Original Article

Postoperative pain and quality of life after lung cancer surgery: a prospective observational study

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Background: We aimed to identify the factors associated with postoperative pain, quality of life, and development of chronic pain after lung cancer surgery, including pain sensation threshold, fentanyl sensitivity, and surgical procedures.

Methods: We conducted a single-center prospective observational study involving lung cancer patients. Brief pain inventory, including nine items concerning pain and quality of life, was investigated at 1 week, 1 month, and 3 months postoperatively. Pain sensation threshold and fentanyl sensitivity were assessed preoperatively.

Results: Of the 146 patients who were enrolled, 100 who met our criteria were analyzed. Thoracoscopic surgery was performed in 42 patients and minimally invasive thoracotomy in 58 patients. Pain sensation threshold and fentanyl sensitivity were normally distributed among the patients and were not significantly associated with brief pain inventory scores at each postoperative time-point. The average pain score 1 week after the operation was significantly higher in the thoracotomy group than in the thoracoscopic surgery group ($P<0.050$). The worst pain scores did not differ between the groups at all the examination periods. Pain sensation threshold, fentanyl sensitivity, and surgical procedures were not related to the incidence of post-thoracotomy pain syndrome.

Conclusions: Individual pain sensation threshold and fentanyl sensitivity were not associated with subjective postoperative pain score, quality of life score, or development of post-thoracotomy pain syndrome.

Keywords: Lung cancer; pain sensation threshold (PST); fentanyl sensitivity (FS); postoperative pain

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Introduction

Patients who undergo thoracotomy may experience post-thoracotomy pain syndrome (PTPS), which is defined by the International Association for Study of Pain as pain that recurs or persists along a thoracotomy scar for at least 2 months after a surgical procedure (1). PTPS is a significant clinical problem with a reported prevalence of 5–65% (1-3). Studies have suggested that video-assisted thoracoscopic surgery (VATS) is less painful than conventional open thoracotomy with a metallic retractor with or without rib resection (4,5); therefore, the incidence of PTPS is low with VATS. However, recent studies have suggested that the incidence of PTPS does not differ significantly between VATS and thoracotomy, thus resulting in a controversy regarding this issue (4-6). Several risk factors, including young age, female sex, genetic and psychosocial factors, presence of preoperative pain and subsequent analgesic usage, and type of surgery, can predict the risk of PTPS (7,8). However, the most significant limitation in such studies of postoperative pain is that the measurement is subjective and an objective method for assessing pain has not been established yet. Hsu *et al.* reported that, preoperative pressure pain tolerance is significant correlated with the level of postoperative pain (9). Since PTPS involves chronic pain, it is important to evaluate not only the pain but also the quality of life (QOL) of the patients and investigate whether pain sensation threshold (PST) and fentanyl sensitivity (FS) other than the surgical procedure can be a risk factor for developing chronic pain.

The aim of this study was to prospectively assess the postoperative pain level and PTPS in patients who underwent curative lung cancer surgery using the standard brief pain inventory (BPI) (10) and evaluate the QOL score. Moreover, the relationships between PST and FS were investigated. We present the following article in accordance with the STROBE reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-22-207/rc).

Highlight box

Key findings
- Individual pain sensation was not associated with postoperative pain score, quality of life score, and post-thoracotomy pain syndrome after lung cancer surgery.

What is known and what is new?
- Pain sensation threshold, fentanyl sensitivity, and surgical procedures were not related to the incidence of post-thoracotomy pain syndrome. Several trials comparing postoperative pain after lung cancer surgery have been reported, but this is the first prospective comparison of postoperative pain, which included individual pain sensitivity.

What is the implication, and what should change now?
- Thoracotomy approach, which involves several protocols for preventing intercostal nerve damage, is as minimally invasive as thoracoscopic surgery. It might be unnecessary to stick to thoracoscopic surgery in lung cancer surgery.

Methods

Patients

We conducted a single center prospective observational study involving lung cancer patients. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Chiba University Medical Faculty (No. 2464) and was performed at Chiba University Hospital between May 2017 and November 2018. All patients provided written informed consent.

