

Is the Isolated Pericardial Fat Pad Sufficient to Cover the Bronchial Stump and Separate the Pulmonary Artery in Order to Prevent Bronchopleural Fistula in Patients with Lung Cancer?

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Abstract. *Background:* The development of a bronchopleural fistula (BPF) is the most serious postoperative complication of thoracic surgery. All surgical techniques that have been reported as preventive measures against BPF have disadvantages. *Patients and Methods:* We herein introduce a new technique (Yatsushashi method) for covering the bronchial stump after right lower lobectomy using isolated pericardial fat tissue (PFT). Between 2012 and 2015, 878 consecutive patients with lung disease underwent surgery at our Institution. Among these patients, 26 underwent right lower lobectomy. Their clinical records were retrospectively reviewed to identify the presence of residual fat, in patients in whom the traditional pedicle method was applied and in those in whom an isolated PFT method was applied. The data on the characteristics, surgical details, and perioperative outcomes were analyzed. *Results:* There were no cases of BPF and the 90-day mortality rate was 0%. The mean period of time from the day of surgery until the computed tomographic examination was 207 days. There were no significant differences in the age, gender, clinical stage, pathological stage, the presence of comorbidities or complications, the duration until computed tomography, nor the presence of residual fat between the patients in whom the isolated PFT (n=17) and the standard pedicle (n=9) methods were applied. Furthermore, no postoperative complications due to the use of isolated PFT itself were observed in the patients who were treated using this method. The existence of residual isolated PFT was also confirmed in five out of six cases who underwent surgical treatment with the novel Yatsushashi

method. *Conclusion:* The simple technique using PFT for covering the bronchial stump after right lower lobectomy was satisfactorily effective and was not associated with any complications.

The need for thoracic surgery has been increasing due to the increased number of patients who are diagnosed with pulmonary disease (1). Unfortunately, postoperative complications occur in some patients (2). The development of a bronchopleural fistula (BPF) is one of the most serious postoperative complications (3). The incidence of stapling failure has been to be reported to be higher in right lower lobectomy (RLL) than in other surgical procedures (4). Various autologous tissues, including intercostal muscle, parietal pleura, pericardial flap, pericardial fat, and omental tissues have been used to prevent the occurrence of BPF (5). Thus, thoracic surgeons have tended to apply several intraoperative techniques to reduce the risk of BPF development (6). These techniques seem to be considerably favorable because of the certainty of stump adherence. However, they may risk actually causing a BPF because the methods involve penetrating the bronchial stump with a needle. In other words, passing a needle into the bronchial stump and the retraction of the surrounding tissue that is caused by the intervening material are associated with risks. Therefore, these methods all have some disadvantages. As previously described, the closure of the bronchial stump remains a controversial topic among thoracic surgeons who seek the best method for preventing postoperative BPF (7). We introduced a novel technique which uses isolated pericardial fat tissue (PFT) to close the bronchial stump. Furthermore, we developed a new method that allows the use of isolated PFT without suturing. A polyglycolic acid sheet with fibrin glue is applied as a fat pad to the bronchial stump to ensure stump adherence (8). This sheet is soft and flexible because of its rough weave, and presumably fits well with an appropriate degree of allowance. Thus, this new technique can

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be applied quickly and easily and can achieve good results. The purpose of this study was to determine the clinical outcomes of patients who were treated using the isolated PFT method, including the new suture-free method, to determine whether residual PFT is sufficient to prevent BPF.

Patients and Methods

Patients. This study was approved by the Saitama Cancer Center Ethics Committee (H27-501). The pretreatment evaluation included a medical history, physical examination, a complete blood cell count and analysis of serum chemistry, which included serum electrolytes, liver enzymes, and bilirubin, creatinine and coagulation levels. Patients were eligible for this study if they were suspected to have non-small cell lung cancer that was deemed to be resectable. Patients were excluded if they had contralateral hilar lymph node metastasis or a serious pre-existing disease (9). Tumor staging was performed based on the chest radiography, chest and upper abdomen computed tomography (CT), and bronchoscopy findings. Positron emission tomography scans were used in clinical staging assessments. Magnetic resonance imaging (MRI) of the brain was routinely employed. Patients underwent a preoperative cardiovascular risk assessment, including electrocardiogram and ultrasound cardiography. The patients' records, including their clinical data, preoperative examination results, histopathological findings and their TNM stages were reviewed.

