Monitoring and improving care in thoracic surgery

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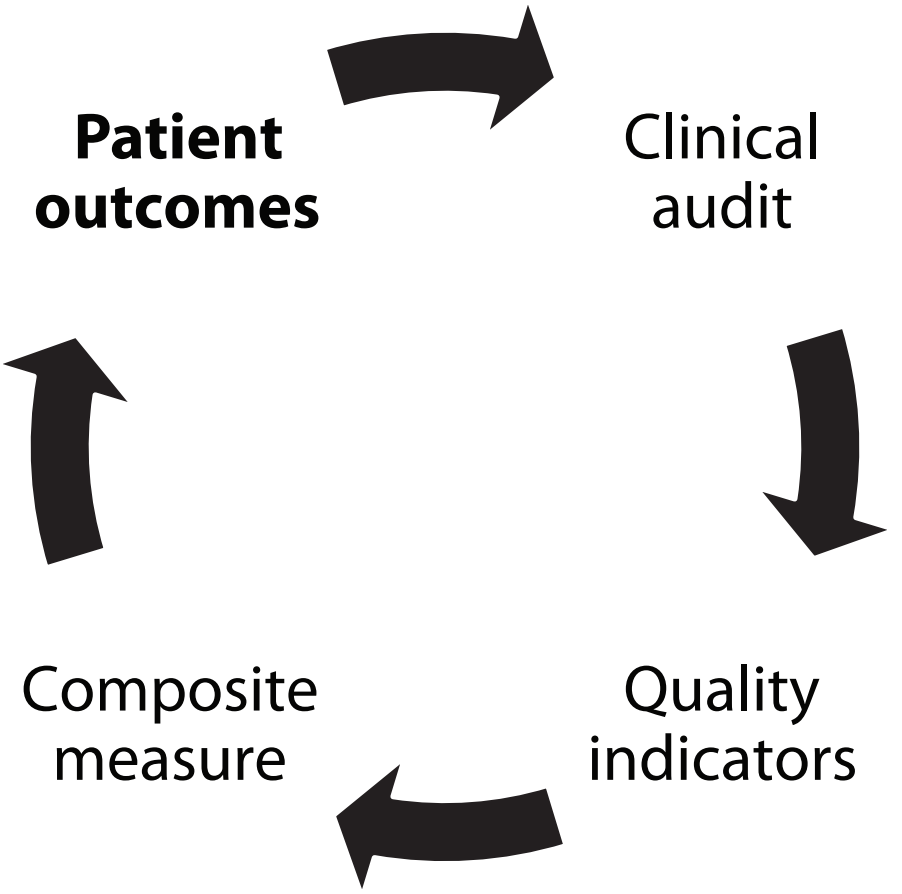
Publication date
2016
Document Version
Final published version


Patient outcomes
Clinical audit
Quality indicators
Composite measure

Chapter 7

Patient Related Outcome Measure: Pain

Can we avoid chronic post-thoracotomy pain?

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European Journal of Anaesthesiology (submitted), 2015.

Abstract

Background

Chronic pain after thoracic surgery is a commonly encountered sequel and seriously impairs the daily functioning of patients. Although extensive research has been performed, until now, no new modifiable risk factors have been identified.

Objectives

The aims of this study were to identify the risk factors attributable to chronic post-thoracotomy pain (CPTP) and its effect on quality of life (QoL) and daily functioning.

Design

A retrospective analysis with prospectively collected data on pain and QoL using the Brief Pain Inventory and SF36 questionnaire.

Setting

The study was conducted at the Netherlands Cancer Institute, one of the tertiary referral centres in the Netherlands specialised in oncological care.

Patients

Patients operated for (malignant) pulmonary lesions from April 2006 to December 2011 (n = 382) were included. Patients being operated on before January 2008 (i.e. when epidural analgesia was not the standard analgesic method, N=83), having recurrent or progressive disease during follow-up (N=27), were excluded. Also, patients receiving adjuvant therapy or any other surgical procedure within 6 months after the primary thoracic procedure (N=59 and N=40, respectively), were excluded.

Main outcome

The risk factors attributable to CPTP and the impact on QoL and daily functioning.

Results

Age (p=0.016), the intensity of preoperative pain (p=0.039), the intensity of direct postoperative pain (pain score>0, p=0.017) and smoking (p=0.016) were strongly associated with an increased chance of CPTP. Patients with CPTP experienced significantly impaired QoL and daily functioning (i.e. general activity, mood,

walking ability, relations with other people, sleep and enjoyment of life) compared to patients without pain (all $p<0.0001$).

Conclusions

Of the predictive factors we analysed, two factors stand out which can be influenced. Rigorously addressing smoking addiction and the reduction of immediate post-operative pain may improve QoL and daily functioning.

Introduction

Post-thoracotomy pain is one of the most frequently observed chronic adverse events after thoracic procedures for (malignant) pulmonary lesions[1,2]. The International Association for the Study of Pain (ISAP) has formulated a strict definition of chronic post-thoracotomy pain (CPTP): 'pain that recurs or persists along a thoracotomy scar at least two months after the surgical procedure'[3]. In literature, other definitions regarding the duration of pain (i.e. ranging from two up to six months after the surgical procedure) have been used[4-8]. Depending on the definition used, incidence varies from 21% up to 75%[4-8].

