Assessment and follow-up of intercostal nerve damage after video-assisted thoracic surgery

Takuro Miyazaki[a], Tetsuya Sakai[b], Tomoshi Tsuchiya[a], Naoya Yamasaki[a], Tsutomu Tagawa[a],

Mariko Mine[c], Yoshisada Shibata[c], and Takeshi Nagayasu[a]

Divisions of [a]Surgical Oncology and [b]Anesthesiology and [c]Atomic Bomb Disease Institute,

Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

Word count of the text: 4710

Correspondence to: Takeshi Nagayasu, MD, PhD

 Division of Surgical Oncology

 Nagasaki University Graduate School of Biomedical Sciences

 1-7-1 Sakamoto, Nagasaki 852-8501, Japan

 Tel: +81-95-819-7304; Fax: +81-95-819-7306

 E-mail: nagayasu@nagasaki-u.ac.jp

Abstract

Objectives: Chronic pain is a common complication after thoracic surgery. The most important factor appears to be intercostal nerve damage. The purpose of this prospective study was to objectively evaluate intercostal nerve damage associated with post-thoracotomy pain after three surgical procedures using current perception threshold testing.

Methods: The 32 patients were classified into three groups: video-assisted thoracic surgery group (n=7), video-assisted mini-thoracotomy with metal retractors group (n=15), and conventional thoracotomy group (n=10). Intercostal nerve function was assessed by a series of 2000-Hz (Aβ - fiber), 250-Hz (Aδ - fiber), and 5-Hz (C - fiber) stimuli using current perception threshold testing (Neurometer CPT/C®). The current perception threshold values were measured before and 1, 2, 4, 12, and 24 weeks after surgery. The intensities of ongoing pain were also assessed using a numeric rating scale (0 – 10).

Results: Video-assisted thoracic surgery group showed no changes in any current perception threshold values and no residual pain more than 12 weeks after surgery. Video-assisted mini-thoracotomy with metal retractors group and conventional thoracotomy group showed significantly higher current perception threshold values at 2000 Hz 1 week after surgery (p = 0.0013, p = 0.0012, respectively), with pain in approximately 70% of patients 12 weeks after surgery. The correlation between current perception threshold values at 2000 Hz and the intensities of going pain after 4 and 12 weeks surgery was significantly observed (p = 0.03, p = 0.04, respectively).

Conclusions: This is the first study that objectively evaluated pain after video-assisted thoracic surgery. The results suggest that the Aβ and Aδ fibers play a significant role in the development of intercostal nerve damage. The current perception threshold values clearly demonstrated that video-assisted thoracic surgery is a less invasive procedure resulting in less post-thoracotomy pain and have some possibilities to objectively evaluate the ongoing pain after surgery.

Abstract word count: 300

1. Introduction

About 50% of patients undergoing thoracic surgery suffer from various intensities of chronic post-thoracotomy pain syndrome (PTPS) [1], which is defined by the International Association for Study of Pain (IASP) as 'Pain that recurs or persists along a thoracotomy scar at least 2 months following a surgical procedure' [2]. Different strategies have been described to reduce acute and chronic post-thoracotomy pain. These have included anticonvulsants, epidural analgesia [3], paravertebral infusion of local anesthetics [4], and continuous intercostal-intrapleural analgesia [5]. Video-assisted thoracic surgery (VATS) is believed to reduce post-thoracotomy pain compared with conventional thoracotomy and is now widely used for many surgical procedures. Several studies have demonstrated the considerable benefits of VATS compared with conventional thoracotomy approaches [6, 7]. More recently, VATS has developed to 'complete VATS', in which all procedures are performed via the multiple ports by visualization through a television monitor [8]. However, the correlation between type of surgical procedure and post-thoracotomy pain is still unclear.

Intercostal nerve injury seems to be the most important pathogenic factor of PTPS, though the precise mechanism is still unknown [9]. The quantitative and selective assessment of intercostal nerve fiber damage has not been fully evaluated. Current perception threshold (CPT) testing with the Neurometer CPT/C® (Neurotron, Baltimore, MD, USA) can evaluate sensory nerve fibers quantitatively and selectively. CPT values with 2000-, 250-, and 5-Hz stimuli indicate the functions of Aβ, Aδ, and C fibers, respectively. Aβ fibers are large myelinated fibers responsible for touch and pressure sensation. Aδ fibers are small myelinated fibers responsible for sharp pain. C fibers are unmyelinated fibers responsible for sensing temperature and dull pain [10, 11]. Recent clinical studies have demonstrated that CPT testing is useful for the quantitative evaluation of sensory function associated with diabetic neuropathy [10], postherpetic neuralgia [12], and chronic sciatica [13]. However, there have been no reports evaluating intercostal nerve function using CPT testing.

