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Comparison of surgical results after pneumonectomy and sleeve lobectomy for non-small cell lung cancer. Trends over time and 20-year institutional experience

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Abstract

Objective: Sleeve lobectomy is a lung-saving procedure for central tumors for which the alternative is pneumonectomy. The purpose of this study was to report the clinical characteristics, operative results, survival, and late outcomes over 20 years in patients who underwent sleeve lobectomy and pneumonectomy at our institution. **Methods:** There were 62 patients who underwent sleeve lobectomy (SL group) and 110 who underwent pneumonectomy (PN group). Comparisons of the demographics, morbidity, and survivals between the groups were performed by unpaired t-test, χ^2-test, and log-rank test. **Results:** Patients who underwent a pneumonectomy showed a significantly advanced pathological stage, and a larger tumor size than those who received a sleeve lobectomy, whereas there were no significant differences in histology, ratio of combined resection and induction therapy, or total morbidity. There were three in-hospital deaths (4.8%) in the SL group and four (3.6%) in the PN group. Local relapse and distant recurrence incidence were similar between the two groups. The 5-year-survival rates of the SL and PN groups were 54% and 33%, respectively ($p < 0.0001$). However, there were no differences in 5-year survivals in patients with pathological stage I/II (SL, 59% vs PN, 63%) and those who received induction therapy (SL, 22% vs PN, 52%) between the groups. **Conclusions:** Both pneumonectomy and sleeve lobectomy were performed with an acceptable risk of operative mortality and satisfactory 5-year survival rate. The indication of pneumonectomy is aimed to perform a curative resection for locally advanced lung cancer, particularly after induction therapy that is otherwise unresectable, and the selected patients will likely benefit from a complete resection.

Keywords: Pneumonectomy; Sleeve lobectomy; Morbidity and mortality; Induction therapy

1. Introduction

The overall operative mortality for lung cancer surgery in Japan has been reported to be satisfactorily low [1], with a 30-day death of 1.3%. In addition, the rate of pneumonectomy (PN) is also relatively low because surgeons generally try a bronchoplasty to avoid pneumonectomy.

A bronchoplastic resection achieves local control and preserves pulmonary function without missing the complete removal of the central located tumors. Since Price-Thomas [2] first applied this procedure for therapeutic option, it has become a basic therapeutic strategy in the general hospitals provided that oncologic radicality and reconstructive aspects are evident during the past 20 years [3,4].

In contrast, pneumonectomy for lung cancer has been reported to be associated with significant morbidity and mortality [5–7], including postpneumonectomy lung edema, adult respiratory distress syndrome (ARDS), bronchopleural fistula, and postpneumonectomy syndrome [7]. Recent studies have compared pneumonectomy and sleeve lobectomy (SL) procedures in terms of late outcome and morbidity using matched patients [8,9]. A meta-analysis [6] of comparisons between a sleeve lobectomy and pneumonectomy in stages I and II non-small cell lung cancer (NSCLC) revealed an advantage of sleeve lobectomy for mortality (4.1% vs 6.0%), while there was no significant difference in 5-year survival rate (51% vs 49%). We always employ a sleeve lobectomy when technically possible, however, a pneumonectomy is inevitable in certain situations, when a complete

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resection could not otherwise be achieved and provided that pulmonary function permits it. Recently induction therapy followed by surgery has emerged as a promising treatment for advance staged NSCLC [10,11], for which an extensive resection is also required by using a sleeve resection or pneumonectomy [12]. In the present study, we retrospectively analyzed our experiences of the two procedures without adding selection bias.

The objective of the present retrospective analysis was to characterize the indications, patient demographics, morbidity, mortality, and late outcomes over time in patients who underwent sleeve lobectomy and pneumonectomy.