Patients meeting the following criteria were included in the study: suspected or diagnosed lung cancer scheduled for anatomical pulmonary resection (lobectomy or segmentectomy); preoperative performance state of 0 or 1; ability to communicate and comprehend the study; eligible for intraoperative general and epidural anesthesia; underwent surgical treatment, such as conventional VATS, robot-assisted thoracoscopic surgery (RATS), axillary thoracotomy, or lateral thoracotomy; and no history of non-steroidal anti-inflammatory drug use preoperatively. The exclusion criteria included preoperative pain or use of analgesic drugs, dementia, malignancy in other organs, and recurrence of lung cancer within 3 months of the surgery.

Thoracoscopy group (VATS or RATS)

Patients who underwent VATS or RATS were included in the thoracoscopy group. VATS procedures were performed under monitor visualization. The main skin incision was 4–5 cm in the intercostal space to enable the removal of the lung from the chest cavity. In most cases, 3–4 ports were created between the anterior and posterior axillary lines using a silicon thoracic opener. RATS was performed using the da Vinci robot surgery type Xi system (Intuitive Surgical, Sunnyvale, CA, USA) with surgeons adopting the complete portal approach with four arms and one assist port as described by Pearlstein (11).

Thoracotomy group

An 8–12-cm vertical axillary or lateral incision was made, and the serratus anterior muscle was divided using electric cautery. The 4th or 5th intercostal space was opened and retracted with a silicon thoracic opener. In some cases, a port was not created for video assistance or using automatic suture device to cut blood vessels and bronchi. A 19-Fr Ethicon Blake Silicon Drain (Johnson and Johnson, USA, NZ) was utilized as the chest drain.

PST and FS

PST for objective method for assessing pain was measured using a pressure algometer (Baseline Evaluation Instruments: Fabrication Enterprises, USA) immediately before the induction of general anesthesia by the anesthesiologists. The pressure was increased gradually using the pressure algometer; the value at which the first sensation of pain was observed was defined as PST. It was measured on the ventral side of the second finger of the arm opposite to the blood pressure cuff as frequent ischemia produced by insufflation of the cuff is likely to change the pain threshold. The maximal value was set at 10 kg/cm^2 based on a previous report (12); however, we used 5 kg/cm^2 to ensure safety. FS was defined as the difference in PST before and after intravenous administration of fentanyl in the induction of general anesthesia. The second PST was performed 3 min after injecting fentanyl at 2 µg/kg/ideal body weight.

Evaluation of postoperative pain in the perioperative and chronic phases

BPI items, including the worst pain, least pain, average pain, general activities, mood, walking, relationship with other people, sleep, and enjoyment of life, were investigated in each patient. Patients graded each item with scores ranging from 0 (best) to 10 (the worst) at 1 week, 1 month (21–40 days), and 3 months (81–100 days) postoperatively. BPI was standardized questionnaire and displayed excellent internal consistently (Cronbach's alpha value of 0.91). PTPS was defined as pain along with the surgical scars with worst pain score >3, which was assessed 3 months after the surgery.

Pain relief

An epidural catheter was placed in each patient for postoperative pain relief according to the incision site. Epidural analgesia with fentanyl at 4 mL/h (median, 800 µg; range, 0–1,500 µg), diluted with 0.125–0.25% levobupivacaine, was usually continued for 2 days. Oral non-steroidal anti-inflammatory drugs (loxoprofen sodium hydrate, 180 mg) were administered from postoperative day one. When patients did not achieve adequate pain relief, tramadol hydrochloride (25 mg) or pregabalin (75 mg) was added to the regimen.

Statistical analysis

Continuous data are presented as average ± standard deviation and range. Categorical data are presented as numbers and percentages. Student's *t*-test was used for continuous variables, and Pearson's chi-square test was used for categorical variables. The Shapiro-Wilk test was used for normality of the distribution in histogram data of PST or FS. Scores for each BPI items are shown as average values. BPI changes were calculated using Student's *t*-test. Considering the relatively different sample size, we relied on Cohen's *d* to describe the difference between the groups. Although interpretations of Cohen's *d* vary, most researchers consider 0.20–0.40, 0.40–0.80, and >0.80 as small, medium, and large effects, respectively (13). PST and FS changes were calculated using the Wilcoxon or Kruskal-Wallis method. The coefficient was used to correlate PST and FS values with BPI of pain or QOL score. The Spearman rank correlation coefficient was used to correlate PST or FS values and BPI of pain or QOL score. All tests were two-sided, and a P value <0.05 was used to define statistical significance. Statistical analyses were performed using JMP v13 (SAS, Cary, NC, USA). Missing data was left as a missing value.

