic radiotherapy or radical radiotherapy for patients with stage I-II NSCLC who were ineligible for surgery; 4) "Palliative, no severe symptoms": palliative treatment to patients with no severe cancer symptoms; 5) "Palliative, severe symptoms": palliative treatment to patients with severe cancer symptoms.

5.2.2 Diagnostic workup procedures

Imaging procedures included chest radiograms, computer tomography (CT), ultrasound (US), magnetic resonance imaging (MRI), positron emission tomography computer tomography (PET CT), bone scan, and octreotide scan.

Exercise tests included the stair-climbing test, six-minute walk-test, and cardiopulmonary exercise test.[113]

Tissue sampling procedures were categorized as bronchoscopy, endobronchial ultrasound-guided trans-bronchial needle aspiration (EBUS TBNA), trans-thoracic needle biopsy, or others. We defined that the method "failed" when another diagnostic procedure was required to diagnose lung cancer, or the patient underwent both bronchoscopy and bronchoscopy with EBUS-TBNA. The histopathological classification of the tissue samples included microscopy, and molecular and genetic profiling.

5.2.3 Medical complexity

In our experience, the factors that influence the timelines the most are the number of tissue sampling procedures required,[81,83,85,114] and delays for medical reasons.[84,85]

We classified **"Medical delay"** as delay of >3 days due to complications to a diagnostic procedure, or treatment for comorbid conditions or intercurrent disease.

We defined **"Non-complex patients"** as having undergone ≤1 tissue sampling procedure and having no medical delays. **"Complex patients"** were classified as having a) >1 tissue sampling procedure, b) medical delay, or c) both >1 tissue sampling procedures and medical delay.

5.2.4 Time axis

Four time points were defined: 1) **"Referral date"**, the date when a referral letter for suspected lung cancer was received at the Department of Thoracic Medicine – or the date when the decision was made to start diagnostic workup in patients with a known single pulmonary nodule; 2) **"Start of diagnostic work-up"**, the date of the first meeting with the pulmonary specialist responsible of lung cancer diagnostic workup; 3) **"Treatment decision"**, the date when such a decision was documented in the electronic medical record; 4) **"Treatment start"**, the date of surgery, first fraction of radiotherapy, first day of intra-venous chemotherapy, or date of prescription of oral cancer therapy.

"Time to treatment" was defined as the number of calendar days from referral until start of treatment. In accordance with current Norwegian recommendations, patients were classified as **"Timely"** when time to treatment was ≤42 days (surgery and radiotherapy) or ≤35 days (systemic therapy). If the intervals were longer, patients were categorized as **"Untimely"**.

Survival was defined as the time from referral until death. Patients were followed for survival until death or 48 months.

5.3 Data analysis and statistics

5.3.1 Statistics

We used chi-square test for group comparisons. Factors influencing the likelihood of timely treatment (patient and disease characteristics as well as PET CT since PET CT was not available at St. Olavs hospital during most of the study period), and the possible impact of an optimized pathway, were explored using logistic regression analysis. Survival differences were compared using log rank statistics.

We used the Stata/IC 13.1, Stata/IC 14.2, and Stata/MP 15.1 packages for Windows for performing the simulation and the statistical analyses. We considered a two-sided p-value of < 0.05 to be statistically significant.

5.3.2 Optimal pathway simulation

All processes were given unique identifiers and intervals for each process were calculated: from referral until start of diagnostic workup; from start of diagnostic workup until referral for a procedure; from referral to a procedure until the result was available in the medical records; from the result of a procedure until the result was actioned upon (by referral to another procedure or making a treatment decision); and from a treatment decision was made until start of treatment (Table 1). The tissue sampling procedures were reviewed, and dummy variables were made to label "failed" procedures, defined as using a method that failed when subsequently applying another method produced the diagnosis and/or stage. Equations for simulating the application of an optimized pathway were built on the basis of the pathway analysis (Figure 5).

Table 1 Intervals used in the simulation model

Interval	Start	End
Startwait	Referral letter received	Start of diagnostic work-up
BaselineCT_int	Start of diagnostic workup	Result of baseline CT if >start of diagnostic workup
CTfollowup_delay	Result of baseline CT, or start of diagnostic workup if result already available	Referral to CT follow-up procedures
CTfollowup_int	Referral to CT follow-up procedures	Result of CT follow-up procedures
Exercisedelay	Start of diagnostic work-up	Referral to exercise testing
Exerciseint	Referral to exercise testing	Result of exercise testing
PETdelay	Start of diagnostic workup	Referral to PET CT
PETint	Referral to PET CT	Result of PET CT
D1delay	Start of diagnostic workup	Referral to first tissue procedure
D1int	Referral to first tissue procedure	Result of first tissue procedure
D2delay	Result of first tissue procedure	Referral to second tissue procedure
D2int	Referral to second tissue procedure	Result of second tissue procedure
D3delay	Result of second tissue procedure	Referral to third tissue procedure
D3int	Referral to third tissue procedure	Result of third tissue procedure
Dfollowup_delay	Date of tissue diagnosis	Referral to follow-up investigation (e.g. cerebral MRI or bone scan in SCLC)
Dfollowup_int	Referral to follow-up investigation	Result of follow-up investigation
PETD1_delay	PET CT result	Referral to the first PET CT follow-up procedure
PETD1_int	Referral to the first PET CT follow-up tissue procedure	Result of the first PET CT follow-up tissue procedure
PETD2_delay	Result of the first PET CT follow-up procedure	Referral to the second PET CT follow-up tissue procedure
PETD2_int	Referral to the second PET CT follow-up tissue procedure	Result of the second PET CT follow-up tissue procedure
PETD3_delay	Result of the second PET CT follow-up tissue procedure	Referral to the third PET CT follow-up tissue procedure
PETD3_int	Referral to the third PET CT follow-up tissue procedure	Result of the third PET CT follow-up tissue procedure
PETfollowup_ delay	PET CT result	Referral to a PET CT follow-up procedure other than tissue sampling procedures
PETfollowup_int	Referral to a PET CT follow-up procedure	Result of PET CT follow-up procedure
Otherinvest_delay	Start of diagnostic work-up	Referral to other investigation
Otherinvest_int	Referral to other investigation	Result of other investigation
Treatdelay	Result of the last diagnostic work-up procedure	Referral to treatment
Treatwait	Referral to treatment	Start of treatment

Figure 5 Equations for calculating actual timelines and estimated timelines if an optimal clinical pathway had been applied

Observed pathway equation:

Diagnosis = D1delay + D1int + D2delay + D2int + D3delay + D3int + Dfollowup_delay + Dfollowup_int

Staging = max ((BaselineCT_int + CTfollowup_delay + CTfollowup_int);
(PETdelay + PETint + max((PETD1_delay + PETD1_int + PETD2_delay + PETD2_int + PETD3_delay + PETD3_int);
(PETfollowup_delay + PETfollowup_int))))

Physical assessment = Exercisedelay+Exerciseint
Other investigation = Otherinvestdelay+Otherinvestint

Time to treatment= Startwait + max (Diagnosis; Staging; Physical assessment; Other investigation) + Treatdelay + Treatwait

Optimal pathway equation:
Assuming that Baseline CT result <Start of diagnostic work-up

Sequence 1 = max(PETint; CTfollowup_int; Exerciseint)

Sequence 2 = max((D1int + D2delay)*d1_yn + (D2int + D3delay)*d2_yn + D3int*d3_yn + Dfollowup_delay +Dfollowup_int;
PETD1_delay*d1_yn + PETD1_int + PETD2_delay + PETD2_int + PETD3_delay + PETD3_int;
PETfollowup_int; Otherinvestint; Treatwait

Time to treatment = Startwait + Sequence 1 + Sequence 2

The dummy variables d1_yn, d2_yn and d3_yn were set to value 0 if the corresponding procedure (D1, D2, D3) applied a method that failed, when another method subsequently produced the diagnosis and/or stage; otherwise the value was set to 1.

5.4 Ethics

A passive consent procedure was applied. All patients who were alive and had a known address received written information about the study and a form giving them the opportunity to decline participation, and prepaid envelopes for returning the opt-out form. Those who did not decline were included in the analyses. The study and this approach for consent was approved by the Regional Committee for Medical and Health Research Ethics West Norway (REK Vest (2014/60)).

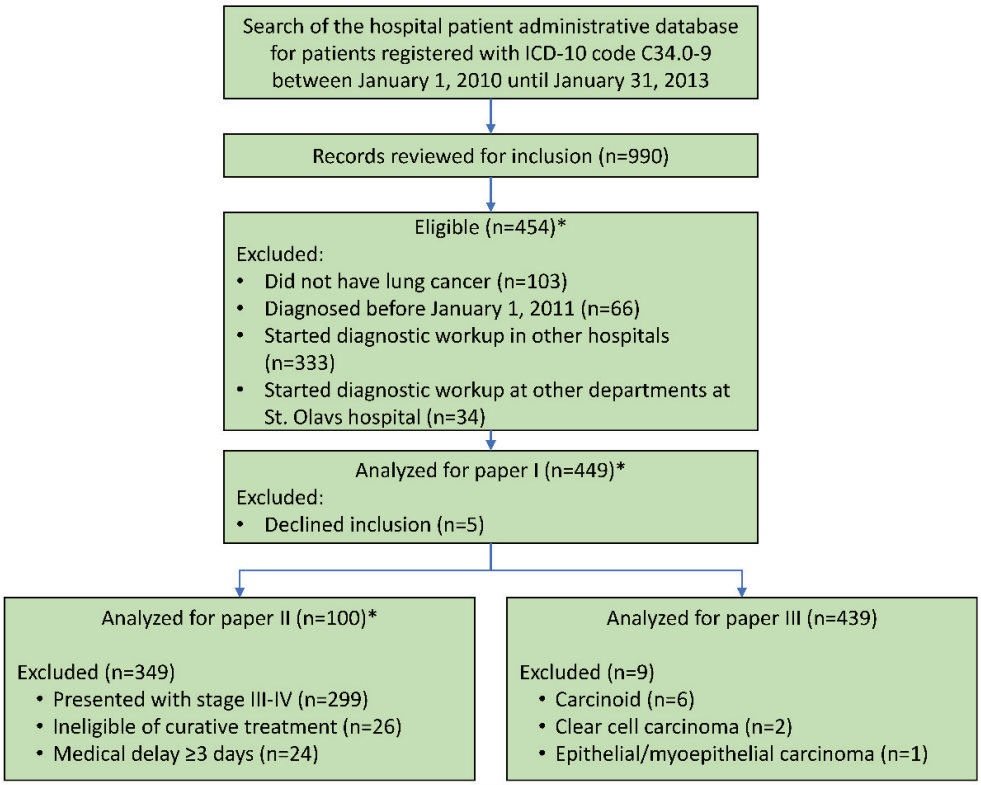
5.5 Financial support

The PhD project was funded by St. Olavs hospital.

6. Summary of papers

6.1 Patient selection

Figure 6 Patient selection



*Includes the two courses of one patient who was diagnosed twice during the study period. Therefore, the number of patients was 448 in paper I and 99 in paper II. In paper III, survival time was counted from the first referral date for that patient.

6.2 Paper I

"Medical complexity and time to lung cancer treatment- a three-year retrospective chart review"

6.2.1 Patients

Nine-hundred ninety records were reviewed, whereof 536 were ineligible because the patient did not have lung cancer (n=103), was diagnosed before January 1, 2011 (n=66), or diagnostic workup started in another hospital (n=333) or another department than the Department of Thoracic Medicine (n=34). Five patients declined participation. Thus, 449 lung cancer courses were analyzed in 448 patients (one patient was diagnosed twice with lung cancer during the study period) (Figure 6).

Median age was 72, 59% were ≥70 years, 46% were women, 34% had stage I-II disease, 26% stage III and 40% stage IV. Tissue diagnosis was NSCLC in 69%, SCLC in 14%, other thoracic malignancy in 2%, and 14% had no confirmed tissue diagnosis. Twenty-six percent underwent surgery, 16% curative radiotherapy, 39% palliative treatment, 18% received no cancer treatment, and 2% died before treatment could start. In total, 33% had a PET CT scan, increasing from 10% in 2011 to 36% in 2012 and 51% in 2013 (Table 2).

6.2.2 Medical complexity

Two-hundred sixty-two patients (58%) were classified as non-complex, and 187 (42%) as complex. Thirty-two percent underwent >1 tissue sampling procedure, and 15% experienced delays due to comorbid or intercurrent disease. The reasons for medical delay were synchronous cancer (n=11), acute cardiovascular disease (n=8), lung- or bronchial infections (n=11), poor lung- or general condition (n=23), traumatic or pathologic fractures (n=5), and 9 other conditions.

The proportion with more than one tissue sampling procedure did not vary statistically by treatment intention (curative or palliative) or stage of disease. The proportions who had medical delays were similar in curative and palliative treatment, but more stage II patients experienced medical delay than stage I, III and IV (p=0.009).

Table 2 Baseline characteristics Paper I

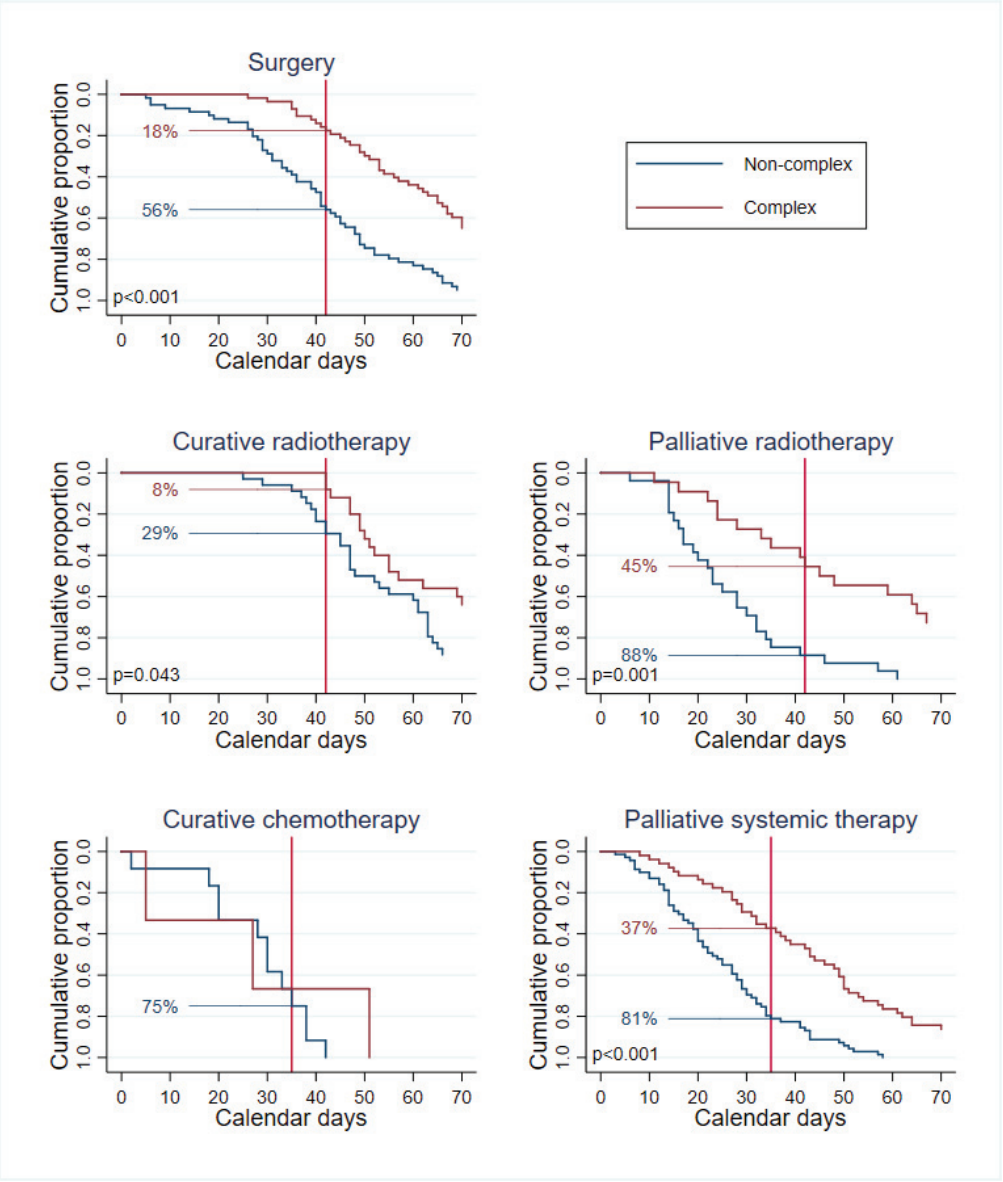
Variables	Total N=449		Non-complex patients* n=262		Complex patients** n=187	
Age						
Median (range)	72	(40-93)	72	(46-93)	72	(40-89)
< 70 years	184	(41%)	107	(41%)	77	(41%)
≥ 70 years	265	(59%)	155	(59%)	110	(59%)
Sex						
Women	206	(46%)	125	(48%)	81	(43%)
Men	243	(54%)	137	(52%)	106	(57%)
TNM stage						
I	112	(25%)	65	(25%)	47	(25%)
II	42	(9%)	18	(7%)	24	(13%)
III	116	(26%)	68	(26%)	48	(26%)
IV	179	(40%)	111	(42%)	68	(36%)
Histology						
NSCLC	312	(69%)	161	(61%)	151	(81%)
SCLC	65	(14%)	49	(19%)	16	(9%)
Other primary lung cancers	9	(2%)	4	(2%)	5	(3%)
No tissue diagnosis	63	(14%)	48	(18%)	15	(8%)
Treatment						
Surgery	116	(26%)	59	(23%)	57	(30%)
***Curative radiotherapy	74	(16%)	46	(18%)	28	(15%)
Palliative radiotherapy	48	(11%)	26	(10%)	22	(12%)
Palliative systemic therapy	120	(27%)	69	(26%)	51	(27%)
Palliative surgery	5	(1%)	2	(1%)	3	(2%)
No cancer treatment	79	(18%)	55	(21%)	24	(13%)
Death before treatment	7	(2%)	5	(2%)	2	(1%)
PET CT						
Yes	146	(33%)	79	(30%)	67	(36%)
No	303	(67%)	183	(70%)	120	(64%)

