Chronic post-thoracotomy pain: a critical review of pathogenic mechanisms and strategies for prevention

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Summary

Chronic pain complaints after thoracic surgery represent a significant clinical problem in 25—60% of patients. Results from thoracic and other surgical procedures suggest multiple pathogenic mechanisms that include pre-, intra-, and postoperative factors. This review attempts to analyse the methodology and systematics of the studies on the post-thoracotomy pain syndrome (PTPS) after lung cancer surgery in adults, in order to clarify the relative role of possible pathogenic factors and to define future strategies for prevention. Literature published from 2000 to 2008 together with studies included in previous systematic reviews was searched recursively using PubMed and OVID by combining three categories of search terms. The available data have major inconsistencies in collection of pre-, intra- and postoperative data that may influence PTPS, thereby hindering precise conclusions as well as preventive and treatment strategies. However, intercostal nerve injury seems to be the most important pathogenic factor. Since there is a general agreement on the clinical relevance of PTPS, a proposal for design of future trials is presented.

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Keywords: Thoracotomy; Chronic pain; Intercostal nerves; Thoracoscopy; Neuralgia; Pre-emptive analgesia

1. Introduction

The term persistent postsurgical pain is now accepted as a clinical entity of medical significance for several surgical procedures [1]. Thus incidences of chronic postoperative pain have been reported after limb amputation to average 60—80% [2], to about 30% after total hip arthroplasty [3], to 5—30% after hysterectomy [4], to about 10% after caesarean section [5,6], to 20—50% after breast surgery [7], to about 10% after groin hernia surgery [8,9], to about 20% after surgery [10], and to 25—60% after thoracic surgery (PTPS) [11—13]. Thoracotomy is, along with limb amputation, considered to be the procedure that elicits the highest risk of severe chronic postoperative pain [1]. The International Association for the Study of Pain (IASP) definition of chronic pain after thoracotomy is ‘Pain that recurs or persists along a thoracotomy scar at least 2 months following surgical procedure.’ [14], but previous authors have chosen to evaluate PTPS at 1 month [15], 2 months [16,17], 6 months or later [18—20] or at multiple points in time [13,21,22].

In order to understand the pathogenic mechanisms and prevention/treatment strategies in PTPS, various approaches of surgical, analgesic and pharmacological interventions to alleviate chronic pain have been attempted with alternating success. In an attempt to minimise the incidence of chronic pain, significant attention has been directed towards reducing the intensity of acute pain, based on the assumption that acute pain is a predictive factor for chronic pain [23,24]. Other risk factors investigated include age [25,26], gender [21,23], preoperative pain [21], type of surgery [20,27,28], perioperative analgesic care and timing [19,21,22,24], radiation/chemotherapy [18,29], tumour recurrence and psychosocial factors [30,31], but all with variable results. Finally the characterisation of PTPS itself and its social consequences have also been somewhat unclear. No studies have so far included all or even most of these risk factors suspected of causing PTPS.

The purpose of this critical review is therefore to:

1. Assess the methodology of clinical trials of PTPS i.e. at least 3 months (12 weeks) after surgery in adult humans undergoing thoracotomy for lung cancer (inclusion criteria).
2. Pair this information with current knowledge from other persistent postsurgical pain states.
3. To present a list of parameters to optimise design of future trials on PTPS.
4. Suggest topics for future trials on methods for prevention/treatment of PTPS.
### Table 1