The purpose of the present study was to objectively evaluate intercostal nerve damage associated with post-thoracotomy pain following various surgical procedures during next 24 weeks using CPT testing prospectively. The correlations between CPT values and the intensities of ongoing pain were also assessed.

2. Patients and methods

2.1. Patients

The study was performed at Nagasaki University Hospital from September 2006 to August 2009. Local ethics committee approval was obtained prior to commencement of the study. All patients gave their written, informed consent. A total of 44 patients (27 men, 17 women; mean age, 68.3 years) participated in this study. All patients had primary lung cancer.

The patients were divided into three groups according to the different surgical procedures performed in our division: VATS (complete VATS, without metal retractors, using the wound retraction system (WR; Alexis Wound Retractor®, Applied Medical, Rancho Santa Margarita, CA, USA), with an incision length within 5 cm); Mini-T (video-assisted mini-thoracotomy with small metal retractors, with a skin incision length within 8 cm); and Conv-T (conventional thoracotomy with metal retractors, either an axillary or a posterolateral incision, with the skin incision length over 8 cm) (Fig. 1A - C).

Patients who underwent pneumonectomy, chest wall resection, and partial resection and those who had a history of prior thoracotomy were excluded from this study. In the follow-up period, patients who required a chest tube for longer than a week were also excluded because such patients sometimes complained of pain around the skin where the chest tube was inserted.

2.2. Surgical technique for lung cancer

All patients were anesthetized using the same general anesthesia technique with propofol and vecuronium. After double lumen endotracheal intubation, the patient was positioned in a lateral position. At first, a 30° thoracoscope was introduced through the sixth intercostal space at the anterior axillary line. Generally, a fourth intercostal thoracotomy in the mid-axillary line was used for upper lobe or middle lobe disease, while a fifth intercostal thoracotomy was used for the lower lobe. Systemic mediastinal or hilar lymph node dissection was performed according to clinical stage, performance status, and lymph nodal status.

VATS (Fig 1A): All procedures were performed by visualization through a television monitor (complete VATS). In most cases, 4 – 5 ports were used. Usually, the main skin incision was just 4 – 5 cm long to remove the lung from the chest cavity with a wound retractor®.

Mini-T (Fig 1B): This procedure was a video-assisted procedure with an approximately 7- to 8-cm mini-thoracotomy using several ports, two small metal retractors, and a wound retractor. This procedure can easily be adapted to cases of advanced lung cancer and cases with intra-operative complications (e.g., dense adhesions and bleeding).

Conv-T (Fig 1C): This is the conventional procedure for thoracic surgery. The length of the skin incision was greater than 8 cm, and either a posterolateral or an axillary incision was chosen. For the posterolateral incision, the latissimus, trapezius, and rhomboid muscles were divided, and for the axillary incision, only the serratus anterior muscle was split. All metal retractors were placed for spreading not only ribs, but also superficial muscle and soft tissue.

2.3. Pain relief

For postoperative pain relief, an epidural catheter was placed according to the site of incision before the induction of general anesthesia. Ropivacaine (8 mg/h) was given for no longer than 5 days. All patients received oral loxoprofen sodium (60 mg), a systemic, non-steroidal, anti-inflammatory drug, three times a day for at least 1 week. When patients did not obtain good pain relief, a diclofenac sodium suppository (25 mg) or intramuscular pentazocine injection (15 mg) was added.

2.4. Current perception threshold and the Neurometer CPT/C$^{®}$

The Neurometer CPT/C$^{®}$ produces constant-current sine-wave stimulation at 2000, 250, and 5 Hz. The sine waves at 2000, 250, and 5 Hz correspond to depolarization periods of 0.25, 2, and 100 ms, respectively. The electrical stimulus selectively excites distinct subpopulations of nerve fibers as a function of the sinusoid frequency [14, 15]. Thus, large myelinated A (Aβ), small myelinated A (Aδ), and unmyelinated C (C) nerve fibers are evaluated with a series of 2000-, 250-, and 5-Hz stimuli, respectively.

A pair of gold-plated surface electrodes was placed just beside the sternum at the site of chest opening. At each frequency (2000, 250, and 5 Hz), the current was slowly increased until the subject reported sensation. The stimulus was then turned off, the intensity was decreased by 0.1 mA, and the stimulus was turned back on. This procedure was repeated until a range of 0.1 mA was established at which level the patient reported feeling the high intensity but could not detect

the lower intensity. Using a double-blind methodology, the patient was then presented with 6 – 20 cycles of randomly selected real and false stimuli above and below the perception threshold level until the exact CPT value could be determined within a ±0.02-mA range. CPTs of 0.01 mA were defined as '1', and CPTs of 10 mA were defined as '1000'. These examinations took approximately 20 minutes for all frequencies. The experiments were carried out with patients in a supine position in an isolated room (Fig 2).

