Review Article

Post-thoracotomy pain syndrome in the era of minimally invasive thoracic surgery

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Contributions: (I) Conception and design: T Miyazaki; (II) Administrative support: All authors; (III) Provision of study materials or patients: T Miyazaki, R Doi; (IV) Collection and assembly of data: T Miyazaki, R Doi; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Post-thoracotomy pain syndrome (PTPS) is defined as pain around the wound that persists for more than 2 months after surgery. Persistent pain not only increases the use of analgesics and their side effects but also causes many social problems, such as decreased activities of daily living, decreased quality of life, and increased medical costs. In particular, thoracic surgery is associated with a higher frequency and severity of chronic pain than is surgery for other diseases. The basic principles of postoperative pain treatment, not limited to thoracic surgery, are multimodal analgesic methods (using combinations of several drugs to minimize opioid use) and around-the-clock treatment (administering analgesics at a fixed time and in sufficient doses). Thoracic surgeons must always be aware of the following three points: acute severe postoperative pain is a major risk factor for chronic pain; neuropathic pain due to intercostal nerve injury is a major cause of postoperative pain after thoracic surgery, and its presence must not be overlooked from the acute stage; and analgesics must be administered in sufficient quantities according to dosage and volume. The frequency of PTPS has decreased compared with that in the standard thoracotomy era because of the development of analgesia and the widespread use of minimally invasive procedures such as thoracoscopic surgery and robot-assisted surgery. However, no consistently effective prevention or treatment strategies for PTPS have yet been established. In this review, we focus on PTPS in the era of minimally invasive surgery and discuss the role of thoracic surgeons in its management.

Keywords: Post-thoracotomy pain syndrome (PTPS); minimally invasive surgery; lung cancer; multimodal analgesia

Submitted Jan 26, 2024. Accepted for publication Apr 07, 2024. Published online May 20, 2024.
doi: 10.21037/jtd-24-158
View this article at: https://dx.doi.org/10.21037/jtd-24-158

Introduction

In the current era of thoracic surgery, a trend toward minimally invasive approaches has become predominant. With the shift from posterolateral thoracotomy involving rib dissection to the advent of video-assisted thoracoscopic surgery (VATS), many surgical procedures have evolved from video-assisted to fully thoracoscopic, dramatically reducing incision sizes. In recent years, robot-assisted thoracoscopic surgery (RATS) and uni-portal VATS (U-VATS) have demonstrated short- and long-term outcomes comparable to those of VATS. Correspondingly, advancements have been made in the minimally invasive nature of lung resections. The effectiveness of segmentectomy for peripheral small-sized lung cancer

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has been reported in randomized controlled trials (RCTs) from both Japan and the United States (1,2). The extent of resection is expected to continue to decrease in future.

Despite this progress, post-thoracotomy pain remains problematic. In the era of open surgery, chronic pain, especially post-thoracotomy pain syndrome (PTPS), was a frequent occurrence. PTPS is inherently associated with the functional decline resulting from lung resection, and it represents a significant complication with the potential to diminish patients' quality of life. Although the prevalence of PTPS has decreased with the rise of minimally invasive surgeries in recent years, it remains incompletely controlled. Several factors have contributed to the limited progress in research on this topic, including the inherently subjective nature of pain assessment, the absence of objective indicators commonly employed in routine clinical practice, the lack of systematic pain management education for surgeons akin to procedural skills training, and a somewhat limited interest in this domain. These factors have collectively hindered substantial advancements in understanding and addressing post-thoracotomy pain, resulting in a lack of significant research progress in this area. In the contemporary era dominated by minimally invasive surgery, we herein review various approaches to addressing post-thoracotomy pain. Through this review, we seek to raise awareness among thoracic surgeons regarding postoperative pain and elaborate on the measures that can currently be undertaken to minimize PTPS.

Definition and evaluation of post-thoracotomy pain

Definition

PTPS, also termed chronic post-thoracotomy pain or post-thoracotomy neuralgia, is defined by the International Association for the Study of Pain as "pain that recurs or persists along a thoracotomy scar at least 2 months following the surgical procedure" (3). PTPS is characterized by an aching sensation in the distribution of the incision, and it usually resolves within 2 months postoperatively. Pain that persists beyond this time or recurs may be accompanied by burning dysesthesia. There may also be a pleuritic component to the pain. Movements of the ipsilateral shoulder worsen the pain. In addition, according to the International Association for the Study of Pain, chronic pain is defined as "pain that persists or recurs for longer than 3 months". Although there are some differences in duration, PTPS and chronic pain can be considered almost identical conditions in the clinical practice of thoracic surgery.