2. Methods

Between January 1984 and December 2003, a pulmonary resection was performed for 1211 consecutive patients with primary NSCLC (920 males, 291 females; average age 62.5 years) at Toneyama National Hospital in Japan. Ten patients who underwent a carinal resection, including five that received a sleeve pneumonectomy were excluded from the analysis. In our institutional experience, tracheo-bronchoplastic procedures using an end-to-end anastomosis were performed [3] in the early era (1984–1993), and then telescoping techniques have been achieved in the recent era (1994–2003) [4], including those who received induction chemoradiotherapy [12]. After induction therapy, re-staging of local tumor extension and nodal status were assessed to determine the operative procedures. Survival, perioperative morbidity, and sites of recurrence were analyzed and compared in 62 consecutive patients who underwent a sleeve lobectomy, and 110 consecutive patients who underwent a pneumonectomy. The sleeve lobectomy procedures included 35 right upper lobectomies, 1 middle lobectomy, 2 upper and middle lobectomies, 6 middle and lower lobectomies, 12 left upper lobectomies, and 6 left lower lobectomies. A concomitant pulmonary angioplasty was performed in 12 patients (19.3%) in the SL group. As for the PN group, we performed 38 right and 72 left pneumonectomies (Table 1).

All patients were evaluated for predicted postoperative function, as we have previously reported [13]. However, patients with borderline pulmonary functional reserve were posed a special preoperative pulmonary rehabilitation if necessary. Furthermore, an aggressive pulmonary toilet, including a bronchoscopy, was performed during anesthesia and prior to extubation. Other postoperative management included, early ambulation, bronchial toilet including bronchoscopy, as necessary and prolonged low-flow nasal oxygen supplementation, as necessary.

Postoperative complications were divided into minor complications, which included pneumonia based on chest radiographic findings that required antibiotics, hypoxemia, atelectasis, a persistent air leak for more than 7 days, chyle leak, and cardiac arrhythmia that could be treated medically, and major complications, which included myocardial infarction, respiratory failure requiring reintubation with mechanical ventilation, and bronchopleural fistula, empyema, and severe chylothorax requiring reoperation. The hospital mortality included 30-day mortality and operation-related death during the same hospitalization for up to 3 months.

Table 1
Comparison of patients' characteristics of sleeve lobectomy and pneumonectomy

	Sleeve lobectomy	Pneumonectomy	p value
Number	62	110	
Age (years)	61.1 ± 10.2	59.3 ± 9.6	0.266
Gender M/F	46/16	92/18	0.196
Location right/left	44/18	38/72	0.0001*
Histology			0.765
Sq	31	57	
Ad	20	38	
Others	11	15	
p-stage			0.0011*
IA/IB	26	24	
IIA/IIB	19	14	
IIIA	12	52	
IIIB/IV	5	18/2	
Tumor size (cm)	3.6 ± 1.7	4.6 ± 2.1	0.0026*
Combined resection	19 (30.6%)	49 (44.5%)	0.0645
Induction therapy	16 (25.8%)	19 (16.8%)	0.196

* Statistically significant.

Most sites of relapses were documented through hospital readmission. A locoregional recurrence being defined as a recurrence that developed within the ipsilateral hemithorax including the mediastinum.

Data are reported as mean ± standard deviation or as a proportion. Survival rate was estimated by the Kaplan–Meier method, and the log-rank test was used to compare survival rates between the two groups. Other comparisons were made using an unpaired t-test or χ^2-test. Significance was accepted as a p value of less than 0.05.

3. Results

Comparisons of the patients' clinical characteristics and operative results for the SL group ($n = 62$) and PN group ($n = 110$) are shown in Table 1. There were no significant differences in age, gender, or prevalence of histological subtypes including adenocarcinomas, squamous cell carcinomas, and others (Table 1). A sleeve lobectomy on the right side and left pneumonectomy were more common than those on the respective contralateral sides ($p = 0.0001$). Pathological staging for the SL and PN groups were as follows: stage IA, B (SL: $n = 29/62$, 46.8%, PN: $n = 24/110$, 21.8%), stage IIA, B (SL: $n = 16/62$, 25.8%, PN: $n = 14/110$, 12.7%), stage IIIA, B (SL: $n = 17/62$, 27.4%, PN: $n = 70/110$, 63.6%), with significant differences found between the groups ($p = 0.0069$) (Table 1). Namely, 72.6% of the SL group was stage I or II disease, whereas those comprised 34.5% in the PN group. Tumor size was significantly greater in the PN group than that of the SL group ($p = 0.0026$). There were no significant differences in the ratio of the combined resection including the chest walls, pericardium, diaphragm, or great vessels (SL, 30.6% vs PN, 44.5%, $p = 0.0645$) or the rate of induction therapy (SL, 25.8% vs PN, 17.2%, $p = 0.236$) between the groups.