* Non-complex, ≤1 tissue diagnostic procedure and no medical delays of >3 days
** Complex, >1 tissue diagnostic procedures and / or medical delay of >3 days
*** Curative radiotherapy includes concurrent radio-chemotherapy and radiotherapy alone

6.2.3 Time to treatment

In the overall population, median time to start of treatment was 42 days (range: 2-296), and 179 (49%) were classified as timely. Among non-complex, 66% were classified as timely compared to 29% among complex ($p<0.0001$). Among patients who were offered surgery or curative radiotherapy, the proportions of timely among non-complex were only 56% and 29% respectively (Figure 7).

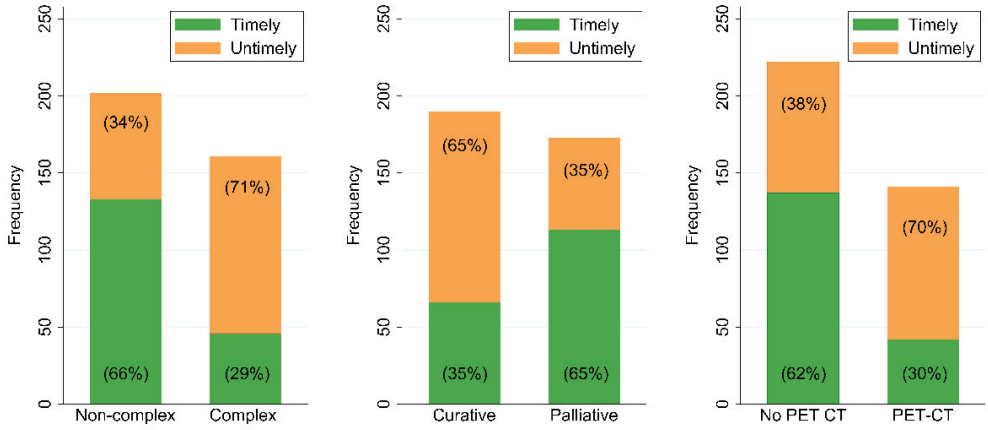
Figure 7 Time to treatment among complex and non-complex



6.2.4 Associations of meeting the recommended timeframes and complexity

The most important predictors of not meeting the recommended timeframes were curative treatment intention ($p<0.0001$), being classified as complex ($p<0.001$), and to have had a PET CT scan ($p<0.0001$) (Figure 8).

Figure 8 Predictors of not meeting the recommended timeframes



6.2.5 Conclusion, Paper I

Overall, only 49% of lung cancer patients started treatment within the Norwegian target timeframes. Even among the least complex, the timeframes were met in only 66%. Consequently, too few lung cancer patients started treatment within the recommended timeframes at St. Olavs hospital.

6.3 Paper II

"Reasons for prolonged time for diagnostic workup for stage I-II lung cancer and estimated effect of applying an optimized pathway for diagnostic procedures"

6.3.1 Patients

150 patients presented with preliminary stage I or II on the baseline CT scan. Twenty-six patients were excluded since they were ineligible of curative treatment; and another 24 were excluded because they experienced delays of ≥3 days due to medical reasons or patient's whish (Figure 9). Thus, 100 patients were included in the analyses. Median age was 70 (54-84), 77% had NSCLC, and 63% were women (Table 3).

Figure 9 Patient selection for Paper II

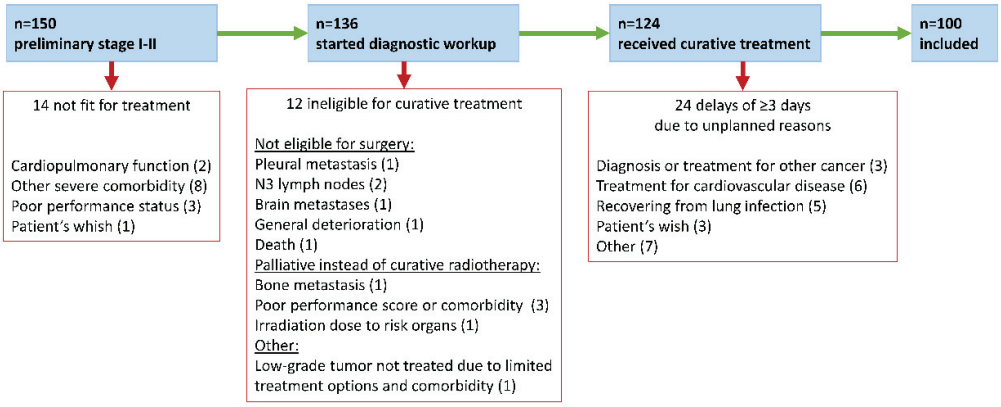


Table 3 Baseline characteristics Paper II

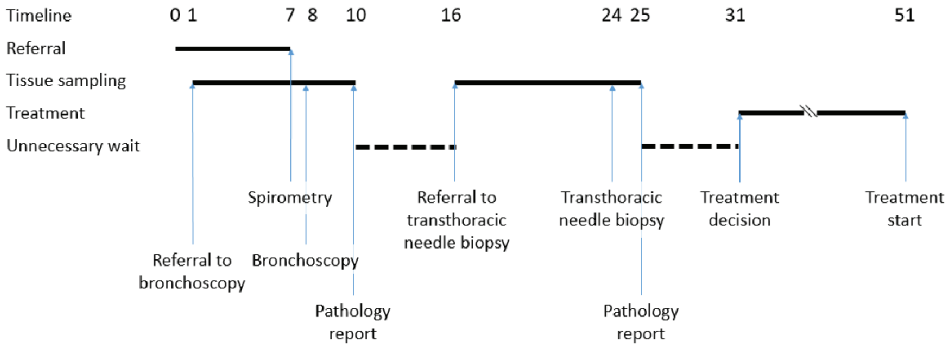
Variables	Included N=100
Age	
Median (range)	70 (54-84)
≥75 years	32 (32%)
Sex	
Women	63 (63%)
Men	37 (37%)
TNM stage	
I	72 (72%)
II	20 (20%)
III	8 (8%)
Treatment	
Surgery	76 (76%)
*Curative radiotherapy	8 (8%)
**Stereotactic radiotherapy	16 (16%)
Histology	
NSCLC	77 (77%)
SCLC	6 (6%)
Another primary lung cancer	5 (5%)
No tissue diagnosis	12 (12%)
* Includes chemo-radiotherapy in limited disease SCLC ** In T1-2N0 NSCLC	

6.3.2 Reasons for delay

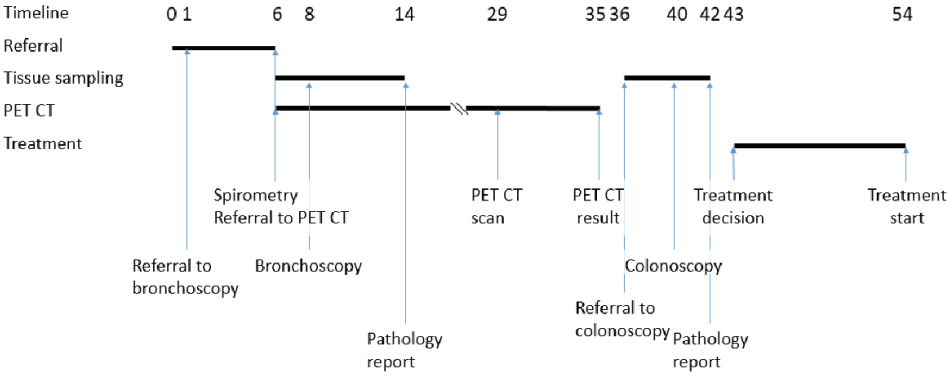
We found several reasons for delay that may be sub-classified as suboptimal planning, resource constraints, or other reasons. Some important mechanisms for prolonged time until treatment start is illustrated in Figure 10.

Figure 10 Illustrations of some important mechanisms for delay

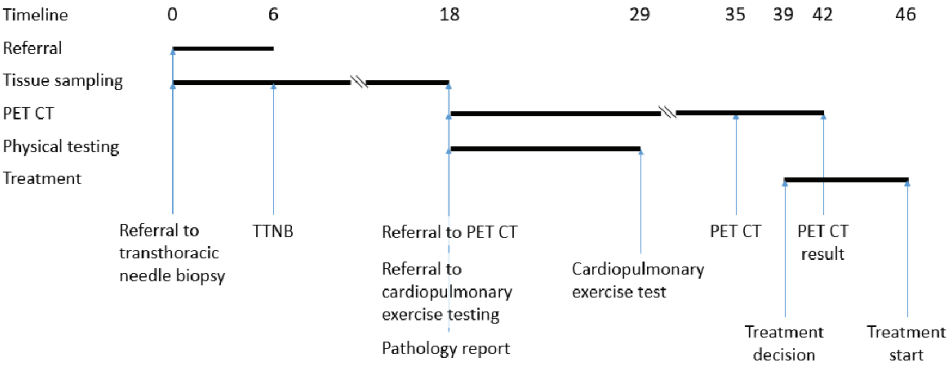
Case 1 Repeated tissue sampling procedures; unnecessary delay (stapled line); long wait for surgery



Case 2 Long wait for pathology report; a late PET CT revealed lesions that caused sequential diagnostic procedures



Case 3 Late referral to PET CT and exercise testing; long wait for pathology report, PET CT and exercise testing



6.3.3 Suboptimal planning

1) CT of the chest and upper abdomen was not done before after the first hospital visit (n=8), or the radiology report was not completed when the first hospital visit took place (n=39).
2) Patients were referred to a PET CT too late, partly because the radiology report of the CT scan was not available (n=27).
3) Patients were referred for an exercise test too late (n=16).
4) Patients underwent subsequent tissue procedures because an attempt of sampling tumor through bronchoscopy failed when it was quite obvious that a transthoracic CT guided biopsy was the method that could result in a diagnosis (n=15).
5) Need for additional diagnostic procedures due to findings on PET CT (n=12).
6) Incomplete workup before the patient was discussed at the tumor board. Thus, the treatment decision was delayed (n=16).

6.3.4 Resource constraints

1) The interval from the hospital received a referral letter until the first hospital appointment exceeded seven days for unexplained reasons (n=50).
2) Long waiting time for PET CT (a median of 20.5 days from referral to result). The PET CT scanner was installed at St. Olavs hospital in October 2013. Since then, the interval from referral until result has been ≤7 days.
3) Long waiting time from a tissue sampling procedure took place until the pathology report was completed (median 4.5 days). Furthermore, patients were routinely given an appointment for information about the pathology report 1-2 weeks after the tissue sampling procedure, which caused further delays when the report was completed earlier or when the sampling procedure failed to produce an analyzable tissue sample.
4) Other important delays occurred due to waiting time for cardiopulmonary exercise testing (median 11 days); and waiting time for a second tissue sampling procedure (median 8 days).
5) Long waiting time for surgery (median 13 days) and radiotherapy (median 22.5 days).

6.3.5 Other reasons:

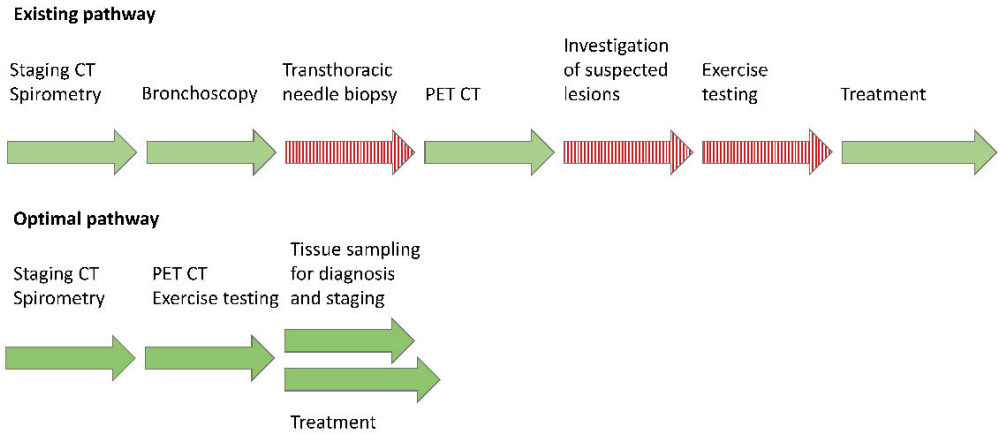
Two patients were medically operable but received chemo-radiotherapy due to SCLC. In all other patients, there was a medical reason when radiotherapy was chosen instead of surgery.

6.3.6 Suggestion for an optimal pathway

Based on our analyses, we defined the following optimal pathway (Figure 11):

1) If a CT of the chest and upper abdomen is not performed before, it should take zero days from a referral letter is received until referral for a CT scan.
2) In patients who are considered eligible and fit for curative treatment, it should take zero days from the first consultation until referral to PET CT.
3) In patients with reduced pulmonary function it should take zero days from the first consultation until referral for exercise testing.
4) Patients should be discussed at a tumor board meeting immediately after completion of exercise tests and PET CT to a) decide how tissue sampling for both diagnostic and staging purposes should be performed; b) make a preliminary plan.
5) It should take zero days from the tumor board meeting until referral to a procedure using a method that is suitable for both diagnosis and staging.
6) It should take zero days from the tumor board meeting until referral to treatment.