Evaluation

Although the numeric rating scale and visual analogue scale (VAS) are commonly used in daily clinical practice, they are subjective assessments performed by the patient. One of the most important risk factors for PTPS is the presence of severe acute postoperative pain (4,5). If the pain score does not improve with conventional analgesics or additional analgesics, the presence of neuropathic pain should be suspected. For example, a 10-point change in the score on a 100-mm VAS for pain would be the minimal clinically important difference, and a VAS score of ≤33 signifies acceptable pain control after surgery (6).

Thoracic surgery is often performed through narrow intercostal spaces, and the presence of neuropathic pain from the time of the first port insertion would not be unexpected. In fact, a neuropathic pain component was observed in about 30% of patients on the fifth postoperative day after VATS (7,8). PTPS is largely due to this neuropathic pain, and its presence should be suspected early in the postoperative period so that its characteristic symptoms are not overlooked. Such pain can be observed not only at the wound site but also around the chest drain insertion site. Screening tools such as the Self-administered Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS) and pain DETECT (9) are used for this purpose, and their sensitivity and specificity are considered high.

We previously performed a study in which we objectively evaluated postoperative pain after thoracic surgery. Peripheral nerves are mainly composed of A fibers (myelinated nerves) and C fibers (unmyelinated nerves). We focused on the fact that the Neurometer™ (Neurotron, Inc., Baltimore, MD, USA) can objectively evaluate nerve damage by stimulating each nerve fiber separately and measuring the current perception threshold (CPT). We measured the CPT using various surgical approaches, including thoracotomy, mini-thoracotomy, and VATS. The results showed that VATS without a chest spreader significantly reduced intercostal nerve damage in A fibers (10). Similarly, when we examined intercostal nerve damage before, during, and after removal of a thoracic drain, we found a significantly higher CPT during drain insertion and a significantly lower CPT after drain removal. These findings indicated that the thoracic drain itself also caused intercostal nerve damage and influenced postoperative pain (11). Thus, the Neurometer™ is useful as an objective measure of nerve

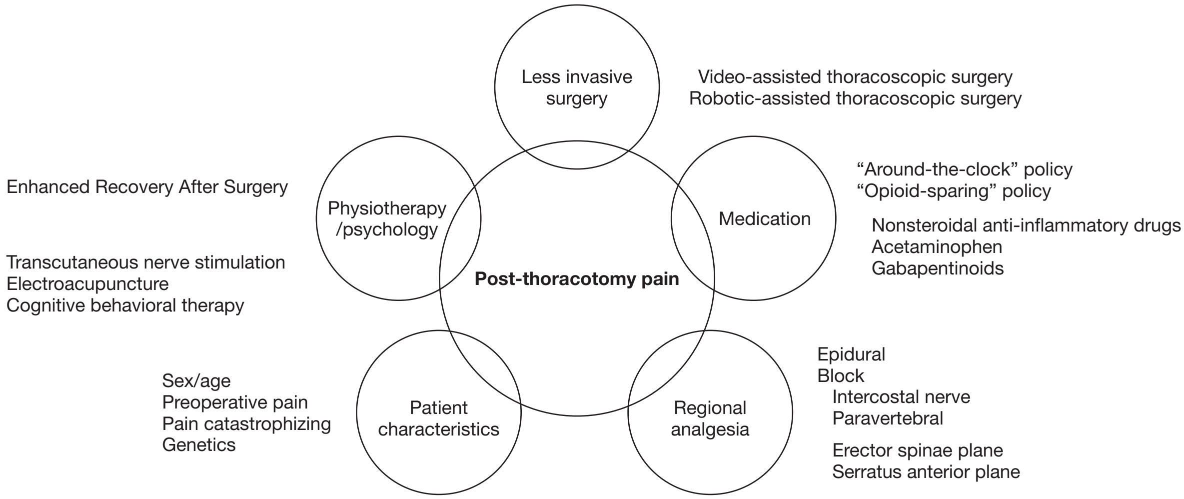

Figure 1 Our strategies for post-thoracotomy pain. Control of postoperative pain after thoracic surgery requires a multidisciplinary approach and collaboration with many departments in the hospital.