Three SL group patients, who received induction therapy, had serious complications, and finally died of empyema or respiratory failure, respectively, while one PN group patient

Table 2
Time trends of surgical results and outcome: sleeve lobectomy versus pneumonectomy

	Sleeve lobectomy	Pneumonectomy	Total procedures
Number	62 (5.1%)	110 (9.1%)	1211
Early era (1984–1993)	23 (5.0%)	72 (15.8%)	456
Recent era (1994–2003)	39 (5.2%)	38 (5.0%)	755
In-hospital mortality			
Early era	1 (4.3%)	1 (1.3%)	
Recent era	2 (5.1%)	3 (6.2%)	
Total	3 (4.8%)	4 (3.6%)	
Overall morbidity			
Early era	10 (43.4%)	23 (31.9%)	
Recent era	18 (46.2%)	22 (45.0%)	
Total	28 (45.2%)	45 (40.9%)	

who underwent a right pneumonectomy following induction chemoradiotherapy died of adult respiratory distress syndrome 6 days postoperatively.

Three cases were considered to be technically hazardous, which consisted of one patient who had a history of tuberculosis pleuritis and underwent a pneumonectomy, and two patients with T4 tumors that had severely invaded to the aortic arch and left atrium, respectively. The 30-day postoperative mortality was 1.6% (1/62) in the SL group and 1.8% (2/110) in the PN group (Table 2). As for the hospital deaths, the rate was 4.8% (3/62) in the SL group and 3.6% (4/110) in the PN group. Comparisons of the early (1984–1993) and recent (1994–2003) eras did not show significant differences in morbidity and mortality, though recent pneumonectomy cases showed a higher rate of mortality

Table 3
Details of description and classification of complications

	Sleeve lobectomy	Pneumonectomy	*p* value
Number	62	110	
Morbidity	28 (45.2%)	45 (40.9%)	0.615
In-hospital deaths	3 (4.8%)	4 (3.6%)	0.704
30-day deaths	1 (1.6%)	2 (1.8%)	0.999
Local relapse	6 (9.7%)	12 (10.9%)	0.800
Distant relapse	18 (29.0%)	47 (42.7%)	0.0913
Non-cancer death	1 (1.6%)	5 (4.5%)	0.421
HOT[a] within 5 years	0	4 (3.6%)	0.298
Respiratory			
Pneumonia	4 (6.5%)	4 (3.6%)	0.461
Atelectasis	3 (4.8%)	3 (2.7%)	0.669
Respiratory failure	3 (4.8%)	5 (4.5%)	0.999
ARDS	1 (1.6%)	2 (1.8%)	0.999
Empyema	6 (9.6%)	9 (8.2%)	0.779
Bronchopleural fistula	2 (3.2%)	4 (3.6%)	0.999
Chylothorax	1 (1.6%)	4 (3.6%)	0.655
Hemothorax	1 (1.6%)	1 (0.9%)	0.999
Vocal cord paralysis	1 (1.6%)	2 (1.8%)	0.999
Airway problem	1 (1.6%)	1 (0.9%)	0.999
Cardiac and others			
Arrhythmias	9 (14.5%)	29 (26.4%)	0.088
Heart failure	1 (1.6%)	2 (1.8%)	0.999
Pulmonary embolism	0 (0%)	1 (0.9%)	0.999
Cerebral infarction	0 (0%)	2 (1.8%)	0.537
GI bleeding	1 (1.6%)	0 (0%)	0.361
Others	3 (4.8%)	7 (6.4%)	0.999

[a] HOT: home oxygen therapy.