Figure 11 Existing pathway and our suggestions for a more optimal pathway



6.3.7 Time to treatment

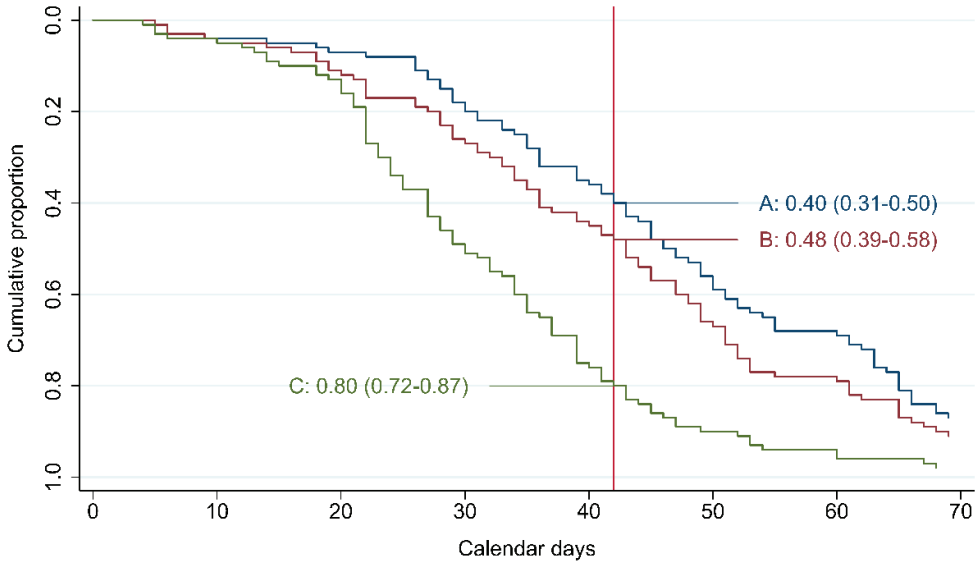
The observed median time to treatment was 46.5 days (5-145), and 40% (95% CI: 31% to 50%) of patients started treatment within the recommended 42 days.

When applying the current waiting time for PET CT (≤7 days), the proportion of patients who could have started timely treatment increased to 48% (95% CI: 39% to 58%) (p=0.255).

Applying the optimal pathway and current waiting time for PET CT (≤7 days), the proportion of patients who could start treatment within 42 days would increase to 80% (95% CI: 72% to 87%) (p<0.001) (Figure 12), and the number of tissue sampling procedures would have been reduced with 16% (from 112 to 92 procedures) without adding extra resources.

Figure 12 Observed timelines and simulated improvements

Time to treatment in A) observed timelines; B) estimated timelines if applying current waiting times for PET CT (≤7 days); C) estimated timelines if applying the optimal pathway and the current waiting time for PET CT



6.3.8 Conclusion, Paper II

Optimal decision making might change the sequence of diagnostic procedures and reduce the number of procedures required for the diagnostic workup for lung cancer at our hospital. Consequently, efficiency of diagnostic workup might be significantly improved without adding resources. By installing a PET CT scanner (already in place) and reducing the time for the most time-consuming steps (pathology processing, exercise testing, surgery and radiotherapy), the proportion receiving timely treatment might be improved even further.

6.4 Paper III

"Timelines for Diagnostic Workup for Lung Cancer Patients and Survival"

6.4.1 Patients

From the original population of 448 patients, we excluded 9 patients with uncommon thoracic malignancies and thus, 439 patients were included in the analyses. Regarding the patient who started treatment for lung cancer twice during the study period, we included the first incidence in the analysis.

Forty-six percent were women, 35% > 75 years, 71% had NSCLC and 14% had no histologically or cytologically confirmed diagnosis. Thirty-three percent had stage I-II disease, 26% stage III, and 41% stage IV. Overall, 180 (51%) received timely treatment. Performance status is the most important prognostic factor in cancer patients but was not assessed since this information was missing in too large a proportion of the medical records.

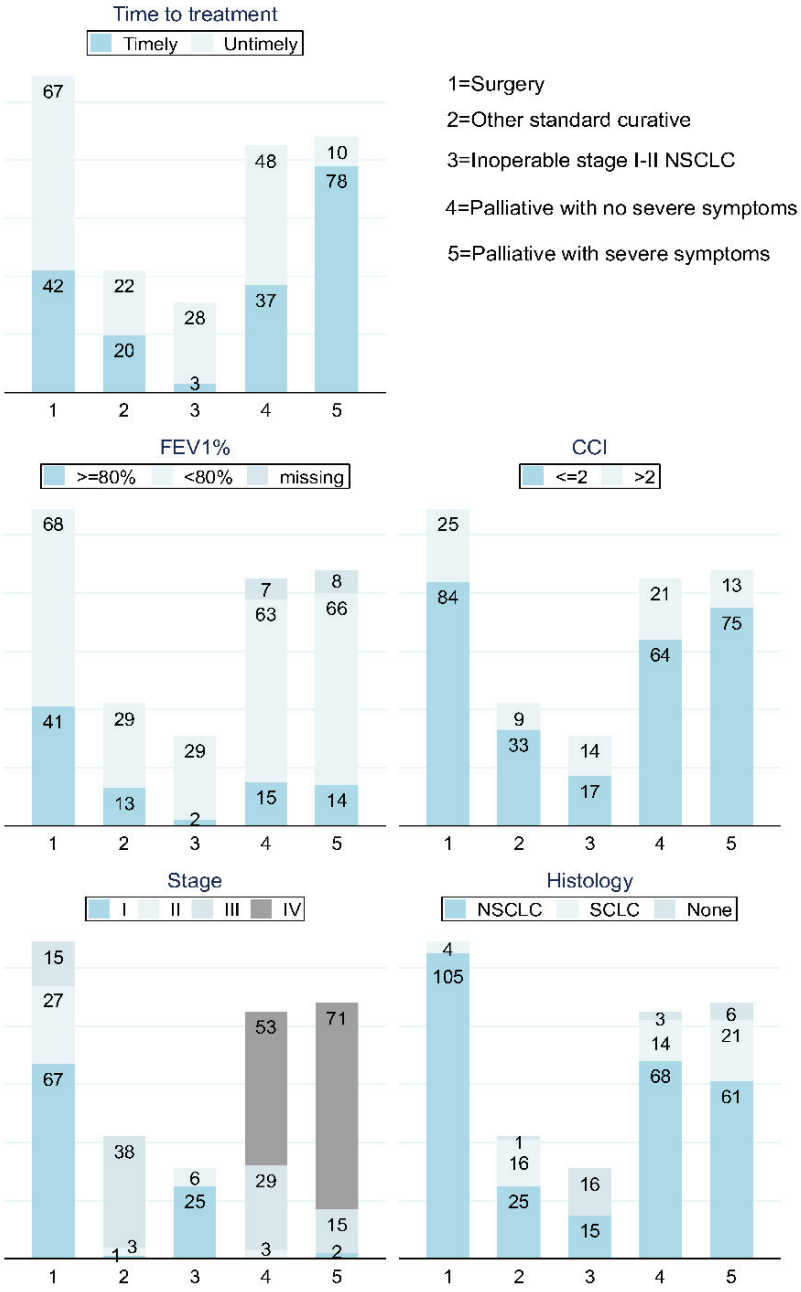
6.4.2 Treatment subgroups

Twenty-five percent underwent surgery, 10% other standard curative treatment, 7% were inoperable stage I-II receiving curative radiotherapy, 19% were palliative without severe cancer symptoms, 20% palliative with severe symptoms. Nineteen percent (n=84) did not receive any cancer therapy, whereof six patients died before treatment could start and one died due to complications of a diagnostic procedure.

The proportion who received timely treatment varied significantly between the treatment groups (p<.001) (Figure 13).

More patients in the inoperable stage I-II curative treatment group than among those who underwent surgery or other standard curative treatment had an FEV1% < 80% of the expected value (p=.004), a CCI of > 2 (p=.033), and no histologically or cytologically confirmed diagnosis (p=<.001). The proportion with stage I disease was higher in inoperable stage I-II patients than in surgery (p=0.052). In the palliative treatment and no severe symptoms group, the proportion with stage I-III disease was significantly higher than among those in the palliative with severe symptoms group (p=.007) (Figure 13).

Figure 13 Variation between the treatment groups



Baseline characteristics were well balanced between those who received timely and those who received untimely treatment within each treatment group, with the exception of a) in the other standard curative treatment group, the proportion of patients aged >75 years was significantly higher in the group who received untimely treatment (45% vs. 15%; p=.033); and b) in the palliative treatment, severe symptoms group, there was a higher proportion of stage I-III disease in the group who received untimely treatment (50% vs. 15%; p=.009).

6.4.3 Survival

Patients who received timely treatment had a shorter overall survival than those who started treatment later than recommended in the Norwegian guidelines. Subgroup analyses revealed that among those who received curative treatment, there was a survival benefit of timely treatment, while those who received untimely treatment lived longer among those who were offered palliative treatment (Figure 14)

When analyzing patients who underwent surgery or other curative treatment separately, there were no survival benefit of receiving timely treatment. Among patients who received palliative treatment, there was no survival benefit of timely treatment among those with no severe symptoms. Among the group with severe cancer symptoms, those who received timely treatment had a significantly shorter survival than those who received untimely treatment (Figure 15)

Figure 14 Survival, overall and by treatment intention

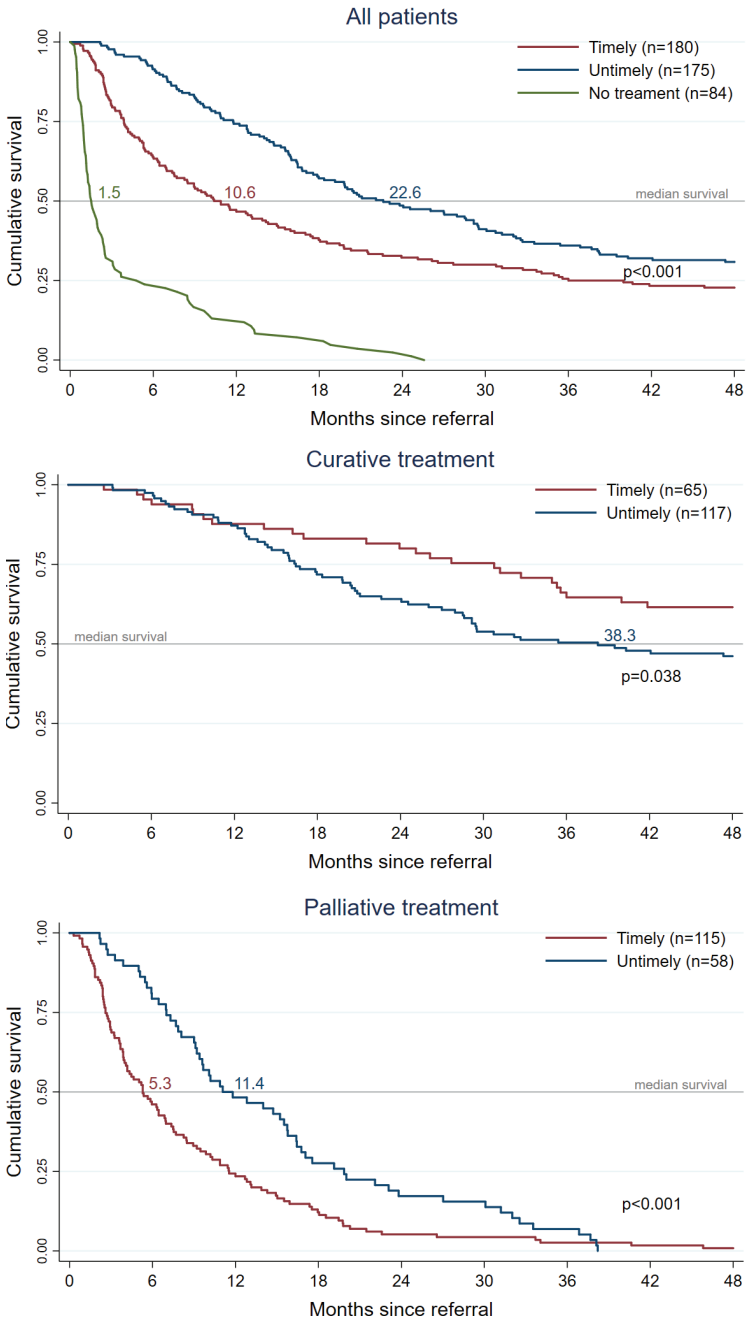
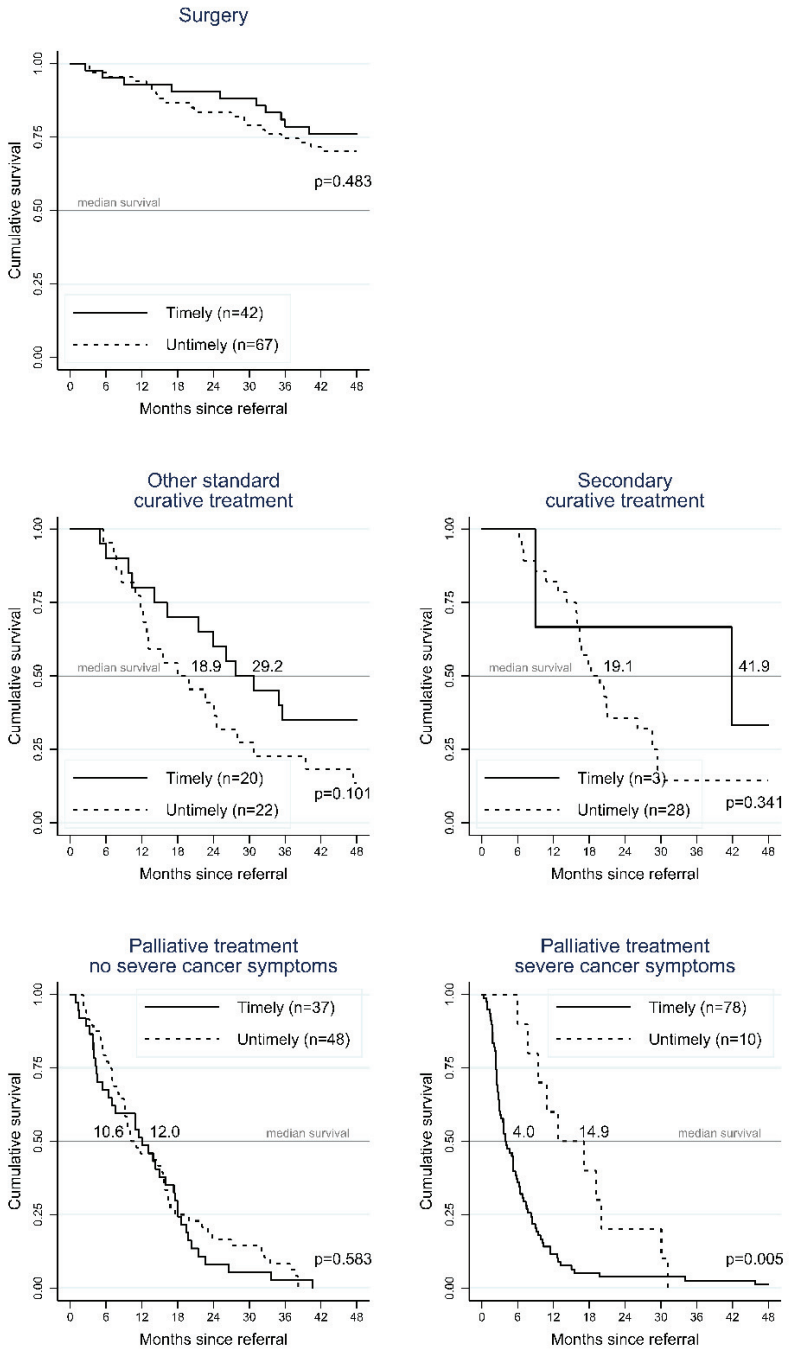


Figure 15 Survival in treatment groups



6.4.4 Conclusion, Paper III

Overall, median survival was significantly shorter among patients who started treatment within the recommended timeframes compared to those waiting longer. However, the associations between timeliness and survival were not uniform in all subgroups, indicating that time until treatment start alone is not prognostic for all lung cancer patients.

7. Discussion

7.1 Comparison with other studies

7.1.1 Timeliness of lung cancer treatment

Our study is not necessarily comparable with others due to differences in recommended timelines and design, but our results seem to be quite similar to what others have found. The Norwegian Patient Registry reported in 2017 that 61% of lung cancer patients in total in Norway started treatment within target time; whereof 49% of those having surgery, 58% of those receiving radiotherapy, and 70% of those receiving systemic therapy.[115] Corresponding numbers in Denmark from 2016 showed that the recommended timeframe of 42 days was met in 52% for surgery, 77% for radio-chemotherapy, 83% for chemotherapy, and 66% for radiotherapy.[116] The National Health Services England reported that 78.5% started treatment within 62 days in the UK in 2013-2014,[16] compared to 70% in our study.