**Incidence studies.**

<table>
<thead>
<tr>
<th>Design</th>
<th>Completing (n)</th>
<th>Psychologya</th>
<th>Nociceptive functionb</th>
<th>Pain elsewhere</th>
<th>Pain</th>
<th>Incision type</th>
<th>Details of surgical procedure</th>
<th>Acute pain evaluation</th>
<th>Pain evaluation (yrs = years, m = months)</th>
<th>Social consequencesc</th>
<th>Pain clinic or physician</th>
<th>Late pain treatment</th>
<th>QSTd</th>
<th>Use of adjuvant therapye</th>
<th>Systematic examination for recurrence</th>
<th>Comments on design and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dajczman et al. [29]</td>
<td>R 56</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>2m–5 yrs</td>
<td>+</td>
<td>+</td>
<td>—</td>
<td>+</td>
<td>—</td>
<td>Questionnaire follow up on 206 journals many post op. factors, incidence 30–73%</td>
<td></td>
</tr>
<tr>
<td>Kalso et al. [12]</td>
<td>R 134</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>15–48 m</td>
<td>—</td>
<td>—</td>
<td>+</td>
<td>—</td>
<td>—</td>
<td>Interview based on review on 214 journals, recall bias, incidence 44%</td>
<td></td>
</tr>
<tr>
<td>Keller et al. [40]</td>
<td>R 238</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>2–20 m</td>
<td>—</td>
<td>+</td>
<td>+</td>
<td>—</td>
<td>—</td>
<td>No data on follow-up, no statistics, incidence 11%</td>
<td></td>
</tr>
<tr>
<td>Sabanathan [36]</td>
<td>R 883</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>1 yr</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>+</td>
<td>—</td>
<td>1000 records reviewed, late pain follow-up methodology unknown, incidence 13.9%</td>
<td></td>
</tr>
<tr>
<td>Benedetti et al. [61]</td>
<td>P 42</td>
<td>+</td>
<td>—</td>
<td>—</td>
<td>PLT</td>
<td>—</td>
<td>+</td>
<td>2–3 m</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Study on abd. reflexes after nerve damage 10% had no abd. reflex, incidence 5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perttunen et al. [13]</td>
<td>P 84</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>PLT</td>
<td>—</td>
<td>—</td>
<td>3, 6, 12 m</td>
<td>+</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Questionnaire follow up on 110 patients, many consequences included, incidence 61–80%</td>
<td></td>
<td></td>
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<tr>
<td>Gotoda et al. [23]</td>
<td>P 85</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>PLT/ant</td>
<td>—</td>
<td>+</td>
<td>1 yr</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Questionnaire follow-up, female gender and acute pain predicts PTPS., incidence 48%</td>
<td></td>
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<tr>
<td>Tiippana et al. [38]</td>
<td>P 111</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>3 + 6 m</td>
<td>+</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Questionnaire follow-up analyzing analgesic method, incidence 41–29%</td>
<td></td>
</tr>
<tr>
<td>Maguire et al. [25]</td>
<td>R 600</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>PLT/VATS</td>
<td>—</td>
<td>—</td>
<td>7 m–7 yrs</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>—</td>
<td>—</td>
<td>Follow-up on patients in database, PTPS decreasing with time, incidence 21–57%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pluijms et al. [18]</td>
<td>R 149</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>PLT</td>
<td>—</td>
<td>+</td>
<td>6–42m</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>+</td>
<td>—</td>
<td>Telephone follow-up, acute pain evaluation based on recall, incidence 44–58%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steegers et al. [26]</td>
<td>R 204</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>PLT/VATS</td>
<td>—</td>
<td>—</td>
<td>6–42m</td>
<td>—</td>
<td>—</td>
<td>+</td>
<td>—</td>
<td>—</td>
<td>Questionnaire follow-up, groups not comparable in regards to cancer, incidence 40–47%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

R, retrospective; P, prospective; *, randomised; +, item included; —, insufficient information; NS, no significant difference; VATS, video-assisted thoracic surgery; PLT, posterolateral thoracotomy; mPLT, muscle sparing PLT; ant, anterior or antero-lateral access.

a Anxiety, depression and coping strategies.
b Clinical examination of nerve function prior to surgery.
c Social, occupational and level of activity evaluated.
d Performed quantitative sensory testing.
e Type of radio-/chemotherapy received described.
f Analgesic consumption registered.
g Does not present data or only presents descriptive data.
h Test of abdominal reflexes.
i Preoperative pain recorded but no intensity or location recorded.
j Acute pain evaluated after 1 week.
Table 2
Evaluation of surgical technique.