The patients were also asked to rate the intensities of ongoing pain using a numerical rating scale (NRS) (0 – 10, with 0 = no pain, 10 = worst pain imaginable). Thus, the NRS and CPTs were measured before surgery and 1, 2, 4, 12, and 24 weeks after surgery.

2.5. Statistical Analysis

The distributions of background characteristics were compared among the three surgical procedures groups using the Kruskal-Wallis test. As concerns the CPT values and the numeric rating scale (NRS) measured in the three groups, we first examined the between patients variation and within patients variation by analysis of variance (ANOVA) for split-plot design, and if either the effects of treatments, time at measurement or the interaction between time at measurements and treatments were significant ($p < 0.05$) or marginally significant ($p < 0.1$), we further examined in the respective treatments the temporal trends by comparing the successive difference in time. In ANOVA, we used Fuynh-Feldt epsilon to adjust the degrees of freedom of F-statistics for dependency. We also evaluated the correlation between CPT values and the numeric rating scale (NRS) measured at 1, 2, 4, 12 and 24 weeks after surgery. The values of continuous variables are presented as means ± standard deviation (SD), and $p < 0.05$ (or if necessary the values adjusted for multiplicity by Bonferroni inequality) was considered statistically significant. GLM and NPAR1WAY in the SAS[R] system were used for

the calculations.

Results

   All patients underwent lung resection for lung cancer; there were 28 cases of lobectomy and 4 cases of segmentectomy. Of the 44 patients, 12 patients were excluded due to prolonged air leakage, refusal to participate in the study after surgery, or drop-out during follow-up. The remaining 32 patients completed the study. None of the patients experienced severe operative or postoperative complications except for prolonged air leakage. No drug-related problems or complications caused by the analgesic procedures and no tumor recurrence were observed during the follow-up period.

   The patients' demographics and the types of surgery are shown in Table 1. No significant difference was observed among the three surgical procedure groups in either age (p = 0.105) or surgery time (p = 0.769), while a significant difference was observed in the length of the skin incision (p < 0.0001).

   At 2000 Hz (Fig 3 A), since the difference in CPT values by treatments was significant (p = 0.0231) and the effects of time at measurement and the interaction between time at measurements and treatments were significant (p < 0.0001 and p = 0.0174, respectively), we compared the successive difference in time for each treatment; no significant difference was observed in the VATS group, while both in the Mini-T and Conv-T groups, the CPT values showed a significant increase 1 week after surgery (an increase of 90.0, 95% CI [confidence interval] = 11.2-168.8, p = 0.0013 in the Mini-T group and an increase of 147.4, 95% CI 36.0-258.8, p = 0.0012 in the Conv-T group) but did not show a significant difference afterward. Similar results held at 250 Hz (Fig 3 B): the difference in CPT values by treatments was marginally significant (p = 0.0907) and the effects of time at measurement and the interaction between time at measurements and treatments were significant (p < 0.0001) and marginally significant (p = 0.0946), respectively); none of the successive difference in time was significant in the VATS group, while both in the Mini-T and Conv-T groups, the CPT values showed a significant increase 1 week after surgery (an increase of 30.4, 95% CI = 5.3-55.5, p = 0.0018 in the Mini-T group and an increase of 49.7, 95% CI 18.4-80.9, p < 0.0001 in the Conv-T group) but did not show a significant difference afterward. At 5 Hz (Fig 3 C), either the difference in CPT values by treatments, the effects of time at measurement or the interaction between time at measurements and treatments

was not significant.

The mean postoperative pain was measured by numeric rating scale (NRS) (Fig 4). The difference in NRS by treatments was significant (p = 0.0014); the NRS was significantly lower in VATS group than in Mini-T and Conv-T groups throughout the time after surgery. Since the effects of time at measurement was significant (p < 0.0001), while the interaction between time at measurements and treatments was not significant (p = 0.6124), we compared the successive difference in time combining three treatments; the decrease in NRS between the time of 1 and 2 weeks after surgery was 1.00 (95% CI = 0.36-1.64, p = 0.0028) and of 4 and 12 weeks after surgery was 1.13 (95% CI = 0.41-1.83, p = 0.0014). Mild pain was still seen 12 and 24 weeks after surgery in the Mini-T and Conv-T groups. Twelve weeks after surgery, 10 (67%) of 15 patients in the Mini-T group and 7 (70.0%) of 10 patients in the Conv-T group still had some post-thoracotomy pain.

A significant correlation was observed between the CPT values at 2000 Hz and the NRS at 4 weeks after surgery (Spearman rank correlation = 0.38, p = 0.0308) and at 12 weeks after surgery (Spearman rank correlation = 0.36, p = 0.0413).