Results

Overall, 146 patients with suspected or diagnosed lung carcinoma who were scheduled for the procedure were screened. Of the 146 patients, 46 were excluded from all analyses (*Figure 1*).

Among the 100 patients who were analyzed, anatomical lung resection for lung cancer was performed using

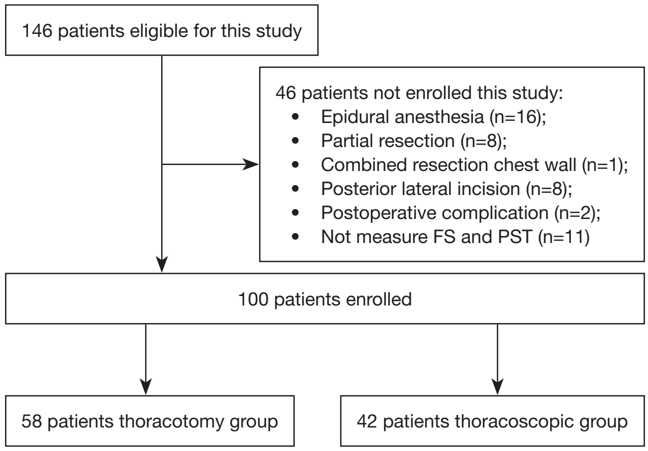

Figure 1 Consolidated Standards of Reporting Trials diagram showing participant flow in the current trial. FS, fentanyl sensitivity; PST, pain sensation threshold.

Table 1 Demographics of patients in the thoracoscopy and thoracotomy groups.

Variable	Thoracoscopy (n=42)	Thoracotomy (n=58)	P value
Age, mean ± SD (years)	68±1.0	70±1.0	0.2976
Sex (male/female)	24/18	35/23	0.8072
Surgery time, mean ± SD (min)	185±8.0	170±7.0	1.0000
Length of skin incision, mean ± SD (cm)	5.0±1.9	9.6±2.7	<0.0001
Blood loss, mean ± SD (mL)	90±18	77±21	0.6056
Past history, n [%]			
Diabetes mellitus	6 [14]	8 [14]	0.7740
Chronic obstructive pulmonary disease	7 [17]	20 [34]	0.1130
Hypertension	16 [38]	26 [45]	1.000
Procedures, n [%]			
Lobectomy	36 [86]	38 [66]	<0.050
Segmentectomy	6 [14]	20 [34]	<0.050

SD, standard deviation.

thoracoscopic surgery in 42 patients and thoracotomy in 58 patients (*Figure 1*). The thoracoscopy group consisted of 30 (71%) and 12 (29%) patients who underwent VATS and RATS. The baseline characteristics are presented in *Table 1*. No significant difference in age (P=0.2976), operation time (P=1.0000), or blood loss (P=0.6056) was observed between the two procedure groups; however, a significant difference was observed in the maximum length of skin incision (P<0.0001) and surgical procedure (P<0.050) (*Table 1*).

Histograms of PST and FS data demonstrated a standard normal distribution (Shapiro-Wilk test P<0.0001) (*Figure 2*). In terms of pain and QOL score, no significant correlation was found between PST and each score and between FS and each score (*Tables 2,3*). Nine patients developed PTPS in this study; three of them had undergone thoracoscopic surgery, while six underwent thoracotomy surgery. PST (P=0.3496) and FS (P=0.4709) were similar between patients with and without PTPS (*Figure 3*).