<table>
<thead>
<tr>
<th>Study Authors</th>
<th>Design</th>
<th>Completing (n)</th>
<th>Psychology</th>
<th>Nociceptive function</th>
<th>Pain elsewhere</th>
<th>Pain type</th>
<th>Details of surgical procedure</th>
<th>Acute pain evaluation (w = weeks, m = months, y = years)</th>
<th>Pain evaluation</th>
<th>Social consequences</th>
<th>Pain clinic or physician</th>
<th>Late pain treatment</th>
<th>QST</th>
<th>Use of adjuvant therapy</th>
<th>Systematic examination for recurrence</th>
<th>Comments on design and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Landreneau et al. [20]</td>
<td>R</td>
<td>335</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>mPLT/PLT +</td>
<td>—</td>
<td>1 y</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Comparison of muscle sparing PLT versus PLT use of pericostal sutures. NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Khan et al. [59]</td>
<td>R</td>
<td>20</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>mPLT/PLT +</td>
<td>—</td>
<td>12–60 m</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Matched comparison of muscle sparing PLT versus PLT difference in division of costae and ligaments. NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ochroch et al. [21]</td>
<td>P*</td>
<td>112</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>mPLT/PLT +</td>
<td>—</td>
<td>12–48 w</td>
<td>+</td>
<td>—</td>
<td>+</td>
<td>—</td>
<td>Randomisation refers to the pre-emptive use of TEA surgical data absent. No incisional difference.</td>
<td></td>
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</tr>
<tr>
<td>Nomori et al. [60]</td>
<td>R</td>
<td>50</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>PLT/ant +</td>
<td>+</td>
<td>3, 6 m</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>h</td>
<td>Comparison of incision in two matched groups less pain with both anterior approaches</td>
<td></td>
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</tr>
<tr>
<td>Nomori et al. [53]</td>
<td>R</td>
<td>84</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>+</td>
<td>PLT/ant +</td>
<td>+</td>
<td>3, 6 m</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>h</td>
<td>Comparison of incisions in three matched groups both anterior approaches better than PLT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kirby et al. [27]</td>
<td>P*</td>
<td>55</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>mPLT/VATS +</td>
<td>—</td>
<td>13 m</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Comparison of muscle sparing PLT versus VATS. NS late pain evaluation method unclear. VATS + PCA group matched to PLT + TEA. NS unclear exactly how follow up was performed Investigation of intraoperative nerve damage, 21% non-lung cancer patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Furrer et al. [64]</td>
<td>P</td>
<td>29</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>PLT/VATS +</td>
<td>+</td>
<td>3–18 m</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Comparison of costal bundle-splitting versus none no data on patients. Bundle-splitting superior</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maguire et al. [50]</td>
<td>P</td>
<td>31</td>
<td>+</td>
<td>—</td>
<td>—</td>
<td>+</td>
<td>PLT +</td>
<td>+</td>
<td>3 m</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Use of intracostal sutures versus pericostal sutures 23–26% with rib fractures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lee et al. [67]</td>
<td>P</td>
<td>56</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>PLT +</td>
<td>+</td>
<td>3, 6 m</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Division of muscle flap versus dangling flap (all had intracostal sutures) dangling flap superior</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerfolio et al. [69]</td>
<td>P</td>
<td>255</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>PLT +</td>
<td>—</td>
<td>3 m</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerfolio et al. [66]</td>
<td>P*</td>
<td>78</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>PLT +</td>
<td>+</td>
<td>12 w</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Cerfolio et al. [68]</td>
<td>P*</td>
<td>144</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>PLT +</td>
<td>+</td>
<td>12 w</td>
<td>+</td>
<td>—</td>
<td>—</td>
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<td></td>
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</tr>
</tbody>
</table>

R, retrospective; C, cohort study; P, prospective; *, randomised; +, item included; —, insufficient information; NS, no significant difference; VATS, video-assisted thoracic surgery; PLT, posterolateral thoracotomy; mPLT, muscle sparing PLT; ant, anterior or antero-lateral access.

a Anxiety, depression and coping strategies.
b Clinical examination of nerve function prior to surgery.
c Social, occupational and level of activity evaluated.
d Performed quantitative sensory testing.
e Type of radio-/chemotherapy received described.
f Arm/shoulder function on operated side.
g Chronic painful condition = exclusion.
h No details on type of treatment.
i Average follow-up time.
j Muscle evoked potential recorded.
k Tested for pinprick sensation.
Table 3
Evaluation of analgesic techniques.

