POSTOPERATIVE PAIN FOLLOWING LUNG CANCER SURGERY - RISK FACTORS AND RECOVERY

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BY
ALLAN VESTERGAARD DANIELSEN

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AALBORG UNIVERSITY
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PhD Thesis 2024

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ENGLISH SUMMARY

Chronic post-thoracotomy pain (CPTP) is common after thoracic surgery with a reported prevalence ranging from 25-60%. A considerable proportion of patients suffering from CPTP endure prolonged and even permanent negative effects of CPTP with many facing a significant negative impact on life quality and long-term limitations in activities of daily life (ADL).

Identification of potential risk factors for CPTP is of particular interest, as it may facilitate implementation and development of new preventive and alleviating measures. Precise risk stratification could potentially pave the way for personalized and tailored treatment strategies based on individual risk profiles. In addition, in-depth comprehension of dynamic postoperative recovery patterns may enable early identification of unfavorable recovery paths and facilitate prompt intervention to alleviate and avert the consequences of CPTP.

The aims of this PhD study were 1) to investigate possible predictors of CPTP including quantitative sensory testing (QST) and screening for anxiety and depression symptoms; 2) to characterize and investigate dynamic pain recovery patterns and 3) evaluate and track pain-related limitations in daily activities after surgery for lung cancer. The hypotheses were 1) that physiological pain inhibitory and facilitating mechanisms, and the severity of anxiety and depression symptoms, were associated with development of CPTP, 2) that patients developing CPTP followed a distinct unfavorable recovery trajectory compared to pain-free patients, and 3) that CPTP was associated with significant limitations in ADL.

This dissertation is based on three separate papers (Paper I-III) from an observational cohort study with repeated assessments of pain symptoms and ADL limitations. Participants underwent preoperative quantitative sensory testing (QST) and psychological screening by Hospital Anxiety and Depression Scale (HADS). Repeated assessments were conducted with bi-weekly pain surveys and bi-monthly ADL assessments to obtain detailed data on the temporal evolvement of recovery paths after lung cancer surgery.

Paper I contains exploratory analyses of potential predictors of CPTP and included baseline characteristics, preoperative QST assessment, and HADS. No associations were observed for QST parameters and HADS, while preoperative pain and maximum acute postoperative pain were associated with CPTP six months after surgery.

In Paper II, pain recovery trajectories were investigated, and three distinct recovery trajectories were identified: Patients following the first trajectory achieved full recovery within two to three months. Another group of patients, following the second trajectory, exhibited protracted recovery and achieved remission only towards the end of follow-up. Finally, a group of patients with incomplete recovery followed a third trajectory with constant pain throughout the entire follow-up period.

Younger age was associated with a protracted recovery trajectory, and acute postoperative pain was associated with incomplete recovery.

The impact of CPTP on ADL recovery patterns was investigated in Paper III. Reported postoperative pain was generally of mild intensity but still resulted in significant and persistent pain-related ADL limitations across several daily activities.

The dissertation specifically focused on recovery after lung cancer surgery and offers detailed insights into recovery paths and consequences of chronic post-thoracotomy pain. With frequent repeated assessments during a 12-month follow-up this work also adds to the ongoing and expanding studies of risk factors, recovery paths, and impact of postsurgical pain in general.

DANSK RESUME

Kroniske smerter efter torakotomi (*chronic post-thoracotomy pain, CPTP)* er hyppige efter lungekræftkirurgi med rapporterede forekomster på 25-60%. En betydelig andel af opererede lungekræftpatienter med CPTP lever med langvarige men og gener, og opnår aldrig fuld bedring. De vedvarende smerter har en udpræget negativ indvirkning på livskvalitet og mange patienter kæmper med betydelige begrænsninger i hverdagsaktiviteter og -gøremål.

Undersøgelsen af mulige risikofaktorer for kroniske postoperative smerter er interessant, da dette kan medføre, at man med større sikkerhed kan udpege patienter i særlig risiko for at udvikle CPTP. Denne viden kan potentielt muliggøre igangsættelse af forebyggende og lindrende behandlingstiltag, skræddersyet ud fra en individuel risikoprofil. Udover en karakteristik af perioperative risikofaktorer, kan en præcis og dynamisk karakteristik af det postoperative rekonvalescensforløb muligvis også bibringe brugbar klinisk information, så man igen kan sætte tidligt ind med behandling til de patienter som udviser ugunstige smerteforløb og/eller manglende bedring, og forhindre udviklingen af langvarige og kroniske postoperative smerter.

Formålet med dette ph.d.-studium var 1) at undersøge om mulige prædiktorer for kroniske smerter efter lungekræftkirurgi, målt med kvantitativ sensorisk testning (quantitative sensory testing, QST) og screening for angst- og depressionssymptomer med Hospital Anxiety and Depression Scale (HADS), medfører øget risiko for CPTP, og 2) at karakterisere og undersøge forskelle i smerteforløb, og 3) smertebetingede begrænsninger i dagligdagsaktiviteter efter lungekræftkirurgi. Hypoteserne var, 1) at fysiologiske smerteinhibitoriske og -faciliterende mekanismer, samt sværhedsgraden af angst- og depressionssymptomer, er associeret med udviklingen af kroniske postoperative smerter, og 2) at patienter, der udvikler kroniske smerter, har et mindre gunstigt rekonvalenscensforløb sammenlignet med patienter uden vedvarende smerter, og 3) at kroniske postoperative smerter afstedkommer betydelige funktionsbegrænsninger i hverdagsaktiviteter.

Afhandlingen tager udgangspunkt i tre separate videnskabelige artikler. Disse artikler er er baseret på et observationsstudium af en kohorte af lungekræftpatienter, som blev fulgt i 12 måneder efter operation. Deltagerne i studiet fik foretaget en præoperativ QST-undersøgelse og screening for angst- og depressionssymptomer. Efter operation og udskrivelse, blev der foretaget gentagen opfølgning med registrering af postoperative smerter, hver anden uge, samt smerterelaterede funktionsbegrænsninger hver anden måned.

Første artikel indeholder en undersøgelse af potentielle prædiktorer for kroniske postoperative smerter efter lungekirurgi, og omfatter parametre fra en præoperativ QST-vurdering og HADS. Vi fandt, at tilstedeværelse af præoperative smerter samt intensiteten af akutte postoperative smerter var associeret med kroniske postoperative smerter seks måneder efter operationen.

Anden artikel beskriver rekonvalescensforløb med hensyn til postoperative smerter efter lungekræftkirurgi. Tre distinkte rekonvalescensforløb kunne karakteriseres baseret på en tæt 12-måneders opfølgning. En gruppe kom sig fuldstændigt efter cirka tre måneder, en anden gruppe havde et protraheret forløb med langsomt aftagende men milde smerter. Den sidste gruppe havde vedvarende milde til moderate smerter gennem hele opfølgningsperioden uden betydende bedring efter 12 måneder. Lavere alder var associeret med et protraheret smerteforløb, mens højere intensitet af akutte postoperative smerter var associeret med manglende bedring.

Den tredje artikel indeholder en karakteristik af smerterelaterede begrænsninger i dagligdagsaktiviteter op til 12 måneder efter lungekræftkirurgi. Selv milde postoperative smerter forårsagede funktionsbegrænsninger i hverdagsgøremål. De patienter der angav kroniske postoperative smerter, rapporterede betydeligt flere og vedvarende funktionsbegrænsninger, sammenlignet med smertefrie patienter.

Denne Ph.d.-afhandling er et bidrag til den eksisterende og igangværende forskning i risikofaktorer og smerteforløb i forhold til kroniske postoperative smerter, med et specifikt fokus på lungekræftkirurgien. Studierne er baseret på en kohorte af lungekræftpatienter som er fulgt gentagne gange de første 12 måneder efter kirurgi. Afhandlingen, inklusiv de tre videnskabelige artikler, bidrager med detaljerede karakteristikker af rekonvalescensforløb efter lungekræftkirurgi og indeholder desuden resultater fra en eksplorativ undersøgelse af præoperative risikofaktorer.

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The work forming the foundation of this dissertation was commenced in 2014 with the conceivement of the PainTrack project by Lars Arendt-Nielsen, Jan Jesper Andreasen, Kristian Kjær-Staal Petersen, Birthe Dinesen and John Hansen, as a collaboration between the Department of Health Science and Technology and the Department of Clinical Medicine at Aalborg University and the Department of Cardio-thoracic Surgery at Aalborg University Hospital. From April 2014 to September 2018, patients were included by Anita Tracey, Dorte Nøhr and Carsten Simonsen, and the study database was designed and compiled by them and John Hansen.

This dissertation and the research Papers presented originates from an extensive cooperation with my coauthors and supervisors. I wish to thank Lars-Arendt Nielsen and Jan Jesper Andreasen, who both acted as principal supervisors in turn, and Kristian Kjær-Staal Petersen, for their expertise, critical inputs, and constructive criticism during the entire process. I also highly appreciate the important contributions by Birthe Dinesen, John Hansen and Carsten Simonsen, which also included providing the raw data and trusting me with the database. Furthermore, Jannie Bisgaard and Kirsten Duch have been of magnificent assistance in the statistical analyses, data interpretation and proof-reading during the writing process of the papers.

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My journey as a PhD student began in the autumn of 2019, through the pandemic, commencement of specialty training and an evolving family life. Through periods of leave, part-time enrolment, many late nights and long days, this dissertation is now submitted. I am truly grateful for the understanding patience and flexibility, and financial and professional support given to me on this journey.

Allan Danielsen
June 2024

LIST OF ABBREVIATIONS

ADL: Activities of daily life

COSMIN: Consensus-based standards for the selection of health measurement instruments

CPM: Conditioned pain modulation

PPSP: Chronic post-surgical pain

CPTP: Chronic post-thoracotomy pain

ERAS: Enhanced recovery after surgery

GBTM: Group-based trajectory modelling

HADS: Hospital anxiety and depression scale

IASP: International Association for the Study of Pain

ICD-11: International Classification of diseases 11th edition

IMMPACT: Initiative on methods, measurement, and pain assessment in clinical trials

NPSI: Neuropathic pain symptom inventory

NRS: Numeric rating scale

NSAID: Non-steroid anti-inflammatory drugs

PDT: Pain detection threshold

POD: Postoperative day

PPSP: Persistent postsurgical pain

PROM: Patient-reported outcome measure

PROSPECT: Procedure specific postoperative pain management

PTT: Pain tolerance threshold

QST: Quantitative sensory testing

TSP: Temporal summation of pain

VAS: Visual analog scale

VATS: Video-assisted thoracoscopic surgery

SCIENTIFIC PAPERS

This PhD dissertation is based on the listed scientific Papers below, referred to by their roman numerals in the text as follows:

I. Danielsen AV, Andreasen JJ, Dinesen B, Hansen J, Petersen KK, Simonsen C, Arendt-Nielsen L. **Chronic post-thoracotomy pain after lung cancer surgery: a prospective study of preoperative risk factors**. Scandinavian Journal of Pain. 2023;29(3):501-510. doi:10.1515/sjpain-2023-0016

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Danielsen AV, Andreasen JJ, Dinesen B, Hansen J, Petersen KK, Simonsen C, Arendt-Nielsen L. **Corrigendum to "Chronic post-thoracotomy pain after lung cancer surgery: a prospective study of preoperative risk factors"** Scandinavian Journal of Pain. Scand J Pain. 2024 Apr 29;24(1). doi: 10.1515/sjpain-2024-0021

II. Danielsen AV, Andreasen JJ, Dinesen B, Hansen J, Petersen KK, Duch KS, Bisgaard J, Simonsen C, Arendt-Nielsen. **Pain trajectories and neuropathic pain symptoms following lung cancer surgery: a prospective cohort study.** European Journal of Pain. Eur J Pain. 2024 Mar 25. doi: 10.1002/ejp.2265. Online ahead of print

III. Danielsen AV, Andreasen JJ, Dinesen B, Hansen J, Petersen, Duch KS, KK, Simonsen C, Arendt-Nielsen L. **Pain-related impairment and functional recovery in daily activities after lung cancer surgery: A 1-year prospective cohort study.** Submitted to European Journal of Pain

TABLE OF FIGURES

FIGURES

TABLES

TABLE OF CONTENTS

CHAPTER 1. INTRODUCTION

1.1. PERSISTENT POSTSURGICAL PAIN

Chronic postsurgical pain is common within most surgical domains, with reported incidences ranging from 15% to 60% [1,2]. It is generally characterized as pain related to the operation area that endures after normal tissue healing, typically extending beyond two to three months after surgery[3]. Recently, the International Association for the Study of Pain (IASP) provided a definition in connection with the incorporation of chronic postsurgical pain as a specific diagnosis in the 11th edition of the International Classification of Diseases (ICD-11). The purpose was to enable an universal classification and differentiate between various chronic pain conditions based on their clinical features and etiology, thereby facilitating both research, clinical management and recognition of chronic postsurgical pain as a condition in itself[4,5]. The definition of now states that any novel pain occurring in relation to the surgical site qualifies as chronic postsurgical pain if it persists or recurs three months or more after the procedure[5].

In this dissertation and the associated papers, the term persistent postsurgical pain (PPSP) is used instead of chronic postsurgical pain. This is because the exact time criterion of three months is not always fulfilled since we include two-month data, and the focus evolves around the dynamic development of chronic pain after surgery from the earliest postoperative weeks and up to 12 months.

Extensive research has been conducted on the transition from acute postoperative pain to PPSP and chronic pain in an endeavor to understand and ultimately prevent chronification of postoperative pain[2,6–11]. Investigations into various risk factors associated with PPSP, including physiological pain mechanisms evaluated through quantitative sensory testing (QST)[12], and psychological factors[13,14], have been conducted extensively and ongoing research continuously delve into the exploration of potential novel risk factors and the field of genetic predictors is evolving rapidly[15].

With the introduction of Enhanced Recovery After Surgery (ERAS) protocols and preemptive analgesia, the attention on risk factors and recovery trajectories has heightened, emphasizing the clinical potential as parameters in risk stratification models and possible targets for focused and individualized intervention to optimize postoperative recovery, including long-term PPSP outcomes[11,16–20].

1.2. CHRONIC POST-THORACOTOMY PAIN

Surgery involving the chest wall, e.g. breast, cardiac and thoracic surgery is considered as high risk surgery in relation to the risk of developing PPSP with incidences ranging from 30 to 80%[1,2,5], depending on evaluation time and pain

intensity cutoffs. Chronic pain after thoracic surgery has been extensively documented and is often referred to as post-thoracotomy pain syndrome or chronic post-thoracotomy pain (CPTP)[21]. This dissertation specifically addresses CPTP following lung cancer surgery. The definition of CPTP used is synonymous with PPSP in general terms, i.e., postoperative pain of any intensity lasting more than two to three months after normal tissue healing[22].

The reported incidence of CPTP varies from approximately 25 to 60% in patients undergoing thoracic surgery by either open thoracotomy or Video-assisted thoracoscopic surgery (VATS) [21,23–33]. Possible risk factors for CPTP have already been subject to prior investigations, and existing evidence consistently indicates that acute postoperative pain and preexisting pain conditions are associated with CPTP[34]. However, current reports are inconsistent regarding other suggested predictors of CPTP in thoracic surgery, such as QST and psychological factors[30,34–39]. Lastly, most existing studies evaluate CPTP outcome based on a single assessment at single timepoint, offering only limited information about temporal changes in recovery, and the consequences of CPTP over time.

1.3. THE CONCEPTS OF THIS DISSERTATION

The purpose of this dissertation is to provide an exploratory investigation of central aspects in relation to the development of CPTP. It presents an integration of findings from exploratory studies of risk factors, pain recovery trajectories, and functional outcomes, in a cohort of patients undergoing surgery for lung cancer. The dissertation contains 1) an investigation of preoperative risk factors for CPTP (Paper I), together with 2) a 12-month trajectory-based analysis of pain recovery (Paper II), and 3) an evaluation of pain-related limitations in activities of daily life (ADL) (Paper III). An overview of the dissertation and adjoining Papers is shown in Figure 1.1.