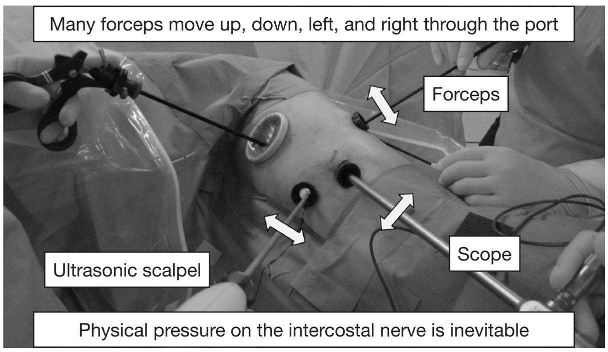

Figure 2 Video-assisted thoracoscopic surgery. The various devices used in thoracoscopic surgery are constantly moving through the narrow intercostal space through the rigid thoracoscopic port, and the pressure exerted is sometimes so great that intercostal nerve injury occurs.

damage.

Treatment options for reducing PTPS

Figure 1 shows a strategic diagram for reducing PTPS. As shown in the figure, a multifaceted approach is necessary. The present review focuses on three areas: the surgical approach, regional anesthesia, and medication.

Surgical approach

The most important goals for thoracic surgeons are ensuring safety and achieving a cure. However, reducing intercostal nerve damage is also important. For this purpose, the number of intercostal spaces to be approached should be reduced as much as possible, and surgery should be performed without applying a metal retractor. In addition, attention should be paid to thoracic drainage tubes. As mentioned above, we previously reported that thoracic drains are a cause of intercostal nerve injury (11). From the perspective of Enhanced Recovery After Surgery (ERAS®), thoracic drains should be removed as soon as possible if no problem has developed, the number of drains should be reduced as much as possible, and smaller-diameter drains made of softer materials should be selected.

VATS

VATS has become the standard approach for thoracic surgery. It is expected to cause fewer intercostal nerve injuries than standard thoracotomy, which requires the application of a metal retractor that compresses the intercostal nerves. However, all thoracic surgeons have encountered patients who develop postoperative pain, even after VATS. This is because the various devices used in thoracoscopic surgery (cameras, forceps, etc.) are constantly moving through the narrow intercostal space through the rigid thoracoscopic port, and the pressure exerted is sometimes so great that intercostal nerve injury occurs (*Figure 2*). Initially, VATS was performed with three to five ports and access wounds of a few centimeters in diameter. In recent years, however, bi-portal and uni-portal surgery have become more popular because of improvements in technique. The European Society of Thoracic Surgeons (ESTS) published a consensus report on the definition of and indications for U-VATS (12). The advantages of U-VATS over standard thoracotomy and multi-portal VATS (M-VATS) with respect to the perioperative and long-term outcomes appear to be well documented (13). Additionally, many reports have indicated that U-VATS induces less pain than M-VATS because it injures fewer intercostal nerves (8,14). However, these were few high-quality prospective studies, and their results should be interpreted with caution.

U-VATS seems to be the technique with the greatest potential to reduce PTPS because theoretically, injury to only one intercostal nerve is required. In recent years, extended procedures such as bronchoplasty have been more aggressively performed (15). Such procedures are expected to become the mainstream approaches in centers where robots have not been introduced.

RATS

Robotic surgery has become more widely used in recent years because of its ease of use and stable field of view (16). The remote center of the da Vinci™ Surgical System (Intuitive Surgical, Sunnyvale, CA, USA), which is currently the most commonly used robotic system, is said to have the potential to reduce postoperative pain with use of the robot because the port position is fixed. This fixed position adds to the somewhat strong pressure manipulation of the camera and forceps by the surgeon and assistant in U-VATS and M-VATS. Several RCTs comparing RATS with VATS and standard thoracotomy have been reported to date, with perioperative outcomes comparable or superior to those of VATS and open chest surgery (17-20). Acute postoperative pain was also evaluated in these studies and was found to be superior to that after standard thoracotomy (17), but with no difference compared with either U-VATS or M-VATS (20). A survey on the number of ports, intercostal insertion sites, and 30-day postoperative pain in patients undergoing RATS and VATS is currently underway (J-RATSIG 01: UMIN000041514), and the results of this analysis are being eagerly awaited.