<table>
<thead>
<tr>
<th>Design</th>
<th>Completing (n)</th>
<th>Psychologya</th>
<th>Nociceptive functionb</th>
<th>Pain elsewhere</th>
<th>Pain Incision type</th>
<th>Details of surgical procedure</th>
<th>Acute pain evaluation</th>
<th>Pain evaluation (m = months, w = weeks)</th>
<th>Social consequencesc</th>
<th>Pain clinic or physician</th>
<th>Late pain treatment</th>
<th>QSTd</th>
<th>Use of adjuvant therapye</th>
<th>Systematic examination for recurrence</th>
<th>Comments on design and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Katz et al. [24]</td>
<td>P* 23</td>
<td>—</td>
<td>+1</td>
<td>—</td>
<td>PLT</td>
<td>—</td>
<td>+</td>
<td>18 m</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Follow-up after multimodal therapy including ICB versus placebo, surgical details absent</td>
</tr>
<tr>
<td>Doyle and Bowler [71]</td>
<td>P* 29</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>PLT</td>
<td>—</td>
<td>+</td>
<td>6, 12 m</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Evaluation of pre-emptive ICB, NS., data from late pain follow-up miniscule</td>
</tr>
<tr>
<td>Obata et al. [78]</td>
<td>P* 58</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>PLT</td>
<td>—</td>
<td>+</td>
<td>3, 6 m</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Evaluation of pre-emptive TEA., pre-emptive analgesia superior, many factors missing</td>
</tr>
<tr>
<td>Octroch et al. [21]</td>
<td>P* 112</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>PLT/mPLT</td>
<td>—</td>
<td>+</td>
<td>12—48 w</td>
<td>+</td>
<td>—</td>
<td>+</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Evaluation of pre-emptive TEA, NS, surgical data absent</td>
</tr>
<tr>
<td>Senturk et al. [19]</td>
<td>P* 69</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>PLT</td>
<td>—</td>
<td>+</td>
<td>6 m</td>
<td>—</td>
<td>—</td>
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<td>—</td>
<td>—</td>
<td>—</td>
<td>Evaluation of pre-emptive TEA, many factors absent, pre-emptive analgesia superior</td>
</tr>
<tr>
<td>Rusbridge et al. [80]</td>
<td>P* 48</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>6 m</td>
<td>—</td>
<td>+</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Cryo + LEA versus LEA. No data, too low follow-up at 6 months for analysis</td>
</tr>
<tr>
<td>Miguel and Hubbell [72]</td>
<td>P* 33</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>12 w</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>4 groups: cryo, LEA, IPA, p.n. opioid cryo and opioid both better than LEA or IPA</td>
</tr>
<tr>
<td>Yang et al. [56]</td>
<td>P* 80</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>3, 6 m</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Cryo + TEA versus TEA, NS, non-analgesic data absent</td>
</tr>
<tr>
<td>Gwak et al. [54]</td>
<td>P* 50</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>3, 6 m</td>
<td>—</td>
<td>—</td>
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<td>—</td>
<td>—</td>
<td>—</td>
<td>I.V. continuous analgesia (ivca) versus ivca + cryo, surgical data absent. NS.</td>
</tr>
<tr>
<td>Ju et al. [55]</td>
<td>P* 77</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>3—12 m</td>
<td>—</td>
<td>—</td>
<td>—</td>
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<td>—</td>
<td>—</td>
<td>Evaluation of cryo versus TEA, NS, consequences less for TEA group, surgical data absent</td>
</tr>
<tr>
<td>Cerfolio et al. [73]</td>
<td>P* 105</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>3—12 m</td>
<td>—</td>
<td>—</td>
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<td>—</td>
<td>—</td>
<td>—</td>
<td>Pre-emptive incisional lidocaine. NS surgical details included</td>
</tr>
<tr>
<td>Hu et al. [31]</td>
<td>R 159</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>6—40 m</td>
<td>+</td>
<td>—</td>
<td>+</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>TEA versus no TEA, NS., includes several postoperative psychosocial variables</td>
</tr>
<tr>
<td>Suzuki et al. [22]</td>
<td>P* 44</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>3, 6 m</td>
<td>+</td>
<td>—</td>
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<td>—</td>
<td>—</td>
<td>TEA and iv. ketamine versus TEA, NS, surgical details absent. Conflicting results at 3 and 6 m</td>
</tr>
</tbody>
</table>

R, retrospective; C, cohort study; P, prospective; *, randomised; +, item included; —, insufficient information; NS, no significant difference; VATS, video assisted thoracic surgery; PLT, posterolateral thoracotomy; mPLT, muscle sparing PLT; ant, anterior or antero-lateral access; LEA, lumbar epidural analgesia; TEA, thoracic epidural analgesia; IPA, intrapleural analgesia; cryo, cryoanalgesia; ICB, inter-costal block.

a Anxiety, depression and coping strategies.
b Clinical examination of nerve function prior to surgery.
c Social, occupational or level of activity evaluated.
d Performed quantitative sensory testing.
e Type of chemotherapy received described.
f Algometer test.
g Chronic pain, or regular use of analgesics = exclusion.
h Yes/no to pain interfering/inconveniencing daily life.
i At follow-up after 6 weeks.
jk No details on type of treatment.
2. Methods

A block search was done May 2008 in PubMed (http://www.ncbi.nlm.nih.gov/sites/entrez/) by combining the three categories of search terms below (procedure AND timing AND measure). OR was used within the categories.

Procedure: Thoracoscopy, thoracoscopic, thoracic surgery, thorascopic surgery, thoracotomy, thoracotomies, VATS, video-assisted surgery, lobectomy, pneumonectomy.

Timing: Postoperative, post operative, post surgical, post-thoracotomy, postthoracotomy.

Measure: Pain, persistent pain, chronic pain, complex regional pain syndrome, neuralgia, neuropathic, residual.

MeSH terms were used in conjunction with free text word combinations as this would uncover papers tagged with unsatisfactory MESH terms and papers not yet fitted with MeSH terms (PreMEDLINE, part of PubMed). Since several related reviews were published in 2000 [7,32] to 2008 [5], we limited our initial bibliographic search to include only articles from 2000 and forth. Results were further limited to articles published in English, including only adults (19+ years) and clinical trials. A similar search was performed in Ovid (http://ovidsp.ovid.com/) still using English language, Emclas classification as clinical and publishing year as 2000–2008. Duplicate publications found were discarded. Finally references from extracted articles, papers already known to the authors and papers published during the review process (using the inclusion criteria in 'My NCBI') supplemented the search strategy.