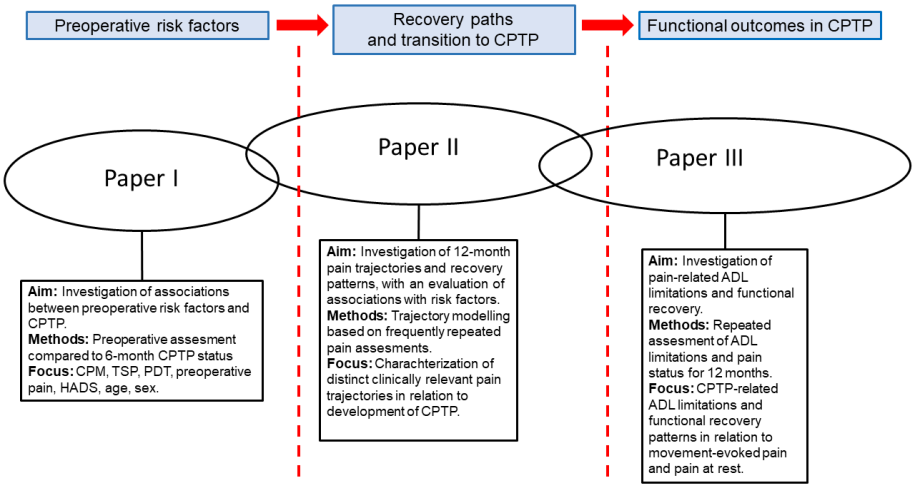

Figure 1.1: Overview of the dissertation Papers. Abbreviations: CPTP, chronic post-thoracotomy pain. CPM, conditioned pain modulation. TSP, temporal summation of pain. PDT, pain detection threshold. HADS, hospital anxiety and depression scale. ADL, activities of daily life.

1.3.1. INVESTIGATION OF RISK FACTORS

Investigations of the predictive value of QST parameters in PPSP-risk within several fields of surgery have so far shown mixed results[12]. The significance of pressure pain detection threshold (PDT), conditioned pain modulation (CPM) and temporal summation of pain (TSP) in the development of CPTP, following either VATS or thoracotomy, have only been sporadically investigated in a few previous studies[35–38]. Likewise, the predictive value of anxiety and depression symptoms evaluated by Hospital anxiety and depression scale (HADS) in relation to CPTP risk has not yet been consistently studied, and further studies are needed to determine the predictive value of HADS in thoracic surgery[34]. Paper I presents results from an exploratory analysis of suggested risk factors for CPTP and contains findings from a preoperative assessment including CPM, TSP and HADS.

1.3.2. PAIN TRAJECTORIES

Recently, focus has increased on the significance of postoperative pain trajectories, with an aim to characterize and determine the potential for identification of unfavorable recovery paths leading to PPSP, ultimately enabling the possibility for early intervention to reduce postoperative pain and improve functional outcomes[40–45]. In Paper II, three distinct 12-month pain trajectories are outlined, derived from frequent bi-weekly pain assessments. Paper II also includes an exploratory analysis

investigating the associations between preoperative risk factors for CPTP and long-term recovery trajectories.

1.3.3. PAIN-RELATED LIMITATIONS AND FUNCTIONAL RECOVERY

Previous studies have examined quality of life in lung cancer patients undergoing surgery, primarily focused on general aspects of health-related quality of life across broader domains such as mental, social and physical functioning[29,32,46–50] Few earlier retrospective studies also specifically examined limitations in activities of daily living (ADL) related to CPTP[23,51,52]. Paper III provides a prospective investigation of functional recovery by repeated and comprehensive assessments of pain-related ADL limitations from two to twelve months after surgery.

1.4. AIMS AND HYPOTHESES

The aims the PhD-study were to investigate HADS and QST parameters as risk factors for CPTP, and to track how postoperative pain and functional recovery paths evolve up to 12 months post-surgery. The hypotheses were:

1) CPTP is associated with decreased preoperative pressure pain detection threshold (PDT), impaired conditioned pain modulation (CPM) response, and facilitated temporal summation of pain (TSP).
2) The severity of preoperative anxiety and depression symptoms, evaluated by Hospital Anxiety and Depression Scale (HADS), is associated with development of CPTP.
3) Patients who develop CPTP follow a distinct pain trajectory which diverges from the trajectory of patients who recover fully.
4) Patients suffering from CPTP experience more limitations in activities of daily life and protracted recovery in physical functioning.

CHAPTER 2. BACKGROUND

This chapter provides an outline of PPSP in general and a brief introduction to lung cancer surgery, followed by a concise summary of current knowledge on specifically CPTP in lung cancer patients.

2.1. PERSISTENT POSTSURGICAL PAIN

Persistent postsurgical pain (PPSP) is highly prevalent with reported incidences ranging from 15 to 60% depending on the type of surgery[1,2]. The development of PPSP is complex and multifactorial, as already acknowledged by the present multidisciplinary and bio-psycho-social approach in both research and management[17,53–56]. Various risk factors have been extensively studied across several fields of surgery and research on PPSP risk stratification has been in focus the past 20 years in an attempt to develop precise risk stratification and identify targets for prevention[2,7,9,11,17].

Current evidence indicate that acute postoperative pain and preexisting pain conditions are consistently associated with PPSP[7,10,56]. This correlation is possibly linked to central pain sensitization, but the complex nature of PPSP still cannot be convincingly attributed to any single-standing risk factor and the effect of acute postoperative pain on subsequent development of PPSP remains controversal[2,6,9,57,58].

2.1.1. THE SURGICAL TRAUMA AND PAIN SENTISIZATION

Iatrogenic tissue and nerve damage are inevitable consequences of surgery. The incision into the skin and deeper tissues triggers the release of local inflammatory mediators and cytokines, activating peripheral sensory neurons with induction of mechanistic changes in excitability and signal transmission through the dorsal root ganglion[2,19,59]. This facilitated peripheral signal transmission can lead to neuroplastic changes in the secondary pain-projecting neurons in the dorsal horn of the spinal cord, resulting in central sensitization and hyperalgesia that persist beyond the normal tissue healing process[19,59]. Additionally, mechanisms of descending pain modulation within the brainstem that connect and integrate sensory pathways and the conscious perception of pain can be altered, causing a more intense and emotionally negative perception and expectation of pain[60].

In general, current hypotheses regarding the development of persistent postsurgical pain revolve around the concept of an inherent maladaptive state arising during recovery, caused by neuroplastic changes occurring in the periphery, dorsal ganglia, and throughout the central nervous system, leading to pain sensitization and alterations in endogenous pain facilitation and inhibition[10,60].

2.1.2. RISK FACTORS FOR PPSP

The body of research on risk factors associated with PPSP is extensive, and the range of known and potential risk factors continues to expand. This expansion of knowledge aims to establish a robust prediction model for PPSP, facilitating preoperative risk stratification, prevention, and customized pain management[17]. While numerous risk factors have already been identified, the causal mechanisms of identified risk factors remain incompletely elucidated, with many risk factors appearing to be interconnected[8,60,61].

Current research into PPSP risk factors is massive and studies employ diverse methods, designs, and definitions of PPSP and risk factors, presumably contributing to some of the inconsistency in present findings. This plethora of studies reported in the literature emphasizes the need for larger-scale studies to determine the true predictive value of individual risk factors[7,60]. Ongoing large multicenter studies, incorporating a multidimensional approach, are attempting to identify new genetic risk factors and validate previously proposed risk factors, in an effort to enhance and offer new evidence to enable the discovery of distinct biosignatures for PPSP[62,63]. Nevertheless, smaller explorative studies within separate surgical specialties may still be warranted for identification of new proposed risk factors and to determine the value in individual surgical populations, as the importance of individual risk factor and underlying mechanisms of PPSP may be influenced by procedure and patient population[11].

Risk factors can be divided into separate subtypes of factors as earlier suggested[10,56]; 1) patient specific factors such as genetic, demographic, lifestyle and psychosocial factors; 2) clinical factors such as comorbidities, preexisting pain and endogenous pain modulation mechanisms; 3) perioperative factors related to surgery, anesthesia and pain management. While single-standing risk factors may be correlated to PPSP, they cannot fully by themselves predict pain outcomes. PPSP-risk is probably rather a combination of risk factors including individual vulnerability, which ultimately result in an overall imbalance in pain homeostasis leading to PPSP (Figure 2.1).

2.1.3. RISK PREDICTION MODELS

Several risk prediction models for PPSP in specific surgical specialties have been reported and many have aimed to provide risk calculators intended for clinical use[64,65]. A general prediction model has been presented by Montes et al., based on a large sample compiled from patients undergoing various procedures within four surgical specialities[66,67]. The risk calculator included six patient-related preoperative factors, easily obtainable by simple clinical screening and questionnaires. The model showed an overall discrimination ability of 70%, with a reported sensitivity of 60%. The positive predictive value was 32% at a risk-cutoff of 20%, meaning that identified patients had at least 20% risk of developing PPSP.

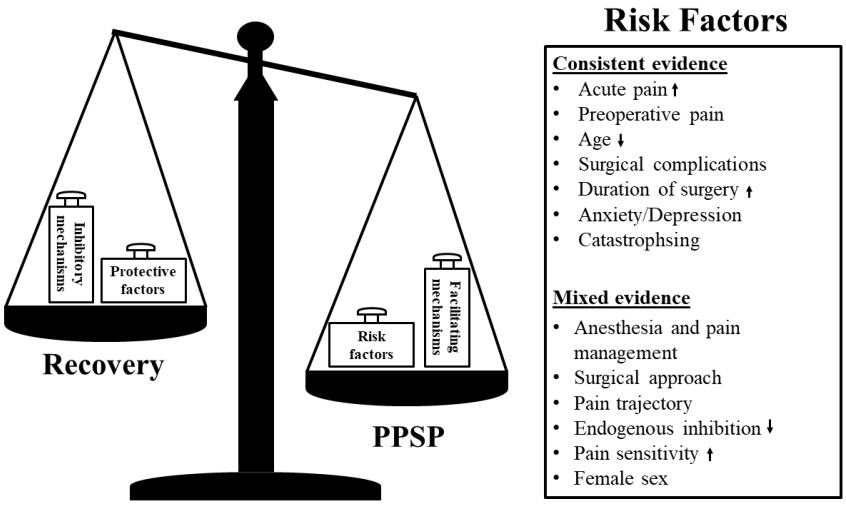

Figure 2.1: Risk factors for persistent postsurgical pain (PPSP) and recovery outcome. The development of PPSP is associated with numerous risk factors and individual differences in facilitatory and inhibitory pain mechanisms. A combination of individual vulnerability and risk factors possibly determine the overall risk of developing PPSP.
Adapted from Glare et al.[10]

Prediction models might be interesting for identifying high risk patients for recruitment to interventional trials, while the clinical applicability yet is limited, if such models are used for individual treatment decisions[68,69]. However, with the advent of even more precise risk models, a clinically valid preoperative risk stratification could enable tailored pain management in the future[10,17].

2.1.4. TRANSITION FROM ACUTE TO CHRONIC PAIN

As mentioned, the development of PPSP is multifactorial and cannot simply be attributed to specific preoperative risk factors, intraoperative aspects, type of surgery or perioperative pain management and central sentisization[8,9,16]. The transition to PPSP and the complexity of underlying mechanisms poses challenges in both prevention and treatment of PPSP[6]. There is a clear association between acute pain and PPSP[10,56]. In the majority of existing studies, PPSP is assessed at an appropriate time, typically around 3 to 12 months after surgery[7]. However, this cross-sectional approach does not convey any temporal information regarding the dynamic course and possible fluctuations during recovery, and the role of subacute pain[11,60].

The assertion that acute postoperative pain is a strong predictor for PPSP and transitions into chronic pain has also been challenged by some due to a shift in pain type, i.e., from acute nociceptive and inflammatory pain to e.g. neuropathic pain[8]. Furthermore, the causal mechanistic link between acute and chronic postoperative pain remains largely unknown, and methodological issues have also been raised in relation to the typical cross-sectional approach in pain evaluations[58,60,70].

2.1.5. PREVENTIVE MEASURES AGAINST PERSISTENT POSTSURGICAL PAIN

Despite ever insisting efforts to prevent PPSP by targeting acute postoperative pain using preemptive anesthesia and optimization of perioperative pain management, the incidence of PPSP has not decreased noticeably over the past decades[60]. This implies that pharmacological interventions cannot stand alone, and there is a need for greater understanding of pain mechanisms and larger scale randomized trials to validate existing and emerging treatments and preventive meassures[16,17,59,71].

Today, it is broadly acknowledged that a biopsychosocial multimodal approach is warranted in addressing preoperative, intraoperative and postoperative risk factors, including psychological factors and subacute to long-term pain management beyond discharge from hospital, ideally based on individual risk profiling[7,10,11,17,60].

2.2. LUNG CANCER SURGERY IN CONTEXT

Despite many efforts and the advent of ERAS programs[72], acute and chronic pain still pose significant challenges in lung cancer surgery[16]. This section offers a brief description of lung cancer surgery and perioperative pain management to provide an overview of the study population this dissertation and Papers I-III are dedicated to.

2.2.1. EPIDEMIOLOGY

Lung cancer is one the most frequently diagnosed malignancies with an estimated incidence of 2.2 million cases annually, and it is the leading cause of cancer deaths worldwide[73]. The incidence of primary lung cancer has increased during the last 20 years and patients are diagnosed at an earlier disease stage, consequently leading to a rise in the number of patients eligible for surgery[74]. Furthermore, new treatment modalities have emerged, significantly increasing the survival of lung cancer patients[75]. Nevertheless, surgical resection remains the cornerstone in the treatment of early-stage non-small cell lung cancer whenever the patient is deemed operable[76–78].

The overall five-year survival among operated Danish lung cancer patients is presently 63%, varying from 72% in the lowest stages to 53% in stage IIIA[79]. Due to increasing resection rates in combination with improved oncological treatment, the number of cancer survivors suffering from CPTP is expected to increase[80].

2.2.2. CLINICAL CHARACTHERISTICS OF SURGICAL PATIENTS

Comprehensive data from all primary lung cancer cases in Denmark have been systematically gathered since 2000 and integrated into the Danish Lung Cancer registry[75]. Currently, about 1,200 lung cancer resections are performed annually at the four Danish university hospitals, corresponding to 28% of the approximately 5,000 lung cancer cases diagnosed each year[79].

The typical lung cancer patient undergoing surgery is about 65 to 70 years of age, and often presents with various comorbidities, predominantly chronic obstructive pulmonary disease and cardiovascular conditions such as hypertension and chronic ischemic heart disease[79,81]. Low-stage non-small cell lung cancer usually only cause discrete symptoms, and the suspicion of lung cancer is often raised when a lung tumor is discovered incidentally in connection with diagnostic work-ups for other conditions[82].

Patients with suspected lung cancer undergo additional tests and scans until the suspicion is either confirmed or denied. The compiled diagnostic results are evaluated by a multidisciplinary team and referred to either oncological or surgical treatment, depending on disease stage, respectability and an evaluation of operability in relation to the patient's over-all health condition, comorbidities and lung function[83,84].

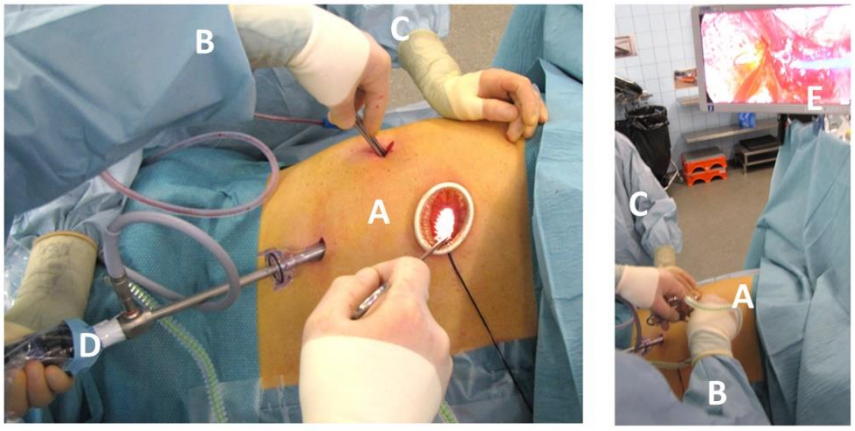

Figure 2.2: Video-assisted thoracoscopic surgery (VATS). Three incisions are placed, typically in the 4th and 7th to 9th intercostal spaces. Surgery is then performed by thoracoscopic visualization with long instruments suitable for the purpose. **A**: Patient lying on left side with the right up. **B**: Surgeon. **C**: Assisting surgeon. **D**: Video-thoracoscope. **E**: Monitor connected to the video-thoracoscope.