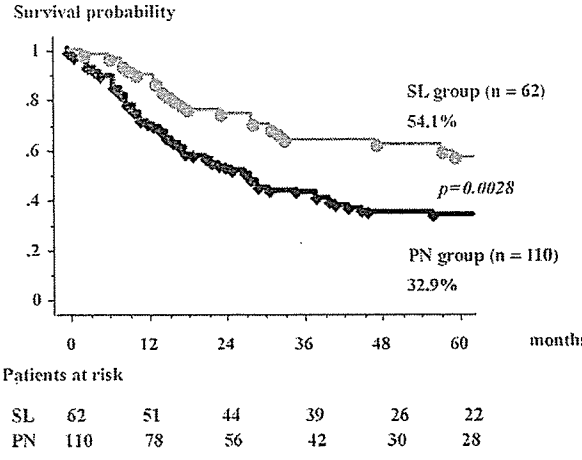

Fig. 1. Overall survival rates for 62 sleeve lobectomy patients (SL group) and 110 pneumonectomy patients (PN group). A significant difference was found between the SL and PN groups ($p = 0.0029$).

than those in the early era (statistically not significant) (Table 2). Regarding respiratory and cardiac complications, there were no significant differences in respective complications or overall morbidity between the groups (SL, 45.2% and PN, 40.9%), as shown in Table 3. Local and distant recurrence rates were 9.7% and 29.0%, respectively, in the SL group. They were 10.9% and 42.7%, respectively, in the PN group, which were not significantly different between the groups (Table 3). Two patients in the SL group were later treated with a completion pneumonectomy without later recurrence. Further four patients in the PN group who were free of relapse required home oxygen therapy (HOT) in the late postoperative period, whereas none in the SL group required HOT throughout the 5-year follow-up period. The overall 5-year survival rates in the SL and PN groups were 54.3% and 32.9%, respectively ($p = 0.0028$) (Fig. 1). However, there was no difference in 5-year survival rate in pathologically stage I and II patients (SL, $n = 45$ and PN, $n = 38$) between the groups (Fig. 1). Moreover, as for the patients who received induction therapy with clinical stage III patients, the PN group ($n = 19$) showed a marginally better survival rate compared to the SL group ($n = 16$) (Fig. 3).

4. Discussion

Resectability for locally advanced lung cancer is improving with recent advances in perioperative care, surgical techniques [4,14,15], and induction therapy [10–12], which downstages the tumors to render them resectable. Thus, avoidance of pneumonectomy can be achieved in particular patients at an early disease stage, and the ratio of sleeve lobectomy to pneumonectomy (SL/PN) has nearly reached 1.0 in the recent reports [8,14–17]. It has been shown that a sleeve resection can offer a better long-term survival and quality of life (QOL) in patients with relatively early stage disease [6,13,15]. In the current retrospective analysis, overall survival in p-stage I/II was similar in both groups.

Over the time, the rate of operative mortality decreased in patients who underwent standard lobectomy at our institution, while there was a slight increase in mortality

Table 4
Literature on operative mortality of lobectomy, sleeve lobectomy, and pneumonectomy for non-small cell lung cancer

	Year	Operative mortality (case number)		
		Lobectomy	Sleeve lobectomy	Pneumonectomy
Author				
Tedder et al. [15][a]	1992	7.5% (1915)		
Mizushima et al. [18][a]	1997		7.4% (122)	
Suen et al. [16]	1999		5.2% (58)	4.9% (142)
Ferguson and Karrison [7]	2000	7.0% (340)		12.0% (102)
Lausberg et al. [14]	2000	2.0% (374)	1.2% (81)	7.5% (40)
Bernard et al. [5]	2001			6.9% (609)
Fadel et al. [19][a]	2002		2.9% (169)	
Ferguson and Lehman [6][a]	2003		4.1% (860)	6.0% (746)
Alexiou et al. [9]	2003	2.4% (374)		8.0% (111)
Stoelben et al. [20]	2003	3.0% (621)	5.3% (152)	6.7% (147)
Deslauriers et al. [21]	2004		1.6% (184)	5.3% (1046)
Ludwig et al. [22]	2005		4.6% (117)	3.6% (194)
Current series	2006	0.5% (956)	4.8% (62)	3.6% (110)
30 days mortality		0.2%	1.6%	1.8%