The etiology of CPTP is not fully understood, although a combination of physical and psychosocial factors has been identified[1]. Nerve damage during surgery is probably the most important source of chronic postoperative pain[9]. Extensive research has been performed to identify patients at risk for chronic postsurgical pain. Pre- and postoperative pain levels are known risk factors and have led to a strict pain management in recent years[10-14]. The effect of adequate epidural analgesia on the development of CPTP is limited, but the use of Video-Assisted Thoracoscopic Surgery (VATS) leads to a decrease in the severity of chronic pain[10, 15, 16].

The negative impact of chronic pain on daily life and society is significant. It does not only reduce quality of life (QoL), but also increases economic costs related to more hospital admissions, general practitioner visits and a loss of productivity[17,18]. These implications urged us to analyse our database with prospectively collected information to identify new risk factors and determine the effect of CPTP on QoL and daily functioning.

Methods

Patient selection

Data were obtained from a cohort study evaluating the effectiveness of a multidisciplinary care path for thoracic cancer surgery in the Netherlands Cancer Institute, one of the tertiary referral centres in the Netherlands specialised in oncological care[19]. All patients with (potentially) malignant pulmonary lesions scheduled for lung resection were invited to participate in this study. Patients who

were under 18 years of age and those who were unable or refused to complete the QoL and pain questionnaires were excluded.

Ethics

Patients included in the study gave written informed consent. Ethical approval for the study was provided by the Institutional Review Board (IRB) of the Antoni van Leeuwenhoek-Netherlands Cancer Institute, Amsterdam, the Netherlands (chairperson prof dr. G.C. de Gast), December 2004. In accordance with the Dutch law, no approval needs to be obtained and no informed consent is required for this retrospective analysis.

Study design

A cohort study was performed and data were prospectively collected. The cohort study was initiated in 2005, evaluating 'usual care' to identify adjustable factors in pre-, peri- and postoperative care (the baseline period). In 2008 a multidisciplinary care path for thoracic cancer surgery was implemented. During this three-year period, detailed clinical data concerning patient, tumour and treatment characteristics as well as outcome data were prospectively collected. Patient characteristics including age, gender, smoking status, history of previous thoracic surgery and performance status, were documented[19]. Details of the surgical intervention (i.e. the surgical technique, duration of the procedure, type of resection, use of a muscle sparing technique) and anaesthesiological proceedings (i.e. the analgesic method, level of epidural insertion, type of analgesia used, additional analgesia used) were collected. Direct postoperative outcome concerning postoperative morbidity and in hospital mortality, length of hospital stay, complications, readmissions, chest tube and epidural duration and detailed pathology data were collected during hospital stay. Pain and QoL were evaluated (using the Brief Pain Inventory and SF-36 questionnaire, respectively), preoperatively and 1, 3 and 6 months postoperatively[20-21]. For this study, we selected all patients who had undergone surgery after the introduction of the multidisciplinary care path (i.e. when a strict pain protocol was implemented). Patients receiving adjuvant treatment (i.e. chemotherapy, radiotherapy or both) or those who had undergone other surgical interventions after discharge up to 6 months postoperative were excluded (with the exception of the removal of (sub)cutaneous lesions) (Figure 1). Participants were followed for at least 6 months after surgery, evaluating pain and QoL.

Functional outcome measurements

Pain

Direct postoperative pain was assessed using a numeric rating scale, ranging from 0 (no pain) to 10 (worse pain), twice on each postoperative day from surgery until discharge. Pain prior to the thoracic procedure and at 1, 3 and 6 months after the operation was assessed using the Brief Pain Inventory (BPI)[20]. This questionnaire quantifies pain intensity and the impact of pain on daily functions. The form consisted of 15 questions, concerning the location of pain and the severity of pain, rated on a 0-10 scale (0 representing 'no pain' and 10 'worse pain imaginable'). Patients were asked to rate their pain intensity at the moment of filling out the BPI, as well as to report their worst and average pain in the past 24 hours. Literature states that for average pain, the postoperative pain score ranging from 1-4 corresponds to mild pain[22]. The BPI also assessed the impact of pain on daily functions, rated on a 0-10 scale (0 representing 'no interference' and 10 'complete interference').

Quality of life

QoL was evaluated with the short-form health survey SF-36, an easy to use and validated questionnaire[21]. The SF-36 questionnaire assesses eight dimensions of perceived well-being. Four physical scales: physical functioning (PF), role-physical functioning (RP), bodily pain (BP) and general health (GH); and four mental scales: social functioning (SF), role-emotional functioning (RE), vitality (VT) and mental health (MH). The scores for all eight dimensions range from 0 to 100, with higher scores representing a better health status. The SF-36 questionnaire was administered, together with the BPI, prior to the thoracic procedure and 1, 3 and 6 months after the operation.