A total of 298 unique articles were found by the search strategy. By abstracts/title alone; 204 articles were discarded because it did not match one or more criteria in purpose 1, leaving 94 articles. These were then again scrutinised in full text for their relevance to the criteria in purpose 1 discarding 78 papers. References from the remaining 16 papers and the above three reviews were recursively followed disregarding publication year, in order to obtain original works fulfilling our inclusion criteria, thus adding 17 original articles for a total of 33 unique trials. Finally three papers were presented via 'My NCBI' during the review process for the final 36 trials presented in Tables 1–3. Evaluation of PTPS included any form of pain score or binary yes/no evaluation. Whenever multiple papers referred to the same investigation, consequently only one of the references was used [21,33–37]. Papers identified presented typically as either prospective (randomised) trials, or retrospective questionnaire investigations.

Data were extracted on preoperative factors, pain score, site of pain, psychological resources and evaluation of nerve function. Intraoperative factors: type of surgery, incision including levels of incisions, muscle/nerve/rib handling and closure technique. Postoperative factors: acute and chronic pain, use of analgesics including type, social consequences and referral to specialist or pain clinic. Also postoperatively, objective estimates of nerve damage, use of radiation and chemotherapy as adjuvant treatment and systematic examination for recurrence of malignancy were recorded.

3. Incidence

The prevalence of PTPS seems to be highly variable (Table 1, incidence studies), but high (about 50%). With the majority experiencing only mild pain, 3–16% experience moderate to severe pain [1,18]. Some authors have chosen to only register PTPS at a certain intensity level of pain [20,38,39] while others have registered PTPS as a binary outcome [12,36] or when a discomfort requiring regular analgesic consumption was present [40], hindering exact interpretation and comparison between studies.

Pain has been reported most profound around the scar, since 82–90% of pain patients relate their pain directly to the surgical site [12,13]. The pain is primarily described as aching, tender, with numbness and to a lesser degree burning [12,25].

The social consequences and subsequent analgesic use have only been recorded in a minority of studies with different design [21,25,29,31,38] leaving impact of chronic pain on daily life unclear. Thus no deduction from intensity or frequency of PTPS to quality of life can be made.

4. Preoperative factors

It is well established in several types of surgery that the risk for chronification is decreased in elderly patients [1] and probably also that the risk is increased in women [1]. Several efforts have been made for a preoperative identification of patients at risk for persistent postsurgical pain [1]. Thus, the pain response to a preoperative nociceptive stimulation test (heat, electrical stimulation, cold pressure test) may be able to identify patients showing an increased acute postoperative pain response [41–44], which otherwise has been demonstrated to correlate with an increased risk for chronification [1]. Subsequently, construction of different cumulated score systems based upon psychological assessments and responses to nociceptive stimulation have also been able to be predictive of severe postoperative pain [45,46]. Finally, recent data suggest that preoperative assessment of the endogenous analgesia system (diffuse noxious inhibitory control (DNIC)) may be able to predict postoperative pain responses [39]. However, except for the latter DNIC-study [39] which was performed before and after thoracotomy, no specific information is available on the ability to predict PTPS from the other studies.

Another predictive factor is the existence of chronic pain complaints from other sites in the body (apart from the surgical site) as shown in hysterectomy [4] and inguinal herniotomy [8], but again no similar specific information is available linking to PTPS.

4.1. Genetics

Sensitivity to physiological nociceptive and clinical pain differs considerably between individuals. Consequently, it has been recognised that genetic factors may be important in pain perception and several pain gene candidates have been identified including genetic polymorphisms of catechol-O-methyltransferase (COMT), genetic variants to determine voltage-gated sodium channels, and GTP cyclohydrolase and tetrahydrobiopterin-related genes among others [47–49].
Because of the complexity of persistent postsurgical pain, the exact roles of genetic disposition have not yet been verified, and especially not when combining different pain gene candidates characteristics. Nevertheless, such studies are extremely important, including in persistent post-thoracotomy pain, where neuropathic pain probably is a main component and occurs with such a high incidence that reasonably large patient series (about 500–1000 patients) should be sufficient to provide clinically relevant answers [48].

4.2. Psychosocial factors

It is well established that several psychosocial conditions can affect perception and consequences of chronic pain conditions, including, anxiety, depression, malignant disease, social network and social status [30]. Only two studies assessed preoperative anxiety/depression in relation to the development of PTPS, both showing no relationship [24,50]. Consequently, more detailed studies are required on the role of psychosocial factors combined with other risk factors of PTPS.

4.3. Preoperative pain

Little information in relation to PTPS is available in contrast to the well documented relationship from hernia [51], hysterectomy [4] and amputation surgery [52]. Pettunen et al. found that 17% of participants had some degree of preoperative pain [13], and one trial used a preoperative pain assessment [53] but did not relate this to PTPS. Katz et al. scored preoperative pain pressure thresholds but found no association with chronic pain [24]. Other authors also found no or inconsequent relation between preoperative pain and PTPS [21,50]. Keller et al. found in a retrospective investigation that among users of preoperative analgesics 52% developed PTPS, as opposed to only 5.5% without daily preoperative analgesic consumption. However pre-, intra- and postoperative factors were not described in detail, hindering exact interpretation. Since preoperative chronic pain or analgesic consumption was an exclusion criterion in many of the clinical trials, the knowledge of the role of pre-surgical pain for PTPS is conflicting [21,50,54–56]. As seen in Tables 1–3, unfortunately no study on PTPS has included specific information on preoperative pain complaints in other sites of the body, which is important, since such complaints have been related to development of chronic pain at the surgical site after hysterectomy [4] and hernia surgery [57,58].