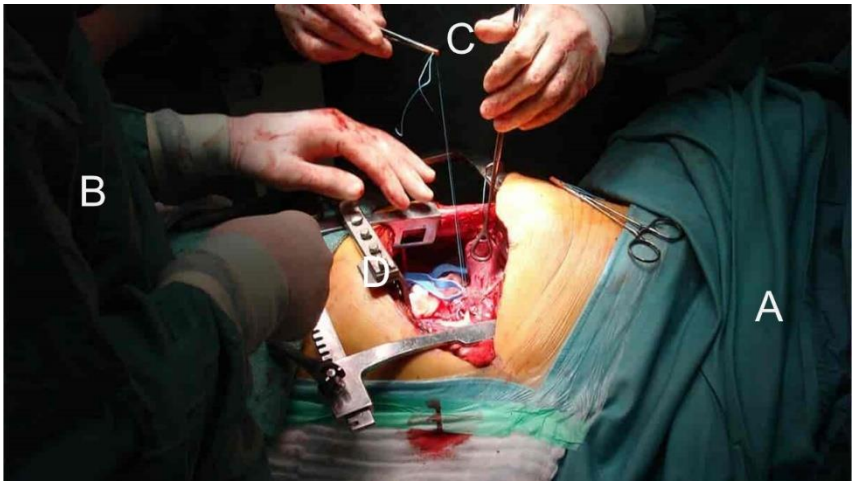

Figure 2.3: Posterolateral thoracotomy. A skin incision is placed in the 4th or 5th intercostal space. Access to the pleural cavity is achieved after placement of a rib retractor. **A**: Patient lying on right side with the left side up. **B**: Surgeon. **C**: Assisting surgeon. **D**: rib retractor.
Picture by Wojciech Filipiak[*]

2.2.3. SURGICAL PROCEDURES AND APPROACH

The current established standard management for resectable lung tumors is anatomical lobectomy if tolerated[77], although sublobar resections and stereotactic body radiation have shown promising results in lower stage disease[85–87]. VATS is considered the approach of choice due to its less invasive nature compared to thoracotomy, resulting in less acute postoperative pain, shorter length of in-hospital stay, and swifter reconvalescence[29,88,89].

Approximately 80% of lung cancer surgeries in Denmark are performed by VATS[79]. The most common approach is the three-port anterior approach (Figure 2.2)[90]. In this method, three smaller incisions are made and access through the chest wall is achieved through the intercostal spaces without the use of a rib retractor.

The traditional approach by open thoracotomy can also be performed with different techniques, depending on the demand for surgical exposure and surgeon preferences. Most often, open access is achieved by either anterolateral[91] or muscle-sparing posterolateral[92] thoracotomy. A classical posterolateral thoracotomy involves partial division of the latissimus dorsi muscle and is perceived as the most invasive, generally associated with higher acute pain and disability[93,94]

[*] *Creative commons license https://commons.wikimedia.org/wiki/File:Lobectomy_-_surgery_of_romoval_of_lung_tomor.JPG#)*

In the open anterolateral thoracotomy, a single skin incision is made, typically in the 4th or 5th intercostal space, following the trajectory of the rib. Access is obtained under direct visualization through the intercostal space, by partial mobilization of the serratus anterior and division of the intercostal muscles, while sparing the nerve and vascular bundle adjacent to the lower rib edge. A steel rib retractor is then placed and surgical access to the pleural cavity is achieved (Figure 2.3).

2.2.4. PERIOPERATIVE CARE AND PAIN MANAGEMENT

Multimodal analgesia is presently incorporated and continuously under refinement in thoracic surgery[95,96]. Effective postoperative pain management is pivotal in avoiding serious complications such as pneumonia and respiratory failure[74]. While there may be differences in local practices, most centers adhere to general principles, presently outlined in the Procedure-specific postoperative pain management (PROSPECT) guidelines[95]. Perioperative preemptive regional analgesia constitutes a fundamental part in acute postoperative pain management[97–99]. Different techniques exist, but the most common are paravertebral or intercostal blocks and thoracic epidural anesthesia (Figure 2.4). In addition to regional anesthesia, paracetamol and NSAIDs are used in an opioid-sparing approach, sometimes in combination with gabapentin, to promote faster mobilization and reduce side-effects and potential addiction issues linked to opioid consumption[100–103].

In recent years, dedicated ERAS programs have emerged in lung cancer surgery with an aim with to minimize pain and opioid usage, facilitate early discharge, and enhance recovery and overall outcomes, including long-term postoperative pain[72]. The programs consists of both preoperative habilitation, protocolized pain management and optimization of the immediate perioperative care[72,104–106].

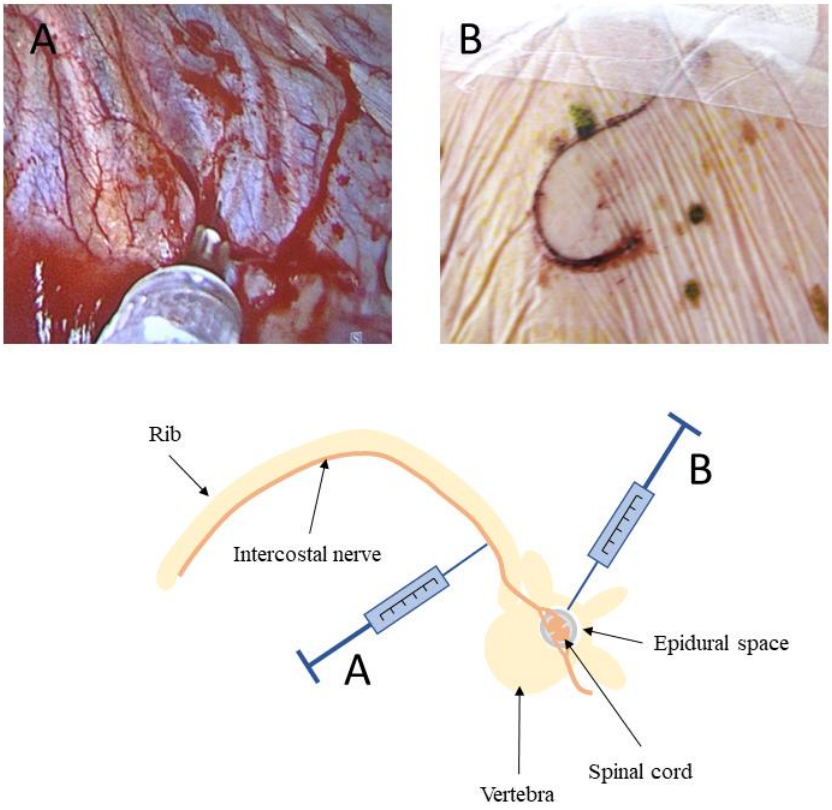

Figure 2.4: Regional analgesia in thoracic surgery. **A**: Intra-operative paravertebral intercostal blockade during video-assisted thoracoscopic surgery (VATS). A local anesthetic is place precisely paravertebrally in each intercostal space under thoracoscopic guidance by puncture of the parietal pleura form the inside of chest. **B**: An epidural catheter is placed after percutaneous puncture through the back of the patient at an appropriate level of the thoracic spine.

2.3. CHRONIC POST-THORACOTOMY PAIN

The occurrence of chronic postsurgical pain following thoracic surgery ranks among the highest across all surgical domains, with a reported prevalence ranging from approximately 30% to 50% up to one year after surgery for lung cancer[23,25,26,33,107–110]. Many lung cancer survivors will experience CPTP regardless of the expanding use of

minimally invasive techniques and multimodal anesthesia. Despite increasing attention to PPSP and extensive research into preventive treatments, the incidence of PPSP has remained high through the past two decades, including CPTP[80,111,112]. This section describes the clinical properties of CPTP and proposed underlying causal mechanisms.

2.3.1. PAIN INTENSITY

As mentioned, CPTP is common, but generally considered to only be associated with mild intensity pain in most cases, and moderate to severe pain in 8-12% of surgical lung cancer patients [23,29,110]. In CPTP specifically, factors such as surgical approach seem to be of significance to the risk for developing CPTP[34,110], but only few studies have investigated the pain intensity of CPTP in relation to surgical approach. While acute pain is higher after open thoracotomy, current studies have not demonstrated the same tendency for chronic pain[29,30,113].

Pain intensity in CPTP is often sporadically reported, and a direct comparison between studies is difficult due to variations in evaluation times and methods[114]. Many studies employ a definition of clinically relevant pain solely based on pain intensity, not recognizing the importance of other pain characteristics such as quality, movement evoked pain, pain at rest, duration, fluctuations, and neuropathic symptoms etc.[115] Lastly, pain-related impairment and the impact on quality of life are seldom reported, but should ideally be included to fully evaluate the clinical importance and consequences of CPTP[114].

2.3.2. INTERCOSTAL NERVE DAMAGE AND NEUROPATHIC PAIN

Neuropathic pain is very frequent following thoracic surgery and are reported by 25 to 50% of patients up to 6 to 12 months post-surgery[110,116]. The influence of surgical approach and the extent of surgery are still subjects of debate, but some studies have found that open thoracotomy appear to be more strongly associated to neuropathic pain compared with VATS[24,117]. However, it is noteworthy that the prevalence of neuropathic symptoms is high in any surgery involving the chest wall in general, regardless of intraoperative factors, including benign conditions in thoracic surgery, cardiac surgery and breast surgery[118–120].

Nerve damage after both VATS and thoracotomy has been demonstrated in previous studies, where loss of sensory function in relation to the scar was detected in immediate connection to the procedure and up to three years after surgery[37,39,121,122]. However, the significance of experimentally confirmed nerve damage and neuropathic pain in CPTP has yet to be established with certainty, since loss of function is not necessarily associated with CPTP[37,39,107,122–124].

The underlying mechanism of the high occurrence of neuropathic pain symptoms after thoracotomy has traditionally been attributed to the surgical trauma, caused by incision into the chest wall between the ribs in close proximity to the intercostal nerves

with high risk of nerve damage[122,125]. Prolonged nerve irritation during surgery has also been proposed as a contributing factor since less evasive approaches, such as VATS and muscle sparing thoracotomies, still exhibit high rates of neuropathic pain, possibly caused by nerve compression from instruments and rib retractors[121].

It has been suggested that VATS may be associated with less intraoperative nerve damage, due to its minimally invasive nature, and some studies indicate a lower incidence of neuropathic pain after VATS compared with open thoracotomy[113,121].

Regardless of the underlying mechanism and the role of neuropathic pain in the development of CPTP, it should still be considered of importance, because studies suggest that neuropathic pain may be associated with more pronounced limitations in daily activities, higher pain intensity and increased need for analgesics, including opioids[25,113].

2.4. RISK FACTORS OF CHRONIC POST-THORACOTOMY PAIN

Numerous studies have specifically investigated risk factors of CPTP. This section contains a summary of established and suggested risk factors with emphasis on those investigated in relation to this dissertation and Papers I-II.

2.4.1. SURGICAL APPROACH AND INTRAOPERATIVE FACTORS

Current evidence suggests a modest, yet statistically significant increased risk of CPTP following open thoracotomy compared with VATS[34]. The used technique also seems to play a role in relation to nerve damage and the development of CPTP, since some studies report lower incidence and intensity of CPTP when employing less invasive approaches such as anterior and muscle-sparing thoracotomies[93,126], although some studies do not detect any difference[127]. Whether uniportal VATS offers any advantage compared with traditional multiportal VATS regarding CPTP risk has yet to be determined but studies indicate less postoperative pain after uniportal VATS[128].

Finally, longer duration of surgery also seem to be correlated to CPTP, suggesting that prolonged nerve compression and irritation are also contributing factors[116,122].

2.4.2. ACUTE POSTOPERATIVE PAIN

High acute postoperative pain is one of the most frequently reported risk factors for PPSP[2,10]. This association has also been reported for CPTP after surgery for lung cancer[30,34,35,38,42,50,129,130]. The used methods for pain evaluation vary between studies, which is also the case for studies investigating CPTP. Some studies specifically assess movement-evoked pain, pain when coughing and neuropathic pain. However, very often only limited information on pain characteristics or provoking factors are reported. The most used evaluation method for quantifying acute postoperative pain

is a recording of maximum pain intensity during the first 24 to 48 hours post-surgery. Others measures also used commonly used are average pain or pain trajectories which enables incorporation of a temporal factors into the data.

The diversity of methods makes direct comparison between studies challenging, and the investigation of the actual association between acute and chronic postoperative pain can be considered problematic due to methodological inconsistencies[58,115].

Finally, whether or not acute pain is a causal mechanism leading to chronic pain can be considered highly controversial[7,8,11]. However, it is certain, that a strong association exists between acute postoperative pain and PPSP, and this is also the case in thoracic surgery[34].

2.4.3. PREOPERATIVE PAIN

Preoperative pain is an established risk factor of PPSP[1,7], and also associated to CPTP after both cardiac and thoracic surgery[34]. However, when scrutinizing specific subpopulations undergoing various types of thoracic surgery, evidence can however be considered somewhat mixed. One of the main issues is that direct comparisons among existing studies can be problematic, due to incomplete information and characterization of preoperative pain with only limited available data in specific surgical populations[21].

Over the past two decades the number of studies reporting preoperative pain in surgical lung cancer patients has increased. Although many studies still include only limited characterization of preexisting pain conditions, a majority report associations between preexisting pain and development of CPTP after lung cancer surgery[30,33,38,42,50,131], although some studies still do not observe any connection[42,132,133].

A detailed characterization in case of preexisting pain appears to be of significance since a strong correlation with preoperative pain located to the operation area has been reported[38,50]. In addition, preexisting pain from other regions of the body, stemming from various etiologies, have also been reported to increase the risk of CPTP[30,33].

2.4.4. PSCYCHOLOGICAL FACTORS

Current evidence shows an association between psychological factors and development of PPSP[14,134]. However, psychological factors such as catastrophizing and anxiety and depression have only been sporadically investigated in thoracic surgery and differing parameters and assessment tools have been used, limiting comparability between studies. Overall, the significance of psychological factors as a contributing factor in CPTP risk is still to established[34].

Preoperative evaluations of depression and anxiety symptoms in lung cancer patients have only been reported in a few studies[30,33,38,42]. These existing studies have not

demonstrated any effect of HADS on CPTP risk which stands in contrast to existing compiled evidence showing a small but significant and consistent effect[134]. This discrepancy could perhaps be explained by differences in patient populations within surgical fields. The most extensive and recent metanalysis of psychological factors and PPSP risk by Giusti et al. included 41 studies, predominantly within orthopedics in patients with benign but painful conditions such as knee osteoarthritis and spine disease[134]. These patients can be considered as quite different from the typical lung cancer patient diagnosed with a malignant disease, which rarely causes any pain in itself.

There is a need for larger studies to supply sufficient and comparable data for assessment of the prognostic value of individual psychological risk factors and evaluation methods in relation to CPTP after surgery for lung cancer.

2.4.5. PAIN MECHANISMS EVALUATED BY QUANTITATIVE SENSORY TESTING

Current research has also explored the predictive value of facilitating and inhibitory physiological pain mechanisms, such as conditioned pain modulation (CPM) and temporal summation of pain (TSP), assessed by preoperative quantitative sensory testing (QST)[†]. Several studies have investigated the importance of variations in QST parameters, with the hypothesis that such variations are linked to individual pian threshold and maladaptation of pain modulation mechanisms, which could ultimately result in increased postoperative pain risk. However, only limited evidence yet exist in relation to PPSP[12,135].

Only a handful of studies have investigated the associations between preoperative QST parameters and the development of CPTP in thoracic surgery specifically[30,35,36,38]. A single study from 2008 by Yarnitsky et al.[35] reported an association with decreased CPM and CPTP. Currently, available data in thoracic surgery is still sparse, based on limited sample sizes in different cohorts of patients undergoing thoracic surgery for both benign conditions and malignancies.

The role of QST variables in CPTP risk stratification and PPSP in general is still to be determined. No consistent evidence has yet been established and existing data are obtained across multiple surgical fields by various methods[12].