Surgery

Eligible patients were planned for surgery using an open approach (i.e. thoracotomy) or a minimally invasive approach (i.e. VATS). The operative technique chosen depended on tumour size, tumour location and patients' health status. When a thoracotomy was performed, a muscle sparing approach was pursued and the thoracic cavity was entered through the 5th intercostal space. When a minimally invasive approach was used, two or three trocars were placed near the target location without spreading the ribs. The extend of the surgical resection depended on tumour size: wedge resection was the

preferred surgical resection for small lesions, larger or centrally located tumours were resected by an anatomical segmentectomy or lobectomy. After surgical resection, a chest tube was placed.

Pain management protocol

Preoperative insertion of the epidural catheter with preoperative infusion of epidural anaesthesia was the favoured option for pain control. A catheter was inserted between the thoracic segments T5-T6 or T6-T7 and tested with a bolus of 0.5% bupivacaine (3 ml). Up to 15 minutes before the incision, 10-25 µg sufentanil was given. Also, depending on the patient characteristics such as height, weight and blood pressure after epidural insertion, 10-15 cc bupivacaine was administered before surgery. Intra-operatively additional boli of bupivacaine were given, aiming for a total volume of 13-15 cc (including the preoperative doses). In case of signs of inadequate pain control (tachycardia, hypertension, sweating etc.), the epidural was topped up with additional boli of bupivacaine 0.5%.

Postoperative analgesia was strictly standardised. First, an epidural infusion of 50 ml 0.5% bupivacaine with 10 mg morphine in 500 ml 0.9% saline was delivered at 20 ml/hr peri- and postoperative up to three days after the thoracic procedure. When a morphine intolerance was recorded, morphine was replaced with 300 µg clonidine. Literature states that a pain scores>3 has a significant effect on general activity, mood, walking ability, and sleep.[21] If a pain score>3 was reported during these three days, a bolus of 0.25% bupivacaine 5 ml was administered. Also, the epidural mixture was adjusted: in case of a morphine-bupivacaine mixture, either clonidine 300 µg would be added, or the bupivacaine dose would be doubled to 100 ml 0.5% bupivacaine plus 10 mg morphine in 500 ml 0.9% saline, delivered at 20 ml/hr. Second, on the fourth postoperative day the infusion rate was diminished with 4 ml/hr every four hours if a pain score≤3 was reported. The infusion was stopped when the infusion rate reached 12 ml/hr. If a pain score>3 was reported, a bolus of 0.25% bupivacaine 5 ml was administered and the infusion rate was increased with 4 ml/hr (until the next day). If pain persisted (i.e. pain score>3) despite an adjustment of the epidural mixture and an increase of the epidural infusion rate, opioids were added (i.e. piritramide 10-15 mg subcutaneously 4-6 times a day). Subcutaneous opioid administration was only used when the epidural mixture did not contain morphine. If so, morphine was replaced with clonidine. Finally, all patients received 1000 mg acetaminophen every 6 hours.

When ipsilateral shoulder pain was reported, a non-steroid anti-inflammatory drug was added to the regime. In case of contra-indications to epidural anaesthesia, technical failure or patient refusal, postoperative pain was managed with the administration of oral opioids.

Statistical analysis

In our study CPTP, was defined as pain (i.e. pain score>0) that recurs or persists along a thoracotomy scar six months after the thoracic procedure. Differences between patients with and without pain 6 months after the thoracic procedure were assessed with the chi squared or Fisher exact test for categorical variables and a Student t-test or Mann-Whitney U-test for continuous variables. An independent sample t-test was used to compare QoL 6 months after the operation between the two groups (i.e. patients with and without pain 6 months postoperatively). Normality was assessed graphically by means of QQ-plots.

From the literature seven variables have been identified as risk factors for CPTP: younger age, female sex, performance status, diabetes, incision type, intensity of preoperative and direct postoperative pain[4-8, 23]. For each of the significant risk factors identified from our univariate analysis (see Table 1, left column) we constructed a regression model for CPTP (after checking for multicolinearity among the variables). Each regression model contained eight independent variables: one risk factor derived from our study (Table 1, left column) and seven 'known' risk factors from the literature (Table 1, right column). Continuous variables such as pack years were allowed to influence the risk of CPTP in a non-linear way by entering them into the logistic regression model through the use of restricted cubic splines. The number of knots was determined chosen as the lowest number of knots such that adding an extra knot no longer significantly improved the model fit. In the concrete case of pack years this led to the use of three knot cubic splines, thus allowing a modest but significant non-linearity in the relation between pack years and risk of CPTP. A p-value <0.05 was regarded to be significant. All statistical analyses were performed in SPSS 20.0.0 and R version 3.0.1.

Table 1. Factors included in the Multiple logistic regression analysis.

Significant variables from univariate analysis	Predictive factors extracted from literature
smoking status	age
pack years	sex
induction therapy	pre operative pain (pain score>0)
operation time	direct postoperative pain (pain score>0)
tumour type	incision type
Physical Functioning	performance status
Role Physical	diabetes
General Health	
Social Functioning	
Role Emotional	
Mental Health	
Vitality	
Mental Composite Scale	
Physical Composite Scale	

Results

From 2006 to 2011, 382 surgical thoracic procedures for (malignant) lung tumours were performed. After excluding patients being operated on before January 2008 (N=83), patients experiencing progressive/recurrent disease (N=27) and patients receiving adjuvant therapy or any other surgical procedure within 6 months after the primary thoracic procedure (N=59 and N=40, respectively), 173 thoracic procedures remained eligible for analysis (Figure 1). Patient, tumour and treatment characteristics are listed in table 2 and 3. From the 173 patients included, pain scores were available for 99 patients. Chart data were retrieved for all patients of whom no pain scores were available (Table 4). Patients of whom pain scores were missing were comparable to patients who completed the pain questionnaires with regard to patient (i.e. age, sex, smoking status, co-morbidity), tumour (tumour type) and treatment characteristics (surgical technique, type of resection, use of neoadjuvant chemotherapy).