Discussion

Intercostal nerve function was measured objectively in lung cancer patients undergoing various surgical procedures using current perception threshold (CPT) testing, because it is well known that intercostal nerve damage is a main cause of post-thoracotomy pain [9]. The present study demonstrated that video-assisted thoracic surgery (VATS) was less invasive to intercostal nerves and resulted in less post-thoracotomy pain.

The results of the present study showed that the function of myelinated fibers ($A\beta$ and $A\delta$ fibers) was significantly impaired following surgery with metal rib retractors. There have been some reports about intercostal nerve injury during thoracotomy. Rogers et al. [16] evoked motor potentials in a series of 13 patients and showed that the use of rib retractors induced intercostal nerve damage. Thus, they found a total intercostal nerve conduction block from retractor-induced nerve injury in 100% of their patients. They also suggested that the rib retractor causes two injuries: direct ischemic injury caused by pressure from the retractor and a stretch injury. Although the intercostal nerves are mixed nerves, and they evaluated only motor conduction, the present results support the notion that myelinated fibers are susceptible to damage by the pressure or stretch from metal retractors. We believe that the compression of intercostal nerves by metal retractors may have been responsible for the elevated CPT values seen in the myelinated fibers in the Conv-T and Mini-T groups. This finding also suggests that myelinated fibers might be sensitive to compression. On the other hand, unmyelinated C fibers were insensitive to mechanical stimuli, which has been previously reported [17].

In the present study, the numerical rating pain scores (NRS) decreased gradually after surgery. The NRS scores were significantly less following VATS than following Mini-T and Conv-T. The most important finding here is that no pain was reported 12 weeks after VATS. In general, about 50% of patients undergoing thoracic surgery suffer from PTPS [1], which is defined as pain for more than at least 2 months after surgery [2]. The present results are similar to these reports and demonstrated that approximately 70% of patients in our study complained of PTPS even 12 weeks after surgery in the Mini-T and Conv-T groups.

In the early stage, 'VATS' with mini-thoracotomy that requires metal retractors was expected to reduce PTPS because of its lesser invasiveness. The following advantages have been described

compared with conventional thoracotomy: shorter skin incision, shorter surgery time and hospital stay, less bleeding, less postoperative pain, and reduction in pulmonary function impairment. However, the use of 'VATS' with mini-thoracotomy may not eliminate intercostal nerve injury, since the wound metal retractors and scopes are heavily manipulated during the procedure, which may cause nerve damage through crushing against the adjacent rib [13, 18]. The present results also showed that even Mini-T performed successfully for lung cancer tended to result in PTPS. Complete VATS has more advantages than 'VATS' with mini-thoracotomy because of a shorter skin incision and less division of muscles. The main skin incision is usually just 4 to 5 cm long to permit removal of the lung from the chest cavity.

For all of these reasons, the procedure without using metal retractors (complete VATS) may be a useful procedure to reduce PTPS. In terms of the cause of post-thoracotomy pain, since 2000 and 250-Hz values were significantly elevated after Mini-T and Conv-T, these results also suggest that damage to the peripheral myelinated fibers (Aβ and Aδ fiber) may play a significant role in the development of PTPS. On the other hand, unmyelinated C (5 Hz) fibers were not damaged by metal retractors, which suggests that C fibers are not responsible for PTPS.

Yamashita et al [19] reported a close correlation between the intensities of ongoing pain and CPT values. They measured CPT values in 48 patients with lumbar disc herniation accompanied by unilateral lower-extremity lumbar radiculopathy and reported correlations between sensory disturbance and leg pain. We found a significant correlation between CPT values at 2000 Hz at 2 and 4 weeks after surgery and the intensities of ongoing pain. The present results imply that the CPT values may be useful for evaluating the intensities of ongoing pain and predicting the development of PTPS. This test does not always correlate with clinical symptoms of pain. We speculate that there are two possible reasons.

First, to date, pain has been assessed subjectively by means of verbal or visual intensity scales and questionnaires [20]. A numeric rating scale (NRS) is also a subjective assessment tool, and pain itself can be ambiguous in each patient. The way pain is expressed is sometimes affected by race, sex, age, and other factors. We speculate that the damaged Aβ fibers, though they are responsible for touch and pressure sensation, sometimes make some patients feel post-thoracotomy 'pain'.

Second, we previously reported the allodynia and pain of postherpetic neuralgia using CPT and

found no correlation between the intensities of ongoing pain and CPT values at any frequencies [12]. We proposed that postherpetic neuralgia might be a pain syndrome including both peripheral and central mechanisms. Steegers et al. [21] reported that up to half of the chronic pain after thoracic surgery was not associated with a neuropathic component. Predictive factors for chronic pain were radiotherapy, pleurectomy, and more extensive surgery (bilobectomy and pneumonectomy). They concluded that damage involving the visceral pain component played an important role in post-thoracotomy pain.