2.5. PREVENTION AND TREATMENT

As described in section 2.2.4, a multimodal analgesic approach is currently the cornerstone in postoperative acute pain management after lung resection. Present

[†] The concepts of TSP and CPM are explained in chapter 3.

focus has been on reducing acute pain by a combination of preemptive regional anesthesia in a combination with systemic central and local-acting analgesics. Acute pain management might hold a potential for prevention of chronic postoperative pain due to a strong association between acute postoperative pain and PPSP[6,50,56,95,100,136,137]. However, evidence indicates that perioperative pharmacological interventions cannot stand alone[59,71]. Despite many trials and attempts with preemptive analgesia, opioid-sparing anesthesia and other perioperative interventions, the incidence of PPSP has not decreased convincingly during the past decades, which is also the case for CPTP specifically[16,17,71].

2.5.1. TREATMENT OF ESTABLISHED CHRONIC POST-THORACOTOMY PAIN

Up to 40% of CPTP patients rely on daily analgesics use, and persistent opioid use is highly prevalent as long-term opioid usage is prevalent, with reports of long-term opioid consumption extending beyond the initial three postoperative months in 20 to 30% of patients[25,101,124,133,138]. Alternatives to traditional analgesics, such as gabapentin, are widely used and may offer some efficacy in the neuropathic component of established CPTP[136,139,140].

Experimental treatments, like cryoneurolysis, have been sporadically tried and reported, but consistent evidence is yet to emerge[141]. A novel treatment modality involving botulinum toxin-induced nerve blockade has also been reported as effective in CPTP case studies[142,143].

Pain clinics offer multimodal care to the most complex chronic pain patients with long-lasting pain stemming from various etiologies, typically extending beyond 12 months. However, many patients suffering from PPSP are not eligible or in need of referral to a pain clinic. In recent years, transitional pain services have emerged to offer specialized treatment and early detection of PPSP which could ultimately prevent chronification[11,144]. However, most lung cancer patients are not offered any specialized treatment for postoperative pain after discharge and are managed by general practitioners alone, often only with prescription medications.

In conclusion, the current treatment options for patients suffering from CPTP after lung cancer surgery are generally limited and could be considered problematic due to the high prevalence of long-term opioid users in this specific subpopulation.

2.6. CHRONIC POST-THORACOTOMY PAIN AND FUNCTIONAL IMPAIRMENT

The reported intensity of CPTP is generally mild to moderate[110]. Although the definition of CPTP does not include specific parameters regarding pain-related impact on quality of life and functional impairment, these aspects hold

significant relevance in understanding the influence of CPTP on health and overall outcomes following lung cancer surgery.

The consequences of CPTP in lung cancer patients have been widely studied, revealing a substantial association with poorer physical health status and limitations in activities of daily life[23,46,50,51,145]. However, little is known about recovery potential in terms of functional impairment and quality of life[49,109], as well the effects of interventions aimed at facilitating recovery and restoring preoperative physical capacity after surgery for lung cancer[146,147].

CHAPTER 3. MATERIALS AND METHODS

The foundation of this dissertation and the adjoining papers are data collected from a study cohort of patients who underwent surgery with lung resection due to lung cancer. This chapter provides a broad outline of the study's framework, data collection process, and phases during the follow-up period. In addition, the statistical methods used in Papers I-III are briefly explained. More comprehensive descriptions of the included parameters and employed methods are provided in the individual papers.

3.1. STUDY POPULATION AND DESIGN

The study population was defined as patients referred for lung resection, due to either presumed or confirmed primary lung cancer. The design was a single-center observational cohort study with a follow-up period of 12 months.

3.1.1. STUDY SAMPLE

The study sample forming the foundation of this dissertation, and Papers I-III on which it is based, is derived from patients scheduled for lung cancer surgery at Aalborg University hospital. The Department of Cardiothoracic surgery at Aalborg University Hospital is one out of four Danish cardiothoracic departments and it services the entire North Denmark Region with 590.000 inhabitants. Approximately 180 lung cancer surgeries are performed annually. The majority of patients (75%) undergo lobectomy[79].

3.1.2. STUDY PROTOCOL

The study was designed as a single-center observational cohort study with a follow-up period of 12 months. The protocol included a preoperative assessment of clinical and demographic variables, a QST assessment by cuff algometry, and screening for anxiety and depression symptoms. The study featured repeated assessments of postoperative pain and ADL-limitations with the intend to track changes during recovery as described in detail below (Section 3.4).

3.1.3. RECRUITMENT

Patients referred for elective surgery via the standardized national program for patients with presumptive or confirmed lung cancer[148], were recruited over a four-year period from March 2014 until April 2018. Patients were consecutively screened and approached for inclusion whenever dedicated research staff were available. The number of surgeries increased gradually during the study period from 131 patients in

2014 to 195 patients in 2018, not counting patients with benign tumors or distant metastasis form other concomitant cancers[149].

Inclusion criteria for the study cohort were age ≥18 years, ability to understand Danish, and scheduled for thoracic surgery by either VATS or open thoracotomy due to either verified or presumptive primary lung cancer. Exclusion criteria were active or prior drug and/or substance abuse, cancellation of surgery or reoperation, inability to cooperate at the preoperative evaluation, and synchronous cancer diagnoses other than primary lung cancer.

3.1.4. DATA COLLECTION AND MANAGEMENT

Participants reported data by answering questionnaires during follow-up, either electronically or by post, according to their preference. Study data were collected, recorded, and stored in compliance with national laws and regulations. The final study database was compiled in REDCap (Research Electronic Data Capture, Vanderbilt University).

3.1.5. ETHICS

At the recruitment process, participants received comprehensive oral and written information regarding the objective of the study and its phases. Included participants provided a signed an informed consent form, and were informed about the opportunity to withdraw, should they wish to.

The study was approved by The North Denmark Region Committee on Health Research Ethics (N-20140062) and conducted in accordance with local regulations and the Declaration of Helsinki.

3.2. PREOPERATIVE ASSESMENT

The preoperative baseline assessment took place one to three days before scheduled surgery. Recruited patients received questionnaires either electronically or on paper. Questionnaires included screening for preexisting pain at any location, preexisting neuropathic pain symptoms and anxiety and depression symptoms. Clinical and demographic baseline characteristics were retrieved from the electronic patient records.

3.2.1. QUANTITATIVE SENSORY TESTING

Participants underwent a QST assessment conducted by the recruiting research staff member. Screening for preoperative neuropathy in the operation area involved standard brush (Somedic production AB, Sweden) to test for allodynia, and pin-prick stimulation for assessing hyperalgesia on the chest wall. Computer controlled cuff

algometry (Cortex Technology and Aalborg University, Denmark) was utilized to assess PDT, CPM and TSP.

Cuff algometry was conducted in the following sequence: Initially, a pressure cuff on the leg corresponding to the side of the operation was ramp inflated. Pressure was gradually increased until the participant reported a VAS≥1 PDT, at which point PDT was determined. Subsequently, cuff pressure was further increased until the participant tapped out due to intolerable pain or a maximum stimulus was reached, defining the pain tolerance threshold (PTT). The magnitude of PTT determined the level of the conditioning stimulus.

Following the first testing cycle, a conditioning stimulus was applied by a pressure cuff on the contralateral leg opposite to the operation side. The cuff on the leg corresponding to the operation side was reinflated with a concomitant constant conditioning stimulus on the opposite leg. PDT with conditioned stimulus was then determined as VAS exceeded 1 during the second stimulation cycle. The CPM effect could then be calculated as the difference in PDT with and without conditioning stimulus. The cuff algometry set-up and the concept of CPM is shown in Figure 3.1, and further described in detail in Paper I[28].

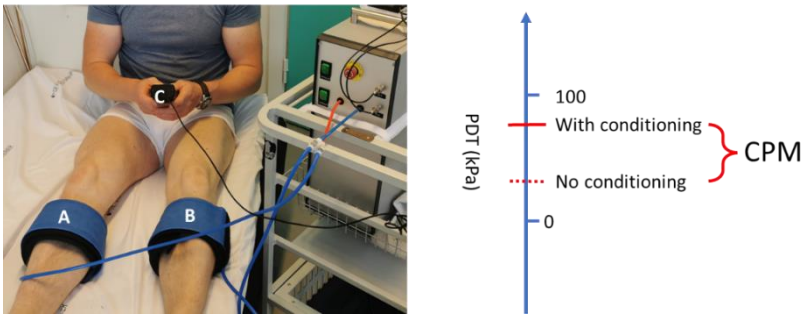

Figure 3.1: Cuff algometry setup. A: Pressure cuff on test leg (operation side). B: Pressure cuff on contralateral leg for pain conditioning. C: Electronic VAS-recorder. Conditioned pain modulation (CPM): Cuff pressure is gradually increased on the test leg (A) until pain detection threshold (PDT) is reached. A constant conditioning stimulus is then applied to the contralateral leg (B). Cuff pressure is again gradually increased on the test leg (A) until PDT with conditioning stimulus is reached. CPM is calculated as difference in PDT with and without conditioning stimulus.

TSP was evaluated through a series of ten cuff inflation pulses with stimulations at the PDT pressure. Participant were instructed to incrementally adjust VAS on the electronic slider if their perceived pain intensity increased between stimulation pulses

(Figure 3.2). TSP was calculated as the difference between mean VAS during the three last and first three stimulation pulses.

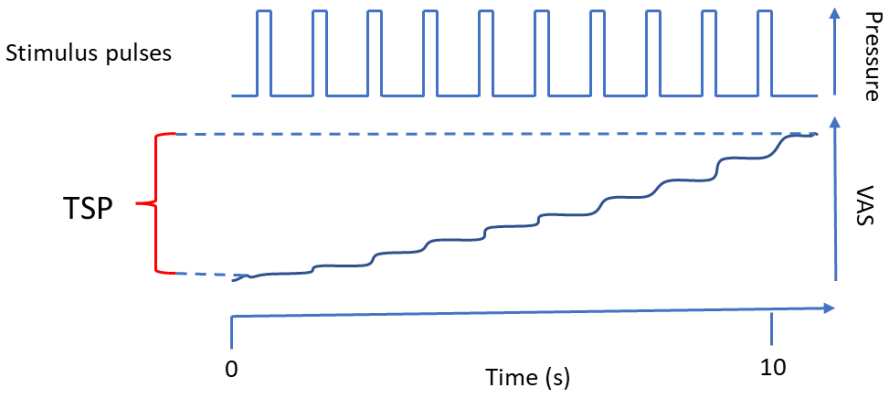

Figure 3.2: Temporal summation of pain. A series of ten stimulation pulses at the same pressure are delivered at a rate of one pulse per two seconds. The test subject reports VAS continuously during the stimulation cycles. VAS is gradually increased if a pulse is perceived as more painful than the previous pulse.

3.2.2. HOSPITAL ANXIETY AND DEPRESSION SCALE

Preoperative anxiety and depression symptoms were assessed by HADS which was originally introduced as a screening tool for anxiety and depression in hospitalized patients[150]. The use has expanded, and HADS is now also used as a screening tool of mood and anxiety disorders in wider contexts, including investigations of associations with chronic postsurgical pain[134].

The questionnaire contains seven items on anxiety symptoms and seven items on depression symptoms, each rated by a descriptive answer corresponding to a score of 0 to 3 for each item. The maximum score for anxiety and depression is 21, with a maximum total combined score of 42. Higher scores indicate greater degree of symptom severity. The Danish version of the HADS questionnaire used in the study can be found in Appendix B.

3.3. SURGERY

The surgical approach and general considerations and practices have already been described in chapter 2. In this section, local practices at the Department of Cardiothoracic Surgery Aalborg University Hospital are briefly outlined.

3.3.1. SURGICAL PROCEDURE

Patients were operated by either VATS or thoracotomy depending on tumor size, location and extend, and surgeon preferences. Conversion from VATS to open thoracotomy was conducted if deemed necessary by the operating surgeon. Duration of surgery and conversion rate were unfortunately not recorded.

3.3.2. ANAESTHESIA AND PAIN MANAGEMENT

General anesthesia was induced and maintained by infusion of remifentanil and propofol as described in Paper I[28]. Generalized muscle relaxation was achieved by administration of rocuronium, supplemented as needed to ensure satisfactory intraoperative conditions. Supplemental fentanyl was administered as required.

VATS patients received an internal thoracoscopic guided paravertebral blockade as described in section 2.2.4. A total weight-adjusted dose of bupivacaine without adrenaline (<60 kg: 150 mg, 60 to 80 kg: 200 mg, >80 kg: 300 mg), was evenly distributed into the 2nd to 9th intercostal spaces. Patients scheduled for open thoracotomy and VATS patients deemed at high risk of conversion to open surgery, had an epidural catheter placed before induction of general anesthesia. The catheter delivered a solution of bupivacaine 2,5 mg/ml and sufentanil 1 µg/ml, typically at rate ranging from 3 to 8 ml/h, depending on patient demand for satisfactory pain control.

Pain management adhered to the established principles outlined in the international PROSPECT guidelines[95]. At discharge form the recovery unit, oral paracetamol at a dosage of 1 g every six hours, and ibuprofen 600 mg in retarded formulation every 12 hours, were initiated as soon as feasible, unless contraindicated. Epidural anesthesia was continued until at least third postoperative day in case of open thoracotomy. Oral and intravenous morphine were administered as rescue analgesics as needed.

3.4. REPEATED ASSESMENTS DURING FOLLOW-UP

Participants were contacted at two weeks intervals via mail or email and invited to reply up to four different questionnaires. A reminder was issued one to two weeks after the initial contact If participants were unresponsive after the initial contact at every assessment time during follow-up. The reminder was followed by either e-mail or phone call if the participants remained unresponsive. Figure 3.3 provides an overview of the data collection phases during the study.

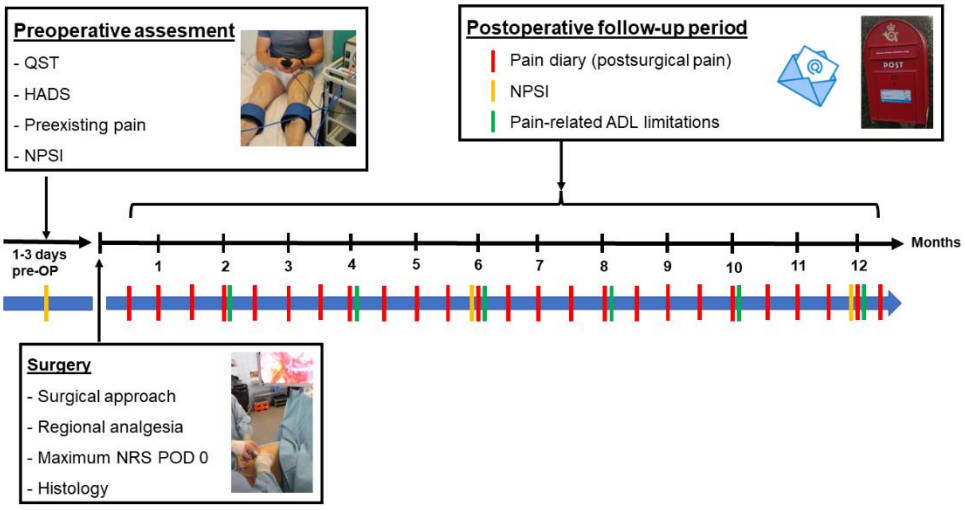

Figure 3.3: Data collection overview and timeline. Abbreviations: QST, quantitative sensory testing. HADS, hospital anxiety and depression scale. NRS, numeric rating scale. POD, postoperative day. ADL, activities of daily life.

3.4.1. PAIN DIARY

Every two weeks up to 12 months after surgery, participants reported pain associated to their lung surgery. Pain intensity was assessed by NRS as movement-evoked pain and pain at rest. Pain courses were characterized as either no pain, constant pain with light fluctuations, constant pain with pain attacks, pain attacks without pain in between, and frequent pain attacks. The Danish version of the questionnaire can be found in Appendix B.

3.4.2. PAIN-RELATED LIMITATIONS IN ACTIVITIES OF DAILY LIFE

Postoperative limitations in ADL were documented on six occasions during follow-up, commencing at two months post-surgery and subsequently repeated every second month, up to 12 months. To capture information on only postoperative pain-related ADL impairment, a procedure specific questionnaire developed by Ringsted et al. was used[52]. This questionnaire not only enables detailed assessment of limitations in individual activities, but also facilitates calculation of a cumulative impairment score to quantify overall pain-related impairment following lung cancer surgery. The questionnaire has undergone external validation in similar populations through previous studies with reproducible results[51,151].