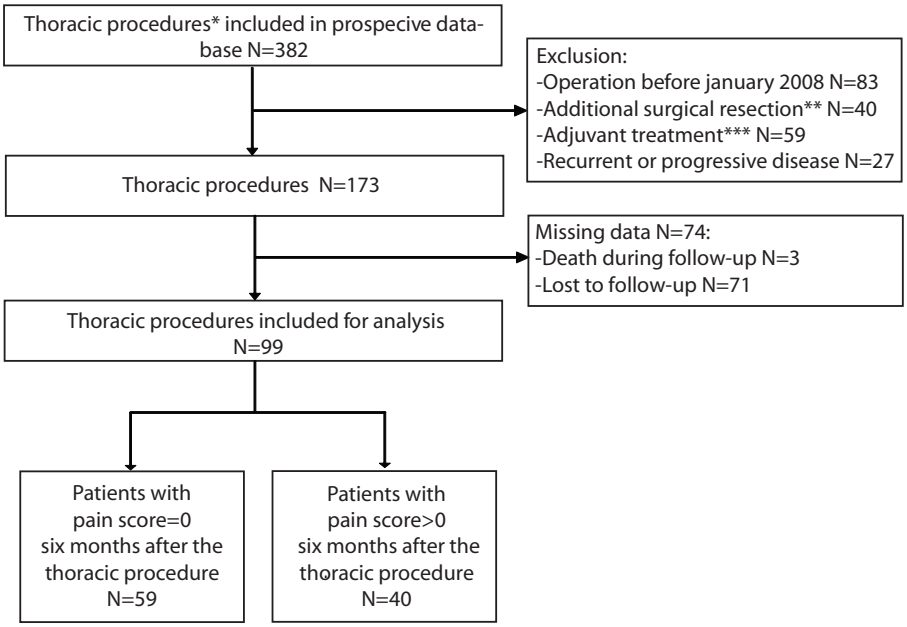

Figure 1. Flow chart inclusion and exclusion criteria.

*Thoracic procedures consisted of 120 VATS procedures and 262 thoracotomies
**Any form of additional surgical resection within 6 months after the primary thoracic procedure
***Adjuvant treatment: chemotherapy, radiotherapy or both within 6 months after the primary thoracic procedure

Patients with CPTP had a longer duration of surgery (p=0.004), more thoracic drainage days (p=0.047) and a longer hospital stay (p=0.019) (Table 2 and 3). Six patients in the group with chronic pain required a chest wall resection compared to no patients in the group without pain (p=0.078). Of these six patients, five reported mild pain 6 months after the operation (three patients reported a pain score of 1 and two patients reported a pain score of 2) and one patient reported moderate pain (a pain score of 5). Although not statistically significant, patients with chronic pain underwent more extensive resections (lobectomy was performed in 46% of the patients with chronic pain and in 22% of the patients without pain 6 months postoperatively, p=0.103) and therefore more open resections were performed in patients with chronic pain (p=0.09).

Table 2. Patient, tumour and treatment characteristics of patients with and without chronic pain 6 months after the operation.

Characteristics	Post-thoracotomy pain (N=59)	No post-thoracotomy pain (N=40)	P value
Age, yrs (Mean, Range)	65 ± 9.9	65 ± 10.1	0.792
Gender (No. of patients, %)			
M:F	27 : 32	19 : 21	0.865
Smoking status			
(No.of patients, %)			
Never	4 (7)	13 (33)	**0.007**
Former	35 (59)	20 (50)	
Current	19 (32)	7 (17)	
Unknown	1 (2)	0 (0)	
Pack Years (median, SD)	32±20	19±22	**0.009**
BMI (mean, SD)	26 ± 4.6	25 ± 3.9	0.381
Co-morbidity			
(No.of patients, %)			
Pulmonary	13 (22)	6 (15)	0.383
Cardiac	6 (10)	4 (10)	0.978
Diabetes Mellitus	7 (12)	3 (8)	0.479
Vascular	19 (32)	11 (28)	0.617
WHO-performance			
(No. of patients, %)			
0 : I : II	44 (75) : 15 (25): 0	35 (88) : 5 (12): 0	0.116
Preoperative FEV1[a]			
(% of expected, SD)	91 ± 17.7	93 ± 20	**0.756**
Preoperative TLCO[b]			
(% of expected, SD)	82 ± 19.7	82 ± 14.0	0.977
Induction (chemo)radiation			**0.031**
(No. of patients, %)	24 (41)	8 (20)	
Surgical technique			
(No. of patients, %)			
Thoracotomy	42 (71)	22 (55)	0.098
VATS	17 (29)	18 (45)	
Site of surgery			
(No. of patients, %)			
Left versus right	21 : 38 (36:64)	16 : 24 (40:60)	0.657
Resections			
(No. of patients, %)			
Wedge	16 (27)	21 (53)	0.090
Segment	10 (17)	6 (15)	
Bi/trisegmentectomy	3 (5)	2 (5)	
Lobectomy	27(46)	9 (22)	
Other	3 (5)	2 (5)	
Muscle sparing			
(No. of patients, %)			
Yes	54 (91)	39 (98)	0.237
No	4 (7)	-	
Unknown	1 (2)	1 (2)	
Additional chest wall resection			
(no. of patients, %)	6 (15)	0 (0)	0.078