Moreover, Maguire et al. [22] studied nerve conduction to assess intercostal nerve function during surgery. They found that the only factors that significantly predict chronic pain were higher pre-operative pain and a higher 6-week postoperative pain score. They suggested that either the amount of intra-operative intercostal nerve damage is not indicative of long-term nerve damage or that there is a more significant cause for chronic pain than intercostal nerve injury. These reports indicate that the cause of neuropathic pain is not simply damage to a single nerve but involves multi-factorial mechanisms.

This present study had two limitations. First, it would be better to provide more data about the number of patients. Small number of patients and the presence of confounding bias through loss of 25% of the patients might weaken the statistical accuracy. Second, we measured and intercostal nerve function by CPT and evaluated post thoracotomy pain from the data with NRS only. Because post thoracotomy pain might have multi-factorial mechanisms, more factors, including age, sex, and visceral pain should be evaluated. Future studies are needed to solve these limitations.

In conclusion, this is the first report to assess intercostal nerve damage after thoracic surgery using current perception threshold testing. The present study demonstrated that VATS is a useful procedure for reducing post-thoracotomy pain. Moreover, this testing has some possibilities to objectively evaluate the ongoing pain after surgery.

Table 1. Patients characteristics by type of surgical procedure

Factor	Type of surgical procedure			p-value[a]
	Video-assisted thoracic surgery (n = 7)[b]	Mini-thoracotomy (n = 15)	Conventional thoracotomy (n = 10)	
Age (year)	62.0±8.3	68.9±8.1	71.0±7.3	0.1053
	65 (48-71)[c]	69 (57-85)	71.5 (63-83)	
Rib retractor device	wound retractor	metal + wound retractor	metal retractor	NA[d]
Surgery time (min)	287±91	294±57	296±57	0.7691
	260 (178-470)[c]	277 (237-456)	300.5 (218-390)	
Length of skin incision (mm)	4.2±0.7	7.5±0.7	14.7±4.9	< 0.0001
	4 (3-5)[c]	8 (6-8)	13.5 (10-23)	
Procedures				NA[d]
Lobectomy	6	12	10	
Segmentectomy	1	3	0	
Clinical stage				NA[d]
I	7	15	3	
II	0	0	4	
III	0	0	3	
IV	0	0	0	
Resected lobe				NA[d]
Right upper	0	8	2	
Right middle	1	1	1	
Right lower	1	2	1	
Left upper	5	2	4	
Left lower	0	2	2	

[a]Based on Kruskal-Wallis test for the homogeneity of three groups.

[b]Number of patients.

[c]Median (minimum- maximum).

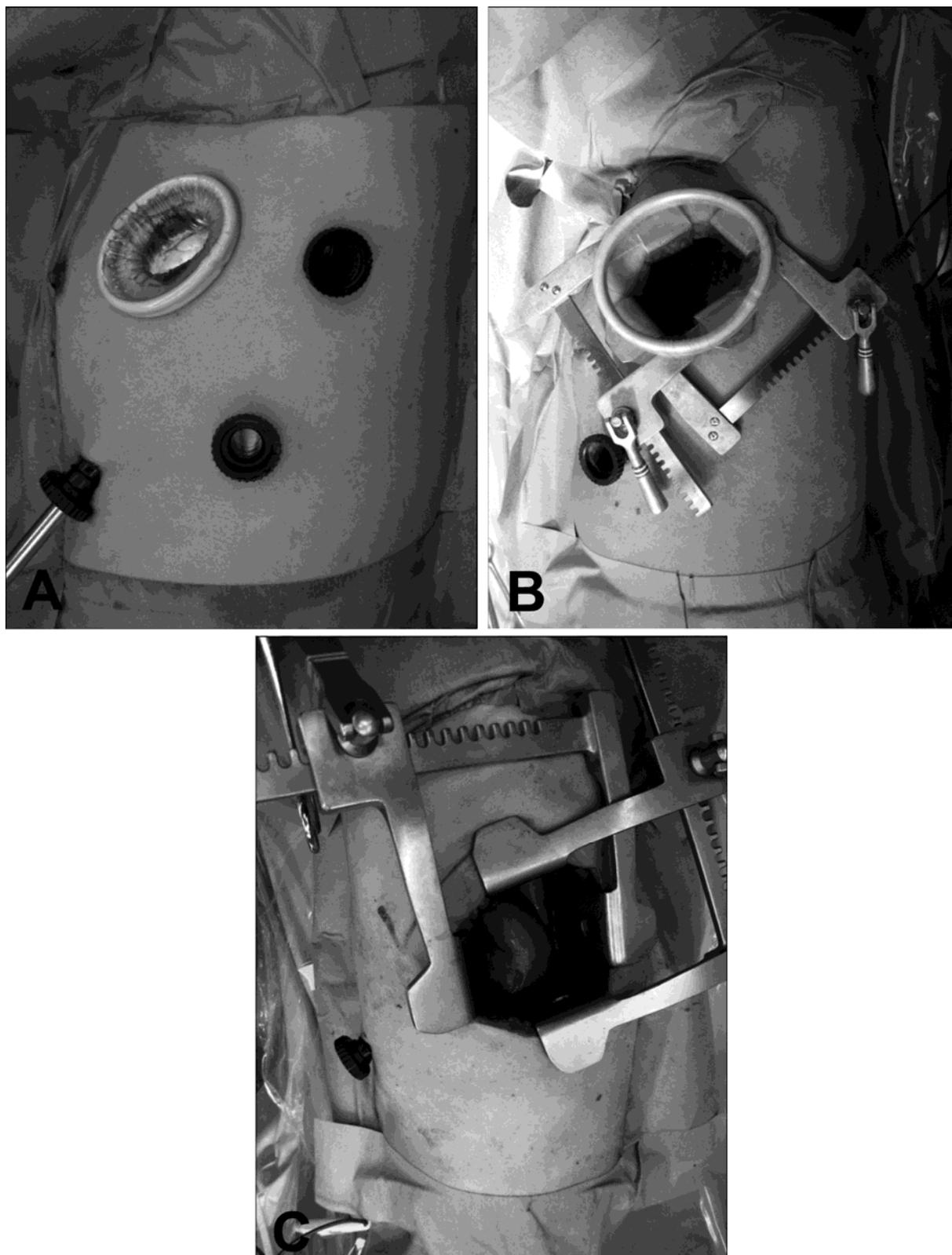[d]Not available.