7.1.2 The reasons for delay

We found no studies aiming to define, or quantify, which patients who should not start treatment within the specified timeframes, although it is a typical expectation that target times can only be achieved in 70-80% of patients. This is a consensus-based number, and the reasons why some delays are accepted are not clear.

None seems to have differentiated between complex and non-complex patients. Our definition of "complex" might not be universally agreed upon, but we would be surprised if the concept of complex and non-complex is considered controversial. In our opinion, when as few as 66% among non-complex start treatment within target time, there is room for significant improvement.

Several studies show that there is an association between the need for repeated tissue sampling procedures and prolongation of the lung cancer diagnostic workup.[81 ,83 ,117] However, it seems to be fairly accepted that repeated tissue sampling may be necessary due to the difficult access to lung tumors. In peripheral tumors, the diagnostic yield is reported to be 14%- 52% for bronchoscopy and 70%-96% for transthoracic

needle biopsy (TTNB), with the lowest sensitivity for tumors < 2 cm.[118-120] Still, because there is a higher risk of complications through TTNB, a bronchoscopy is often chosen as the first procedure even if the success-rate is low. Complications, most often pneumothorax, occur in 2% in bronchoscopy[121] and 15% in TTNB.[122] However, our results strongly indicate that TTNB is underused as the primary tissue sampling procedure in our study. That does not mean that bronchoscopy does not play a role, as unexpected findings occur, but we recommend that a TTNB should be planned in parallel with a bronchoscopy and not after failure to obtain a tissue sample through bronchoscopy, at least when the pulmonologist consider the chances for a successful sampling through bronchoscopy to be low.[123,124] Current Norwegian and European guidelines recommend a bronchoscopy as the first tissue sampling procedure and a PET CT scan following primary diagnosis in potentially curative disease.[74,125] The Danish, Swedish and NICE guidelines recommend a PET CT scan before the tissue sampling procedures if the CT scan indicate curable disease, and a transthoracic needle biopsy as the first procedure in peripheral tumors.[90,126,127] Our data strongly suggest that the latter guidelines should be applied also in Norway.

Endobronchial ultrasound transbronchial needle aspiration (EBUS TBNA) increases the numbers of one-step simultaneous diagnosis and staging in clinical stage II disease,[114,128,129] and at St. Olavs hospital, we found that EBUS TBNA was the preferred first procedure among patients presenting with stage III disease on the baseline CT. However, we observed that the personnel performing EBUS TBNA was not always available on the day the procedure was scheduled. We also observed that some patients with parabronchial tumors first had a negative conventional bronchoscopy when EBUS TBNA was the method that succeeded.[130] This calls for better planning.

Relatively few patients in our study underwent a PET CT scan, and the proportion who had a PET CT increased during the study period (10% in 2011 – 57% in 2013). At the time of our study, there were 6 PET CT scanners in Norway, compared to 32 in Denmark. The lack of capacity may explain why referral to PET CT took place late, usually after a thorough multidisciplinary board discussion. However, even when

applying the current waiting time for PET CT (≤ 7 days), only a few patients would finish the diagnostic workup within the recommended timeframes.

We conclude that delays occurred because the best medical practice was not always applied at our hospital. The reasons for this was both suboptimal planning and insufficient capacity for essential procedures. Better and more extensive surveillance by the most competent physicians is highly recommended in order to improve the timeliness and quality of the diagnostic workup.

7.1.3 The optimal lung cancer pathway

Several studies demonstrate the efficacy of organizational interventions on timeliness of care. The methods include clinical pathways,[87,131] rapid diagnostic programs,[88,128,132,133] multidisciplinary teams,[89] and nurse coordinators.[134] One study described the efficiency of a program using PET CT for invasive test planning.[135] There is one ongoing study aiming to compare the cost-effectiveness of different diagnostic pathways.[136] The only Norwegian study, from 2011, described the implementation of Lean methodology to improve time from the first pathological chest image until start of lung cancer treatment.[86] Their analysis resulted in an alert system and altered administrative routines which led to decreased waiting times until start of diagnostic workup, and they implemented target times for the intervals from referral to treatment until treatment start. Organizational interventions may clearly speed up the processes, but often include extra resources while other mechanisms for improvement are poorly described.[87,88]

Referring patients to treatment before the diagnosis is histologically verified might be controversial because it will, in some cases, cause cancellations and sudden changes of treatment plans. In our study only three medically operable patients received chemoradiation instead of surgery, but we expect the number of changes in treatment plans to increase when including patients with stage III disease.

7.1.4 Associations between time to treatment and survival in other studies

Some studies have found associations between long intervals and poorer survival, but the intervals in these studies were longer than the time-to-treatment observed in our study. In one study, many patients progressed and had a poorer survival if the interval

from treatment decision until surgery exceeded 2-3 months[99]; and in other studies, survival decreased if the interval from diagnosis until surgery exceeded 8 weeks[98] or 3 months[137] for stage Ia disease.

Studies stratifying for stage and treatment type do not find an association between timeliness and survival,[138] except in advanced stage where longer intervals are associated with better survival.[139-142] One study found an association between ≤35 days from diagnosis until treatment and improved survival in localized disease, but there was also an association between longer intervals and receiving chemoradiation, indicating a higher proportion of stage III disease and limited disease SCLC among those with the worst prognosis.[143]

One study randomized patients with suspected stage I-IIIA lung cancer to either "conventional diagnosis and staging" (usually the first procedure was a bronchoscopy or TTNB), or EBUS TBNA as the first procedure. In this study, a PET CT scan was usually undertaken after the first tissue sampling procedure. They found that those starting with an EBUS TBNA underwent fewer procedures than the control group. Furthermore, the EBUS TBNA group had better survival, but in the authors' opinion, this was due to superior selection of patients eligible for surgery and not the fact that the EBUS TBNA group had a median of 15 days shorter diagnostic interval.[114]

Existing studies have limitations since most studies are retrospective and many are based on administrative registries. E.g., some studies did not include data on important characteristics such as stage of disease and treatment intention.[101 ,144] Thus, it remains unclear how long lung cancer patients can safely wait until they receive treatment.

7.2 Strengths, limitations and external validity

This work is based on a comprehensive review of the individual electronic medical records, and the data are complete. Data collection is done by a physician not involved in lung cancer diagnostic workup or treatment but has experience with care for patients with gynecological cancers. The project group consisted of a gynecologist, a lung oncologist, and two pulmonary physicians specializing in lung cancer diagnosis and treatment.

St. Olavs hospital was the primary hospital for all patients in the study, and the patients were diagnosed consecutively. The proportion with stage I-II disease (34%) was higher compared with Denmark (23%),[80] Canada (26%),[145] and UK (21% among non-missing),[146] but otherwise, baseline characteristics among patients in these countries seem to be similar to ours. We therefore consider our study population to be representative of lung cancer patients in countries with comparable healthcare systems.[147]

It is a single center, retrospective study, since a prospective study was not feasible within the timeframes of the project. Furthermore, one can argue that a prospective study would have been an intervention in itself. Due to the lack of standards we had to make our own definitions in many settings. E.g. the definition of "optimal pathway" was made based on analyses of a limited group of patients because there was a need to reduce the complexity. Also, the estimated improvement was simulated and was not tested in clinical practice, and we were unable to investigate if improving the timelines would improve lung cancer survival in this observational study.

Diagnostic workup for lung cancer varied considerably during the study period which may have limited our abilities to examine if there actually was a survival benefit of starting treatment within the recommended timeframes. Finally, performance status was not routinely recorded and often not possible to estimate from the medical records, reasons for delay may have been overseen or not registered, and decisions may have been made for good reason, but not well documented.

Our results may not be applicable to other healthcare systems, due to variations in defined timelines, prehospital pathways, access to resources (PET CT in particular), and attributes of the Norwegian public healthcare system, but we believe that our data might be of interest when discussing lung cancer logistics at other Norwegian hospitals and in other countries.

7.3 The current status

The data presented in this project are outdated. In our experience, the pathway for lung cancer diagnostic workup at our hospital has improved and much have happened since the end of the study period. The concept of clinical pathways is now accepted; the team-

leader function may be better implemented; and the functions of a weekly meeting of pulmonary physicians and a lung oncologist (lung oncologic meeting) that launched during the study period has taken on forms. An electronic database for the reporting of clinical pathway time metrics has been developed at St. Olavs hospital, and thus, real-time performance data are available for the time-indicator.

Much more patients now undergo a PET CT scan, which was applied to lung cancer patients relatively late at St. Olavs hospital. Also, national and international guidelines have been revised several times. A national quality register for lung cancer care was established in 2013, and national cancer pathways were implemented in Norway on January 1, 2015.

There have also been significant differences in therapeutic options. During the study period, few patients received first-line oral systemic therapy (n=6). Now, molecular characterizations of all newly diagnosed NSCLCs are performed, and a larger proportion are offered oral targeted therapy and immunotherapy with checkpoint inhibitors. However, according to the Lung Cancer Quality Register, only 44.7% started treatment within target time among patients starting treatment for lung cancer at St. Olavs hospital in 2018.

7.4 The clinical impact of the project

Due to medical complexity and numerous potential confounders, a randomized study design would be the best way to investigate associations of timelines and survival, but that may not be feasible. We believe that one has to ensure a high quality of diagnostic workup and implementation of good systems for registering and oversee the sequence of diagnostic procedures before such a randomized trial might be performed.

We do, however, strongly believe that the results of this project have had impact on implementation and refining the lung cancer clinical pathway at St. Olavs hospital. This thesis provides evidence which may be used in future efforts to overcome barriers to clinical pathway implementation and consequently improve the quality of cancer care at our hospital.

7.5 The time indicator

Performing the process mapping from referral until treatment start enabled us to identify mechanisms why lung cancer diagnostic workup until treatment start took too long. In our case, the most efficient pathway was not obvious and had to be defined,[148-150] in other cases the data may be used directly to evaluate performance against medical standards. An alternative approach would be to systematically review the charts of all patients exceeding the timelines, but our project clearly indicates that there is also room for improvement in the care of patients even when the timelines are met. Unexplained variance in medical practice entail a risk that patients receive suboptimal care and should be understood and minimized regardless of timelines.

The time indicator is not an operational indicator and cannot be used in plan-do-study-act improvement. Examples of applicable metrics from our study are "number of sequential tissue sampling procedures" and "waiting time for PET CT". These indicators may help explain the performance of the time indicator, and they allow studying implementation of improved pathways.[151-153]

To our knowledge, there are no publications of studies attempting to foresee how improved medical practice may impact timelines. It is our opinion that simulations may aid targeting the right goals, reduce the number of inefficient interventions, and optimize the sequence of procedures.

7.6 Clinical pathway organization

We acknowledge that competent decision making is the most important factor for improving the quality of lung cancer diagnostic workup. We also want to highlight the role of the MDT meetings. Traditionally, patients are discussed at the MDT meeting at the end of diagnostic workup, while involving the MDT earlier may improve planning of both the workup and treatment, and save time and money. [42 ,154]

The leader function is a main component of the clinical pathway concept at St. Olavs hospital, the leader being responsible of the development, implementation and follow-up to make sure that things are done right, and to provide feedback to the other members of the multidisciplinary team. Since the weekly number of new lung cancer

patients is limited, it is our opinion that it might be feasible that the multidisciplinary team (MDT) leader is continuously updated on all patients entering the pathway. However, leaders of multidisciplinary teams usually contribute with all kinds of general clinical work including duty shifts. In our opinion, this is a major barrier towards successful implementation and a change in organization of the hospital is needed in order to improve clinical practice to a maximum.

Solely presenting the time metrics is not sufficient for quality control.[155,156] The lack of IT systems to aid the teams to continuously measure, understand, and analyze their practice is another major obstacle.

Finally, ownership and involvement of leaders at all levels and all involved departments are necessary. E.g. the waiting times for imaging are currently too long. Joint meetings should be kept between MDT leaders, Heads of involved departments, the Hospital Managing Director, and the Medical Director on a regular basis in order to optimize care for our cancer patients.

8. Conclusions

- All lung cancer patients cannot comply with timelines for medical and/or technical reason, but too few patients at St. Olavs hospital started treatment within the recommended timeframes. Among all patients, 49% started timely treatment and even among the non-complex, only 66% started timely treatment.
- Delays occurred because too many tissue sampling procedures were performed, patients were referred for PET CT and exercise testing too late, and were referred to treatment later than necessary. Changing the sequence of actions may significantly reduce the number of tissue sampling procedures, and provided a sufficient capacity for PET CT, the numbers who could start timely treatment among patients presenting with stage I-II on the baseline CT and who received curative treatment, could improve from 40% to 80%. Interestingly, applying a more optimal pathway would reduce the number of procedures and hence costs.
- Overall, meeting the timeframe recommendations was associated with decreased survival, but the associations varied significantly within important subgroups.

9. Implications and directions of future research

Our data strongly suggest that adhering to our optimal pathway will improve timeliness of lung cancer treatment significantly without requiring more resources. We suggest implementing the pathway and allocating trained personnel to continuously evaluate adherence and timeliness. Personal feedback during training is probably required in order to increase the number of physicians who are able to perform diagnostic procedures in an optimal way.

There are several requirements for building a solid evidence base through future research on time indicators, the role of clinical pathways and continuous improvement of clinical practice:

- There is a need for uniform definitions. E.g. according to the Norwegian Lung Cancer Quality Register, there is a variation in what proportions of lung cancer patients who are included in a pathway, possibly indicating that the definition of eligible patients varies significantly.
- There is a need to define an optimal lung cancer pathway for more complex patients than stage I-II patients.
- There is a need for IT-systems that enable trained personnel to continuously monitor adherence to guidelines and optimal pathways and outcomes of following these recommendations. On the National level, the quality registers collect process and disease-specific information through an electronic reporting system, but this information needs to be continuously available at the hospital level. A new system for medical records will be implemented in Central Norway in 2021. A main element in the solution is structured electronic health records, and this system may facilitate the collection of relevant process data, provided that the system is designed in collaboration with experts in medicine and process analysis.
- The quality of the treatment and not only the diagnostic workup significantly influences survival. A comprehensive registry of administered treatment is needed in order to fully evaluate the importance of timelines until treatment start. Such a registry has been created, but not all data are reported since no resources for reporting data has been allocated to the hospitals.

- Finally, we did not investigate the patients' preferences and opinions about timelines due to the retrospective nature of our study.

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Paper I

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RESEARCH ARTICLE Open Access

Medical complexity and time to lung cancer treatment – a three-year retrospective chart review

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Abstract

Background: The time from a referral for suspected lung cancer is received at a hospital until treatment start has been defined as a quality indicator. Current Norwegian recommendation is that ≥70% should start surgery or radiotherapy within 42 calendar days and systemic therapy within 35 days. However, delays can occur due to medical complexity. The aim of this study was to quantify the proportion of patients who started treatment within the recommended timeframes; and to assess the proportion of non-complex patients for which there were no good reasons for delays.

Methods: We performed a retrospective chart review of all patients diagnosed with lung cancer at a university hospital during 2011–2013. We defined "non-complex" patients as those who underwent ≤1 tissue diagnostic procedure and had no delays due to comorbidity, intercurrent disease or complications to diagnostic procedures ("Medical delays") of more than three days.

Results: Four hundred forty-nine cases were analyzed; 142 (32%) had >1 tissue diagnostic procedures; 67 (15%) had medical delays >3 days; 262 (58%) were non-complex and 363 (81%) received treatment for lung cancer. Median number of days until surgery or radiotherapy was 48 (overall) and 41 (non-complex patients). The proportions who started surgery or radiotherapy within 42 days were 41% (overall) and 56% (non-complex). Corresponding numbers for systemic therapy were 29 days (overall) and 25 days (non-complex), and 64% (overall) and 80% (non-complex).

Conclusion: Fewer lung cancer patients than desired started treatment within the recommended timeframes. Even among the least complex patients, too few patients received timely treatment. The reasons need to be identified and understood, and changes in the organization appear to be necessary in order to offer timely treatment to more patients.