Table 2. Patient, tumour and treatment characteristics of patients with and without chronic pain 6 months after the operation. (Continued)

Characteristics	Post-thoracotomy pain (N=59)	No post-thoracotomy pain (N=40)	P value
Operation time in minutes (Mean±SD)	116 ± 63	162 ± 83	**0.004**
Tumour type after operation (No of patients, %)			
NSCLC[c]	41 (70)	17 (43)	**0.046**
Metastasis	12 (20)	14 (35)	
No tumour localisation/other	6 (10)	9 (22)	
Tumour stage after operation (No of patients, %)			
Stage I	15 (38)	25 (42)	0.266
Stage II	1 (2)	6 (10)	
Stage III	0	2 (3)	
Stage IV	15 (38)	15 (25)	
Other	9 (22)	11(19)	

[a] FEV1, forced expiratory volume in 1 s.
[b] TLCO, carbon monoxide transfer factor.
[C] NSCLC, Non-Small Cell Lung Cancer

Table 3. Outcome characteristics of patients with and without post-thoracotomy pain 6 months after surgery.

Characteristics	Post-thoracotomy pain (N=59)	No post-thoracotomy pain (N=40)	P value
Thoracic drainage (days) (Mean±SD)	6 ± 5	4 ± 2	**0.047**
Hospital stay (days) (Mean±SD)	10 ± 9	7 ± 3	**0.019**
Epidural analgesia (days) (Mean±SD)	5 ± 3	5 ± 2	0.135
Complications (No. of patients, %)			
Air leakage>7days	0	0	-
Chylothorax	0	0	-
Postoperative bleeding	1 (2)	1 (1)	1.000
Torsion	1 (2)	0	1.000
Empyema	0	0	-
Pneumothorax	2 (3)	0	0.514
Re-intervention (No. of patients, %)	3 (5)	1 (3)	0.645
Readmission (No. of patients, %)	2 (3)	1 (3)	1.000
In hospital Mortality (No. of patients, %)	0	0	-

Table 4. Patient tumour and treatment characteristics of patients who completed and did not complete the questionnaires.

Characteristics	Patients with completed data (N=99)	Patients with missing data (N=74)	P value
Age, yrs (Mean, Range)	65 ± 10.0	62 ± 14.1	0.101
Gender (No. of patients)			
M:F	46 : 53	32 : 42	0.674
Smoking status			
(No.of patients, %)			
Never	17 (17)	16 (22)	0.554
Former	55 (56)	35 (47)	
Current	26 (26)	23 (31)	
Unknown	1 (1)	0 (0)	
Co-morbidity			
(No.of patients, %)			
Diabetes Mellitus	10 (10)	8 (11)	0.856
Cardiac	10 (10)	10 (14)	0.487
Vascular	30 (30)	25 (34)	0.627
Pulmonary	19 (19)	19 (26)	0.308
Induction (chemo)radiotherapy			
(No. of patients, %)	32 (32)	17 (23)	0.177
Surgical technique			
(No. of patients, %)			
Thoracotomy	64 (65)	53 (72)	0.332
VATS	35 (35)	21 (28)	
Resections			
(No. of patients, %)			
Wedge	37 (37)	30 (41)	0.941
Segment	16 (16)	12 (16)	
Bi/trisegmentectomy	5 (5)	2 (3)	
Lobectomy	36 (36)	27 (36)	
Other	5 (5)	3 (4)	
Muscle sparing			
(No. of patients, %)			
Yes	93 (94)	73 (99)	0.202
No	4 (4)	0 (0)	
Unknown	2 (2)	1 (1)	
Additional chest wall resection			
(No. of patient, %)	6 (6)	5 (7)	0.853
Tumour type after operation			
(No of patients, %)			
NSCLC[a]	58 (59)	41 (55)	0.515
Metastasis	26 (26)	26 (35)	
No tumour localisation/other	15 (15)	7 (10)	
Thoracic drainage (days)			
(Mean±SD)	5 ± 4.3	6 ± 6.5	0.224
Hospital stay (days)			
(Mean±SD)	9 ± 7.4	10 ± 11.2	0.210
Epidural analgesia (days)			
(Mean±SD)	6 ± 2.7	7 ± 3.3	0.161

Table 4. Patient tumour and treatment characteristics of patients who completed and did not complete the questionnaires. (Continued)

Characteristics	Patients with completed data (N=99)	Patients with missing data (N=74)	P value
Readmission (No. of patients, %)	3 (3)	4 (5)	0.433
Mortality (No of patients, %)	0	1 (1)	0.507