The patients were basically evaluated every 3 months after surgery by a physical examination, chest roentgenography, analysis of blood chemistry and by the measurement of tumor marker levels. As a general rule, chest and abdominal CT scans, brain MRI and a bone scintigraphy were performed every 6 months for the first 2 years after surgery and annually after surgery for 5 years or more. Additional examinations were performed if any symptoms or signs of recurrence were detected.

Surgical technique. Video-assisted thoracic surgery assisted lobectomy-assisted lobectomy with systematic mediastinal lymph node dissection (en-bloc removal of the mediastinal fatty tissue containing the lymph nodes) was performed in all cases. The bronchi were closed transversally using an automated suturing device (10). The bronchial stump was checked for air leakage with a sustained airway pressure of 20 cm H₂O. After the completion of each surgical procedure, the required amount of pedicle, isolated PFT or intercostal muscle pedicle was harvested. In the case of pedicle PFT, fixation to the bronchial stump was performed using 4-0 prolene suture thread (Ethicon, Somerville, NJ, USA) (two sutures). In cases in which suturing was not performed, fibrin-glue (Beriplast P; Marburg, Germany or Bolheal: The Chemo-Sero-Therapeutic Research Institute, Kumamoto, Japan) was applied to achieve adhesion between the PFT and the stump. Next, an absorptive sheet of 0.15 mm in thickness (Neoveil: NV-M- 015G; Gunze Ltd, Kyoto, Japan), was used to cover the PFT and the stump (8). One milliliter of liquid thrombin was then placed, in a drop-wise manner onto the sheet, followed by fibrinogen and thrombin (1.0 ml of each). Fixation was then performed for a few minutes. Thus, the PFT was coated with a PGA sheet (Neoveil, Gunze Ltd, Kyoto, Japan) maintaining appropriate placement which might otherwise be disturbed by gravity or postoperative coughing. The appearance of the produced 'patch' is strikingly similar to a

Table I. *The associations between clinicopathological characteristics and use of the pedicle and isolated pericardial fat tissue (PFT) methods.*

| Characteristic | Total | Pedicle | Isolated PFT | p-Value |
|----------------------|-------|---------|--------------|---------|
| All cases | 26 | 9 | 17 | |
| Age (years) | | | | |
| <72 | 11 | 3 | 8 | 0.683 |
| ≥72 | 15 | 6 | 9 | |
| Gender | | | | |
| Male | 16 | 6 | 10 | >0.999 |
| Female | 10 | 3 | 7 | |
| c-Stage ^a | | | | |
| I | 12 | 4 | 8 | 0.999 |
| II-IV | 13 | 5 | 8 | |
| p-Stage ^a | | | | |
| I | 13 | 5 | 8 | 0.999 |
| II-IV | 12 | 4 | 8 | |
| Comorbidity | | | | |
| Yes | 18 | 4 | 14 | 0.078 |
| No | 8 | 5 | 3 | |
| Complication | | | | |
| Yes | 9 | 2 | 7 | 0.417 |
| No | 17 | 7 | 10 | |
| Time until CT (days) | | 256 | 182 | 0.198 |
| Residual fat | | | | |
| Yes | 23 | 8 | 15 | >0.999 |
| No | 3 | 1 | 2 | |

CT: Computed tomography. ^aOne case was excluded because a pathological examination revealed a metastatic carcinoma from rectal cancer.

Yatsunashi, a Japanese cake which is made in Kyoto. We therefore dubbed this method the "Yatsunashi method".

Detection of the residual fat pad. Enhanced chest CT was performed postoperatively to determine whether PFT was present (plain CT was performed in one case due to bronchial asthma). The mediastinal sagittal section was examined from a lateral view to detect the presence of a residual PFT. The identification of apparent fat that remained intact with a low CT value confirmed the existence of PFT (Figure 1).

Statistical analysis. A p-value <.05 was considered to indicate statistical significance. The data were analyzed using the Stat View software program (Abacus Concepts, Inc., Berkeley, CA, USA).