The questionnaire version used in this study for collection of data presented in Paper III can be found in Appendix B. The questionnaire and calculation method for cumulative impairment scores are further described in Paper III.

3.4.3. NEUROPATHIC PAIN SYMPTOM INVENTORY

Neuropathic symptoms were evaluated by the Neuropathic pain symptom inventory (NPSI) which contains evaluation of five separate neuropathic pain qualities (burning, pressing, paroxysmal, evoked and dysesthesia) rated using NRS[152]. Participants reported preoperative neuropathic pain at any location at baseline and NPSI was then reassessed after six and 12 months. The Danish version of the NPSI used in this study can be found in Appendix B.

3.5. STATISTICAL ANALYSES

This section summarizes the statistical methods employed in this dissertation and its associated papers. It contains a brief explanation and rationale for the chosen approaches. More details can be found in the individual papers (Papers I-III).

3.5.1. ESTIMATION OF SAMPLE SIZE

To investigate risk predictors, a power calculation was conducted to determine the study sample size. The calculation relied on a standardized difference between two groups (those with and without development of PPSP), defined as a 30% difference in PDT divided by the standard deviation, as previously described[153]. The following formulae and assumptions were applied:

$$n = \frac{2}{d^2} \cdot k$$

The standardized difference *d*, was calculated from a standard deviation (SD) of 91.4 kPa, derived from a study of PPSP after hernia repair, where patients reported a combined mean PDT of 161 kPa[154]. The constant *k* was defined as 7.9 derived from a predetermined power of 0.8 ($\beta = 0.2$) and a level of statistical significance at $p < 0.05$ ($\alpha = 0.05$). The estimated sample size was calculated to 112 participants in case of equal sized groups, as n=56. With a presumed CPTP prevalence of 29%, derived from a previous study in our department[26], the study sample was adjusted by:

$$N = \frac{2n(1+k)}{4k}$$

N is the adjusted sample size, where *n* denotes the number of required subjects in each group assuming equal-sized groups, and *k* is the expected proportion of subjects with

CPTP. Thus, the number of required subjects was determined to be N=188. Accounting for anticipated withdrawals and losses to follow-up at 10%, the final target for inclusion was set at 206 subjects.

3.5.2. DESCRIPTIVE AND INTERFERENTIAL STATISTICS

Normally distributed data are presented as means accompanied by 95% confidence intervals (95% CI) or SD. Non-parametric data are presented as medians accompanied by the first to third interquartile range (IQR). The assumption of normality was assessed graphically using QQ-plots and the Shapiro-Wilk test. Binomial proportions are presented as percentages with exact binomial 95%CIs (Clopper–Pearson).

Statistical comparisons and evaluations of associations involving normally distributed data were conducted using the t-test and analysis of variance (ANOVA). Tukey's post hoc test was utilized following ANOVA for discrimination in multiple comparisons. For non-parametric data, differences were assessed using the Wilcoxon rank-sum test, Kruskal-Wallis test, and Mann-Whitney U-test. Categorical variables were compared using Pearson's Chi-square test and Fisher's exact test.

All calculations were performed in STATA Version 16.1, StataCorp. College Station, Texas. Statistical tests were conducted at a power of $\beta=0.8$ and level of statistical significance at $\alpha=0.05$. Thus, p-values less than 0.05 were considered statistically significant.

3.5.3. RISK FACTOR ANALYSIS (PAPER I)

Associations between CPTP, QST parameters and HADS were evaluated in univariate analysis, as described above. To account for multiple comparisons, p-values were adjusted by the Holm-Bonferroni method.

To assess the effect of the included risk variables, a modified Poisson regression approach was employed to obtain estimates of risk ratio (RR). Exploratory models were developed for each of the incorporated exploratory QST-parameters (PDT, CPM and TSP), and combined HADS scores. The models were adjusted for earlier reported CPTP risk factors (age, sex, surgical approach, and maximum acute pain) to determine the influence of the exploratory variables on CPTP-risk.

3.5.4. PAIN TRAJECTORY MODELLING AND RISK FACTORS (PAPER II)

For the investigation of recovery trajectories, group-based trajectory modeling (GBTM) was utilized. This approach enables data-driven modelling whereby subjects are allocated to a predetermined number of groups, based on all available observations within each subject[155]. A normal censored model was selected, since the reported outcome for each measurement was reported on a NRS scale ranging from 0 to 10.

In an exploratory approach, three models consisting of two to four groups were computed. Trajectories for each group were evaluated as first 1st and 2nd order polynomials within each model. This method was chosen because long-term recovery patterns were expected to follow a steady decline in pain intensity, and this assumption was based on existing reports were the prevalence of CPTP seems to decline with time. The final model selection was based on clinical applicability and the principle of parsimony, in combination with evaluation of fit statistics as described in Paper II.

Lastly, univariate analyses were conducted to explore associations between identified pain trajectories and selected risk factors. Due to relatively small sample size, no multivariate analyses were performed.

3.5.5. MULTILEVEL MIXED-EFFECTS LINEAR REGRESSION (PAPER III)

For analysis of impairment and limitations in daily life in relation to CPTP, a multi-level mixed effect modelling approach was chosen. The advantage of this method is the capacity to adjust for potential influential factors on functional level, such as preexisting pain, shifting pain status, possible patient adaptation or compensation in limitations, and overall time interaction.

Pain interference in relation to pain intensity was separately reported for each assessment time and evaluated by linear regression.

3.5.6. MISSING DATA

No imputation of missing data was used. The numbers of participants with available data for individual analyses are indicated throughout reported results in Papers I-III.

CHAPTER 4. FINDINGS AND DISCUSSION

Chapter 4 presents the principal findings and results from Papers I-III, along with a concise discussion and some supplemental analyses. Detailed results, data descriptions and discussion can be found in the individual papers comprising the foundation of this dissertation.

4.1. PREDICTORS FOR CHRONIC POST-THORACOTOMY PAIN

In Paper I, an exploratory analysis of risk factors associated with CPTP was conducted. This investigation included QST, HADS and various clinical parameters. None of the QST parameters (PDT, CPM, TSP) or HADS demonstrated any significant associations with CPTP. However, neuropathic pain symptoms and maximum acute postoperative pain on the day of surgery were found to be significantly associated with CPTP in the primary univariate analyses, following correction for multiple testing. It must be mentioned, that HADS was initially reported as significantly associated with CPTP in the original version of Paper I due to a mistake in data management, but after correction of this error, HADS was not associated with CPTP. The corrected data and results have been published in a corrigendum[156].

Paper I also included secondary risk modelling analyses. Four exploratory multivariable models were computed from available data for each of the included risk predictor variables of interest, i.e., PDT, CPM, TSP and HADS. Each model was adjusted for earlier reported risk factors for CPTP (preoperative pain, age, sex, surgical approach, and maximum pain on POD 0). CPM was the only variable of interest independently associated with CPTP risk. Preoperative pain and maximum acute pain on POD 0 contributed significantly to CPTP six months post-surgery in all models, in accordance with existing evidence[34].

The previous described error in HADS calculations slightly altered the risk estimates initially reported in Paper I, but conclusions remained the same; that HADS was not independently associated with CPTP risk in the secondary multivariable analysis. A corrected version of the results from multivariable analyses are brought in the aforementioned corrigendum[156].

In Paper II, associations between HADS, maximum acute pain on POD 0, demographic variables, and perioperative factors were also investigated in relation to recovery paths and CPTP in patients without preoperative pain. The findings revealed that maximum acute pain on POD 0 was linked to two distinct recovery trajectories: 1) a protracted trajectory characterized by mild but declining pain, and 2) an incomplete trajectory, where no reduction in pain intensity was observed. No

significant differences in HADS scores were observed in the protracted or incomplete recovery trajectories when compared to patients without CPTP.

4.1.1. INTERPRETATION OF FINDINGS IN RELATION TO PREOPERATIVE ASSESSMENTS AND ASSOCIATIONS WITH CHRONIC POST-THORACOTOMY PAIN

Results reported in Paper I and II reflect existing evidence regarding the significance of maximum acute postoperative pain which is considered established risk factors of CPTP and PPSP in general[2,10,17,34,56]. Preoperative assessment by QST and HADS were not associated with CPTP in primary analyses, and the data in Papers I and II contribute to the limited available knowledge on the significance of these variables as possible risk predictors of CPTP.

Quantitative sensory testing

When assessing the predictive value of preoperative QST assessment in CPTP risk, none of the investigated parameters demonstrated statistical significance in the primary analysis presented in Paper I. However, in the secondary exploratory analysis, risk estimates indicated a statistically significant effect of CPM on CPTP risk. This implies that preoperative impaired central pain inhibitory mechanisms could potentially contribute to the development of CPTP, as previously suggested for PPSP in general[12]. However, it is essential to interpret these results with caution as the clinical implications may be questionable, given a modest relative risk of 0.98 per kPa and a mean difference of 9.9 kPa (95% CI 2.3; 17.5) between patients without CPTP and those with CPTP. Thus, the corresponding decrease in CPTP risk ranges from 0.5 to 35.0%, reflecting the uncertainty of the risk estimates and limited sample size. Nevertheless, the presented data in Paper I are still of interest and offer additional insights, since only few studies have reported CPM and TSP in surgical lung cancer patients, predominantly in relation to acute postoperative pain response[35,37,38,157].

Hospital anxiety and depression scale

HADS was not associated with CPTP in the reported results from Papers I and II. An earlier report evaluating HADS and CPTP 12 months did not find any association either[38]. These results stand in contrast the compiled existing literature, where a recent metanalysis found that psychological factors are of importance and significantly associated with development of PPSP, although associations are considered weak[134]. A recent review and metanalysis specifically concerning CPTP after thoracic and cardiac surgery did not include psychological factors due heterogeneity between exiting studies and limited data[34].

The observed discrepancies between CPTP and PPSP in general probably reflect that psychological factors may be modified by other variables. Furthermore, these variables most likely vary among different patient populations. For instance,

preexisting pain could influence psychological factors such as catastrophizing, anxiety and depression, as earlier reported for HADS[132].

In conclusion, larger studies, and perhaps also a standardized approach, is needed to determine the actual effect of psychological factors on CPTP risk after lung cancer surgery. Since HADS is widely used, this measure was chosen for the purpose of our investigations. However, a formalized evaluation of assessment tools and agreement upon which measure tool to use would strengthen comparability and validity in future studies. This aspect is further discussed in Chapter 5, under Methodological considerations in section 5.3.

Preoperative pain

Preoperative pain was included in Paper I and dichotomized as "pain" versus "no pain". The prevalence of preoperative pain at any location was 28% and no significant associations with CPTP were observed after adjustment for multiple testing. Upon closer examination, the intensity of preoperative pain was mild to moderate regardless of CPTP outcome.

In contrast, preoperative neuropathic pain intensity, evaluated by NPSI, revealed a significant association with CPTP in univariate analysis. Thus, a detailed characterization of preoperative neuropathic pain symptoms seems important, when evaluating the association between preoperative pain and development of chronic pain, since patients without CPTP did not report any markable neuropathic symptoms (median NPSI 0 IQR (0.0; 0.0)), while patients who developed CPTP reported few but significantly more neuropathic pain symptoms (median NPSI 0.5 IQR (0.0; 5.3), p=0.014).

In the secondary analyses in Paper I, preoperative pain was associated with CPTP risk after adjustment for possible confounders, which supports current evidence. However, it must be kept in mind that these results may be underpowered due to loss to follow-up, missing data, and withdrawals. Nevertheless, findings reflects current evidence that preoperative pain is an independent risk factor for development of CPTP[34].

It is important to notice that the collected data on preoperative pain presented in Paper I and III did not contain information on pain location. Thus, some patients classified as CPTP-patients might already have suffered from pain in the surgical area before surgery which would lead to a misclassification in CPTP-status. However, early-stage lung cancer does not usually cause pain, and the observed prevalence of CPTP is similar to others reported in existing literature[110].

In conclusion, the presented data and results on preoperative pain form Papers I and III offer a general descriptive picture of the prevalence and intensity of preoperative pain in surgical lung cancer patients and associations with CPTP. In addition, findings underline the necessity of a more precise characterization of preoperative pain, including neuropathic pain symptoms.

4.1.2. CONCLUSIONS

The results from the evaluation of possible preoperative risk factors of CPTP did not reveal any significant associations with preoperative mechanistic pain profile assessed by QST, and HADS (Paper I). Likewise, investigation of 12-month pain trajectories did not show any association between preoperative HADS and development of CPTP (Paper II).

4.2. POSTOPERATIVE PAIN TRAJECTORIES AND PAIN CHARACTHERISTICS

Paper II of this dissertation introduces a model of 12-month postoperative pain recovery trajectories in lung cancer patients without any preoperative pain. Utilizing a data driven approach by GBTM, our analysis revealed three distinct and clinically relevant pain trajectories. The model was based on numerous bi-weekly observations up to 12 months after surgery with a high response rate throughout follow-up.

A group of patients achieved full recovery and only experienced mild pain which resolved entirely within the first two to three months after surgery. Another group of patients followed a protracted recovery trajectory with mild intensity pain extending beyond three months after surgery. This group exhibited only a slow decline in pain intensity until the pain eventually resolved approximately after six to 12 months. The last group followed an incomplete recovery trajectory and consistently reported moderate pain throughout follow-up without any noteworthy decline in pain intensity.

Patients following a protracted or incomplete recovery path reported more neuropathic pain symptoms. However, neuropathic pain symptoms returned to baseline levels as none of the trajectory groups reported any significant increase in neuropathic pain after 12 months.

4.2.1. THE SIGNIFICANCE OF PAIN TRAJECTORIES

The relationship between acute postoperative pain trajectories and chronic postoperative pain has been explored in previous studies examining PPSP[158,159] and specifically CPTP[38]. These investigations suggest an association between the patterns of acute pain trajectories in the immediate postoperative period and the likelihood of developing long-term chronic postoperative pain.

As previously discussed, acute postoperative pain is strongly association with development of PPSP and might also constitute an independent risk factor and potential target for intervention. This prompts the question of whether a trajectory-based approach offers advantages over other methods of quantifying postoperative pain measured as an average over two to three days or at a single timepoint during admission e.g., on POD 0.

In Paper II, a trajectory-based classification of CPTP was employed instead of the established IASP-definition which is based on pain outcome evaluated three months post-surgery[5]. A comparison of the two classification approaches is presented in Table 4.1 where data is derived from participants included in both of the study samples from Papers I and II.

		CPTP outcome 3 months post-surgery *(Paper I)*		
		No pain	Pain	Total
CPTP trajectory *(Paper II)*	Complete recovery	37 (90.2)	4 (9.8)	41 (100.0)
	Protracted recovery	6 (20.7)	23 (79.3)	29 (100.0)
	Incomplete recovery	0 (0.0)	10 (100.0)	10 (100.0)
	Total	43 (53.8)	37 (46.2)	80 (100.0)

Table 4.1: Comparison of CPTP outcomes among participants included in both Paper I and Paper II. Pain outcomes were determined by 12-month recovery trajectories in Paper II and by a single assessment of pain status three months after surgery in Paper I.

There seems to be good agreement between the two approaches, although it is observed that 9.8% of patients reporting pain beyond three months followed the complete recovery trajectory. This indicates that the time to complete recovery extends beyond three months in some cases. In contrast, 20.7% of patients who did not report pain at the three-month evaluation, had in fact not fully recovered as they reported pain at other assessment times and followed a protracted recovery trajectory.

So, what does a trajectory-based approach offer in addition to the established definition of chronic post-surgical pain? Evaluation of CPTP outcomes at a single timepoint might lack accuracy due to fluctuations in pain symptoms and intensity. On the other hand, it is straightforward and generally a reproducible way to assess and compare the incidence of CPTP among study populations. The method is also easily applied in both clinical practice and scientific studies. However, temporal information during the transition from acute to chronic pain is lost, and no indication on recovery paths can be assessed. This issue might be of significance in treatment decisions and clinical trials, since recent findings indicate distinct and differing long-term recovery trajectories in CPTP patients[42,44].