5. Intraoperative factors, surgery

Thoracotomy may be performed by a posterolateral (PLT) access or the modified version, muscle-sparing posterolateral access (mPLT) denoting whether the latissimus dorsi is divided or not [20] or by an axillary or anterior (ant) approach. In the latter three approaches, the muscles are mobilised and retracted to allow optimal exposure of the rib cage. In this review the term ‘muscle sparing’ is only used when M. latissimus dorsi is neither incised nor severed.

5.1. Open surgery; incision type

Our current knowledge on the effect of open surgical access on PTPS consists of retrospective investigations and a single sub-analysis on a prospective work, all of which omit most details on pre-, intra- and postoperative data (Table 2, Evaluation of surgical technique).

Only two studies [20,59] (n = 335 and n = 20) had a primary goal to present data on the difference between muscle-sparing posterolateral thoracotomy versus traditional posterolateral thoracotomy and none of them found any difference between the two methods. Data from the prospective study primarily designed to measure the pre-emptive effect of thoracic epidural analgesia (TEA) [21], showed no difference in chronic pain incidence based on the type of incision.

When considering the classical posterolateral access versus an anterior access, two retrospective investigations by the same authors [53,60] found the anterior access to result in reduced PTPS. Methodologically, different rating scales for acute and chronic pain were used and both investigations consisted of retrospectively matched groups.

Benedetti et al. [61] assessed the superficial abdominal reflex impairment as a measurement of nerve damage after PLT, showing that acute and chronic pain both contain elements of nerve damage. Increased chronic pain and analgesic consumption were found more often in the group with postoperative absence of superficial abdominal reflexes. In a later study evaluating pain and nerve function after only 1 month, muscle-sparing posterolateral thoracotomy (mPLT) had more preservation of superficial abdominal reflexes than traditional posterolateral thoracotomy as well as pain after 1 month was improved in the mPLT group [62].

Summarising, the lack of prospective studies with details on relevant pre-, intra- and postoperative factors does not allow any firm conclusions as to the consequences of type of open surgery technique in relation to the development of PTPS, although nerve damage seems to be a risk factor.

5.2. Video-assisted thoracic surgery (VATS)

The introduction of video-assisted thoracic surgery (VATS) was expected to reduce PTPS based on the assumption that several minute incisions, although at multiple intercostal levels, are preferable compared to one long surgical incision. However, although minimally invasive, the use of VATS may not eliminate intercostal nerve injury since the scopes are heavily manipulated during the procedure, which may cause the nerve to be crushed against the adjacent rib. Also operation time in VATS has been suspected of being prolonged [63]. Finally, since the resected part of the lung must be evacuated from the thoracic cavity, at least one port has to be expanded to allow extraction of the lung tissue. During this process the use of rib retractors is sometimes used (assisted-VATS) which may cause intercostal nerve injury, and the use of rib retractors in VATS has made some surgeons refer to the procedure as a mini-thoracotomy [27].

Two prospective trials [27,64], one comparing mPLT to VATS (n = 55) and one comparing PLT to VATS (n = 29) found no differences on the incidence of PTPS. In contrast, a retrospective study [28], with a complete follow-up on 343 patients found VATS to reduce PTPS compared to a muscle-
spared incision (Table 2, Evaluation of surgical technique). However, pre- and postoperative patient related factors and several surgical details are missing thereby precluding firm conclusions as to the potential role of VATS to reduce PTPS.

5.3. Other surgical techniques

Rogers et al. [65] evoked motor potentials in a series of 13 patients and showed that the use of rib retractors induced intercostal nerve damage. Thus, a total nerve conduction block from retractor induced nerve injury was measured in 100%, respectively 92%, of patients in the intercostal nerve sparing incision (Table 2, Evaluation of surgical technique). However, pre- and postoperative patient related factors and several surgical details are missing thereby precluding firm conclusions as to the potential role of VATS to reduce PTPS.

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In conclusion, these studies [65–69] suggest that pronounced nerve injury takes place during thoracotomy, and that this may contribute to development of PTPS. However, in all the above studies there is insufficient information on all other pathogenic mechanisms and there is no quantitative sensory test (QST) assessment of degree of nerve injury at the chronic pain site, or a specific assessment of symptoms or neuropathic pain characterisation. Accordingly, there is a severe need of future high-quality studies on the exact role of nerve injury in PTPS in relation to preoperative (genetic) factors and surgical approach, including closure technique, and late psychosocial factors.