Figure legends

Fig. 1. Classification of the three main thoracotomy procedures. **A.** Video-assisted thoracic surgery with multiple ports and a wound retractor®. **B.** Mini-thoracotomy with small metal retractors and a wound retractor®. **C.** Conventional thoracotomy.

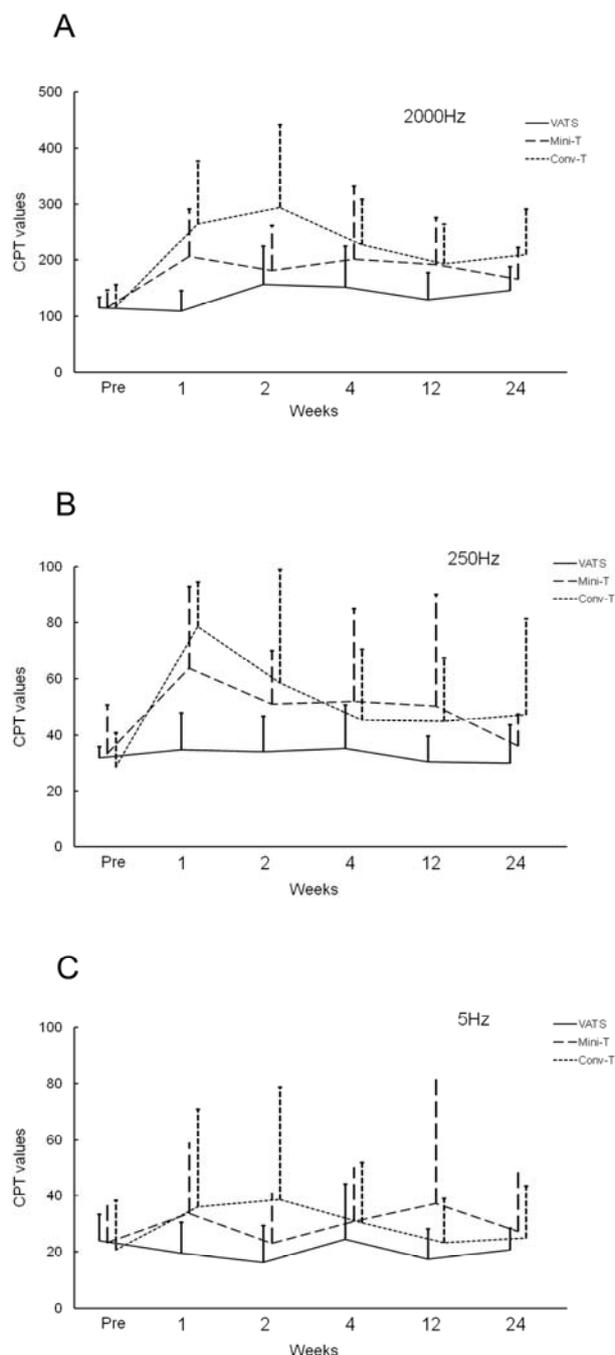**Fig. 2.** Neurometer CPT/C® for measurement of current perception threshold (CPT) values.