Furthermore, it is well established that the prevalence of CPTP declines beyond three months and continues to decline up to several years after surgery, implying that time to full recovery can vary considerably[25,110,133]. In addition, some patients might even

experience a delayed onset of CPTP, which could be missed if the patient's pain status is only assessed at single time-point within the first three to six months[107,160]. By a trajectory-based approach, with repeated and frequent assessments during follow-up, these circumstances can be accounted for to some extent, thereby reducing the risk of CPTP-outcome misclassification.

Implications of tracking long-term recovery paths

The characterizations of long-term pain recovery paths presented in Paper II offer valuable insights into the trajectories of postoperative pain after discharge following lung cancer surgery. The presented trajectory analyses are also interesting in the context of the expansion of transitional pain clinics which were conceived to optimize postoperative pain management and long-term treatment strategies in order to alleviate pain after discharge, reduce opioid consumption, and possibly prevent the development of PPSP[10,17,54].

Knowledge on how recovery paths evolve could be of clinical relevance in treatment decisions and monitoring of therapeutic response in patients suffering from PPSP. However, a trajectory-based approach is more laborious and requires additional resources. It is still unknown if tracking pain trajectories is superior to the traditional single time-point definition when evaluating CPTP and more studies are needed to determine whether the method offers any additional advantages in both research and clinical settings.

4.2.2. PAIN CHARACTERISTICS

The pain trajectories presented in Paper II are derived from data on movement-evoked pain only. The importance of distinguishing between movement-evoked pain and pain at rest has earlier been pointed out since the intensity of pain at rest and when active only seem to be moderately correlated[58]. Additionally, it is also of clinical relevance to distinguish and further characterize postoperative pain when considering functional outcomes and pain interference in general[115].

We chose to only report trajectories for movement-evoked pain in Paper II, because we did not have a sufficient sample size to conduct the GBTM exclusively for pain at rest after exclusion of patients with preoperative pain and unknown pain status. This decision was necessary in accordance with current IMMPACT recommendations[114], as the main aim in Paper II was to evaluate pain trajectories for CPTP only, and data on the location of preexisting pain were not collected.

Neuropathic pain symptoms

Chronic neuropathic pain is common after thoracic surgery with a general prevalence of 30%[110]. To provide a more comprehensive understanding of neuropathic symptoms in CPTP, a repeated evaluation of neuropathic pain symptoms was also included in Paper II. The relevance of a detailed characterization of CPTP with evaluation of

neuropathic pain has been emphasized by existing reports which indicate that increased functional impairment may be associated with higher neuropathic pain in patients suffering from CPTP[25].

In our studies (Paper II), all trajectory groups exhibited a significant increase in neuropathic symptoms during the first six months post-surgery, which suggests a transition from early nociceptive and inflammatory pain to the development of a neuropathic pain component. Interestingly, the intensity of neuropathic pain symptoms returned to preoperative levels after 12 months, which is a phenomenon earlier described after thoracotomy and VATS[37,161], even despite experimentally verified lasting nerve damage[37,122,123].

In Paper II, neuropathic pain symptoms were correlated to higher pain intensity as earlier reported[25,46,113,124]. The use of a trajectory approach also revealed that neuropathic pain was associated with a protracted pain recovery and incomplete recovery, which indicates that the presence of neuropathic pain symptoms could influence recovery time. Hence, our findings suggest that neuropathic pain symptoms are associated to an unfavorable recovery path not only in relation to pain intensity, but also recovery time.

4.2.3. CONCLUSIONS

Although the implications of findings reported in Paper II may not be directly applicable in clinical settings, they show that distinct and clinically relevant long-term recovery paths may be identifiable in the early postoperative period after hospital discharge. This insight could potentially aid the detection of patients at risk of developing CPTP by an extended focus on postoperative pain assessments beyond the immediate postoperative pain assessments. The results also contribute to the growing body of knowledge supporting more individualized and targeted approaches to postoperative pain management since patients do not necessarily follow identical recovery paths.

4.3. POSTOPERATIVE PAIN-RELATED IMPARIMENT

Paper III contains results form a repeated assessment of postoperative pain-related impairment. Findings showed a significant association between CPTP and substantial ADL limitations across various activities. The daily activities most affected by CPTP were carrying bag/groceries, arm elevation, climbing stairs, cleaning floors, and coughing, where 50-70% of patients reported limitations during the entire follow-up up to 12 months after surgery.

A total of six ADL-assessments were performed by questionnaire surveys. The first survey was performed two months post-surgery and repeated by two months intervals until 12 months after surgery. Pain intensity data for movement-evoked pain and pain

at rest were obtained separately from the pain diaries. The observed pain intensities were generally mild to moderate (NRS 1 to 3).

Total pain-related impairment was also investigated and quantified as a cumulative impairment score, calculated from reported limitations in 14 individual daily activities. Here, results showed that the presence of pain at rest in conjunction with movement-evoked pain was associated with greater total cumulative impairment across all daily activities.

4.3.1. CHRONIC POST-THORACOTOMY PAIN AND LIMITATIONS IN PHYSICAL FUNCTIONING

The observed pain intensities reported in Papers I-III was predominantly mild to moderate (NRS 1-3), comparable to existing reports on CPTP[110], and the significance of lingering pain among operated lung cancer patients may seem modest if only evaluated by pain intensity. Nevertheless, our analyses presented in Paper III revealed significant associations between even mild intensity CPTP and physical impairment, where up to 80% of patients with CPTP experienced limitations within several daily activities. Furthermore, findings also indicated only modest improvement in ADL-limitations up to 12 months after surgery.

The results presented in Paper III align with earlier findings in lung cancer patients[50,130,162]. In addition, our findings contribute to the knowledge of dynamic recovery patterns in physical functioning after surgery for lung cancer and further highlights the clinical relevance of even mild intensity CPTP.

4.3.2. EVALUATING FUNCTIONAL RECOVERY

The scope of Paper III was confined an evaluation of the consequences of CPTP on daily activities outside the context of overall preoperative functional levels. This is why we utilized the procedure specific questionnaire by Ringsted et al.[52] which only evaluates postoperative ADL limitations attributed to pain only. Therefore, our study did not include a baseline assessment of ADL limitations, and we are unable to compare overall functional levels before and after surgery.

This choice of method should be taken into consideration when interpreting the findings form Paper III because it restricts the ability to evaluate total changes from preoperative to postoperative functional levels. Patients only reported pain-related limitations attributed to their lung surgery, but not limitations due to other causes and preexisting chronic conditions that might affect the patient's ability to perform certain activities. For instance, postoperative dyspnea[163] could affect higher intensity activities such as climbing stairs or cleaning floors.

Another reservation is that evaluation of impairment by questionnaire might not reflect the actual physical capacity, when compared to an objective assessment by direct observation of the patient performing various activities.

On the other hand, it can be considered a strength that a procedure-specific ADL assessment method was used which enables us to determine the patient-reported limitations attributed to CPTP alone. The insights offered by this approach is of relevance when evaluating the possible benefits of preventing and alleviating CPTP seen from the patient´s perspective.

The presented result from Paper III offer in addition to earlier reports employing the same ADL assessment method[51,151], is a repeated assessment of ADL-limitations with a distinction between movement-evoked pain and pain at rest.

4.3.3. CONCLUSIONS

A repeated assessment of functional pain-related impairment showed a significant and enduring difference in ADL-limitations among CPTP patients compared to pain-free patients during a 12-month repeated follow-up. Prescence of pain at rest was associated with higher cumulative impairment.

The observed pain intensity of CPTP was generally mild but patients consistently reported substantial pain-related ADL-limitations, emphasizing the necessity for further research into underlying mechanisms, perioperative risk stratification, and the exploration and development of new treatments and rehabilitation.

CHAPTER 5. GENERAL DISCUSSION

This dissertation has presented investigations of associations between chronic postoperative pain and selected possible risk factors of CPTP and have further provided detailed descriptions of the transition to chronic pain and pain-related impairment. Paper I reported new results from a preoperative assessment by QST and HADS screening while Papers II-III presented analyses of 12-month post-operative pain trajectories and functional recovery paths.

The nature of the presented studies reported in Papers I-III are explorative and observational. They have been conducted with the aim to further elucidate possible underlying contributors to CPTP risk and describe recovery patterns to convey a deeper understanding of how CPTP evolves in patients undergoing surgery for lung cancer.

In this chapter, main findings from Papers I-III are discussed in relation to general concepts in preoperative risk stratification and perioperative pain management. These topics are followed by some methodological considerations and limitations pertaining to the presented analyses in the Papers.

5.1. RISK STRATIFICATION

The clinical value of quantitative sensory testing

Evidence of the predictive value of preoperative QST-assessments is yet to be studied under universally standardized settings in larger observational studies[12]. It is doubtful whether a single QST-parameter could be "that one" risk predictor in preoperative PPSP risk stratification in general. However, QST-assessments still offer insights into the significance of preoperative mechanistic pain profiling and possible correlations with PPSP risk. In addition, it may play a role, not only as a risk factor, but also a predictor of postoperative pain treatment response[164].

Risk prediction models

As previously discussed[‡], some authors have devised risk calculators intended for clinical use[64]. Certain risk factors such as acute pain, various psychological factors, and preoperative pain, seem independent of surgical specialty, but the compatibility between studies within and between specialties is still limited. Another factor to

[‡] Chapter 2, Section 2.1.2, p. 7.

consider is the complexity of both surgery specific and general models. Some factors might be more influential and common in certain surgical fields than others. Patient populations within different surgical fields may be quite different, and some surgeries are undoubtedly associated with more chronic pain than others[2].

A general risk stratification model for clinical use should not be too complex and preferably contain all relevant variables form all domains within the biopsychosocial model in pain medicine. The question is which variables to include in preoperative risk assessment and whether the collection of these variables is feasible in clinical practice. If all patients were to undergo a QST-assessment by cuff algometry, as conducted in Paper I, the information gathered should be of high value in treatment decisions, because the procedure is time consuming and requires dedicated staff and training. In contrast, preoperative pain status and HADS could easily be assessed by questionnaires.

Clinical risk prediction models must be based on firm evidence if used in treatment decisions, and an evaluation of the benefits and possible harm to patients should be thoroughly investigated before broader implementation. To facilitate model synthesis, the first and foremost matter is to identify and validate PPSP risk predictors in larger scale studies, several of which are currently under way[62,63]. Nonetheless, smaller exploratory studies are still warranted for early investigation and identification of new potential risk factors. Paper I contributes to this aspect with results from a preoperative QST-assessment by cuff algometry.

5.2. ENHANCED RECOVERY AND BEYOND DISCHARGE FROM HOSPITAL

Preoperative risk predictors may help identify patients at risk of PPSP, but perioperative factors such as acute pain and emerging complications also contribute to PPSP risk[10,165]. Obviously, such factors cannot be assessed beforehand but should be held in mind if the patient's risk profile changes early in the postoperative period.

Enhanced recovery after surgery

With the advent of ERAS protocols, heighted attention has been brought to preoperative optimization and focus on early postoperative complications and pain management after surgery. The overall long-term benefits of ERAS in itself remain sparsely elucidated, but sufficient pain control and early mobilization, which form a cornerstone in the ERAS concept, are pivotal factors to prevent complications and ensuing poorer long-term outcomes[137].

In a retrospective study, ERAS did not effectively reducing long-term opioid use in surgical lung cancer patients[166], while other studies report a decrease[104,105]. Because

these existing studies are retrospective and only contain limited data beyond the earliest postoperative period, conclusions regarding an effect of ERAS on the development of CPTP cannot be drawn. Consequently, even though ERAS do benefit multiple aspects of recovery and possibly reduces the need for persistent opioid treatment after surgery for lung cancer, long-term benefits have yet to be demonstrated.

Transitional pain services

Transitional pain clinics have emerged to fill the gap in pain management after discharge with the purpose to improve postoperative pain care and functional recovery through a multimodal approach. The aim is to optimize pain management in the entire perioperative period, including extended care after discharge, particularly in complex pain patients at elevated risk for developing PPSP[54,144]. The initiative was devised to close the gap in pain care from discharge and until referral to a chronic pain clinic in case of manifest chronic postsurgical pain (Figure 5.1).

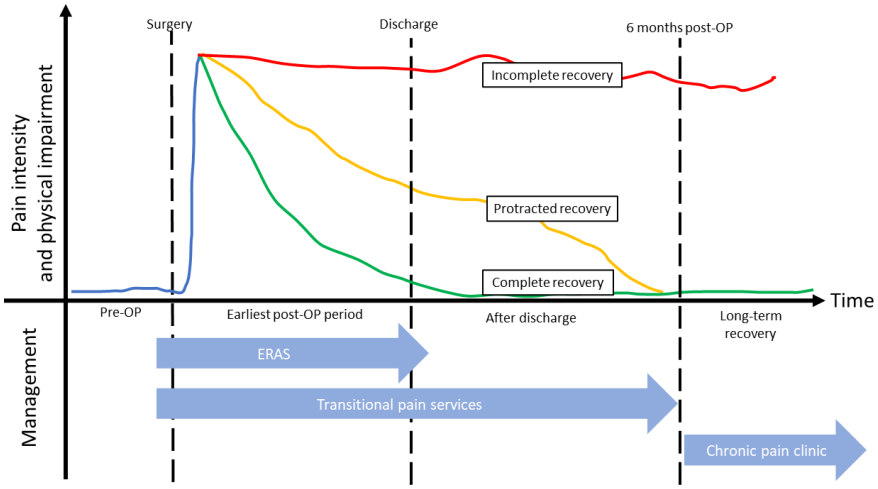

Figure 5.1: Recovery paths and postoperative pain management in the age of ERAS and transitional pain services. Transitional pain services offer perioperative comprehensive care to patients at elevated risk for an unfavorable recovery path and chronic post-surgical pain, extending beyond the scope of ERAS.

Lung cancer patients are gradually being discharged earlier, usually within two to four days after surgery, and this tendency has only increased over the past years. Since

CPTP is highly prevalent after lung resections and patients are discharged within a few days, this subpopulation constitutes a highly relevant target for focused intervention and follow-up from transitional pain services.

The obtained clinical information from a formalized follow-up is not only of importance to clinicians in treatment decisions, but also of immense value to pain researchers. As we also experienced, it can be challenging to obtain sufficient data on pain measurements, e.g., for calculation of valid pain trajectories, especially beyond discharge. This information must be considered of particular interest, since the changes in pain quality and the underlying pain mechanism are yet not fully understood with the respect to the transition from acute nociceptive pain to inflammatory pain, and in some cases eventually to neuropathic pain[8].

Furthermore, the study of pain trajectories may be of interest in future treatment decisions, since results from Paper II demonstrated that distinct recovery paths could be detected. These results were based on frequent pain assessments by a simple questionnaire, which could conveniently be accumulated "in real life" by a dedicated transitional pain service, as earlier proposed[11,144,167].

Ideally, more knowledge and heightened attention to proactive multimodal peri- and postoperative pain management could help alleviate or prevent PPSP, which is one of the goals of ERAS and transitional pain services. However, larger randomized trials in various surgical populations are necessary to convincingly demonstrate improved long-term pain outcomes, despite recognition of the many benefits already established.

5.3. METHODOLOGICAL CONSIDERATIONS

In this section, general methodological considerations, and limitations in connection to the presented studies form Paper I-III are highlighted. In-depth discussions of methods and limitations can be found in the individual Papers.

5.3.1. MEASSUREMENT METHODS

Traditionally, the assessment of postoperative pain recovery has been confined to a limited evaluation of pain intensity and quality, often lacking insight into the mental, physical, and social dimensions of pain. Over the past decade, there has been a notable shift towards a more comprehensive understanding of pain recovery with emphasis on the importance of pain interference and patient-reported outcome measures (PROMs). These measures encompass a broader array of dimensions directly derived from patient experiences, and provide a more holistic and patient-centered perspective containing more clinically meaningful outcome domains in addition to simple pain charachteristics[168].

What should we measure, and how?