No significant difference was observed between the two surgical groups in terms of PST (P=0.3209) or FS

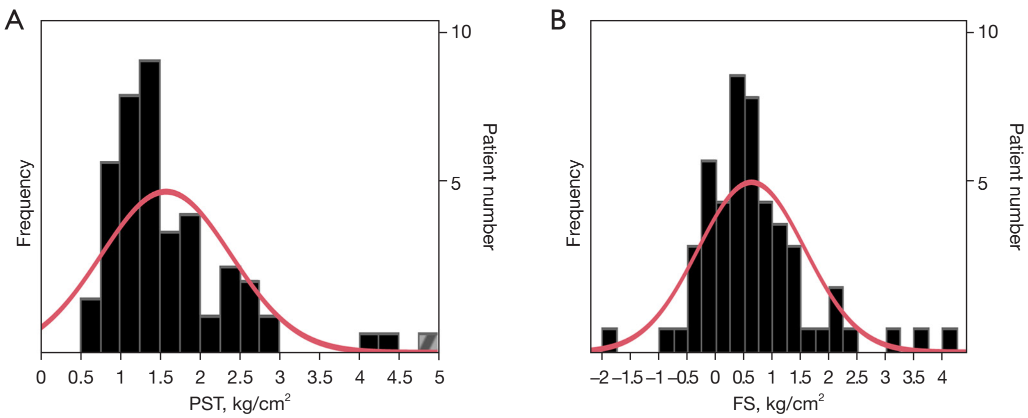

Figure 2 Histogram of PST and FS. Data of PST and FS demonstrate standard normal distribution. (A) PST; (B) FS. PST, pain sensation threshold; FS, fentanyl sensitivity.

Table 2 Relationship between BPI and PST after surgery for lung cancer

Item	PST								
	1 week			1 month			3 months		
	SRCC	95% CI	P value	SRCC	95% CI	P value	SRCC	95% CI	P value
Worst pain	−0.2127	−0.2 to 0.026	0.0840	0.0304	−0.24 to 0.29	0.8222	−0.2111	−0.43 to 0.0084	0.0751
Least pain	0.0513	−0.17 to 0.33	0.6899	0.0958	−0.14 to 0.36	0.4712	−0.1675	−0.35 to 0.10	0.1596
Average pain	−0.1555	−0.33 to 0.16	0.2236	0.0693	−0.19 to 0.33	0.6020	−0.1889	−0.36 to 0.087	0.1120
Activities	−0.1409	−0.35 to 0.15	0.2828	−0.0328	−0.31 to 0.20	0.8049	0.0374	−0.22 to 0.29	0.7768
Mood	−0.0350	−0.28 to 0.23	0.7189	−0.0475	−0.33 to 0.18	0.7208	−0.2020	−0.35 to 0.15	0.1217
Walking	−0.0997	−0.34 to 0.13	0.4448	−0.0079	−0.31 to 0.20	0.9529	−0.1220	−0.19 to 0.31	0.3531
Work	−0.1083	−0.35 to 0.21	0.4314	0.0220	−0.24 to 0.28	0.8685	−0.0932	−0.25 to 0.25	0.4789
Relationship other	−0.0639	−0.35 to 0.21	0.6306	−0.0381	−0.32 to 0.20	0.7765	−0.1523	−0.43 to 0.0641	0.2452
Enjoyment life	−0.0915	−0.33 to 0.18	0.4946	−0.0519	−0.31 to 0.21	0.6961	−0.1872	−0.33 to 0.16	0.1418

BPI, brief pain inventory; PST, pain sensation threshold; SRCC, Spearman's rank correlation coefficient; 95% CI, 95% confidence interval.

(P=0.1088) (*Figure 4*). Compared with patients in the thoracotomy group, those in the thoracoscopy group demonstrated significantly lower average pain scores 1 week after the surgery (P<0.050, *d*=0.63) and lower QOL scores on activities, mood, relationships, and enjoyment in life during the same time point (P<0.050, *d*=0.46; P<0.050, *d*=0.47; P<0.050, *d*=0.54; P<0.050, *d*=0.47, respectively) (*Table 4*). Average pain score and each item of QOL between the groups showed no significant difference after one or three months after surgery. No significant difference was observed in terms of the worst pain score and least pain scores between the groups during the all-examination periods (*Table 4*).