Fig. 3. Temporal patterns of CPT values after surgery at 2000 (A), 250 (B), and 5 Hz (C) by surgical procedure. The vertical lines depict standard deviations of the CPT values by surgical procedure at each time point after surgery. **A.** In VATS group, no significant difference was observed in the successive difference in time throughout the observation period, while both in the Mini-T and Conv-T groups, the CPT values showed a significant increase 1 week after surgery (an increase of 90.0, 95% CI [confidence interval] = 11.2-168.8, p = 0.0013 in the Mini-T group and an increase of 147.4, 95% CI 36.0-258.8, p = 0.0012 in the Conv-T group) but did not show a significant difference afterward. **B.** None of the successive difference in time was significant in the VATS group, while both in the Mini-T and Conv-T groups, the CPT values showed a significant increase 1 week after (an increase of 30.4, 95% CI = 5.3-55.5, p = 0.0018 in the Mini-T group and an increase of 49.7, 95% CI 18.4-80.9, p < 0.0001 in the Conv-T group) but did not show a significant difference afterward. **C.** At 5 Hz, either the difference in CPT values by treatments, the effects of time at measurement or the interaction between time at measurements and treatments was not significant.

(Pre, pre surgery; CPT, current perception threshold; VATS, video-assisted thoracic surgery; Conv-T, conventional thoracotomy with metal retractors; Mini-T, video-assisted mini-thoracotomy with small metal retractors)
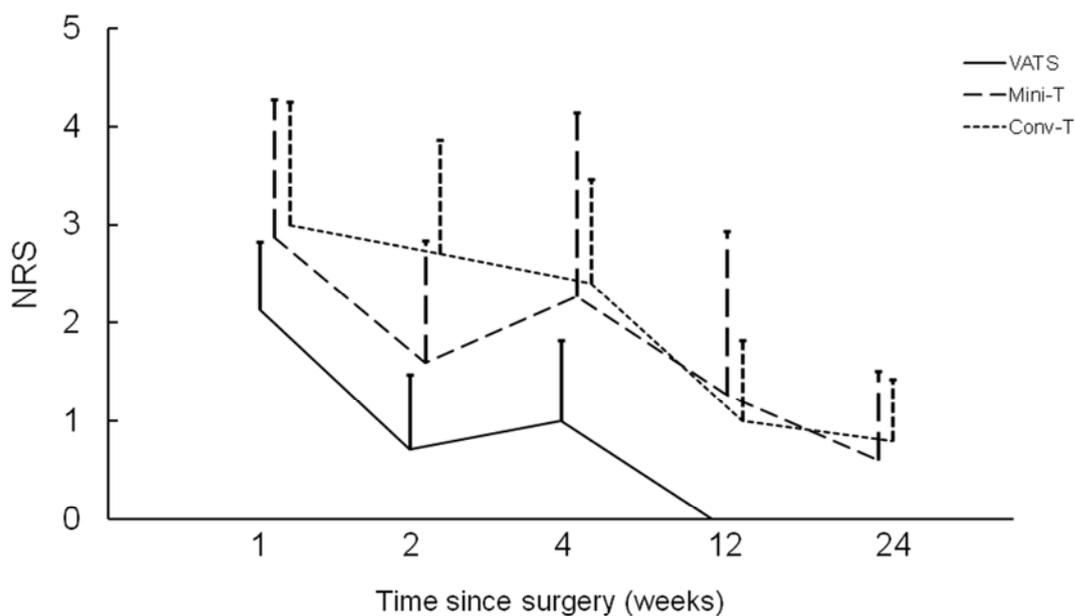
Fig. 4. The NRS was significantly lower in VATS group than in Mini-T and Conv-T groups throughout the time after surgery. The decrease in NRS between the time of 1 and 2 weeks after surgery was 1.00 (95% CI = 0.36-1.64, *p* = 0.0028) and of 4 and 12 weeks after surgery was 1.13 (95% CI = 0.41-1.83, *p* = 0.0014). The vertical lines depict standard deviations of the NRS by surgical procedure at each time point after surgery.

(NRS, numeric rating scale; VATS, video-assisted thoracic surgery; Mini-T, video-asssisted mini-thoracotomy with small metal retractors; Conv-T, conventional thoracotomy with metal retractors;

References

[1] Rogers ML, Duffy JP. Surgical aspects of chronic post-thoracotomy pain. Eur J Cardiothorac Surg **2000**;18:711-6.

[2] Merskey H, Bogduk H. Classification of chronic pain. In: Merskey H, Bogduk H, editors. Descriptions of chronic pain syndromes and definitions of pain terms. Second Edition, Seattle, WA: ISAP. Press; **1994**:143-4.