In pain research, various outcome measures have been used to evaluate postoperative pain and pain-related outcomes, often making direct comparison of studies difficult and sometimes unreliable. The PROMPT/IMI-PainCare project aims to standardize pain and pain-related measurements in pain trials. Four domains were defined in four surgical procedures, including sternotomy, with the primary focus on acute perioperative pain[169]. Within the pain domain, it was concluded, that a distinction between pain intensity during activity and pain during rest should be made, as also emphasized by Gilron et al.[115]. This is especially relevant in relation to pain-related limitations in physical functioning, which was the second domain identified.

The next question pertains to which tool to use for evaluation of each domain and whether the same tool would be appropriate across all surgical procedures and patient populations. The Consensus-based standards for the selection of health measurement instruments (COSMIN) initiative was established to promote transparency and consistency in the assessment of measurement methods in clinical research. A COSMIN-checklist has been introduced to aid clinicians and researchers to evaluate chosen measurement methods in relation to reliability, validity, responsiveness, and interpretability of measures[170]. To my knowledge, no specific consensus-based recommendations have been developed for CPTP after VATS and thoracotomy.

The selection of outcome domains and measurement tools in Papers I-III was based on the research questions raised and included assessments of pain and physical functioning. However, general guidelines for outcome domains have been proposed for chronic pain trials in the IMMPACT recommendations, which also include emotional functioning, PROM ratings of global improvement after treatment, treatment adherence, and adverse events, in addition to pain assessments and physical functioning.

The data and studies presented in Papers I – III and are purely observational and contains no intervention outcomes, but emotional functioning could have been included to further strengthen the results with regard to total pain interference. The decisions regarding questionnaire selection were primarily based on existing literature in comparable study populations.

5.3.2. RISK OF BIAS

Patients were consecutively approached during study recruitment when research staff was available. No reasons were recorded in case of refusal, and selection bias should be considered as the sample size is relatively small. However, when comparing our cohort to previous reports, baseline demographics, prevalence, and intensity of CPTP are similar, indicating that the study samples in Papers I-III are representative of the intended study population.

Information bias should also be considered, particularly concerning misclassification regarding CPTP outcomes (Paper I), pain trajectory groups (Paper II), and recovery paths classifications (Paper III). Measurement methods need to be accurate and standardized for reliable internal and external comparison. Follow-up was entirely based on questionnaire surveys, and although validated questionnaires were used, this can pose challenges as patients may find it difficult to differentiate between CPTP and preexisting pain or concomitant pain from other causes. In addition, even though our results correspond to previous findings, a clinical examination is necessary to genuinely evaluate and distinguish CPTP, avoid misclassification, and truly assess the objective extent of pain-related limitations.

Finally, reporting bias should also be kept in mind, as there could be a tendency to either less or more withdrawals and missing data dependent on CPTP status.

5.3.3. CONFOUNDING

Confounding in clinical research refers to a situation where the association between an exposure (independent variable) and an outcome is distorted or masked by the presence of unrecognized additional factors. A confounding variable that is associated with the exposure and/or outcome can lead to an erroneous conclusion regarding causality and/or associations if not recognized.

In our studies, Paper I and II included exploratory investigations of associations between various possible CPTP risk factors, and adjusted estimates were only reported in Paper I. As outlined in the background chapter, many possible risk factors have been identified, but only a few can be considered established risk factors. Different methodologies, insufficient power, and a lacking understanding of underlying causal mechanisms in many instances, make it difficult to compile sound evidence for many proposed risk factors. The interaction and correlations between risk factors are other aspects to consider when drawing conclusions, especially when including multiple risk factors in statistical analyses. The presented analyses of associations and CPTP risk presented in Paper I and II should be interpreted keeping these universal issues in mind.

5.3.4. LIMITATIONS

Study sample and missing data

Due to limited sample size and missing data, the analyses of associations between CPTP and the included risk factors should be interpreted with care. Given the explorative nature of our studies, power calculations were based on PDT estimated form a previous study in herniotomy patients available at the time of study initiation.

Our original aim was to include 206 participants, but the study sample size fell short of the number intended for primary analysis which reduces the power of our results.

No sensitivity analyses were performed since only limited data beyond baseline were available from withdrawals and loss to follow-up.

Risk and causality

We found no significant associations between the QST parameters and HADS in relation to CPTP. The limited available data did not allow for further meaningful analysis of risk predictors.

Generally, the selection of individual risk factors can introduce risk of bias and confounding. Considering the vast existing literature, CPTP cannot reasonably be attributed to just a single or some selected few risk factors. However, smaller explorative studies investigating new and suggested biomarkers in relation to PPSP risk are still warranted within specific patient populations. Presently, larger studies containing a multitude of risk factors within several domains are underway, and this will hopefully further elucidate the complexity and interconnection of both risk and causal factors in chronic postsurgical pain[63].

Defining of CPTP

According to the definition of CPTP, only persistent novel pain occurring after thoracotomy can be considered as such. Our data do not contain any information on the location of preoperative pain, which could result in an overestimation of CPTP. Although preoperative pain in relation to the operation area is less common in lung cancer surgery, patients with preoperative pain should be excluded when evaluating CPTP. In Paper I, patients with preoperative pain were not excluded, as associations between preoperative pain were investigated. The prevalence of CPTP with any NRS≥1 was 46.3%, corresponding to previous reports[110]. In Paper II, patients with unknown or any preoperative pain were excluded, and here the prevalence of CPTP at six months was 49.4%. Both papers are based on the same cohort, and the six-month CPTP prevalence is comparable, indicating that CPTP was not drastically overestimated in Paper I, despite the lacking the distinction of preexisting pain location. Nevertheless, it would have been most accurate to discern between pain in relation to the operation area and other body locations, which is mandatory in the current IASP definition of chronic postsurgical pain.

CHAPTER 6. PERSPECTIVES

The primary goal in the development of cancer treatment, including surgery, has traditionally been to improve survival rates. However, secondary outcomes, notably pain and physical function, cannot be ignored. With ever more effective treatments and improved survival rates, there has been an expansion in the population of patients who suffer from the side effects and consequences of previous cancer treatment. In surgical patients, PPSP poses a significant clinical problem among cancer survivors, resulting in decreased quality of life and functional impairment.

Despite increasing focus and the development of new surgical techniques and extensive research, the incidence of PPSP has remained largely unchanged in the past decades. This somewhat disappointing picture is also observed after thoracic surgery, despite the widespread adaptation of minimally invasive procedures by VATS.

6.1.1. THE SIGNIFICANCE OF RISK FACTORS

The underlying causality and pathophysiology of CPTP have yet to be fully elucidated, and many potential modifiable risk factors have been proposed, primarily related to perioperative pain control and surgical approach. Nonetheless, targeting single perioperative risk factors, such as acute pain, has not proven to be effective alone. Most likely, multiple risk factors must be considered in order to precisely predict the risk of CPTP in individual patients.

The identification and validation of risk factors is ongoing and necessary for development of precise risk stratification models. For practical reasons and clinical applicability, included variables should be easily obtainable and intuitive to both the health care provider and the patient. In Paper I, we explored preoperative risk factors, and while neither HADS nor the QST-assessments were independently associated with CPTP, this still needs to be determined in larger observational studies.

Risk factor interactions also need to be considered since CPTP cannot be attributed to any single standing risk factor identified so far. The total risk might rather be a combination of risk factors interacting dynamically with each other and perhaps changing, not simply perioperatively, but during the entire recovery period.

Nevertheless, risk stratification based on a combination of risk factors could help optimize perioperative pain management. In addition, further research into established and novel biomarkers within defined patient populations may facilitate even more precise models for clinical use and enable individualized tailored treatment strategies[10,20] .

6.1.2. CLINICAL IMPLICATIONS OF PAIN TRAJECTORIES

Papers II and III gave detailed descriptions of recovery paths and showed a significant impact of CPTP in recovering lung cancer patients. Our studies showed that recovery trajectories diverged early, suggesting that a trajectory-based approach possibly could be utilized to identify patients at risk of transitioning to CPTP. Our findings also suggest that that early intervention is warranted during the early post-operative period after discharge, since we observed little to no spontaneous remission in pain intensity (Paper II) or ADL-limitations (Paper III) among patients who eventually developed CPTP.

The development of PPSP is complex and multifactorial, and while preoperative risk prediction models may help identify patients at elevated risk, many perioperative factors also seem to significantly influence the transition to PPSP, particularly acute perioperative pain. In Paper II, we presented pain recovery trajectories stretching far beyond discharge and demonstrated that unresolved early postoperative pain within the first two to twelve weeks was present in some patients.

Early detection and treatment in case of an unfavorable or pathologic recovery path may be more effective to alleviate and prevent chronification and transition to CPTP. Whether or not this potential "window of treatment opportunity" is feasible, must however be investigated in randomized trials.

6.1.3. CLINICAL PRACTICE AND RESEARCH

Optimization of pain management

Current experience from transitional pain services shows that a dedicated effort in pain control extending beyond discharge is beneficial in many aspects. Meanwhile, a question that remains is how to intervene in order to prevent PPSP? Most current studies focus on preventive measures against acute pain during admission to hospital. This immediate perioperative period constitutes a more controlled and convenient setting for clinical pain trials and acute pain is an easy target easily recognized, although the notion that acute pain causes sensitization and increases the risk for development PPSP is still controversial. Nevertheless, acute pain is definitely relevant in relation to other surgical complications, and thus seemingly an obvious low hanging fruit to be picked first[100].

The dedicated efforts instituted with existing ERAS programs within several surgical fields have already proven effective to minimize opioid consumption, increase patient satisfaction, and enhance functional recovery. However, research into specialized pain management beyond discharge should not be neglected. Expanded knowledge on recovery trajectories beyond discharge similar to the data presented in Paper II and III offer new insights in this aspect.

Testing of new treatments

Continued exploration of new anesthetic drugs and targets should still be encouraged. Preemptive longer-lasting nerve blocks such as liposomal bupivacaine could be of interest in the perioperative pain management after VATS, although existing trials have shown mixed results[171].

The testing of novel treatments such as an even more long-lasting blockade with botulinum neurotoxin have shown promising results in the treatment of post-mastectomy pain syndrome[173], which could be considered analogous to CPTP. In my opinion, this could be interesting to investigate in a VATS setting, not only as treatment of established CPTP, but also as preemptive analgesia. Botulinum toxin could be injected in an appropriate dosage just like the traditional perioperative paravertebral or intercostal blockade with bupivacaine, and perhaps even in combination.

Assessments of persisting postsurgical pain

Recently, there has been an increasing focus on how to evaluate PPSP in trials, leading to a recognition that more standardized and detailed approaches to pain measurements are needed to facilitate comparability between studies.

It has recently been proposed that pain assessments should also include an evaluation of the consequences of PPSP, including procedure-specific functional measures[115]. Such measures need to be clinically relevant, but also meaningful to the patient in relation to the disease treated. For example, walking and mobility might be the main challenge in knee replacement surgery, while carrying grocery bags or coughing might be the most impacted activity in CPTP patients.

The relevance of evaluating pain interference is supported by the findings from Paper III which showed that pain-related impairment was significant, although the observed pain intensity was generally mild among patients suffering from CPTP. In addition, our results also indicated that future studies ideally should include a distinction between movement-evoked pain and pain at rest, since presence of the latter was associated to higher impairment.

Lastly, in my opinion, we need more studies containing clinical assessments of pain-related impairment due to CPTP. Such studies would allow for method validation by correlating clinical observations to survey-based methods since patients might unconsciously compensate and adapt or avoid pain provoking activities, leading to an underestimation of the actual pain-related limitations.

CHAPTER 7. CONCLUSIONS

This dissertation offers insights into chronic post-thoracotomy pain in surgical lung cancer patients and contains investigations of preoperative risk factors, 12-month pain trajectories, and pain-related physical impairment.

No associations were observed between preoperative QST parameters and 6-month incidence of CPTP. Maximum acute pain on the first postoperative day and preexisting pain at any location were associated with development of CPTP. The six months prevalence of CPTP was 46.3%, and the pain intensity was predominantly mild with an NRS≤3.

An investigation of 12-month pain trajectories identified three distinct recovery paths. One group of patients achieved full recovery within two to three months after surgery and did not develop CPTP. Another group followed a protracted recovery path with persisting pain beyond three months. These patients predominantly experienced mild pain but did eventually recover within the 12-month follow-up period. The last group of patients did not achieve any significant recovery and reported constant pain of moderate intensity throughout follow-up.

Patients suffering from CPTP reported considerably more long-term physical impairment with permanent ADL limitations compared to pain-free patients. Only modest recovery was observed, and presence of pain at rest was associated with more ADL limitations.

Our findings underline that CPTP continues to constitute a common and significant clinical challenge after surgery for lung cancer. Pain-related physical impairment among patients suffering from CPTP are substantial and enduring beyond 12 months after surgery.

Insights offered from this dissertation and associated papers indicate that risk stratification and early identification of unfavorable recovery paths are possible. The ability to identify and monitor patients at risk of unfavorable recovery paths could potentially facilitate an opportunity for early intervention to prevent or alleviate chronic post thoracotomy pain and pain-related impairment among patients undergoing surgery for lung cancer.

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APPENDIX A. PAPERS

Paper I

Danielsen AV, Andreasen JJ, Dinesen B, Hansen J, Petersen KK, Simonsen C, Arendt-Nielsen L. **Chronic post-thoracotomy pain after lung cancer surgery: a prospective study of preoperative risk factors**. Scandinavian Journal of Pain. 2023;29(3):501-510. doi:10.1515/sjpain-2023-0016

Corrigendum to Paper I:

Danielsen AV, Andreasen JJ, Dinesen B, Hansen J, Petersen KK, Simonsen C, Arendt-Nielsen L. **Corrigendum to "Chronic post-thoracotomy pain after lung cancer surgery: a prospective study of preoperative risk factors"** Scandinavian Journal of Pain. Scand J Pain. 2024 Apr 29;24(1). doi: 10.1515/sjpain-2024-0021

Paper II

Danielsen AV, Andreasen JJ, Dinesen B, Hansen J, Petersen KK, Bisgaard J, Simonsen C, Arendt-Nielsen. **Pain trajectories and neuropathic pain symptoms following lung cancer surgery: a prospective cohort study.** European Journal of Pain. 2024; preprint. doi: 10.1002/ejp.2265

Paper III

Danielsen AV, Andreasen JJ, Dinesen B, Hansen J, Petersen, Duch KS, KK, Simonsen C, Arendt-Nielsen L. **Pain-related impairment and functional recovery in daily activities after lung cancer surgery: A 1-year prospective cohort study**

APPENDIX B. QUESTIONNAIRES

Hospital Anxiety and Depression Scale (HADS)

Pain dairy

Limitations in activities of daily life

Neuropathic pain symptom inventory (NPSI)

Hospital anxiety and depression scale (HADS)

SMI CENTER FOR SENSORY-MOTOR INTERACTION Dato for besvarelse:_____

PID 044 Humør 01 : DKSS-56LR-P72N

Humør spørgeskema

Vejledning: Nedenfor finder du en række udsagn, der beskriver, hvordan folk har det. Ved disse udsagn bedes du vælge det svar, som bedst beskriver, hvordan du har haft det i den sidste uges tid.