Keywords: Quality indicator, Organization, Performance, Timeliness, Complexity

Background

Waiting while undergoing investigations for suspected cancer is distressing for patients and their families [1–3], and waiting for cancer treatment to start is perceived as a medical risk that may affect treatment outcomes [4, 5]. It is not clear that shorter time to treatment influences survival [6–9], but there is fair evidence that prompt management improves patient satisfaction and reduces anxiety [1, 2, 10–12]. Thus, efficient organization of cancer diagnosis and treatment is a public and political goal. Political strategies to improve organization include development of indicators and standards for timely diagnosis and treatment.

The British Thoracic Society and the Danish Lung Cancer Group presented the first specifications for timely lung cancer diagnosis and treatment in 1998 [8, 13]. In June 2011, the first Norwegian recommendations regarding timelines for diagnosis and treatment of cancer were presented. At that time, at least 80% of all cancer patients were to start treatment within 20

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working days from a referral letter for suspected cancer was received at a hospital. National guidelines for cancer care organization were developed, and the National Standard for lung cancer diagnosis and treatment was presented on January 1, 2015 [14]. For suspected lung cancer, the first hospital appointment should be offered within seven calendar days of receiving a referral letter; a treatment decision should be made within 28 calendar days; systemic therapy should start within 35 calendar days, and surgery or radiotherapy within 42 calendar days. The overall aim is that more than 70% of lung cancer patients start treatment within these timeframes [15].

The metrics for timely lung cancer care vary between health care organizations [16–18], but all accept that good reasons for delay exist and tolerate longer timeframes for a specified proportion of patients. Diagnostic workup for lung cancer may be complex and it is not clear whether it is realistic or medically correct that all patients start treatment within 35 or 42 days. Tissue sampling may be difficult; the number of lesions that should be punctured varies; and complications to diagnostic procedures occur. Many patients are elderly and suffer from co-existing conditions. Thus, intercurrent diseases are common, and some patients want breaks between the diagnostic procedures or before starting treatment [19]. Most studies do not consider these factors, since they are based on registry data. Thus, there is no established method for assessing complexity in diagnostic work-up for lung cancer [20].

Aims of the study

The main aims of the study were to investigate how many patients at a university hospital who started treatment for lung cancer within the timeframes recommended in Norway; and to quantify the proportion of patients who had delays due to complex diagnostic workup, intercurrent disease or patients' wish.

Methods

Study setting

The Norwegian health care is mainly public, and the national health insurance system cover expenses exceeding € 233 per year [21]. Approximately 700 000 people live in Central Norway. There are seven hospitals in the region. All hospitals diagnose lung cancer and offer systemic therapy. Radiotherapy is offered at two sites. Complex cases are referred to St. Olavs Hospital, which is the university hospital in the region, but also serves as the primary hospital for 380 000 inhabitants. Most patients within the primary catch-up area lives within 30 min from the hospital. St. Olavs Hospital has all facilities for diagnostic workup for lung cancer including the only PET CT (Positron Emission Tomography Computer Tomography) scanner in the region (since October 2013), and all lung cancer surgery is performed here. PET CT was performed outside our health region during most of the study period (until October 2013). From 2009 to 2013, the annual world standardized lung- and tracheal cancer rate in Norway was 34.9 in men and 26.0 in women [22]. The annual incidence in the primary catchment area of St. Olavs Hospital was similar to the incidence in all of Norway.

The Department of Thoracic Medicine is responsible of lung cancer diagnosis and they offer systemic therapy. The Cancer Department provide radiotherapy, and surgery takes place in the Department of Cardio-Thoracic Surgery. Diagnostic workup for lung cancer is mainly done on an outpatient basis. A weekly, regional, multidisciplinary tumor board meeting is held between pulmonary physicians, thoracic surgeons, an oncologist specializing in lung cancer (Norwegian oncologists are trained in both medical oncology and radiotherapy), a thoracic radiologist, a specialist in nuclear medicine, a pathologist and a nurse coordinator. Between September 1, 2012 and January 31, 2013, the multidisciplinary team revised the routines and procedures for lung cancer diagnosis and a standardized care pathway was developed that included the national recommendations for timeliness. The pathway did not include protocols that could limit timeliness. They also assigned a pulmonary phycician specializing in diagnosis, staging and treatment of lung cancer as the leader of the multidisciplinary team.

Study design

The study is a retrospective analysis of all cases that started diagnostic work-up and were diagnosed with lung cancer from January 1, 2011 to December 31, 2013, at the Department of Thoracic Medicine at St. Olavs Hospital – Trondheim University Hospital, Trondheim, Norway.

Case selection and data collection

Patients registered with ICD 10 codes C34.0-9 ("lung cancer") were identified from the hospital patient administrative system. Patient data were collected from the hospital electronic medical records.

Stage of disease was assessed according to the 7th edition of the TNM classification of lung cancer [23]. Patients were classified as having non-small-cell lung cancer (NSCLC); small-cell lung cancer (SCLC); other primary lung cancers; or no tissue diagnosis. Treatment was classified as curative treatment (surgery, radical radiotherapy or radio-chemotherapy of stage I-III disease); palliative treatment; or no cancer treatment/death before start of treatment. First treatment was either surgery or radiotherapy, or systemic therapy (including when chemotherapy was administered concurrently with

radiotherapy). Patients were classified as "hospitalized" when admitted to the hospital due to the patient's condition at start of diagnostic work-up, otherwise they were classified as "outpatient".

Complexity

In our experience, the factors that influence the timelines the most are the number of tissue diagnostic procedures required [24–27], and delays for medical reasons [27, 28].

Tissue diagnostic procedures are performed to diagnose lung cancer; to do molecular and histopathological classification; and to assess extent of disease. These procedures include bronchoscopy; endobronchial ultrasound-guided trans-bronchial needle aspiration (EBUS TBNA); transthoracic needle biopsy; or others. Delays in diagnostic workup for medical reasons were categorized as hospitalization caused by complications to a diagnostic procedure; synchronous investigation for other cancer; synchronous treatment of other cancer; treatment of comorbidity; or intercurrent disease.

We defined "non-complex patients" as having undergone ≤1 tissue diagnostic procedure and having no medical delays of >3 days. "complex patients" were subclassified as having >1 tissue diagnostic procedures and no medical delays of >3 days; ≤1 tissue diagnostic procedure and medical delays of >3 days; or >1 tissue diagnostic procedures and medical delays of >3 days.

Intervals

We defined start time as the date when a referral letter for suspected lung cancer was received by the Department of Thoracic Medicine – or the date when the decision was made to start diagnostic workup in patients with a known single pulmonary nodule (SPN). We defined the time for treatment decision as the date when such a decision was documented in the EMR. We defined start of treatment as date of surgery, first fraction of radiotherapy, first day of intra-venous chemotherapy, or date of prescription of oral cancer therapy. Time to treatment treatment was defined as the number of calendar days from start time until start of treatment.

According to Norwegian recommendations, start of treatment within 42 days (surgery or radiotherapy) or 35 days (systemic therapy) was considered "timely treatment" [14].

Statistical analyses

We used chi-square test for univariate analysis. Factors influencing the likelihood of timely treatment (patient and disease characteristics as well as PET CT – since PET CT was not available at St. Olavs Hospital during most of the study period) were explored using logistic regression analysis. We used the Stata/IC 13.1 package for Windows for the statistical analyses, and considered a p-value of < 0.05 to be statistically significant.

Results

Case selection and baseline characteristics

Nine hundred ninety patients were identified with "lung cancer" for the first time in the hospital registry in the study period. Four hundred three started diagnostic workup in other hospitals ($n = 333$) or other departments at St. Olavs Hospital ($n = 34$); 66 were diagnosed before January 1, 2011; 103 patients did not have lung cancer, and five patients declined to participate in the study. Thus, 449 patients were analyzed. St. Olavs Hospital was the primary hospital for 436 (97%) of these.

The proportion at an age ≥70 was higher in 2013 (67%) than in 2011 (52%) and 2012 (57%) ($p = 0.04$) due to a variation in the proportions <70 and 70–74. The proportion aged 75 or higher was stable. The proportion who underwent PET CT increased from 10% in 2011, 36% in 2012 to 51% in 2013 ($p < 0.0001$). Otherwise, there were no significant variations in baseline characteristics or treatment between 2011, 2012 and 2013. 42% received curative treatment, 39% palliative, and 18% received no cancer treatment. Seven patients (1.6%) died before a treatment started (Table 1).

Complexity

Forty-nine (11%) of patients underwent no tissue diagnostic procedure, 258 (57%) had one, 100 (22%) had two, and 42 (9%) had more than two procedures. Five hundred and ninety-five procedures were performed (279 bronchoscopies, 150 EBUS-TBNA, 166 other procedures).

Sixty-seven patients (15%) had a medical delay: 11 due to synchronous cancer, 8 had acute cardiovascular disease, 11 lung or bronchial infection, 23 poor lung- or general condition, 5 fracture or trauma, and 9 other conditions. There were delays ≥1 week due to patients' personal preferences or no show in 13 (3%). Among these, eight had >1 tissue diagnostic procedure and/or medical delay of >3 days.

Two hundred and sixty-two patients (58%) were classified as non-complex, and there was no significant variation between years (2011: 56%, 2012: 55%, 2013: 63%; $p = 0.37$). Among complex patients, 120 (64%) had >1 tissue diagnostic procedure, 45 (24%) had medical delay of >3 days, and 22 (12%) had both >1 tissue diagnostic procedure and medical delay of >3 days. The proportion of complex among patients with NSCLC/other primary lung cancers was 49% ($n = 156$); SCLC, 25% ($n = 16$); no tissue diagnosis, 24% ($n = 15$) ($p < 0.0001$). Among patients who received treatment the proportion of complex was 44% ($n = 161$); no treatment, 30% ($n = 26$) ($p = 0.02$). There was no significant difference in the

Table 1 Baseline characteristics

Variables	Total	2011	2012	2013	Non-complex patients[a]	Complex patients[b]
	N = 469	*n* = 147	*n* = 146	*n* = 156	*n* = 262	*n* = 187
Age, median (range)	72 (40–93)	70 (40–90)	71 (46–91)	73 (54–93)	72 (46–93)	72 (40–89)
Age ≥ 70 years, *n* (%)	265 (59%)	77 (52%)	84 (57%)	104 (67%)	155 (59%)	110 (59%)
Women	206 (46%)	62 (42%)	76 (52%)	68 (44%)	125 (48%)	81 (43%)
TNM stage						
I	112 (25%)	29 (20%)	39 (27%)	44 (28%)	65 (25%)	47 (25%)
II	42 (9%)	19 (13%)	10 (7%)	13 (8%)	18 (7%)	24 (13%)
III	116 (26%)	43 (29%)	34 (23%)	39 (25%)	68 (26%)	48 (26%)
IV	179 (40%)	56 (38%)	63 (43%)	60 (38%)	111 (42%)	68 (36%)
Histology						
NSCLC	312 (69%)	105 (71%)	110 (75%)	97 (62%)	161 (61%)	151 (81%)
SCLC	65 (14%)	18 (12%)	19 (13%)	28 (18%)	49 (19%)	16 (9%)
Other primary lung cancers	9 (2%)	2 (1%)	1 (1%)	6 (4%)	4 (2%)	5 (3%)
No tissue diagnosis	63 (14%)	22 (15%)	17 (11%)	25 (16%)	48 (18%)	15 (8%)
Treatment						
Surgery	116 (26%)	37 (25%)	39 (27%)	40 (26%)	59 (23%)	57 (30%)
Curative radiotherapy[c]	74 (16%)	18 (12%)	22 (15%)	34 (22%)	46 (18%)	28 (15%)
Palliative radiotherapy	48 (11%)	19 (13%)	15 (10%)	14 (9%)	26 (10%)	22 (12%)
Palliative systemic therapy	120 (27%)	38 (26%)	43 (29%)	39 (25%)	69 (26%)	51 (27%)
Palliative surgery	5 (1%)	1 (1%)	1 (1%)	3 (2%)	2 (1%)	3 (2%)
No cancer treatment	79 (18%)	31 (21%)	24 (16%)	24 (15%)	55 (21%)	24 (13%)
Death before treatment	7 (2%)	3 (2%)	2 (1%)	2 (1%)	5 (2%)	2 (1%)
Out-patient investigation	290 (65%)	93 (63%)	98 (67%)	99 (63%)	163 (62%)	127 (68%)
PET CT	146 (33%)	15 (10%)	52 (36%)	79 (51%)	79 (30%)	67 (36%)

[a]Non-complex, ≤1 tissue diagnostic procedure and no medical delays of >3 days
[b]Complex, >1 tissue diagnostic procedures and/or medical delay of >3 days
[c]Curative radiotherapy includes concurrent radio-chemotherapy and radiotherapy alone

proportios who were complex in patients who had a PET CT (46%, $n = 67$) compared to those who did not have a PET CT (40%, $n = 120$) ($p = 0.21$) (Table 1).

The proportion with more than one tissue diagnostic procedure was higher among those who received treatment (33% in curative and 36% in palliative treatment), than among those who did not receive cancer treatment or died before treatment started (19%) ($p = 0.01$); while the proportions with medical delay were similar (curative treatment, 19%; palliative treatment, 12%; no treatment or death before treatment, 13% ($p = 0.12$)) (Fig. 1).

There were no significant differences in the numbers who had >1 tissue procedure depending on stage of disease (stage I: 34 (30%); stage II: 16 (38%); stage III: 38 (33%); stage IV: 54 (30%) ($p = 0.77$). The proportion of medical delays of >3 days was highest for stage II patients (stage I: 21 (19%); stage II: 12 (29%); stage III: 17 (15%); stage IV: 17 (10%) ($p = 0.009$)).

PET CT was performed in 20 (11%) of stage IV patients, and 126 (47%) of stage I-III patients ($p < 0.0001$), and the proportion was consequently higher among those receiving curative treatment (113, 59%) than those offered palliative treatment (28, 16%) or no treatment/death before treatment (5, 6%) ($p < 0.0001$).

Intervals

Median time to treatment decision was 26 days (range: 0–283), and 247 (56%) had a decision within 28 days. Among patients who did not receive any cancer treatment, median time to that decision was 18 days (range: 0–100), and was reached in ≤28 days in 78%.

In the overall population, median time to start of treatment was 42 days (range: 2–296), and 179 (49%) received timely treatment. The proportion who received timely treatment was lowest among those eligible for surgery or curative radiotherapy (Fig. 2). More patients received timely treatment among non-complex (133, 66%) than complex patients (46, 29%) ($p < 0.0001$); among those offered palliative treatment (113, 65%) than patients receiving curative treatment (66, 35%) ($p < 0.0001$);

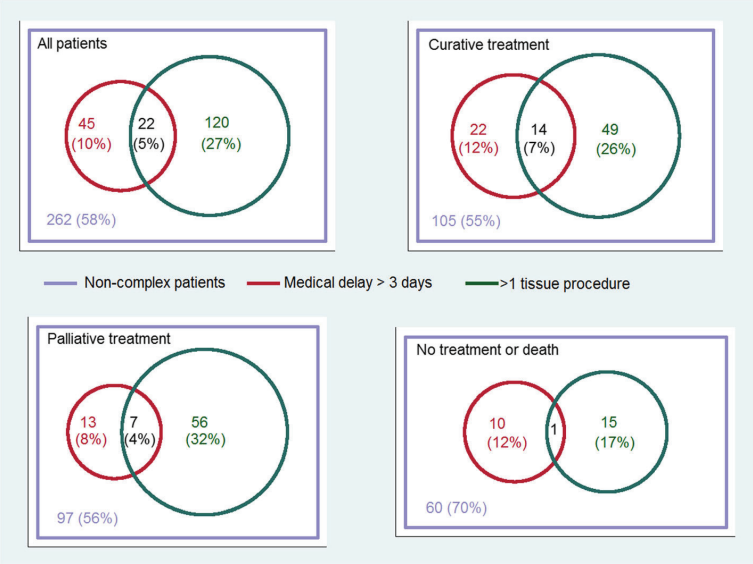

Fig. 1 Proportions of patients with >1 tissue diagnostic procedure and medical delay >3 days. Distribution in the overall population, and split for treatment intention. Complex patients were defined as having >1 tissue diagnostic procedure and/or medical delay of >3 days.

and among those who did not have a PET CT (137, 62%) than patients who underwent PET CT (42, 30%) ($p < 0.0001$) (Fig. 3).