Some retrospective observational studies showed that although there was no difference in long-term pain between RATS and VATS, RATS was inferior to VATS in terms of quality of life (21). In a post-hoc analysis of the RVlob RCT (22), patients were evaluated using the European Organization for Research and Treatment of Cancer (EORTC) Core Quality of Life Questionnaire (QLQ-C30), EORTC Quality of Life Questionnaire in Lung Cancer (QLQ-LC13), and European Quality of Life 5 Dimensions (EQ-5D) at 4, 24, and 48 weeks postoperatively. The results showed that RATS and VATS were comparable in all measures except that RATS showed a higher pain score at 4 weeks postoperatively. In addition, an RCT is currently underway with postoperative quality of life as the primary endpoint (23).

Furthermore, the use of uni-portal RATS (U-RATS) has been reported (24). The difficult maneuverability of U-VATS may become more manageable with use of robotic systems that feature easy multi-joint manipulation. There are currently no detailed reports on postoperative pain after U-RATS, and future studies are being eagerly awaited. We believe that the uni-portal subxiphoid approach, whether used in VATS or RATS (25), will become the most popular procedure in the future because it has the lowest risk of intercostal nerve injury, surpassing even intercostal approaches. We should continue to strive for the most minimally invasive surgery possible.

Regional anesthesia

The ERAS® guidelines established by the ESTS strongly recommend regional analgesia to reduce postoperative opioid use, and this recommendation is based on high-level evidence (26). Even in minimally invasive surgery, the use of regional analgesia may decrease the progression of acute pain and prevent its transition to chronic pain. Therefore, it is advisable to perform one of the regional anesthesia procedures described below. Because the surgeon can perform the procedure from within the operative field, they should consult with the anesthesiologist and perform the procedure with which the hospital is most familiar.

Epidural analgesia is the gold standard for post-thoracotomy pain management and can be started before or after the surgical incision. One meta-analysis compared whether starting epidural anesthesia before the skin incision reduces acute and chronic pain compared with epidural anesthesia started after the skin incision (27). The meta-analysis showed that initiation of epidural anesthesia before the skin incision suppressed not only pain at rest and coughing in the early postoperative period, but also pain from 1 to 6 months postoperatively. However, low-quality evidence indicated that pre-emptive epidural analgesia reduces the intensity of acute pain and the incidence of chronic pain after thoracotomy in adults.

Guidelines from 69 RCTs limited to VATS (28) recommend paravertebral block or erector spinae plane block as the first choice and serratus anterior plane block as the second choice. These blocks are equally effective (29) and have a low incidence of the side effects sometimes seen with epidural anesthesia, such as procedural complications (e.g., dural puncture, bleeding), hypotension, and nausea and vomiting (29). Therefore, these guidelines no longer recommend epidural anesthesia as postoperative analgesia in patients undergoing VATS.

Medication

The three basic concepts of pharmacotherapy for postoperative pain are the use of various analgesic methods to minimize the use of opioid drugs and their side effects (30), "around-the-clock" administration of sufficient analgesic drugs at a fixed time (31), and administration of the drug in accordance with the package insert and with simultaneous monitoring of liver and kidney function. As mentioned above, it is very important to provide sufficient analgesia in the acute phase and to prevent the pain from becoming chronic (32). Among the many medications available, the key ones other than opioids are described below.

Nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen

NSAIDs and acetaminophen are fundamental postoperative pain medications, and the ESTS guidelines strongly recommend that they are regularly administered unless the patient has contraindications. This recommendation is based on high-level evidence (26). Acetaminophen, in particular, can be administered in sufficient doses by intravenous infusion even when oral intake is not possible immediately after surgery. Dexamethasone, which is highly recommended for pain relief and prevention of postoperative nausea and vomiting in the ESTS guidelines despite its low level of evidence, is not routinely administered in our practice because it may inhibit wound healing.

Gabapentinoids

Gabapentinoids are primarily used for neuropathic pain. Because intercostal nerve injury is highly prevalent in thoracic surgery via the intercostal approach, as previously discussed, early administration of gabapentinoids may be effective if neuropathic pain is suspected, regardless of the postoperative time frame. Pregabalin and mirogabalin are structural analogs of γ-aminobutyric acid. They function by acting on the α2δ subunit of voltage-dependent calcium channels, leading to a reduction in the release of neurotransmitters (33). Pregabalin and mirogabalin are commonly used in the treatment of neuropathic pain. Many papers have reported the usefulness of pregabalin for relief of neuropathic pain when administered after thoracic surgery (34,35); however, our RCT did not demonstrate its efficacy (34). The recently introduced drug mirogabalin is reportedly useful and safe for various neuropathic pain conditions, including diabetic neuropathy, postherpetic herpes zoster, and lumbar spinal stenosis (33,36,37). Furthermore, a pooled analysis of two phase-III clinical trials showed that mirogabalin relieves pain as early as 2 days after administration (38). However, there was no evidence for this in the field of thoracic surgery.