Jeg føler mig anspændt:

☐ Næsten hele tiden

☐ Meget af tiden

☐ En gang imellem

☐ Slet ikke

Jeg nyder stadig de ting, som jeg tidligere har nydt:

☐ Helt, som jeg plejer

☐ Ikke helt så meget

☐ Kun lidt

☐ Næsten ikke

Jeg er bange for, at der skal ske noget frygteligt:

☐ Helt bestemt og meget voldsomt

☐ Ja, men så slemt er det ikke

☐ Lidt, men det bekymrer mig ikke

☐ Slet ikke

AALBORG UNIVERSITETSHOSPITAL REGION NORDJYLLAND

Jeg kan le og se det morsomme i en situation:

☐ En stor del af tiden

☐ Meget af tiden

☐ En gang imellem, men ikke så tit

☐ Kun lejlighedsvis

Jeg gør mig bekymringer:

☐ Lige så meget som jeg plejer

☐ Ikke helt så meget nu

☐ Helt klart ikke så meget nu

☐ Slet ikke

Jeg føler mig glad:

☐ Slet ikke

☐ Ikke så tit

☐ Nogle gange

☐ Det meste af tiden

Jeg kan sidde roligt og føle mig afslappet:

☐ Helt bestemt

☐ Som regel

☐ Ikke så tit

☐ Slet ikke

Jeg føler det som om, jeg fungerer langsommere:

☐ Næsten hele tiden

☐ Meget ofte

☐ Nogle gange

☐ Slet ikke

Jeg føler mig bange, som om jeg har "sommerfugle i maven":

☐ Slet ikke

☐ Lejlighedsvis

☐ Temmelig tit

☐ Meget ofte

Jeg har mistet interessen for mit udseende:

☐ Fuldstændig

☐ Jeg er ikke så omhyggelig, som jeg burde være

☐ Måske er jeg knap så omhyggelig som før

☐ Jeg er lige så omhyggelig, som jeg altid har været

Jeg føler mig rastløs, som om jeg hele tiden skal være i bevægelse:

☐ Virkelig meget

☐ Temmelig meget

☐ Ikke særlig meget

☐ Slet ikke

PID 044 Humør 01 : DKSS-56LR-P72N

Jeg glæder mig til ting, som skal ske:

☐ Lige så meget som før

☐ Noget mindre, end jeg plejer

☐ Helt klart mindre, end jeg plejer

☐ Næsten ikke

Jeg får en pludselig fornemmelse af panik:

☐ Særdeles ofte

☐ Temmelig ofte

☐ Ikke særlig ofte

☐ Slet ikke

Jeg kan nyde en god bog eller et radio/TV program:

☐ Ofte

☐ Nogle gange

☐ Ikke særlig tit

☐ Meget sjældent

Tak for din besvarelse

Pain diary

SMI CENTER FOR SENSORY-MOTOR INTERACTION Dato for besvarelse:_____

PID 204 Smertedagbog 27 : ND27-L8YR-R4D1

Smertedagbog

Hvordan vil du vurdere styrken af dine smerter i hvile?

- ☐ 0 - Ingen smerter
- ☐ 1
- ☐ 2
- ☐ 3
- ☐ 4
- ☐ 5
- ☐ 6
- ☐ 7
- ☐ 8
- ☐ 9
- ☐ 10 - Værst tænkelige smerter

Hvordan vil du vurdere styrken af dine smerter under gang?

- ☐ 0 - Ingen smerter
- ☐ 1
- ☐ 2
- ☐ 3
- ☐ 4
- ☐ 5
- ☐ 6
- ☐ 7
- ☐ 8
- ☐ 9
- ☐ 10 - Værst tænkelige smerter

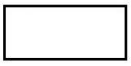
AALBORG UNIVERSITETSHOSPITAL REGION NORDJYLLAND

PID 204 Smertedagbog 27 : ND27-L8YR-R4D1

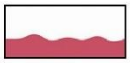
Hvordan vil du vurdere dine smerter under fysisk aktivitet?

- ☐ 0 - Ingen smerter
- ☐ 1
- ☐ 2
- ☐ 3
- ☐ 4
- ☐ 5
- ☐ 6
- ☐ 7
- ☐ 8
- ☐ 9
- ☐ 10 - Værst tænkelige smerter

Vælg det billede, der bedst beskriver dine smerter



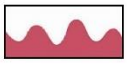
☐ Ingen smerter



☐ Konstante smerter med lette udsving

☐ Konstante smerter med smerteanfald

☐ Smerteanfald, ingen smerter mellem anfaldene



☐ Hyppige smerteanfald, med smerter mellem anfaldene

Tak for din besvarelse

Limitations in activities of daily life

SMI CENTER FOR SENSORY-MOTOR INTERACTION Dato for besvarelse:_____

PID 204 Daglige aktiviteter 06 : NJCS-6GQM-PR41

Daglige aktiviteter

Føler du at smerter fra din lungeoperation påvirker dig, når du skal bære indkøbsposer, tunge tasker eller lign.?

- ☐ Udfører aldrig denne aktivitet pga. smerter
- ☐ Udfører aldrig denne aktivitet
- ☐ Smerter forhindrer mig meget
- ☐ Smerter forhindrer mig noget
- ☐ Smerter forhindrer mig lidt
- ☐ Smerter forhindrer mig slet ikke

Føler du at smerter fra din lungeoperation påvirker dig, når du skal vaske hår, løfte armen, bevæge skulderen eller åbne skabe over skulderhøjde?

- ☐ Udfører aldrig denne aktivitet pga. smerter
- ☐ Udfører aldrig denne aktivitet
- ☐ Smerter forhindrer mig meget
- ☐ Smerter forhindrer mig noget
- ☐ Smerter forhindrer mig lidt
- ☐ Smerter forhindrer mig slet ikke

Føler du at smerter fra din lungeoperation påvirker dig, når du skal støvsuge eller vaske gulv?

- ☐ Udfører aldrig denne aktivitet pga. smerter
- ☐ Udfører aldrig denne aktivitet
- ☐ Smerter forhindrer mig meget
- ☐ Smerter forhindrer mig noget
- ☐ Smerter forhindrer mig lidt
- ☐ Smerter forhindrer mig slet ikke

Føler du at smerter fra din lungeoperation påvirker dig, når du skal gå 1 km?

- ☐ Udfører aldrig denne aktivitet pga. smerter
- ☐ Udfører aldrig denne aktivitet
- ☐ Smerter forhindrer mig meget
- ☐ Smerter forhindrer mig noget
- ☐ Smerter forhindrer mig lidt
- ☐ Smerter forhindrer mig slet ikke

Føler du at smerter fra din lungeoperation påvirker dig, når du skal gå op af trapper?

- ☐ Udfører aldrig denne aktivitet pga. smerter
- ☐ Udfører aldrig denne aktivitet
- ☐ Smerter forhindrer mig meget
- ☐ Smerter forhindrer mig noget
- ☐ Smerter forhindrer mig lidt
- ☐ Smerter forhindrer mig slet ikke

PID 204 Daglige aktiviteter 06 : NJCS-6GQM-PR41

Føler du at smerter fra din lungeoperation påvirker dig, når du skal sidde på hug eller bøje dig forover?

- ☐ Udfører aldrig denne aktivitet pga. smerter
- ☐ Udfører aldrig denne aktivitet
- ☐ Smerter forhindrer mig meget
- ☐ Smerter forhindrer mig noget
- ☐ Smerter forhindrer mig lidt
- ☐ Smerter forhindrer mig slet ikke

Føler du at smerter fra din lungeoperation påvirker dig, når du skal stå op i 30 min.?

- ☐ Udfører aldrig denne aktivitet pga. smerter
- ☐ Udfører aldrig denne aktivitet
- ☐ Smerter forhindrer mig meget
- ☐ Smerter forhindrer mig noget
- ☐ Smerter forhindrer mig lidt
- ☐ Smerter forhindrer mig slet ikke

Føler du at smerter fra din lungeoperation påvirker dig, når du skal stå ud af sengen?

- ☐ Udfører aldrig denne aktivitet pga. smerter
- ☐ Udfører aldrig denne aktivitet
- ☐ Smerter forhindrer mig meget
- ☐ Smerter forhindrer mig noget
- ☐ Smerter forhindrer mig lidt
- ☐ Smerter forhindrer mig slet ikke

Føler du at smerter fra din lungeoperation påvirker dig, når du skal svømme?

- ☐ Udfører aldrig denne aktivitet pga. smerter
- ☐ Udfører aldrig denne aktivitet
- ☐ Smerter forhindrer mig meget
- ☐ Smerter forhindrer mig noget
- ☐ Smerter forhindrer mig lidt
- ☐ Smerter forhindrer mig slet ikke

Føler du at smerter fra din lungeoperation påvirker dig, når du skal cykle?

- ☐ Udfører aldrig denne aktivitet pga. smerter
- ☐ Udfører aldrig denne aktivitet
- ☐ Smerter forhindrer mig meget
- ☐ Smerter forhindrer mig noget
- ☐ Smerter forhindrer mig lidt
- ☐ Smerter forhindrer mig slet ikke

Føler du at smerter fra din lungeoperation påvirker dig, når du skal køre bil?

- ☐ Udfører aldrig denne aktivitet pga. smerter
- ☐ Udfører aldrig denne aktivitet
- ☐ Smerter forhindrer mig meget
- ☐ Smerter forhindrer mig noget
- ☐ Smerter forhindrer mig lidt
- ☐ Smerter forhindrer mig slet ikke

Føler du at smerter fra din lungeoperation påvirker dig, når du skal ligge på den opererede side?

- ☐ Udfører aldrig denne aktivitet pga. smerter
- ☐ Udfører aldrig denne aktivitet
- ☐ Smerter forhindrer mig meget
- ☐ Smerter forhindrer mig noget
- ☐ Smerter forhindrer mig lidt
- ☐ Smerter forhindrer mig slet ikke

Føler du at smerter fra din lungeoperation påvirker dig, når du skal hoste eller tage en dyb indånding?

- ☐ Udfører aldrig denne aktivitet pga. smerter
- ☐ Udfører aldrig denne aktivitet
- ☐ Smerter forhindrer mig meget
- ☐ Smerter forhindrer mig noget
- ☐ Smerter forhindrer mig lidt
- ☐ Smerter forhindrer mig slet ikke

Føler du at smerter fra din lungeoperation påvirker dig, når du skal sidde i en stol i 30 min.?

- ☐ Udfører aldrig denne aktivitet pga. smerter
- ☐ Udfører aldrig denne aktivitet
- ☐ Smerter forhindrer mig meget
- ☐ Smerter forhindrer mig noget
- ☐ Smerter forhindrer mig lidt
- ☐ Smerter forhindrer mig slet ikke

Føler du at smerter fra din lungeoperation påvirker dig, når du skal koncentrere dig om at se fjernsyn?

- ☐ Udfører aldrig denne aktivitet pga. smerter
- ☐ Udfører aldrig denne aktivitet
- ☐ Smerter forhindrer mig meget
- ☐ Smerter forhindrer mig noget
- ☐ Smerter forhindrer mig lidt
- ☐ Smerter forhindrer mig slet ikke

Føler du at smerter fra din lungeoperation påvirker dig, når du skal sove?

- ☐ Udfører aldrig denne aktivitet pga. smerter
- ☐ Udfører aldrig denne aktivitet
- ☐ Smerter forhindrer mig meget
- ☐ Smerter forhindrer mig noget
- ☐ Smerter forhindrer mig lidt
- ☐ Smerter forhindrer mig slet ikke

Tak for din besvarelse

Neuropathic pain symptom inventory (NPSI)

SMI CENTER FOR SENSORY-MOTOR INTERACTION

Dato for besvarelse:_____

PID 204 Nerverelaterede smerter 03 : TR9H-82QQ-PL2P

Nerverelaterede smerter

Du lider muligvis af smerter i forbindelse med beskadigelse af nervesystemet. Disse smerter kan være af flere typer. Der findes spontane smerter, det vil sige smerter, der kommer uden nogen som helst stimulering, som kan være længerevarende eller komme i form af korte smerteanfald. Der findes ligeledes smerter, der fremprovokeres via forskellige stimuleringer (gnidning, tryk, kuldekontakt). Du kan føle en eller flere typer af smerter.

Vi vil gerne vide, om du har spontane smerter, det vil sige smerter, der kommer uden nogen som helst stimulering. For hvert af følgende spørgsmål vælges det tal, der svarer bedst til **gennemsnittet af intensiteten af dine spontane smerter i løbet af de seneste 24 timer**. Vælg 0, hvis du ikke har følt denne type smerte.

Føles din smerte som en brænden?

- ☐ 0: Ingen brænden
- ☐ 1
- ☐ 2
- ☐ 3
- ☐ 4
- ☐ 5
- ☐ 6
- ☐ 7
- ☐ 8
- ☐ 9
- ☐ 10: Værst tænkelige brænden

Har du smerteanfald, som kan sammenlignes med knivstik?

- ☐ 0: Ingen knivstik
- ☐ 1
- ☐ 2
- ☐ 3
- ☐ 4
- ☐ 5
- ☐ 6
- ☐ 7
- ☐ 8
- ☐ 9
- ☐ 10: Værst tænkelige knivstik

Hvor mange af disser smerteanfald har du haft i løbet af de sidste 24 timer? :

Afkryds det svar, der passer bedst til din tilstand

- ☐ Mere end 20
- ☐ Mellem 11 og 20
- ☐ Mellem 6 og 10
- ☐ Mellem 1 og 5
- ☐ Ingen smerteanfald

Vi vil gerne vide, om du har smerter, der er blevet fremprovokerede eller forstærkede af berøring, tryk, eller kontakt med kolde genstande på det smertende område. For hvert af følgende spørgsmål vælges det tal, der svarer bedst til **gennemsnittet af intensiteten af dine fremprovokerede smerter i løbet af de seneste 24 timer**. Vælg 0, hvis du ikke har følt denne type smerte.

Har du smerter, der fremprovokeres eller forstærkes af kontakt med en kold genstand på det smertende område?

- ☐ 0: Ingen smerte
- ☐ 1
- ☐ 2
- ☐ 3
- ☐ 4
- ☐ 5
- ☐ 6
- ☐ 7
- ☐ 8
- ☐ 9
- ☐ 10: Værst tænkelige smerte

Vi vil gerne vide, om du har unormale fornemmelser i det smertende område. For hvert af følgende spørgsmål vælges det tal, der svarer bedst til **gennemsnittet af intensiteten af dine unormale fornemmelser i løbet af de seneste 24 timer**. Vælg 0, hvis du ikke har haft denne type fornemmelse.

Har du en prikkende fornemmelse?

- ☐ 0: Ingen prikken
- ☐ 1
- ☐ 2
- ☐ 3
- ☐ 4
- ☐ 5
- ☐ 6
- ☐ 7
- ☐ 8
- ☐ 9
- ☐ 10: Værst tænkelige prikken

Føles dine smerter som en klemning i en skruestik?

- ☐ 0: Ingen klemning
- ☐ 1
- ☐ 2
- ☐ 3
- ☐ 4
- ☐ 5
- ☐ 6
- ☐ 7
- ☐ 8
- ☐ 9
- ☐ 10: Værst tænkelige klemning

Føles dine smerter som et tryk?

- ☐ 0: Ingen tryk
- ☐ 1
- ☐ 2
- ☐ 3
- ☐ 4
- ☐ 5
- ☐ 6
- ☐ 7
- ☐ 8
- ☐ 9
- ☐ 10: Værst tænkelige tryk

Har du smerter, der fremprovokeres eller forstærkes af let berøring (f.eks. ved at stryge en tot vat) henover det smertende område?

- ☐ 0: Ingen smerte
- ☐ 1
- ☐ 2
- ☐ 3
- ☐ 4
- ☐ 5
- ☐ 6
- ☐ 7
- ☐ 8
- ☐ 9
- ☐ 10: Værst tænkelige smerte

Har du smerter, der fremprovokeres eller forstærkes af tryk på det smertende område?

- ☐ 0: Ingen smerte
- ☐ 1
- ☐ 2
- ☐ 3
- ☐ 4
- ☐ 5
- ☐ 6
- ☐ 7
- ☐ 8
- ☐ 9
- ☐ 10: Værst tænkelige smerte

I løbet af de sidste 24 timer har dine spontane smerter været til stede:

Afkryds det svar, der passer bedst til din tilstand

- ☐ Hele tiden
- ☐ Mellem 8 og 12 timer/dag
- ☐ Mellem 4 og 7 timer/dag
- ☐ Mellem 1 og 3 timer/dag
- ☐ Mindre end 1 time/dag

Vi vil gerne vide, om du har korte smerteanfald. For hvert af de følgende spørgsmål, vælges det tal, der svarer bedst til **gennemsnittet af intensiteten af dine smerteanfald i løbet af de seneste 24 timer**. Vælg 0, hvis du ikke har følt denne type smerte.

Har du smerteanfald, som kan sammenlignes med elektriske stød?

- ☐ 0: Ingen stød
- ☐ 1
- ☐ 2
- ☐ 3
- ☐ 4
- ☐ 5
- ☐ 6
- ☐ 7
- ☐ 8
- ☐ 9
- ☐ 10: Værst tænkelige stød

Har du en kriblende ("sovende") fornemmelse?

- ☐ 0: Ingen kriblen
- ☐ 1
- ☐ 2
- ☐ 3
- ☐ 4
- ☐ 5
- ☐ 6
- ☐ 7
- ☐ 8
- ☐ 9
- ☐ 10: Værst tænkelige kriblen

Tak for din besvarelse