6. Intraoperative factors, analgesia

6.1. Interpleural analgesia, paravertebral block (PVB) and intercostal block

Katz et al. and Doyle and Bowler all found no difference in PTPS when investigating the timing of intercostal nerve block [24,71]. Interpleural analgesia was in a small prospective study found to be inferior to both cryoanalgesia and opioid treatment [72]. Cerfolio et al. [73] performed a prospective trial with systematic injections of local analgesics at the incision site without significant effect on incidence of PTPS. Though one author finds an incidence of 14% in a retrospective investigation of 883 patients receiving continuous extrapleural intercostal nerve block [36] no extrapolation of this study can be done since methodological details are absent. From ‘Table 3, Evaluation of analgesic techniques’ it is apparent that the absence of exhaustive data to uncover other underlying causes of PTPS prohibits exact interpretation of the role of these techniques to reduce PTPS.

6.2. Thoracic epidural analgesia (TEA)

Randomised double-blinded trials on thoracic epidural analgesia in relation to PTSP mainly deal with the concept of timing in relation to a pre-emptive effect (see Section 6.4). TEA was compared to TEA supplemented by iv. ketamine with conflicting results at 3 and 6 months [22] (n = 44) and in a
retrospective follow-up trial TEA did not decrease PTPS among 159 completing participants [31], (Table 3, evaluation of analgesic techniques). Summarising, the role of TEA on PTPS remains unclarified and questionable based upon studies from other procedures [74].

6.3. Cryoanalgesia

In the one randomised prospective trial matching TEA against cryoanalgesia (n = 77) [55] no difference on incidence of PTPS was observed. When comparing prospective randomised trials of cryoanalgesia (CA) alone with CA + TEA [56] or to CA + intravenous continuous morphine [54] again no effect on PTPS has been found, corresponding to reports of no effect of cryoanalgesia on acute pain [75]. In a small prospective study with four arms each containing 10 patients, cryoanalgesia resulted in less PTPS after 12 weeks compared to lumbar epidural morphine and intrapleural analgesia [72].

In summary, as shown in Table 3, the data on intraoperative analgesic technique suffer from severe methodological difficulties in particular with regards to details on surgical technique and do not allow any conclusion on the development of PTPS.

6.4. Pre-emptive analgesia

Pre-emptive analgesia attempts to reduce post-injury pain hypersensitivity by early onset of analgesic treatment i.e. prior to surgery in order to reduce postoperative pain. Recent reviews on effect of pre-emptive analgesic strategy have presented few trials on the relation to chronic pain [76] and only five RCTs have evaluated the pre-emptive effect of analgesia on PTPS [77]. Two of the RCTs including 69 patients [19] and 58 patients [78] found TEA to reduce PTPS. In contrast, three prospective randomised trials, two on multimodal therapy including intercostal nerve blocks [24,71] and another on pre-emptive use of TEA (n = 112) [21] found no advantage. However, all of the above studies had insufficient methodology regarding follow-up (telephone interviews), lack of detailed pain assessment, consequences and lack of information on all other potential pathogenic mechanisms. Finally, transferable evidence on the effect of pre-emptive analgesia used in other surgical procedures [74,76,77], is also inconclusive regarding the effects on chronic postsurgical pain.

7. Postoperatively

7.1. Acute postoperative pain

Several studies from other procedures have demonstrated the intensity of acute postoperative pain to be a risk factor for persistent postsurgical pain [3,9,79]. However acute pain has not been registered consistently in relation to PTPS (Tables 1–3, acute pain evaluation within first postoperative week). Furthermore, the study design is vital since retrospective investigations on the relationship between acute and chronic pain may be influenced by a significant recall bias. Some studies registering acute pain did not present data on acute pain scores in relation to PTPS, but used analgesic consumption as an indirect measurement [20,59]. Several investigations found that acute postoperative pain was related to PTPS [18,23,24] while others found no association [12,13,38]. Trial design and lack of attention to important pre-, intra and postoperative aspects of PTPS aetiology make conclusions impossible on the exact relationship between acute and chronic postoperative pain. Although it seems plausible based upon information from other procedures [1].

7.2. Consequences of PTPS on daily activities

Several authors have evaluated social consequences of PTPS to some extent [13,21,25,29,38]. However, the quality and type of assessment vary from pain interfering with daily life (not well defined) to effect on standing, sitting, getting up, different levels of activity, sleep etc. A few have tested subjective shoulder function or strength on the operated side [20,28,59]. To sum up, sufficient evaluation of subjective disability and key physical activities relating to daily life has not been consistently evaluated (Tables 1–3, column 'social consequences'), and the exact role of PTPS on social consequences of PTPS remains to be determined.