[a] Collective series.

over the time in both the SL and PN groups. An explanation may be due to differences in the severity of disease in the recent era, while the use of extended resection and/or induction therapy may also be related. All three patients with hospital death in the SL group received induction chemoradiotherapy. In the light of this trend, 35 (40.2%) of the 87 patients in the recent era received induction therapy, which may adversely affect the surgical morbidity and mortality [10–12]. In addition, our series indicate that the recent sleeve lobectomy and pneumonectomy procedures encompassed a variety of additional procedures, including combined resection of adjacent organs, mainly because of locally advanced cancer [12,14].

There have been many retrospective analyses of the operative mortality and morbidity of sleeve lobectomy and pneumonectomy for NSCLC [5–7,9,14–22] (Table 4). Recent reports have shown that a sleeve lobectomy can be performed with a much lower rate of operative mortality (1.2–7.5%) as compared to a pneumonectomy (4.9–12.0%) [6,14,20–22]. In some reports [4,15], sleeve lobectomy is safer than pneumonectomy even in patients who received induction therapy.

Considering the high percentage of patients who underwent an extended resection and/or induction therapy, the present surgical results for both procedures seemed to be acceptable in terms of morbidity and mortality [12]. In the current series, no significant differences were found for local relapse rates between the SL and PN groups, which were similar to those of the previous reports [16,19,23]. We consider that a pneumonectomy following induction therapy for complete resection of locally advanced NSCLC is a last option and a difficult challenge to the thoracic surgeons.

Regarding the late outcome (Fig. 1), it was considered that the two groups did not have the same biologic disease and stage for an adequate comparison of survival for the total patients. It is well documented that TNM stage and nodal status are important to obtain the best benefits of a sleeve lobectomy or pneumonectomy [5,8,21–25]. A 5-year survival was similar in patients of the stage-matched (p-stage I/II) was also demonstrated (Fig. 2). On the other hand, pneumonectomy following induction therapy (Fig. 3) resulted in a marginally better survival rate than that of sleeve lobectomy in the clinical stage III patients. Fair 5-year survival of patients with pneumonectomy after induction therapy is an encouraging result in the current study. Furthermore, we believe that an optimal preoperative functional evaluation of cardiorespiratory risks [12], meticulous surgical techniques, and perioperative care, led to the acceptable immediate results in the present study.

Based on our results, we did not think that there are any drawbacks to a pneumonectomy in terms of morbidity, mortality, and overall survival as compared to a sleeve resection, despite our finding that pneumonectomy procedures were associated with 49 combined resections of the adjacent organs and 19 resections following induction therapy. Just one opponent was that four pneumotectomized patients required HOT and eventually died without cancer recurrence, implying a potential of late cardiorespiratory failure in terms of QOL.

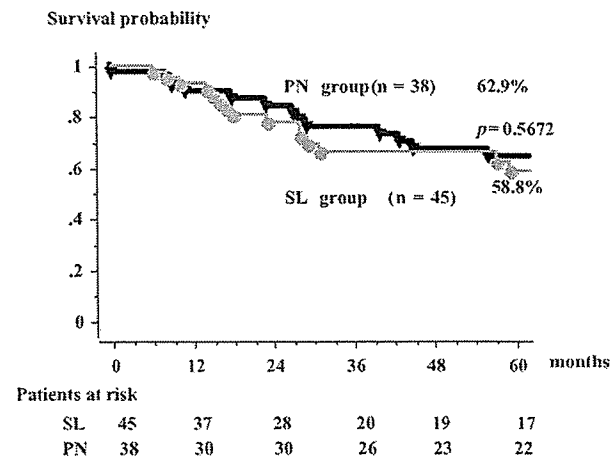

Fig. 2. Overall survival rates for 45 sleeve lobectomy patients (SL group) and 38 pneumonectomy patients (PN group) with pathological stages I and II. No significant difference was found between the SL and PN groups ($p = 0.567$).