[a] NSCLC, Non-Small Cell Lung Cancer

Chronic post-thoracotomy pain

The overall incidence of CPTP in our population (i.e. pain score>0, six months after surgery) was 59% (59 patients). Five patients (5%) reported a pain score>4, six months after the operation. In three out of five patients (60%) with a pain score>4 three months postoperative, the pain persisted six months after the surgery. Two out of eighty-two patients (2%) with a pain score<4, three months postoperative, reported a pain score of 5 or 6, six months postoperative, whereas no patients with severe pain (pain score>7) were seen. In the group with chronic pain, more patients smoked (p=0.007) and the severity of the addiction was more pronounced (i.e. more pack years, p=0.007). Also, more patients were diagnosed with primary lung cancer (NSCLC) (p=0.046) and received induction therapy (p=0.031) (Table 2).

Epidural analgesia was used in 98 of the 99 patients (99%); in one patient the insertion failed due to calcification of the posterior longitudinal ligaments. Adequate analgesia was achieved in 96 out of 98 patients (98%), whereas two patients reported inadequate pain control. For these two patients, pain was controlled with the addition of 25 microgram sufentanil to the epidural mixture. In both cases a pain score≤4 was reported six months after the operation. In one patient, a ketamine perfusor was started during surgery in addition to the epidural analgesia (for this patient a ketamine perfusor was used during previous abdominal surgery). In this case, only mild pain was reported 6 months after the operation. A shorter duration of epidural analgesia was not associated with technical failure of the epidural catheter; ninety percent of the patients with a short duration of epidural analgesia (1-4 days), could leave the hospital within 3 days after the removal of the epidural catheter. In case of five patients, severe postoperative pain was present due to technical failure of the epidural catheter. For three patients

the epidural catheter was replaced, resulting in adequate pain control. In the remaining two patients, oral opioids were used to control postoperative pain. In all patients a pain score≤4 was reported six months after the operation.

After constructing the logistic regression models for CPTP with each 8 variables (i.e. one significant independent variable from our univariate analysis combined with the seven known risk factors from literature, see Table 1), the intensity of pre-operative pain (p=0.039), the intensity of pain in the direct postoperative period (p=0.017), age (p=0.028) and pack years (p=0.009) were independently associated with chronic post-thoracotomy pain .

Impact of pain on quality of life and daily functioning

Patients with pain experienced a significantly worse physical and mental QoL compared to patients without pain six months postoperatively (Physical QoL scales: PF, BP, RP all p<0.0005, GH p=0.004. Mental QoL scales: SF p=0.006, RE scale p=0.005, MH p=0.037 and VT p<0.0005). Figure 2a and 2b show the physical and mental QoL evolvement up to 6 months after the thoracic procedure. With the BPI we were able to assess the impact of pain on daily functioning. Pain interfered significantly with all functionalities (activity, mood, walking ability, relations with other people, sleep and enjoyment of life etc.) 6 months after the operation (all p<0.0001).