7.3. Postoperative pain treatment due to PTPS

Surprisingly few trials have registered analgesic consumption including type and/or referral to pain clinics and specialists [12,21,29,38,71] or simply do not present sufficient data (Tables 1–3). Since the data show highly variable results and have insufficient information on pre-, and intraoperative factors no firm conclusions can be made, calling for further well-described studies of the analgesic requirements in PTPS.

7.4. Adjuvant radio- and chemotherapy

Four of the retrospective incidence studies registered the use of radio- or chemotherapy [18,26,29,36] and two prospective studies [66,68], however none reported details on therapy thereby in relation to PTPS precluding relevant interpretation and conclusions of the role in PTPS.

7.5. Systematic examination for recurrence of malignancy

Recurrence may obviously cause PTPS. However, in the only study describing a systematic clinical assessment for recurrence, no evidence of recurrence is found in a clinical follow-up within 3 months of questionnaire contact [28]. In contrast, Keller et al. mentioned that 20 out of 25 PTPS patients with temporary loss of pain control had recurrence [40], but methodology of recurrence assessment was not described. The lack of systematic follow-up on recurrence makes it difficult to elucidate the role of tumour recurrence for the development of PTPS.

8. Future trial design issues

Roughly one third of the PTPS data in the literature found is based on retrospective studies and even in the prospective
RCTs, detailed description of the blinding and randomisation procedures are infrequently present. Previous trials have evaluated mixed categories of patients with malignant diagnoses including pleural and chest wall resections [25,36,40,55,80] or mixed patients with malignant and benign diagnoses [26,28,59] thereby mixing different surgical procedures and patients of different morbidity and mortality.

Thorough registration of preoperative data relating to potential factors of PTPS such as multiple chest surgery, preoperative pain, pain location and intensity, medication, psychosocial background and objective nerve assessment must be included in standard preoperative patient evaluation. The same comprehensive data collection is necessary in regards to intraoperative surgical technique. Details on open type surgery or VATS in regards to incision level, type and size, amount and size of ports, use of retractor (time), identification and handling of intercostal nerves, and use of sutures on closure of the chest to such an extent that the exact procedure can be reproduced, must be standard in future trials. Likewise details on method of anaesthesia and in particular timing and effect of regional or neuroaxial block must be standard for investigations to come. Therefore, detailed information and stringent methodology in order to reveal causality between surgical/anaesthetic methods and PTPS is necessary for future trials. Considering that it is still unclear for how long the local inflammatory response can sustain postsurgical pain, future investigations should consider including pain evaluation later than the current IASP definition of chronic pain of 2 months. Importantly, in future PTPS studies, postsurgical pain must be discerned from other forms of pain not relating to the surgical site (migraine, low-back pain, fibromyalgia, etc.).

Specific areas of pursuit must include investigations on nerve handling, and nerve damage as dissection studies show the intercostal nerves to be at considerable risk in both open and videoendoscopic surgery. The subcostal groove changes into a sharp edge after the angle of the rib [81] and the nerve only continues in the classical subcostal position in 17% of cadavers [82], thereby leaving the intercostal nerves susceptible to injury. That nerve identification and handling is vital for the understanding of PTPS is further supported by trials showing nerve impingement following use of rib retractors [65] and reduced nerve conduction after closure with pericostal sutures [50]. Furthermore, studies identifying the intercostal nerves and thereby being able to protect these [67,68] or using intracostal sutures [69] saw a reduced risk of PTPS. Thus nerve injury may be a prerequisite for the development of PTPS although not sufficient since other factors (genetic, psychosocial, and others) may contribute. Some authors have argued that less than 50% of PTPS is due to nerve injury based upon neuropathic ‘specific’ questionnaires [26], but screening tools may miss 10—20% of patients with diagnosed neuropathic pain [83]. It is therefore mandatory in future trials that objective assessment of nerve function with quantitative sensory testing is performed as has been done in persistent pain states after other procedures [70]. Better systematics, careful inclusion of all suspected factors in the pre-, intra and postoperative phases of a study including thorough investigation into nerve damage appears crucial for future understanding of PTPS.

A suggested ‘checklist’ to obtain uniform assessment for future trials is presented in Table 4.

9. Conclusion

In this updated critical review on PTPS, a uniform comparison of PTPS between current studies was impossible due to the heterogeneity of data (Tables 1—3), illustrating the need to increase the quality of the systematics in data collection in order to further understand the pathogenesis and the development of prevention/treatment strategies, which have rarely included factors known to be relevant in chronic pain studies from other surgical procedures. Current knowledge of surgical risk factors for PTPS is almost entirely based on non-randomised clinical trials and relative low-quality randomised clinical trials. Therefore, future investigations of PTPS must include exhaustive information on all pre-, intra-, and postoperative factors that may influence the pain condition and consequences in order to optimise preventive or treatment strategies.

References