Discussion

PST is reported to be elevated in patients with neurotic disorders, such as diabetic neuropathic foot (9,14), and affects the pain sensation. Preoperative pressure pain assessment as PST might predict the level of postoperative pain in those who undergo lower abdominal gynecologic surgery (13,14). The primary aim of our study was to evaluate pain following thoracic surgery with standardization of the individual PSTs. However, correlations were not found between PST and BPI or between PST and QOL. Conversely, these results imply that the individual pain threshold did not affect BPI and

Table 3 Relationship between BPI and FS after surgery for lung cancer

Item	FS								
	1 week			1 month			3 months		
	SRCC	95% CI	P value	SRCC	95% CI	P value	SRCC	95% CI	P value
Worst pain	0.1015	−0.092 to 0.38	0.1439	−0.064	−0.26 to 0.26	0.9623	0.1990	−0.12 to 0.34	0.0939
Least pain	−0.1379	−0.31 to 0.19	0.2811	−0.1137	−0.30 to 0.21	0.3910	0.0118	−0.20 to 0.26	0.9214
Average pain	−0.1352	−0.34 to 0.15	0.2907	0.1022	−0.34 to 0.17	0.4413	0.1504	−0.14 to 0.32	0.2074
Activities	−0.0959	−0.30 to 0.21	0.4662	−0.0292	−0.28 to 0.24	0.8263	−0.1504	−0.52 to −0.0051	0.2513
Mood	−0.0630	−0.28 to 0.22	0.6297	−0.1528	−0.33 to 0.18	0.2478	−0.0287	−0.15 to 0.11	0.8276
Walking	−0.0542	−0.23 to 0.27	0.6784	−0.1469	−0.34 to 0.17	0.2668	−0.1660	−0.48 to −0.092	0.2049
Work	−0.0001	−0.30 to 0.23	0.9996	−0.0101	−0.23 to 0.28	0.9397	−0.0882	−0.48 to 0.0025	0.5030
Relationship other	−0.0339	−0.26 to 0.26	0.7985	0.0105	−0.26 to 0.26	0.9376	−0.0254	−0.23 to 0.27	0.8526
Enjoyment life	−0.1240	−0.37 to 0.14	0.3535	−0.0564	−0.28 to 0.23	0.6712	0.2411	−0.16 to 0.33	0.0570

BPI, brief pain inventory; FS, fentanyl sensitivity; SRCC, Spearman's rank correlation coefficient; 95% CI, 95% confidence interval.

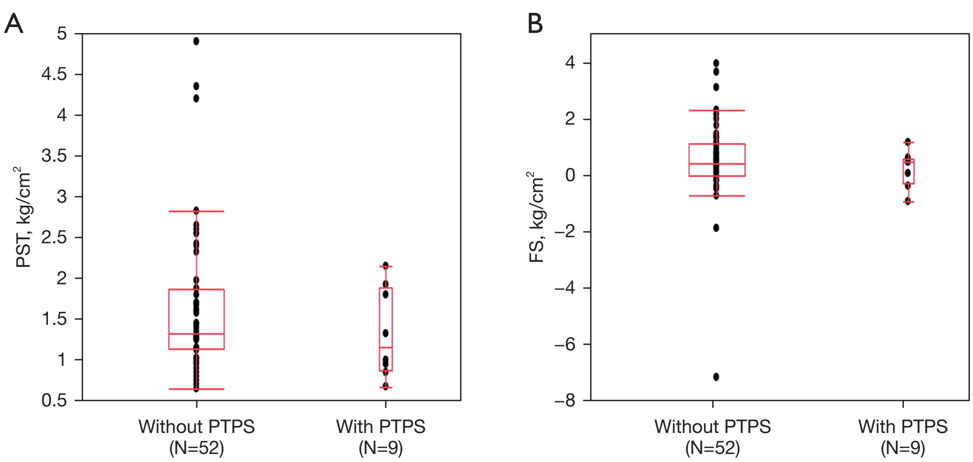

Figure 3 PST and FS scores in patients without and those with PTPS. PST and FS are not associated with the incidence of PTPS. (A) PST; (B) FS. PST, pain sensation threshold; PTPS, post-thoracotomy pain syndrome; FS, fentanyl sensitivity.

might support the obtained BPI and QOL data. There was a significant difference in the average pain scores and several items of QOL scores in the acute phase between the groups although the difference was not observed in the chronic phase. VATS has been associated with increased QOL and fewer complications, shortened length of hospitalization, and reduced postoperative pain (4). One study demonstrated that pain scores after VATS and thoracotomy were similar for the first 12 months after surgery, whereas another study reported that VATS was less invasive to the intercostal nerve and that PTPS had a higher chance of being neuropathic with open thoracic surgery (15,16). Bendixen *et al.* were the first to report that VATS was associated with less operative pain than open surgery (4). For early-stage lung cancer, surgery is the mainstay treatment; VATS or RATS has become the treatment of choice. However, patients who underwent RATS, VATS, or thoracotomy had no significant differences in postoperative numerical rating scores; the pain score only differed by 1–2 points between the uniport and three- or four-port VATS (17-19). Young *et al.* reported that, considering the subjective assessment of pain scores, the clinical significance of these differences was