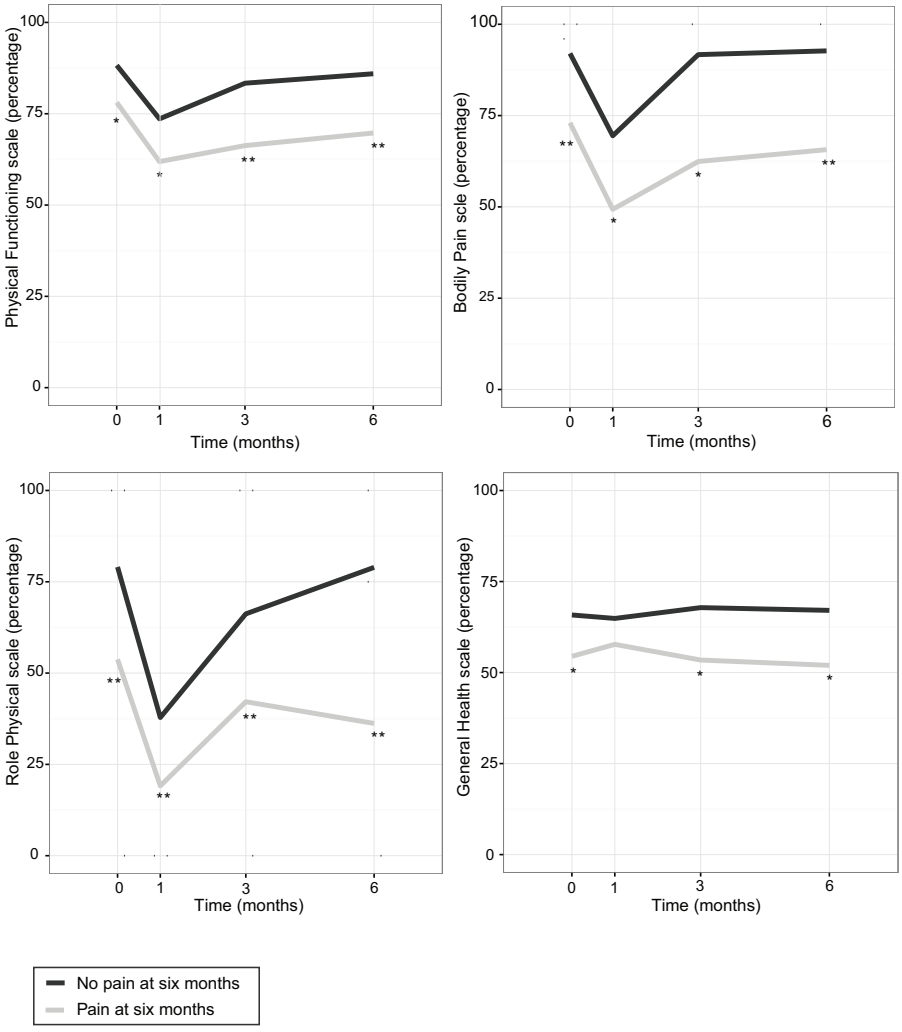

Figure 2. Quality of life Physical Subscales.

The lines connect the means of each assessment. *p<0.05. **p≤0.001

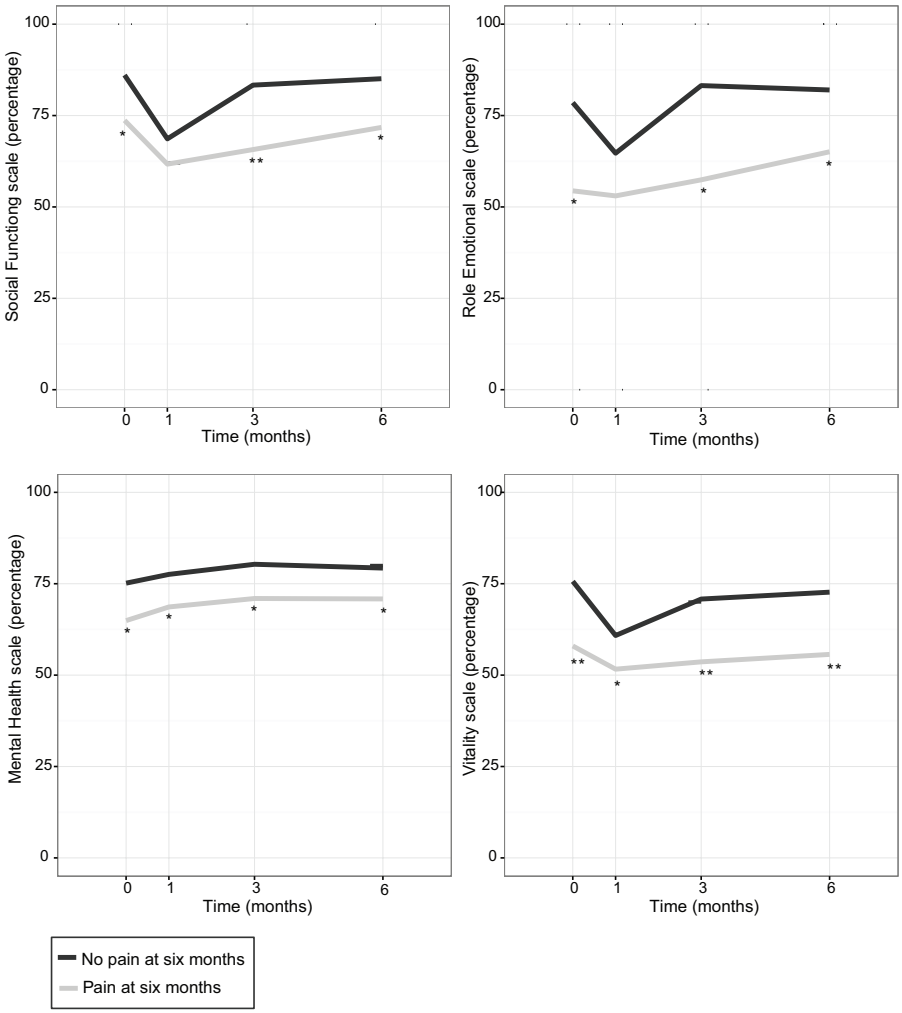

Figure 2b. Quality of Life Mental Subscales.

The lines connect the means of each assessment. *p<0.05. **p≤0.001

Discussion

With our study, we tried to identify new reversible factors, which contribute to the development of CPTP. By using our prospective database we were able to identify a new risk factor for the development of CPTP and assess the impact of chronic pain on QoL and daily functioning. Patients with CPTP reported more severe preoperative and acute postoperative pain. Factors that can be influenced are the direct postoperative pain severity and, unexpectedly, the number of pack years or the continuation of smoking. Once established, patients with CPTP experience seriously impaired QoL and daily functioning.