[3] Sakai T, Tomiyasu S, Sumikawa K. Epidural ropivacaine infusion for the treatment of pain following axillary muscle-sparing thoracotomy: a dose-evaluation study. J Anesth **2007**;21:320-4.

[4] Davies RG, Myles PS, Graham JM. A comparison of the analgesic efficiency and side-effects of paravertebral vs epidural blockade for thoracotomy - a systemic review and meta-analysis of randomized trials. Br J Anaesth **2006**;96:418-26.

[5] Forcella D, Pompeo E, Coniglione F, Gatti A, Mineo TC. A new technique for continuous intercostal-intrapleural analgesia in videothoracoscopic surgery. J Thorac Cardiovasc Surg **2009**;137:e48-9.

[6] Craig SR, Leaver HA, Yap PL, Pugh GC, Walker WS. Acute phase responses following minimal access and conventional thoracic surgery. Eur J Cardiothorac Surg **2001**;20:455-63.

[7] Yim APC, Wan S, Lee TW, Arifi AA. VATS lobectomy reduces cytokine responses compared with conventional surgery. Ann Thorac Surg **2000**;70:243-7.

[8] Yamashita S, Chujo M, Kawano Y, Miyawaki M, Tokuishi K, Anami K, Yamamoto S, Kawahara K. Clinical impact of segmentectomy compared with lobectomy under complete video-assisted thoracic surgery in the treatment of stage I non-small cell lung cancer. J Sur Res **2009**;Article in Press, Corrected Proof.

[9] Wildgaard K, Ravn J, Kehlet H. Chronic post-thoracotomy pain: a critical review of pathogenic mechanisms and strategies for prevention. Eur J Cardiothorac Surg **2009**;36:170-80.

[10] Masson EA, Boulton AJM. The neurometer: validation and comparison with conventional tests for diabetic neuropathy. Diabet Med **1991**;8:563-6.

[11] Masson EA, Veses A, Fernando D, Boulton AJM. Current perception threshold: a new, quick, and reproducible method for assessment of peripheral neuropathy in diabetes mellitus. Diabetology **1989**;32:724-8.

[12] Sakai T, Tomiyasu S, Yamada H, Sumikawa K. Evaluation of allodynia and pain associated with postherpetic neuralgia using current perception threshold testing. Clin J Pain **2006**;22:359-62.

[13] Sakai T, Aoki H, Hojo M, Takada M, Murata H, Sumikawa K. Adhesiolysis and targeted steroid/local anesthetic injection during epiduroscopy alleviates pain and reduces sensory nerve dysfunction in patients with chronic sciatica. J Anesth **2008**;22:242-7.

[14] Katims JJ, Naviasky EH, Ng LK, Rendell M, Bleecker ML. New screening device for assessment of peripheral neuropathy. J Occup Med. **1986**; 28: 1219-21

[15] Katims JJ, Naviasky EH, Rendell MS, Ng LK, Bleecker ML. Constant current sine wave transcutaneous nerve stimulation for the evaluation of peripheral neuropathy. Arch Phys Med Rehabil. **1987**; 68:210-3.

[16] Rogers ML, Henderson L, Mahajan RP, Duffy JP. Preliminary findings in the neurophysiological assessment of intercostal nerve injury during thoracotomy. Eur J Cardiothorac Surg **2002**;21:298-301.

[17] Meyer RA, Davis KD, Cohen RH, Treede RD, Campbell JN. Mechanically insensitive afferents (MIAs) in cutaneous nerves of monkey. Brain Res. 1991;561:252-61

[18] Jutley RS, Khalil MW, Rocco G. Uniportal vs standard three-port VATS technique for spontaneous pneumothorax: comparison of post-operative pain and residual paraesthesia. Eur J Cardiothorac Surg **2005**;28:43-6.

[19] Yamashita T, Kanaya K, Sekine M, Takebayashi T, Kawaguchi S, Katahira G. A quantitative analysis of sensory function in lumbar radiculopathy using current perception threshold testing. Spine **2002**;27:1567-70.

[20] Maguire MF, Ranvenscroft A, Beggs D, Duffy JP. A questionnaire study investigating the prevalence of the neuropathic component of chronic pain after thoracic surgery. Eur J Cardiothorac Surg **2006**;29:800-5.

[21] Steegers MAH, Snik DM, Verhagen AF, van der Drift MA, Wilder-Smith OHG. Only half of the chronic pain after thoracic surgery shows a neuropathic component. J Pain **2008**;9:955-61.

[22] Maguire MF, Latter JA, Mahajan R, Beggs FD, Duffy JP. A study exploring the role of intercostal nerve damage in chronic pain after thoracic surgery. Eur J Cardiothorac Surg **2006**;29:873-9.