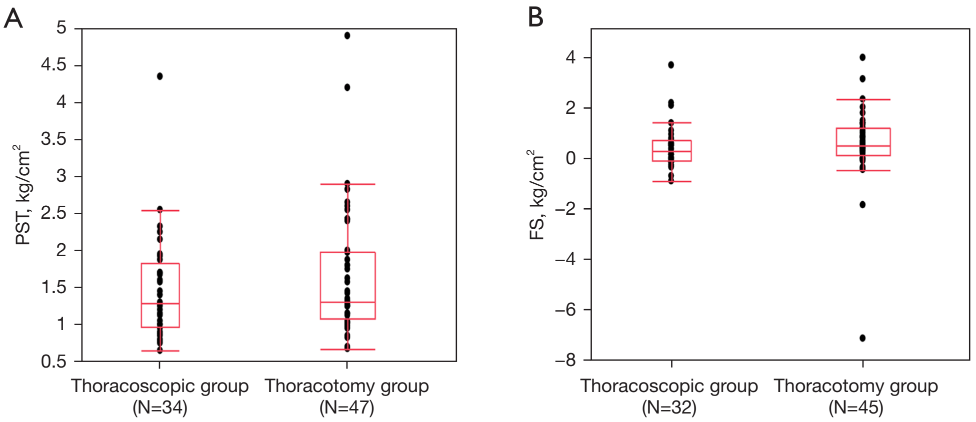

Figure 4 PST and FS scores between the thoracoscopy and thoracotomy groups. No significant difference is observed between the two surgical groups in terms of preoperative PST or FS. (A) PST; (B) FS. PST, pain sensation threshold; FS, fentanyl sensitivity.

Table 4 Relationship between the thoracotomy and thoracoscopy groups on postoperative average score of BPI

Item	1 week				1 month				3 months			
	Thoracoscopy	Thoracotomy	P value	Cohen's d	Thoracoscopy	Thoracotomy	P value	Cohen's d	Thoracoscopy	Thoracotomy	P value	Cohen's d
Worst pain	3.92±2.41	3.65±2.41	0.6045	0.11	2.42±2.12	3.29±2.47	0.1090	0.37	1.02±1.67	1.43±1.66	0.2390	0.25
Least pain	0.829±0.95	1.31±1.57	0.1063	0.36	0.76±1.07	1.70±2.03	<0.050	0.55	0.39±0.77	0.64±1.33	0.2847	0.22
Average pain	1.80±1.47	3.04±2.24	<0.050	0.63	1.68±1.55	2.41±1.83	0.0619	0.43	0.56±1.25	1.20±2.13	0.0572	0.40
Activities	1.69±1.76	2.85±2.95	<0.050	0.46	1.29±2.29	1.93±2.21	0.2122	0.29	0.64±1.69	1.20±2.13	0.2027	0.29
Mood	1.60±1.83	2.84±3.06	<0.050	0.47	1.41±2.43	1.78±2.21	0.4690	0.16	0.50±1.46	0.87±1.56	0.2770	0.24
Walking	1.54±1.80	2.31±2.82	0.1634	0.31	1.35±2.56	1.61±2.03	0.6192	0.11	0.58±1.79	0.80±1.77	0.5778	0.12
Working	1.88±2.07	3.05±3.29	0.076	0.41	1.44±2.26	2.17±2.46	0.1769	0.31	0.52±1.68	1.24±2.16	0.1080	0.36
Relationship other	1.06±1.39	2.43±3.13	<0.050	0.54	1.03±2.25	1.22±1.86	0.6778	0.090	0.19±0.21	0.74±1.54	0.0551	0.47
Enjoyment life	1.65±2.27	2.98±3.18	<0.050	0.47	1.35±2.44	1.96±2.46	0.2791	0.25	0.55±1.52	0.95±1.79	0.2698	0.24

Data are presented as mean ± SD. BPI, brief pain inventor.

small (20). Minimally invasive surgery results in less acute and chronic pain postoperatively; however, no significant differences were observed between the subjective pain scores of patients who underwent RATS/VATS and those who underwent thoracotomy (21). In our study, significant difference between the pain scores of the two groups was only observed in the acute phase.