The proportions who received timely treatment did not vary significantly from 2011 until 2013 in the overall population, but the proportion of non-complex patients that started surgery or radiotherapy within 42 days decreased from 2011 ($n = 27$, 75%), until 2012 ($n = 16$, 47%), and 2013 ($n = 25$, 49%) ($p = 0.03$) (Fig. 4).

Median number of days until surgery or radiotherapy was 48 days (range: 5–296) among all patients (non-complex: 41 days (range: 5–145), complex: 59 days (range: 11–296)). Surgery or radiotherapy started within 42 days in 93 (41%) of all patients (non-complex: 68 (56%), complex: 25 (23%)).

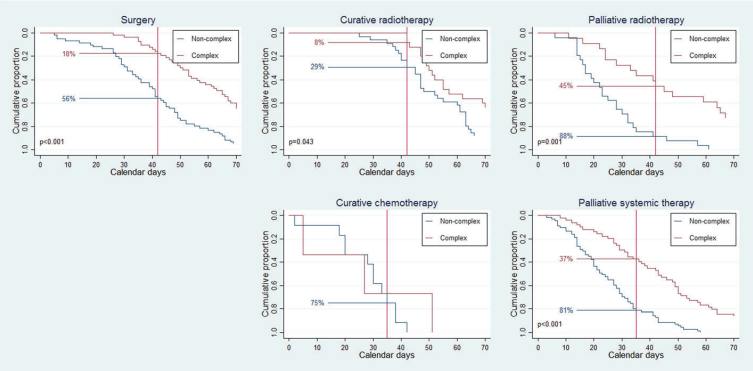

Fig. 2 Timeliness for different treatments, split for complexity. Calendar days from the when the hospital received the referral letter for suspected lung cancer until the different treatments started. Non-complex patients were defined as having ≤1 tissue diagnostic procedure and no medical delay of >3 days, complex patients as having >1 tissue diagnostic procedure and/or medical delay of >3 days. The reference lines refer to the Norwegian recommendations for timely lung cancer treatment, which are 42 days for surgery and radiotherapy, and 35 days for systemic therapy

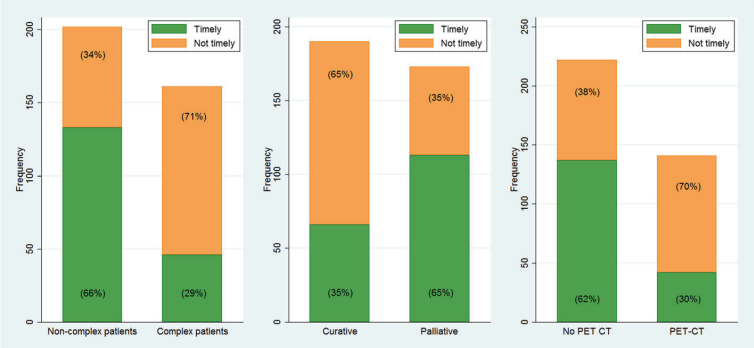

Fig. 3 Proportions that received timely lung cancer treatment. Distributions of timely and not timely treatment in non-complex versus complex, curative versus palliative treatment, and having a PET CT versus no PET CT

Overall, 43 (37%) underwent surgery within 42 days (non-complex: 33 (56%), complex: 10 (18%); $p < 0\text{-}0001$). Corresponding numbers for curative radiotherapy was 12 (20%) (non-complex: 10 (29%), complex 2 (8%); $p = 0.04$); and for palliative radiotherapy 33 (69%) (non-complex: 23 (88%), complex: 10 (45%); $p = 0.001$) (Fig. 2).

Median number of days until systemic therapy was 29 days (range: 2–201) among all patients (non-complex: 25 days (range: 2–58), complex: 43 days (range: 5–201)). Systemic treatment started within 35 days in 86 (64%) of all patients (non-complex: 65 (80%), complex: 21 (39%)). Among those 15 patients with limited disease small-cell lung cancer who received curative chemo-radiotherapy, 12 (80%) were non-complex, and 11 (73%) received timely systemic treatment (thoracic radiotherapy was administered concurrrent with the second chemotherapy-course). Palliative systemic therapy was administered timely in 75 (63%) (non-complex: 56 (81%), complex: 19 (37%); $p < 0.0001$) (Fig. 2).

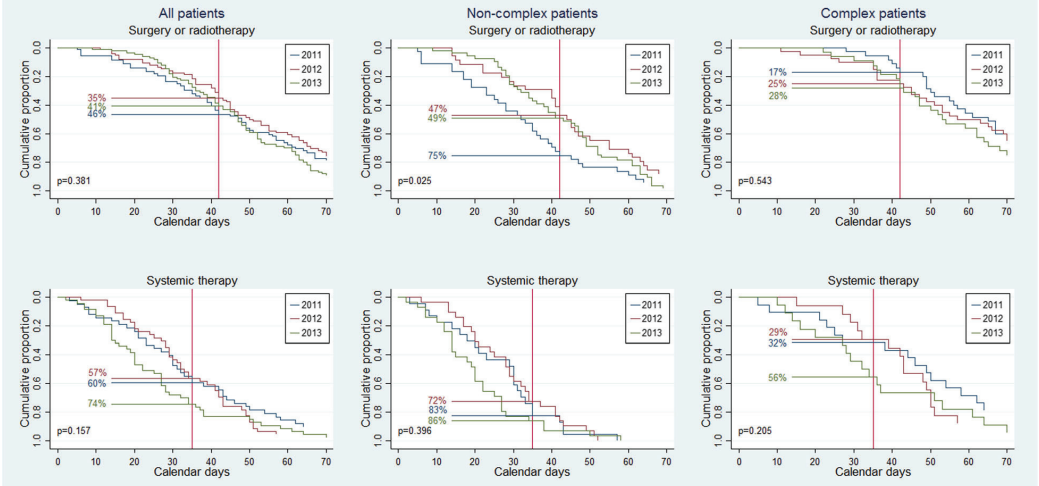

Fig. 4 Time to treatment split for year. Calendar days from the when the hospital received the referral letter for suspected lung cancer until start of treatment. Non-complex patients were defined as having ≤1 tissue diagnostic procedure and no medical delay of >3 days, complex patients as having >1 tissue diagnostic procedure and/or medical delay of >3 days. The reference lines refer to the Norwegian recommendations for timely lung cancer treatment, which are 42 days for surgery and radiotherapy, and 35 days for systemic therapy

Associations of complexity with timely treatment

Multivariate logistic regression analysis adjusted for patient characteristics (age <70/≥70, sex, outpatient/hospitalized), year and tumor characteristics (tissue diagnosis, stage) showed that complex patients were in significant risk of not timely treatment (OR, 0.16; 95% CI, 0.09-0.27). The increased risk remained significant when we adjusted for treatment intention, and whether the patient underwent PET CT or not (OR, 0.15; 95% CI, 0.09–0.26). There was no significant difference in the risk of not timely treatment between patients receiving palliative (reference category) and curative treatment (OR, 0.80; 95% CI, 0.37-1.68); while undergoing PET CT was a significant risk factor (OR, 0.32; 95% CI, 0.17-0.61). There was also no significant difference between patients with NSCLC/other primary lung cancers (reference category), SCLC (OR, 1.05; 95% CI, 0.49-2.28), and no tissue diagnosis (OR, 0.35; 95% CI, 0.12-1.04). The risk of not timely treatment was lower in stage IV than stage I-III patients (OR, 2.72; 95% CI, 1.22-6.06); and lower in hospitalized patiens than outpatients (OR, 2.35; 95% CI, 1.28-4.31).

Discussion

In this cohort of 449 patients diagnosed with lung cancer at a regional cancer center, we found that time to start of treatment exceeded the Norwegian recommendations in 51% of those 363 that started treatment. Overall, timely treatment started in 41% of those who underwent surgery or received radiotherapy, whereas systemic therapy started within the recommended timeframe in 64%. Among the least complex patients, the timeframes where met for those who were offered systemic therapy, but not for those who underwent surgery or radiotherapy.

Interestingly, the proportion who was offered timely sugery or radiotherapy decreased from 2011 until 2013. The reason appears to be significant increase in the use of PET CT for staging of these patients due to changes in guidelines and increasing capacity in Norway. The average time for PET CT was 20 days, and in the multivariate analysis, PET CT was significantly associated with longer timeframes than recommended.

Time to treatment is a commonly used indicator of health care efficiency, but the timeframes vary in different studies and guidelines [16–18, 29]. Most commonly used are the intervals from "day of first abnormal chest image" [9, 30, 31], or "day a referral letter for suspected lung cancer was received" [6] until admission for surgery, the date of surgery, the first fraction of radiotherapy or first day of systemic therapy.

The Danish guidelines recommend that time from receiving a referral letter for suspected lung cancer until start of treatment should be ≤42 days in ≥85% of cases. In a publication from 2013 [32], they reported that the proportions of patients that started treatment within this timeframe were 63.2% ($n = 714$) for surgery, 73.5% ($n = 687$) for radiotherapy and 78.4% ($n = 1660$) for chemotherapy. The key indicator defined by the Swedish Lung Cancer Study Group is the interval from a referral letter for suspected lung cancer is received until a treatment decision is made. The goal is that a decision is made within 28 days in ≥80% of patients. In 2012–14, the goal was met in 47% ($N = 10,369$) [33], while a treatment decision was made within 28 days for 56% of our patients. The National Health Services (NHS) England recommends that patients start treatment within 62 days following an urgent general practitioner (GP) referral in ≥85% of patients. In 2013–14, 78.5% ($N = 12,075$) started treatmentwithin this timeframe [34], while 75% started treatment within 60 days in our cohort. We have not found any documentation of the rationale for the definition of the Norwegian timeframes, though they appear to be quite similar to the Danish – which are based on observations [17].

The results are not necessarily comparable due to varying lung cancer incidence [35], and there are probably differences in the organization of the health care services and availability of PET CT. Still, it appears that the situation at our hospital is similar to what was observed in Sweden and England, whereas time to surgery and radiotherapy is longer at our center than in Denmark.

The mean number of tissue diagnostic procedures was higher in Denmark [36] (1.66 vs. 1.33 in our cohort) - which might explain the higher proportion of patients with confirmed tissue diagnosis (94% vs. 86% in our cohort). The use of PET CT was much lower in our cohort (33%) than in Denmark (62%) [36]. The proportion of patients who received lung cancer treatment (81%) was higher than in Denmark (74%) [36] and England and Wales (60%) [37]. We cannot offer any obvious explanation since the study was not designed to investigate this aspect. Possible reasons include that lung cancer patients are treated in our public health care system that provides equal care for all inhabitants, and that a large proportion of patients in our area live close to the hospital.

No national guidelines recommend that all patients start treatment within the specified timeframe. Thus, it appears to be accepted that the diagnostic workup takes more time in some cases. We are, however, not aware of any studies aiming at quantifying the number of patients that should start treatment within the given timeframes. Some studies have shown that treatment is delayed if a patient has comorbidity [28, 38], or an adequate tissue sample is not obtained at first attempt [24, 25], —supporting our definition of "complex patients". Our definition is

further supported by the large difference in proportions who started timely treatment between non-complex and complex patients. We consider our defintion to be conservative. In our opinion, the health care services are not optimally organized if it takes more than 35 or 42 days to start treatment if only one tissue diagnostic procedure is required to complete diagnostic workup and there are no delays for medical reasons. One might argue that it should be possible to conduct at least two tissue procedures within the recommended timeframes. In our cohort, the results do not change much if such a cut-off value is applied – the proportion of non-complex patients receiving timely treatment changes from 66 to 58%. We have, however, chosen to use the cut-off of one tissue procedure since we presume that it is difficult to argue that this represents a non-complex patient.

The proportion of non-complex was higher among those who did not receive any lung cancer treatment. This has to be interpreted with caution. Many of these patients did not undergo an appropriate diagnostic workup since many were considered ineligible for treatment due to poor performance status or significant comorbidity, or, in some cases, because the patients did not want a complete workup.

The main limitation of our study is the retrospective design, which prohibited a uniform and systematic assessment of medical delays and delays caused by the patients' preferences or no show. Furthermore, this is a single institution study, and not population-based. On the other hand, we are not aware of any other studies of timeliness in diagnostic workup and start of treatment for lung cancer that have assessed diagnostic complexity and medical delays. Our data are based on studies of individual medical records and not registry-based. The population represents consecutive patients diagnosed and treated at a single institution, and the patient characteristics are similar as in other unselected lung cancer polpulations [39].

Overall, the time to treatment was much longer than recommended in our cohort, – even among non-complex patients. Possible explanations include suboptimal organization, failure to comply with guidelines for diagnostic workup, low capacity for key procedures and a general lack of resources. It goes beyond the scope of this first sub-study of our project to perform value stream analyses, but we have collected these data which will be analyzed to better understand how delays can be avoided. The results will be presented in a separate article. Thus, we have currently not evaluated whether the recommended timeframes are feasible or realistic in this first sub-study of our project, but the results might provide valuable information about the proportion of patients who should receive timely lung cancer treatment. Considering that 56% of patients who started treatment were non-complex, using a conservative definition of complexity, the goal of timely treatment in 70% of cases does not appear to be unrealistic.

Conclusion

49% of all lung cancer patients diagnosed at a university hospital started treatment within the official Norwegian timeframes. Among the least complex lung cancer patients, only 66% of patients received timely treatment. The reasons for delays needs to be identified and organization needs to be improved in order to meet the recommended timeframes.

Additional files

Additional file 1: Medical complexity and time to lung cancer treatment. (DTA 38 kb)

Additional file 2: Medical complexity and time to lung cancer treatment. (DO 25 kb)

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Availability of data and materials
The dataset supporting the conclusions of this article is included within the article and Additional files 1 and 2.

Authors' contributions
All autors have approved the manuscript. TS contributed to conception and design, data collection, analyses, and writing of the manuscript. BHG, SS, and TA contributed to conception and design, analyses and writing of the manuscript.

Competing interests
The authors declare that they have no competing interests.

Consent for publication
Not applicable.

Ethics approval and consent to participate
A passive consent procedure was applied. All patients who were alive and had a known address received written information about the study and a form giving them the opportunity to decline participation, and prepaid envelopes for returning the opt-out form. Those who did not decline were included in the analyses. The study was approved by the Regional Committee for Medical and Health Research Ethics West Norway (REK Vest (2014/60)).

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Paper II

REASONS FOR PROLONGED TIME FOR DIAGNOSTIC WORKUP FOR STAGE I-II LUNG CANCER AND ESTIMATED EFFECT OF APPLYING AN OPTIMIZED PATHWAY FOR DIAGNOSTIC PROCEDURES

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DECLARATIONS

Ethics approval and consent to participate

A passive consent procedure was applied. All patients alive received written information about the study and were given the opportunity to decline participation by completing a form and return it in an enclosed, prepaid envelope. The study and the passive consent procedure were approved by the Regional Committee for Medical and Health Research Ethics in Western Norway (REK Vest (2014/60).

Consent for publication

Not applicable

Availability of data and material

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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The first author received a grant from St Olavs hospital for the conduct of this study.

Authors' contributions

TS collected and analyzed the data. BHG and TS were major contributors in writing the manuscript. All authors read and approved the final manuscript

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ABSTRACT

Introduction

Minimizing the time until start of cancer treatment is a political goal. In Norway, the target time for lung cancer is 42 days. The aim of this study was to identify reasons for delays, and estimate the effect on the timelines when applying an optimal diagnostic pathway.

Methods

Retrospective review of medical records of lung cancer patients, with stage I-II at baseline CT, receiving curative treatment (n=100) at a regional cancer center in Norway.

Results

Only 40% started treatment within 42 days. The most important delays were late referral to PET CT (n=27) and exercise test (n=16); repeated diagnostic procedures because bronchoscopy failed (n=15); and need for further investigation after PET CT (n=11). PET CT referral-result took a median 20.5 days. Applying current waiting time for PET CT (≤7 days), 48% would have started treatment within 42 days (p=0.254). "Optimal pathway" was defined as 1) referral to PET CT and exercise test immediately after the CT scan and hospital visit, 2) tumor board discussion to decide diagnostic strategy and treatment, 3) referral to surgery or curative radiotherapy, 4) tissue sampling while waiting to start treatment. Applying the optimal pathway and current waiting time for PET CT, 80% of patients could have started treatment within 42 days (p<0.001), and the number of tissue procedures could have been reduced from 112-92 (16%).