Results

From 2012 April through 2015 July, 878 consecutive patients with lung disease underwent surgery at our Institution. Of these, 28 patients with NSCLC who underwent RLL with systematic mediastinal lymph-node dissection were included in this study. The study population included 18 males and 10 females (mean age=68.9 years; range=40-80 years). All the patients were Japanese. The histological types included lung cancer (n=27) and metastatic carcinoma from rectal cancer

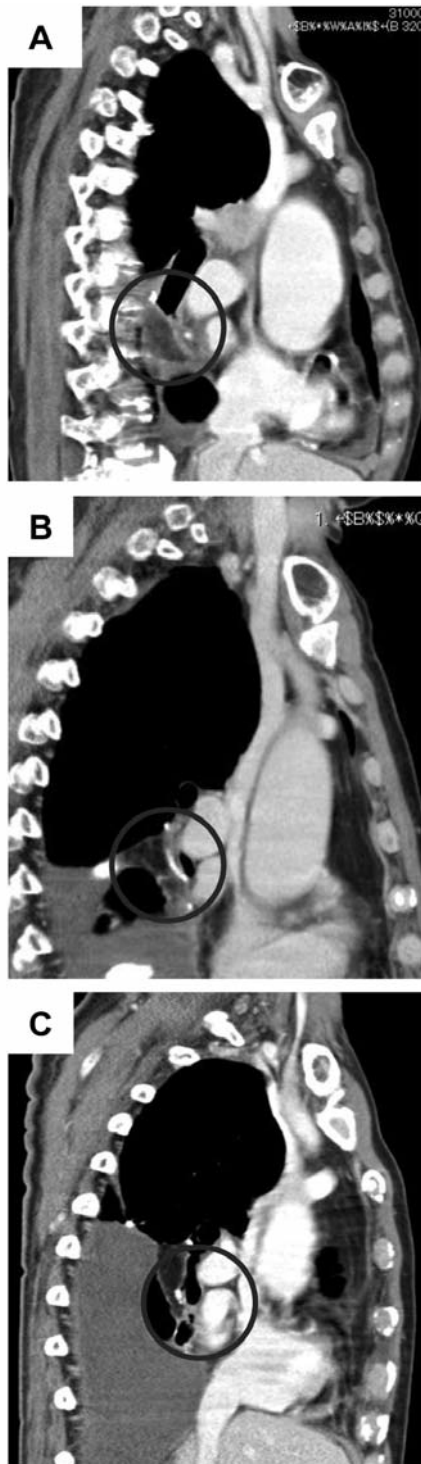


Figure 1. A: Chest computed tomography (CT) of Case 2, showing residual pedicle pericardial fat tissue (PFT) (black circle) around the bronchial stump in the right thoracic cavity (time from surgery until CT: 639 days). B: Chest CT of Case 9, showing residual isolated PFT around the bronchial stump (183 days). C: Chest CT of Case 27 in case in which the Yatsuhashi method was applied, showing residual isolated PFT (108 days).

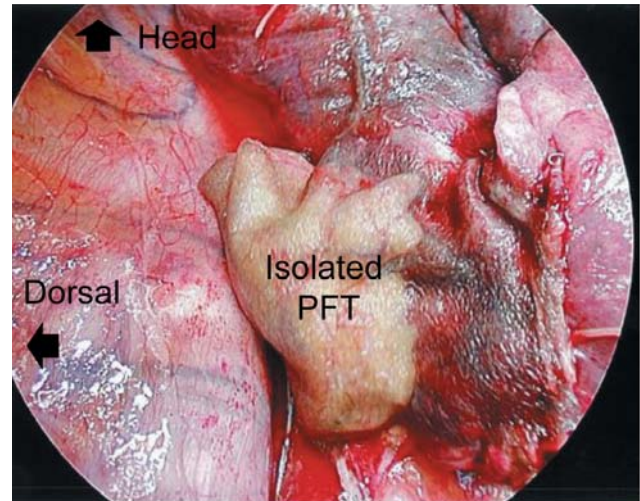


Figure 2. An intraoperative image shows the fixation technique. Firstly, a few drops of fibrinogen were placed around the bronchial stump. Liquid thrombin was then administered to the stump in a drop-wise manner. The stump was covered with an isolated fat pad and covered with an absorptive sheet. Next, 1.0 ml of liquid thrombin was placed onto the sheet in a drop-wise manner, followed by fibrinogen and thrombin (1.0 ml of each). Fixation was performed for a few minutes.