We observed that severe smoking was a risk factor for developing CPTP. Recently, Yu et al. reported the effect of nicotine dependence on the required postoperative opioid administration for patients undergoing thoracic surgery. Patients with high nicotine dependence required a higher postoperative dosage of sufentanil[24]. In addition, the severity of postoperative pain and the need for self-administered sufentanil correlated with the degree of nicotine dependence in smokers. Several physiological mechanisms contributing to these results have been postulated. Long-term nicotine exposure results in the down-regulation of the hypothalamic-pituitary adrenal (HPA) axis, which is associated with the processing of painful stimuli[25]. When a painful stimulus is present, analgesia mediated via the activation of the HPA axis is reduced. Furthermore, cross-tolerance between nicotine and opioids is shown in nicotine-tolerant mice, reducing opioid receptor-mediated analgesia[26]. These results and subsequent explanatory mechanisms apply to the direct postoperative period and it is possible that these mechanisms also explain the risk of developing a chronic pain syndrome in patients with a severe smoking habit. To prevent this, the emphasis should be on education. Both physicians and patients know the risks of smoking, but in those patients who need multiple surgical interventions (i.e. patients with metastatic disease), the emphasis should be on education and promoting smoking cessation. Therefore, physicians' knowledge of the effect of smoking on pain perception is very important. Physicians can identify patients with a severe smoking addiction beforehand and perhaps additional local analgesia (i.e. an intercostal catheter or paravertebral block) can prevent chronic surgical pain.

In line with the literature, we identified the intensity of preoperative pain and direct postoperative pain as risk factors associated with the development of CPTP[7,8]. The severity of direct postoperative pain could be related to the extensiveness of the operation. Although not significant, we showed that patients with chronic pain more frequently were operated through an open approach (i.e. thoracotomy) and had more extensive tumour resections (i.e. lobectomy). More extensive surgery (i.e. open approach with or without chest wall resections) results in more tissue injury and probably more nerve damage. To control this postoperative pain, strict pain management protocols have been implemented in recent years[10-14]. Preoperative epidural analgesia has not always been successful[10-14]. Five RCTs were included in a meta-analysis by Bong et al., comparing pre-emptive thoracic epidural analgesia (TEA) with TEA initiated after the completion of surgery[10]. This meta-analysis showed that pre-emptive TEA did not influence the incidence of chronic pain. Other analgesic methods have been evaluated in literature, such as an intercostal catheter (ICC) and a paravertebral block (PVB) with bupivacaine. Wildgaard et al. (2012) found that adequate analgesia can be obtained by using ICC and PVB in patients undergoing VATS lobectomy for NSCLC[27]. Further studies need to address the effect of specific pain management protocols and different analgesic methods, not only on pain, but also its impact on QoL.

In a review by Wildgaard et al. (2009), it became clear that the social consequences of chronic pain have only been reported in a minority of studies[28]. Kinny et al. (2012) evaluated the impact of chronic pain on QoL and found a significant decrease in Physical Functioning and Vitality in patients experiencing post-thoracotomy pain three months after surgery[18]. Our study included data up to 6 months postoperative and found a compromised mental functioning as well, a result not seen in the study of Kinny et al. When the effects of chronic pain are translated into real life, we found that CPTP seriously undermines daily activities.

Our study has some limitations. First, it is a single centre study with a limited patient number. Our limited patient number prevented us from constructing a model containing more than eight risk factors at a time, because this would certainly have led to overfitting on one hand and inflation of type II error on the other. The rationale behind including the known risk factors from the literature, even if some of them (most notably sex) show no relation to CPTP in our own data, is related to the issue of the limited sample size. It is a way to include some information about patients

that are not included in our own sample, thereby increasing (if only marginally) the external validity of the regression models. Second, we realise not all the modifiable risk factors are investigated in our study (e.g. the type of epidural mixture, duration of epidural infusion, preventive intravenous analgesia). Third, the response rates of the pain questionnaires after 1 and 3 months were acceptable, though at 6 months it was forty percent (71 patients lost to follow-up). Patients who did not return the pain and QoL questionnaires were comparable to patients who completed all the pain questionnaires. Also, no significant differences in preoperative, direct postoperative pain trajectory and pain scores 1 and 3 months after the operation, could be seen (data not shown). With this in mind, a selection bias is less likely. And finally, the initial collection of pain data was used to evaluate the implementation of our multidisciplinary care path[19]. For this purpose, we used the BPI, which gives excellent information on the intensity of the pain and the interference with daily functioning[20]. Unfortunately, this questionnaire does not give insight into the character of chronic pain (i.e. neuropathic component). It could be that patients with higher reported pain scores suffer from more intense neuropathic pain due to the more extensive operations with more associated nerve damage.

Although we know severe postoperative pain has been identified as a risk factor for the development of CPTP, we chose to compare patients with and without pain 6 months after surgery, because the primary goal of surgery is to achieve a radical resection without any chronic morbidity[29]. In our study, 94.9 percent of the patients reported a pain score ≤4 six months after the operation. This shows us that mild pain is quite common and that choosing a higher cut-off score could give a better reflection of pain of a clinically relevant dignity. Because in our study population only 5.1 percent of the patients reported a pain score >4, using a higher cut off score results in a small study population which in turn hampers adequate statistical analysis.

In conclusion, our data show that age, the intensity of preoperative pain and direct postoperative pain are risk factors associated with the development of CPTP. We also identified that the severity of a smoking addiction (i.e. more pack years) appears to be an important predictor of chronic pain. This study helps to identify patients who could be at risk of developing CPTP and it emphasizes: (1) the importance of smoking cessation and (2) the importance of the identification of patients whom are at risk of developing CPTP due to its serious effect on QoL and daily functioning.

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