Conclusion

Changing sequence of investigation would significantly reduce the time until start of treatment in curative lung cancer patients at our hospital, and reduce the resources needed.

Keywords

Pathway, timeliness, diagnostic efficacy, organization

INTRODUCTION

Long intervals for completion of diagnostic workup and start of treatment causes distress among cancer patients,[1] and is conceived as a medical risk that may negatively

impact survival.[2-4] Thus, it is a political goal that diagnostic workup for suspected cancer should be performed efficiently and with no delays except those who are due to medical reasons. Consequently, programs for timely care have been developed, e.g. the two-week-wait referral pathway in the UK,[5,6] and the national cancer pathway intervention in Denmark.[7,8]

Diagnostic workup for lung cancer has become complex due to the increasing number of treatment options. More patients are eligible for potentially curative therapy due to less invasive surgery and advanced radiotherapy techniques but require more extensive tissue sampling for correct staging of disease, and targeted therapies are selected according to molecular profiling of tissue samples. Thus, a multidisciplinary approach including sufficient resources for imaging, tissue sampling and analyses is required, necessitating a good organization across departments and health care levels.

In Norway, current national guidelines recommend that a patients' first hospital visit should take place within 7 calendar days after the hospital receives a referral letter for suspected lung cancer; a treatment decision should be made within 28 days; systemic therapy should start within 35 days; and surgery or radiotherapy within 42 days.[9] The timeframes are consensus-based.

There are few studies of the logistics of lung cancer diagnostic work-up, and mechanisms for delays are poorly described.[10] In a previous study, we found that only a minority of lung cancer patients started treatment within the recommended timeframes at our hospital.[11] The aims of this study were to identify reasons for delays, define an optimal pathway for diagnostic procedures, and estimate the effect on the timelines of applying this pathway. Due to the heterogeneity and complexity of lung cancer patients in general, we limited the present study to patients presenting with stage I-II on the base-line CT scan, who were eligible for potentially curative treatment.

MATERIALS AND METHODS

Study setting

St. Olav's Hospital, Trondheim University Hospital, in Trondheim, Norway, is the primary hospital for 380 000 people, the regional cancer center for the Central Norway Health Region with a population of approximately 700 000 people, and the only hospital in the region to offer lung cancer surgery and PET CT (since October 2013).

Lung cancer diagnosis take place at the Department of Thoracic Medicine by pulmonologists specializing in lung cancer diagnosis and treatment, and they also offer systemic therapy; the Cancer Department provides radiotherapy, oncologists are trained in both medical oncology and radiotherapy; and surgery take place in the Department of Cardio-Thoracic Surgery. A tumor board of pulmonologists, thoracic surgeons, oncologists, thoracic radiologists, specialists in nuclear medicine, pathologists and a patient coordinator, meets every week.

Study design, patients and data collection

We performed a retrospective analysis of the individual hospital medical records of all lung cancer patients presenting with stage I-II disease at the baseline CT scan, who were diagnosed at the Department of Thoracic Medicine, and who underwent surgery or curative radiotherapy at St. Olavs hospital between January 1, 2011 until December 31, 2013. More details about the conduct of our study is included in a previous publication.[11] Patients with a delay of ≥3 days caused by comorbidity, intercurrent disease, or the patients' wish were excluded. Stage of disease was assessed according to the 7th edition of the TNM classification of lung cancer.[12]

Exercise tests included stair-climbing test, six-minute walk-test, and cardiopulmonary exercise test.[13] We defined tissue diagnostic method as either bronchoscopy, bronchoscopy and endobronchial ultrasound transbronchial aspiration (EBUS-TBNA), or transthoracic needle biopsy; and that the method “failed” when the diagnosis was confirmed by subsequently using another method, or the patient underwent both bronchoscopy and bronchoscopy with EBUS-TBNA.

We registered a) the date when a referral letter for suspected lung cancer was registered at the Department of Thoracic Medicine, or the date when diagnostic workup for suspected LC was initiated in a patient with a single pulmonary nodule who had been previously observed (“Receiving a referral letter”); b) the date of the first appointment with a pulmonologist (“First consultation”); c) for each diagnostic work-up procedure: c) type of procedure, d) date of referral to the procedure, e) the date it took place, and f) the date when the result of a procedure was documented in the patient’s medical record; g) the date a treatment decision was documented in the patient’s medical record (“Treatment decision”); h) the date of surgery or first day of

radiotherapy or chemotherapy ("Start of treatment"). "Time to treatment" was defined as interval in calendar days from receiving a referral letter for suspected lung cancer until start of treatment; "Timely", ≤ 42 days; "Untimely", >42 days.

Data analysis

The sequences of actions were ordered and intervals in calendar days were calculated: from receiving a referral letter until first consultation; from first consultation until referral for diagnostic work-up procedure(s); from referral to a procedure until the result was available in the electronic medical record; from the result of a procedure until this result was actioned upon (by referral to another procedure or making a treatment decision); from treatment decision until start of treatment.

Models for simulating improvements were built by manipulating the sequence of actions. The numbers who could start timely treatment were compared using logistic regression. Analyses were performed using the Stata/IC 14.2 package for Windows.

RESULTS

Patient characteristics

Four hundred fifty-four patients were diagnosed with lung cancer between January 1, 2011 and December 31, 2013. Five patients declined inclusion,[11] and among the other 449 patients, 150 presented with preliminary stage I or II. Twenty-six patients were excluded since they were ineligible for curative treatment; and another 24 were excluded because they experienced delays of ≥3 days due to medical reasons or patient's whish (Figure 1). Thus, 100 patients were included in the present analyses. Median age was 70 (54-84), 77% had NSCLC, and 63% were women (Table 1).

Table 1 Baseline characteristics	Included N=100	Unplanned delay n=24	Ineligible of curative treatment n=26
Median age (range)	70 (54-84)	70.5 (56-86)	81 (58-89)
Age ≥75 years	32 (32%)	9 (38%)	19 (73%)
Women	63 (63%)	12 (50%)	13 (50%)
Stage I	72 (72%)	16 (67%)	10 (38%)
Stage II	20 (20%)	7 (29%)	8 (31%)
Stage III	8 (8%)	1 (4%)	3 (12%)
Stage IV			5 (19%)
Surgery	76 (76%)	15 (63%)	
Curative radiotherapy*	8 (8%)	1 (4%)	
Stereotactic radiotherapy**	16 (16%)	8 (33%)	
Palliative treatment			12 (46%)
NSCLC	77 (77%)	18 (75%)	11 (42%)
SCLC	6 (6%)	1 (4%)	2 (8%)
Another primary lung cancer	5 (5%)	1 (4%)	1 (4%)
No tissue diagnosis	12 (12%)	4 (17%)	12 (46%)

* Includes chemo-radiotherapy in limited disease SCLC

** In T1-2N0 NSCLC

Causes for delayed treatment

We found several factors that led to delayed start of treatment. We have presented the actual pathway for three patients in Figure 2 to illustrate some of the most common causes for delay. The most important causes for delay were:

1) CT of the chest and upper abdomen was not done before after the first hospital visit (n=8, median of 15.5 days later, range: 2-98 days), or the radiology report was not

completed when the first hospital visit took place (n=39, median 2 days later, range: 1-55 days).

2) Patients were not referred to a PET CT at the first consultation (n=27, median of 8 days later, range: 1-36 days), partly because the radiology report of the CT scan was not available. In total, 60 patients had a PET CT.

3) Patients were not referred for an exercise test at the first hospital visit (n=16, median of 10 days later, range: 2-28 days). In total, 21 patients underwent exercise testing.

4) Patients underwent subsequent tissue procedures because an attempt of sampling tumor through bronchoscopy failed when a transthoracic CT guided biopsy was the method that produced a diagnosis (n=15).

5) Need for additional diagnostic procedures due to findings on PET CT (n=12; FDG upload in mediastinal lymph nodes (n=3), the thyroid gland (n=2), parotid gland (n=1), pharynx (n=1), small intestine (n=1), colon (n=2), heart (n=1), and genitals (n=1)).

6) Incomplete investigation before the patient was discussed at the tumor board (10 patients were referred to PET CT, and 6 to exercise testing). Thus, the treatment decision was delayed (n=16).

7) Interval from the hospital received a referral letter until the first hospital appointment exceeded seven days for unexplained reasons (n=50). Of these, 18 patients waited 14 days or more.

8) Long waiting time for PET CT. When the study was conducted, patients had to be referred to other hospitals for PET CT, and the median time until the PET CT reports were available was 20.5 days (range: 7-49). A PET CT scanner was installed in our hospital in October 2013, and the current waiting time is now seven days or less.

9) Long waiting time from a tissue sampling procedure took place until the pathology report was completed (median of 4.5 days, range: 0-14 days). Furthermore, patients were routinely given an appointment for information about the pathology report 1-2 weeks after the tissue sampling procedure, which caused further delays when the sampling was unsuccessful.

10) Other important delays occurred due to waiting time for cardiopulmonary exercise testing (median of 11 days, range: 1-19 days); and waiting time for a second tissue sampling procedure (median of 8 days, range: 1-14 days).

11) The median interval from referral to treatment until surgery was 13 days (range: 4-48 days), and until radiotherapy 22.5 days (range: 6-37 days).

We also found that two patients were medically operable but received chemo-radiotherapy due to SCLC. In all other patients, there was a medical reason when radiotherapy was chosen instead of surgery.

Time to treatment

The median time to treatment was 46.5 days (5-145), and 40% (95% CI: 31% to 50%) of patients started treatment within the recommended 42 days.

When applying the current waiting time for PET CT (≤7 days), the proportion of patients who could have started timely treatment increased to 48% (95% CI: 39% to 58%) (p=0.255).

Based on our analyses, we defined the following optimal pathway (Figure 3):

1) If a CT of the chest and upper abdomen is not performed before, it should take zero days from a referral letter is received until referral for a CT scan.

2) In patients who are considered fit for curative treatment, it should take zero days from the first consultation until referral to PET CT.

3) In patients with reduced pulmonary function it should take zero days from the first consultation until referral for exercise testing.

4) Patients should be discussed at a tumor board meeting immediately after completion of exercise tests and PET CT to a) decide how tissue sampling for both diagnostic and staging purposes should be performed; b) make a treatment decision.

5) It should take zero days from the tumor board meeting until referral to a procedure using a method that is suitable for simultaneous diagnosis and staging.

6) It should take zero days from the tumor board meeting until referral to treatment.

Applying this optimal pathway and current waiting time for PET CT (≤7 days), the proportion of patients who could start treatment within 42 days would increase to 80% (95% CI: 72% to 87%) (p<0.001) (Figure 4), and the number of tissue sampling procedures would have been reduced with 16% (from 112 to 92 procedures).

DISCUSSION

We have previously found that few lung cancer patients started treatment within the recommended national timeframes at our hospital.[11] In the present study, we analyzed the individual patients' pathways in order to investigate the reasons for delay, including patients who presented with stage I-II disease on the baseline CT scan who received curative treatment. We found that only 40% of patients started treatment within the recommended timeframe in Norway of 42 days, and suboptimal planning was an important explanation for this. Specifically, the main reasons were that patients were referred to a PET CT late during the diagnostic workup, leading to unnecessary delay and sequential procedures; the optimal method for tissue sampling was not chosen first, leading to repetition of procedures; and exercise tests were not performed before the patient was discussed at the tumor board meeting, leading to delayed treatment decision. There were long waiting times for PET CT during the study period, but when applying current waiting time for PET CT (≤7 days), the proportion of patients who could start treatment within 42 days only increased to 48%. Based on our analyses, we defined a more optimal sequence of actions. By applying this optimal pathway and current waiting time for PET CT, the proportion of patients who would have started treatment within 42 days increased to 80% and the number of diagnostic procedures would have decreased with 16%. Thus, implementing a more optimal pathway could improve timeliness of treatment and save resources.

Several interventions aiming at improving the timeliness of diagnostic workup and start of treatment have been proposed - including care pathways; patient navigators; fast-track programs; and different multidisciplinary decision making procedures.[14] Some studies indicate that such interventions may lead to improvement, but most include allocation of more resources and the exact mechanisms leading to improvement are poorly described.[15-24] Some have investigated the impact of different medical approaches. In a randomized trial of patients with suspected stage I-IIIA lung cancer, performing endobronchial ultrasound transbronchial needle aspiration (EBUS-TBNA) as the first procedure led to fewer procedures and shorter time until a treatment decision was made when compared to bronchoscopy or a transbronchial needle biopsy as the first procedure.[25] Similarly, a prospective study of tumors that based on chest CT were accessible to EBUS-TBNA showed that EBUS-TBNA improved the diagnostic yield

when compared to bronchoscopy and transbronchial biopsy.[26] Several studies have shown that delays occur and if the first tissue procedure fails,[27-29] complications and costs increases,[30] suggesting that procedure for collection of tissue samples should be discussed at a multidisciplinary tumor board.[31]

There are several limitations to our study. It is a single-center study and the mechanisms for delay may not necessarily be relevant for other hospitals or other health care systems. E.g. the health care system in Norway is public, and the PET CT availability may have been more limited during the study period than in otherwise comparable health care systems. Furthermore, we decided to limit our study to stage I-II patients due to the complexity and heterogeneity of patients with more advanced stage.

We are not aware of any internationally accepted definition of an optimal pathway for diagnostic workup for lung cancer. Our definition is only based on what we consider most time-effective and may be questioned. Unsuspected endobronchial involvement occurs, and one can argue that a bronchoscopy should be one of the first diagnostic procedures when lung cancer is suspected.[32,33] Furthermore, it is not always obvious which method for tissue sampling that has a highest chance of success, and bronchoscopy entails less risk of complications than a CT guided transthoracic biopsy.

Norwegian guidelines are not explicit on whether PET CT should be done before or after a diagnosis has been confirmed.[9] Access to PET CT is limited, and many patients have to travel long distances for a PET CT. But if reducing time to treatment is the highest priority, our data strongly indicate that a PET CT should be performed as soon as possible after the CT scan in preliminary stage I-II.

Referring patients for treatment before all procedures have been completed may be more controversial. In our cohort, the treatment plan changed in only 2% of cases after PET CT, but will still cause cancellations of planned treatment, which requires good administrative systems to fully utilize the capacity in operating theatres and radiotherapy departments. Finally, the impact on timelines of applying our optimal pathway is simulated and not validated in an intervention trial.

The main strength of our study is that we have performed a comprehensive review of the individual patients' trajectories from the individual medical records. Most other studies investigating timeliness of lung cancer care, utilize registry data and investigate associations between demographic data, hospital and patient characteristics

with timelines.[10,34-41] Our study group is multidisciplinary (pulmonologists, an oncologist and a gynecologist not involved in diagnosis or treatment of lung cancer), and there were few changes in the staff of pulmonologists who worked at our hospital during the study period.

We believe that our study strongly suggests that the time until start of treatment can be greatly reduced by analyzing current pathways for diagnostic workup and applying a more rational pathway without adding more resources. Furthermore, the number of diagnostic procedures would have been reduced if the optimal pathway had been applied. Still, time until treatment would have been further reduced if waiting time for radiology- and pathology reports, exercise testing, surgery and radiotherapy were shortened.

The most common role of tumor board meetings seems to be to discuss treatment alternatives, and thus facilitate a fast and correct treatment.[22,42] Our study indicate that the patients can in most cases be referred for treatment while the tissue procedures are being performed since the treatment recommendation will change in very few. The tumor board might also play a role in selecting the most correct diagnostic procedures, suggesting that patients should be discussed by a tumor board after the initial imaging and physical examinations have been performed. It is possible, though, that applying our pathway including the early discussion at a tumor board and early referral for treatment is only applicable at larger hospitals.