(n=1). The clinical stages of the patients were as follows: stage IA: n=8, IB: n=4, IIA: n=5, IIB: n=3, IIIA: n=4, and IIIB: n=1. The pathological stages were as follows: IA: n=9, IB: n=4, IIA: n=3, IIB: n=4, IIIA: n=3, IIIB: n=1 and IV: n=1. Comorbidities such as hypertension, diabetes mellitus, lung emphysema, interstitial pneumonia were present in 18 cases. The average intraoperative blood loss during the operation was 220 ml.

PFT was used to cover the bronchial stump in all but two cases, one of which was covered by an intercostal muscle pedicle, the other was not. The presence of residual PFT could therefore be evaluated in 26 patients (2.9%: 26/ 878). The characteristics of these evaluable patients are shown in Table I. The traditional pedicle method was applied in nine cases, while isolated PFT methods were applied in 17 cases. The Yatsuhashi method was applied in six out of the 17 cases (Figure 2). Postoperative complications, including pleural effusion and prolonged air leak, occurred in nine out of the 26 cases. Thus, the morbidity rate was 32.1%. However, there were no cases of BPF and the 30-day and 90-day mortality rates were both 0%. The mean period of time from the date of surgery until the CT examination was 207 days (range=39-639 days).

We compared the clinicopathological characteristics of the patients in whom the new isolated PFT (n=17) and classical pedicle methods (n=9) were applied. There were no significant differences between the two types of methods with regard to age, gender, clinical stage, pathological stage, the presence of comorbidities or complications, the duration

until CT, or the presence of residual fat (Table I). Furthermore, no postoperative complications due to the use of isolated PFT itself were observed in the patients who were treated with the isolated PFT methods. The existence of residual isolated PFT was confirmed in five out of the six cases in which the Yatsushashi method was applied.

Discussion

We herein reported the development of a new method involving the use of isolated PFT to prevent BPF. The greatest problem with the use of isolated fat pads is blood streaking due to isolation. We initially anticipated that the isolated PFT might recede over a relatively short period of time. However, we found that the appearance of the PFT was good and that the volume and size were maintained over a period of 5 months (*e.g.* Case 17). This period seemed to be sufficient because BPFs typically occur at 1 week to 3 months after surgery, with the greatest incidence at 8-12 days (6). In fact, the mean follow-up period until postoperative CT for the cases in which an isolated PFT pad was used was 182 days, which was consistent with previous data (11). Why do isolated tissues survive in the thoracic space? We hypothesize that in an appropriate environment, the isolated fat tissue is fed by oxygen and angiogenic cytokines from pleural effusion (11, 12). Ichinose *et al.* reported that, in basic experiments, the intensity of neovascularization induced by PFT was the same as that induced by the omentum and significantly greater than that induced by intercostal muscle (13). In addition, PFT is mainly composed of fat cells, macrophages, and fibroblasts (13). *In vitro*, the enlargement of adipocytes would increase the intercapillary distance, resulting in relatively decreased blood perfusion to each adipocyte. However, the enlargement of adipocytes may also result in decreased metabolic demands. Thus, adipocytes may not necessarily suffer from tissue hypoxia (14).

We believe that there are seven potential advantages associated with the Yatsushashi method and no apparent disadvantages. (i) It is easy to perform. (ii) It takes just a few minutes to perform. (iii) The new method does not require suturing (which might cause local strangulated blood circulation disorder); this also avoids causing the fat to shrink. (iv) It allows excessive traction on the PFT to be avoided. (v) It does not risk causing the compression of neighbor vessels (a problem which is associated with pedunculated PFT) (15). (vi) It might also be useful in situations other than RLL such as neoadjuvant therapy followed by surgery (9), pneumonectomy (7), bronchoplasty or other stump types in patients with severe diabetes mellitus. (vii) Furthermore, this method may be feasible at all institutions given that it has no special technical requirements. We are therefore of the opinion that the present technique can be performed easily and quickly, with good results.

Nevertheless, our study is associated with several limitations. The study was retrospective in nature and was performed at a single institution. There were imbalances in the patient characteristics that cannot be excluded due to the small number of patients with isolated PFT. To overcome these limitations and for this method to gain widespread popularity, prospective studies in a larger cohort of patients at different institutions will be necessary.

In conclusion, we presented a novel method for preventing BPF that can be applied quickly and easily and which can achieve good results.

Conflicts of Interest

There were no conflicts of interest or financial interest in association with this study for any of the Authors.

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