Neuropathic pain has been demonstrated to play a role in chronic pain after VATS, although this has been associated with the access incision, because the rib retractors can induce intercostal nerve damage (22). However, the introduction of a silicon thoracic opener improves the visualization and decreases postoperative pain (23,24). Several studies have demonstrated that, when using small silicon drains, patients did not complain of pain at the drain site (25,26). Therefore, avoidance of metal retractors and conventional drains in thoracotomy may be an effective approach to reducing PTPS. In the chronic phase, the present results demonstrated no difference between the thoracoscopy and thoracotomy groups. Additionally, there was no significant difference in the number of patients with PTPS. PST and FS were suspected to be correlated with PTPS; however, there were no differences in PST and FS between patients with and without PTPS.

Recently, much attention has been paid to "enhanced recovery after surgery" (ERAS) pathways. ERAS are designed to attenuate the homeostatic disturbances and stress response that is characterized by catabolism and increased oxygen demand, thereby diminishing postoperative organ dysfunction (27,28). ERAS pathways in thoracic surgery have demonstrated benefits, such as reduced pain, reduced length of hospitalization, decreased hospital costs, and fewer complications (29). There is scope for further improvement in most components of ERAS, and minimally invasive surgery is an important key. Generally, VATS and RATS are less invasive than thoracotomy; however, surgeons have ingeniously reduced destruction of the intercostal nerves and irrigation of the periosteum of the ribs, and recent approaches in thoracotomy are even less invasive (18). We also developed a less invasive thoracotomy approach ("organic approach"), which consists of 8–12-cm vertical-axillary incision, muscle sparing procedure, non-spreading device, small silicon drains, epidural and intercostal anesthesia, and 1–2 ports to contribute to the QOL of patients and enhance recovery. Our results, however, demonstrated that significantly stronger pain was observed in the thoracotomy group; therefore, the organic approach is still optional in patients who are not fit for VATS/RATS.

The significance of FS remains to be elucidated. In our study, FS might have affected subjective pain during the postoperative period of epidural analgesia protocol until 2–3 days after the surgery. If FS affects pain or QOL after removing of the epidural tube, the effect is deemed preemptive. Factors that affect FS remain to be investigated.

Study limitations

This study has some limitations. First, it consisted of a small number of patients, which could have affected the statistical accuracy. Second, this was a non-randomized study performed at a single institute. Third, the number of ports and port positions of thoracoscopic surgery were different in study, it became difficult to compare postoperative pain of VATS and RATS. For this reason, these surgical procedures were not possible to compare postoperative pain in our study. Forth, we evaluated the pain-related QOL used Brief Pian Index. This questionnaire asks if pain affects activities, moods, walking, relationships, and enjoyment of life. Patients with dementia who do not understand the question are excluded, so it is unlikely that QOL will be affected by symptoms other than pain. Dyspnea may occur depending on the surgical procedure, which may reduce the QOL. It cannot be denied that this study affected QOL due to the difference in the number of cases of lobectomy and segmentectomy by surgical approach. Finally, a major limitation of our study is that we did not obtain complete BPI, PST, and FS data in all patients. Future studies are needed to address these limitations.

Conclusions

PST and FS were not significantly associated with PTPS and the thoracotomy approach, which involves several protocols for preventing intercostal nerve damage, is as minimally invasive as thoracoscopic surgery. We were able to improve the postoperative pain in the chronic phase to the same extent as thoracoscopic surgery by making various efforts in thoracotomy surgery. In this study, PST and FS could not predict patients with PTPS. Future studies needed to find alternative measurements of pain predictors. We believe that the results of this study will be beneficial for patients who may undergo thoracotomy. The authors will continue to examine the pain predictors for thoracic surgery.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-22-207/rc

Data Sharing Statement: Available at https://apm.amegroups.com/article/view/10.21037/apm-22-207/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-22-207/coif). The 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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Chiba University Medical Faculty (No.

2464), and informed consent was taken from all individual participants.

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