In conclusion, we found that only 40% of preliminary stage I-II lung cancer patients started treatment within the recommended 42 days at our hospital. When applying the current waiting time for PET CT (≤7 days), the proportion increased to 48%. If also a more optimal pathway had been applied, the proportion could increase to 80% and the number of diagnostic procedures could be reduced with 16%.

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Figure legends

Figure 1.

Patient selection. Preliminary stage was defined as TNM stage according to the baseline CT scan.

Figure 2.

Patient cases demonstrating some common reasons why treatment was delayed: several procedures were performed when it was evident that the last procedure was most likely to succeed (Case 1); a late PET CT revealed lesions that caused sequential diagnostic procedures (Case 2); unnecessary delays because the pathology reports were not acted upon (and the patients were not informed) until several days after they were completed (Case 1, marked with a stapled line); late referral to PET CT and cardiopulmonary exercise testing (Case 3); long waiting time for pathology report (Case 2 and 3), PET CT (Case 2 and 3), and cardiopulmonary exercise testing (Case 3); and long waiting time for treatment (Case 1).

Figure 3.

A) reasons for delays in preliminary stage I-II lung cancer patients who received curative treatment: patients were referred to a PET CT late during the diagnostic workup, leading to unnecessary delay and sequential procedures; the optimal method for tissue sampling was not chosen first, leading to repetition of procedures; and exercise tests were not performed before the patient was discussed at the tumor board meeting, leading to delayed treatment decision.

B) our suggestions for a more efficient diagnostic work-up: referral to PET CT (and exercise testing when in doubt) immediately after it was clear that the patient could be eligible of curative treatment; a tumor board meeting to discuss tissue procedures both for diagnostic and staging purposes immediately after having the result of PET CT and exercise testing; to save time, patients could be referred for treatment at the same time, because the treatment plan would change in very few (2% in our cohort) after this point.

Figure 4.

Time to treatment in calendar days from receiving a referral letter for suspected lung cancer in lung cancer patients with stage I-II on the baseline CT scan and who received

curative treatment. A) observed timelines; B) estimated timelines when applying current waiting time for PET CT (≤ 7 days); C) estimated timelines when applying a better sequence of actions and current waiting times for PET CT. The reference line at 42 days refer to the Norwegian Guidelines for timely lung cancer treatment.

Figure 1

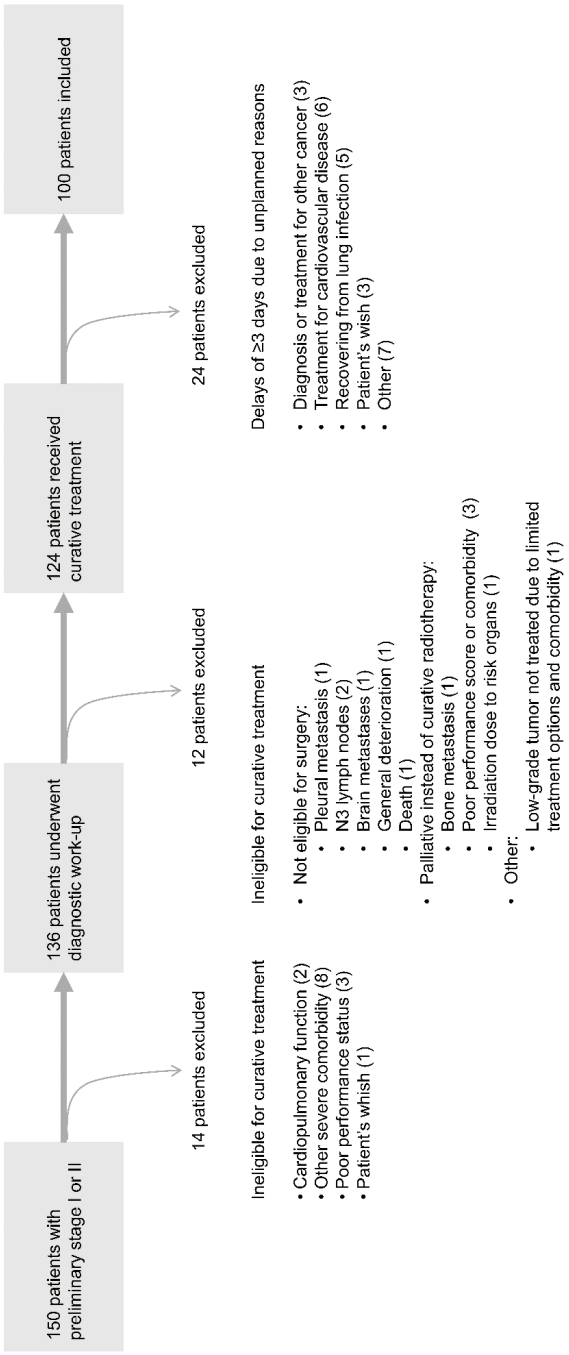

150 patients with preliminary stage I or II
14 patients excluded
Ineligible for curative treatment
• Cardiopulmonary function (2)
• Other severe comorbidity (8)
• Poor performance status (3)
• Patient's whish (1)
136 patients underwent diagnostic work-up
12 patients excluded
Ineligible for curative treatment
• Not eligible for surgery:
• Pleural metastasis (1)
• N3 lymph nodes (2)
• Brain metastases (1)
• General deterioration (1)
• Death (1)
• Palliative instead of curative radiotherapy:
• Bone metastasis (1)
• Poor performance score or comorbidity (3)
• Irradiation dose to risk organs (1)
• Other:
• Low-grade tumor not treated due to limited treatment options and comorbidity (1)
124 patients received curative treatment
24 patients excluded
Delays of ≥3 days due to unplanned reasons
• Diagnosis or treatment for other cancer (3)
• Treatment for cardiovascular disease (6)
• Recovering from lung infection (5)
• Patient's wish (3)
• Other (7)
100 patients included

Figure 2

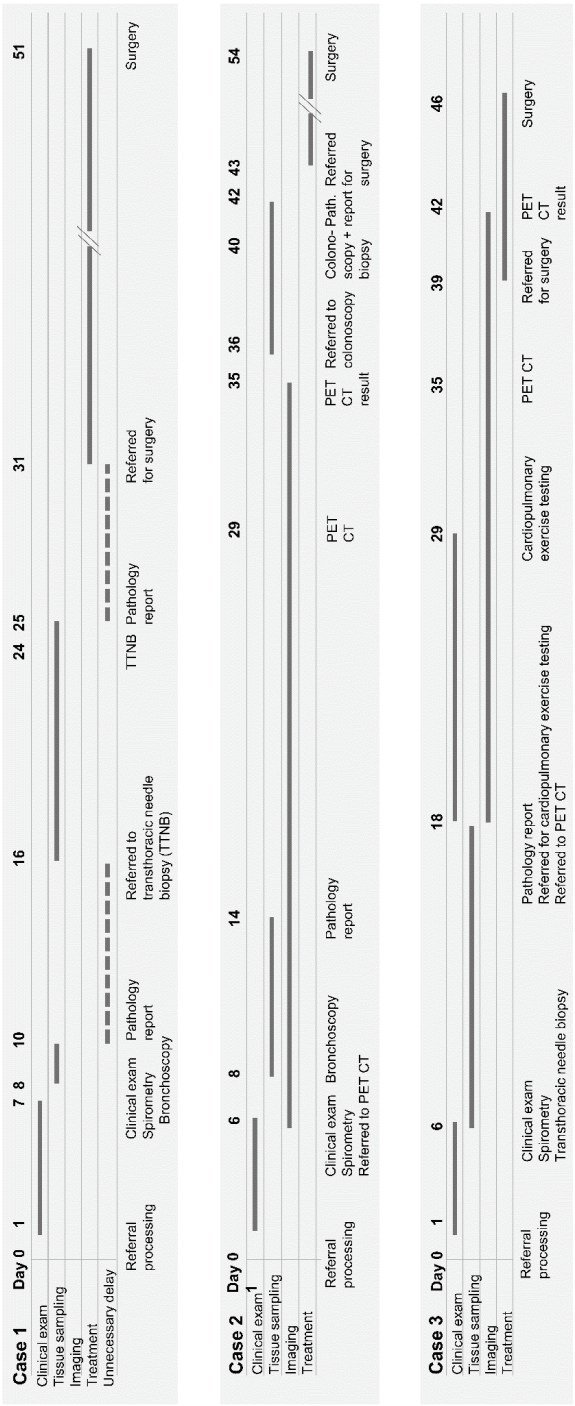

Case 1
Day 0
1
7 8
10
16
24 25
31
51
Clinical exam
Tissue sampling
Imaging
Treatment
Unnecessary delay
Referral processing
Clinical exam
Spirometry
Bronchoscopy
Pathology report
Referred to transthoracic needle biopsy (TTNB)
TTNB
Pathology report
Referred for surgery
Surgery
Case 2
Day 0
1
6
8
14
29
35
36
40
42
43
54
Clinical exam
Tissue sampling
Imaging
Treatment
Referral processing
Clinical exam
Spirometry
Referred to PET CT
Bronchoscopy
Pathology report
PET CT
PET CT result
Referred to colonoscopy
Colono-scopy + biopsy
Path. report
Referred for surgery
Surgery
Case 3
Day 0
1
6
18
29
35
39
42
46
Clinical exam
Tissue sampling
Imaging
Treatment
Referral processing
Clinical exam
Spirometry
Transthoracic needle biopsy
Pathology report
Referred for cardiopulmonary exercise testing
Referred to PET CT
Cardiopulmonary exercise testing
PET CT
Referred for surgery
PET CT result
Surgery

Figure 3

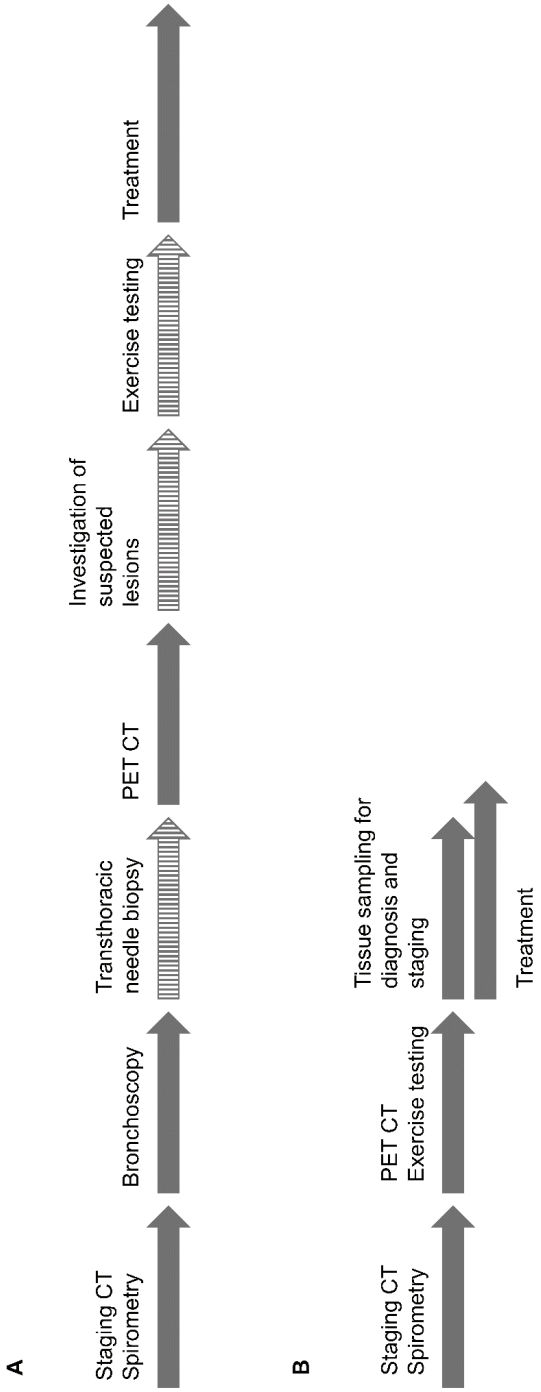
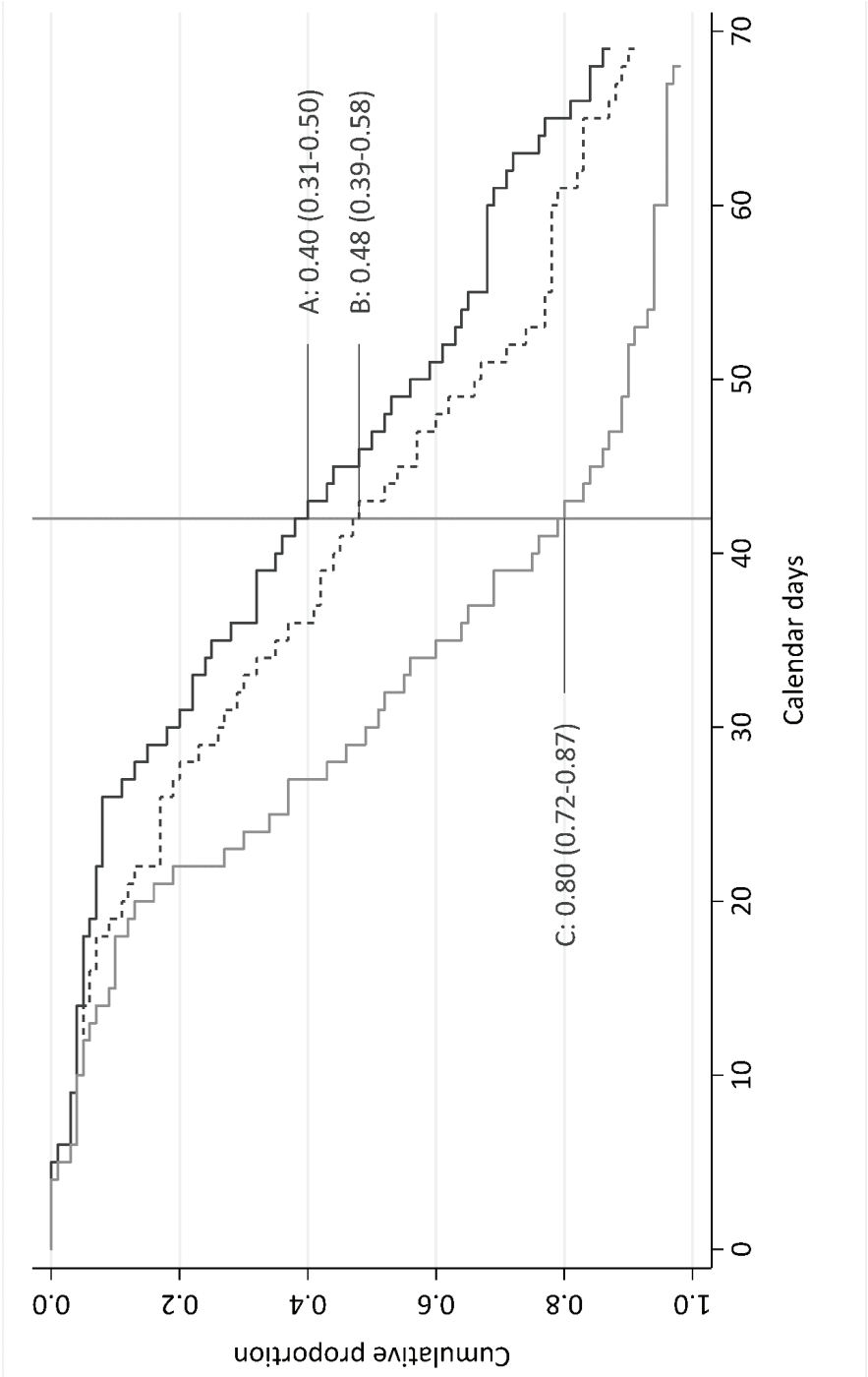

A
Staging CT
Spirometry
Bronchoscopy
Transthoracic
needle biopsy
PET CT
Investigation of
suspected
lesions
Exercise testing
Treatment
B
Staging CT
Spirometry
PET CT
Exercise testing
Tissue sampling for
diagnosis and
staging
Treatment

Figure 4


A: 0.40 (0.31-0.50)
B: 0.48 (0.39-0.58)
C: 0.80 (0.72-0.87)
Cumulative proportion
0.0
0.2
0.4
0.6
0.8
1.0
Calendar days
0
10
20
30
40
50
60
70

Paper III

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