Therefore, we designed a multicenter open-label RCT (ADMIT-NeP study) to investigate this issue. Patients with a VAS score of ≥40 mm and neuropathic pain in the wound or around the drain after removal of a thoracic drain following thoracic surgery were assigned to two groups. One group received NSAIDs and acetaminophen (conventional treatment), and the other group received conventional treatment with additional mirogabalin (39). At the primary endpoint of 8 weeks postoperatively, there was no significant difference in the change in the VAS score. However, in patients with a baseline S-LANSS score (used for neuropathic pain screening) of ≥12, the mirogabalin add-on group exhibited a greater decrease in the VAS score with increasing baseline S-LANSS scores. This trend was not observed in the conventional treatment group (post hoc analysis). In addition, regarding activities of daily living and quality of life, changes in the Pain Disability Assessment Scale score and the EQ-5D-5L index value from baseline to week 8 showed significantly greater improvement in the mirogabalin add-on group than in the conventional treatment group. These findings demonstrated that addition of mirogabalin to conventional therapy significantly improved the activities of daily living and quality of life in patients with peripheral neuropathic pain after thoracic surgery (40).

Others

It has been widely practiced for post thoracotomy pain by rehabilitation and external warming methods. Kol *et al.* (41) investigated that the effects of active external warming of patient concurrently with application of ice to incision site on thoracotomy pain and analgesic consumption and demonstrated that active external warming and ice application on the incision area, could reduce opioid consumption the intensity of thoracotomy pain. Transcutaneous electrical stimulation has been used as a form of physical therapy for postoperative pain after thoracic surgery (42,43). The mechanism has been attributed to gate control theory and endogenous opioid release; cytokine suppression has also been shown (44). Moreover, electroacupuncture for post-thoracotomy pain has been performed (45). However, no high-quality RCTs have focused on these issues to date, and future studies are expected.

There are important issues regarding objective pain assessment, especially using methods that assess pain based on brain function. Common functional neuroimaging techniques include magnetic resonance imaging, functional magnetic resonance imaging, near-infrared spectroscopy, electroencephalography, magnetoencephalography, and positron emission tomography (46).

In addition, recent developments in artificial intelligence have been used in many medical applications and may lead to rapid developments with respect to pain objectification in future (47).

Studies have also been at the molecular level, including assessment of the association between chronic pain after cardiac surgery through a median sternotomy and catechol-O-methyl transferase activity (48) and examination of genetic polymorphisms that predispose to inadequate pain control after U-VATS (49). Such research holds promise for "tailor-made treatment," which is now a routine practice in the treatment of lung cancer.

The association between the intestinal microbiota and the effects of immune checkpoint inhibitors is an area of particular interest (50). An interesting study has endeavored to find a relationship between the intestinal microbiota and chronic pain (51), and we hope that such research will continue.

In conclusion, we strongly recommend that pain treatment is not performed only by thoracic surgeons but also by a multidisciplinary team comprising anesthesiologists, pain clinicians, physiatrists, psychiatrists, nurses, pharmacists, clinical psychologists, physical and occupational therapists, and other specialists.

Nagasaki University, the author's institution, is conducting research with the aim of becoming a university that contributes to Planetary Health (52). The control of chronic pain, including that after open heart surgery, not only improves patients' quality of life but also reduces the use of analgesics, avoids side effects, prevents abuse, and ultimately leads to lower medical costs. We would like to contribute to this improvement in global health by continuing our research in this field.

Conclusions

This review has focused on postoperative pain after thoracic surgery in the current era of minimally invasive surgery. Although minimally invasive surgery is at its peak, there are still many issues regarding postoperative pain after thoracotomy, and we hope that various high-quality studies such as RCTs will be conducted in the future.

Acknowledgments

We thank Angela Morben, DVM, ELS, from Edanz (https://jp.edanz.com/ac) for editing a draft of this manuscript.
Funding: None.

Footnote

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-158/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-158/coif). T.M. serves as an unpaid editorial board member of *Journal of Thoracic Disease* from October 2022 to September 2024. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Miyazaki T, Doi R, Matsumoto K. Post-thoracotomy pain syndrome in the era of minimally invasive thoracic surgery. J Thorac Dis 2024;16(5):3422-3430. doi: 10.21037/jtd-24-158