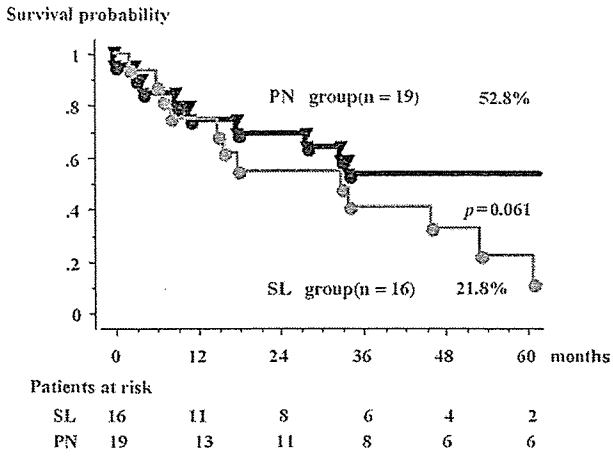

Fig. 3. Overall survival rates for 16 sleeve lobectomy patients (SL) and 19 pneumonectomy patients (PN group) who received induction therapy. No significant difference was found between the SL and PN groups ($p = 0.061$).

In retrospect, the sleeve lobectomy and pneumonectomy procedures performed for the central tumors, presumably with different stages, were done efficiently, with acceptable morbidity, mortality, and 5-year survival. The present indication of pneumonectomy is aimed to perform a curative resection of locally advanced lung cancer in particular following induction therapy as a final surgical option otherwise unresectable, and the properly selected patients will likely benefit by a complete resection with a pneumonectomy.

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Efficient clinical application of percutaneous cardiopulmonary support for perioperative management of a huge anterior mediastinal tumor

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Herein we summarize our experience with 4 patients who had huge tumors that compressed mediastinal neighboring organs. Patient findings are summarized in Table 1, with computed tomographic (CT) images shown in Figure 1.

Clinical Summary

PATIENT 1. The patient was referred to our hospital with chest pain. Chest radiography and CT (Figure 1, *A*) images revealed a mediastinal mass 14 cm in diameter that was compressing the right main pulmonary artery (PA) and left main bronchus. Serum β-human chorionic gonadotropin (β-HCG) was 0.8 ng/mL (cutoff <0.2 ng/mL), whereas the α-fetoprotein (AFP) level was within the normal limit (<5 ng/mL). We began performance of an incisional biopsy under general anesthesia. During the operation, ventilation insufficiency with severe hypoxemia occurred, and fiberoptic bronchoscopy revealed a left bronchial occlusion. After emergency application of percutaneous cardiopulmonary support (PCPS; Capiox emergency bypass system; Terumo, Tokyo, Japan), we performed PA tomography and found a total occlusion of the right PA. Thus, mediastinal compression by the huge tumor induced a complete ventilation-perfusion imbalance after general anesthesia with muscular relaxation. We performed an emergency tumor extirpation.

PATIENT 2. A patient with a testicular tumor associated with intrathoracic metastases was treated with a right high orchiectomy followed by chemotherapy in the department of urology. After normalization of serum AFP (maximum 1265 ng/mL) and HCG (maximum 7 ng/mL), we attempted a metastasectomy of the mediastinal tumor, which was causing bronchial stenosis (Figure 1, *B*). Ventilation insufficiency was anticipated during the induction of general anesthesia; therefore, we initiated PCPS with left axillary artery and right femoral vein cannulation. Thereafter, we safely resected the mediastinal tumor.

PATIENT 3. Patient 3 presented with chest pain and a fever. Chest radiograph and CT images revealed a huge mass that occupied one fourth of the right thorax. Serum AFP and HCG concentrations were increased to 10,100 and 490 ng/mL, respectively. We performed an incisional biopsy under infiltration anesthesia for histologic diagnosis. During the biopsy, a portion of the tumor had fallen into the thorax, and tracheal intubation was required. However, after several needle biopsy attempts, mechanical ventilation became impossible. Fiberoptic bronchoscopy showed an airway obstruction at the level of the carina, and CT demonstrated tumor expansion caused by an intratumorous hemorrhage (Figure 1, *C*). The patient was placed in a hemi-left upside position, and the airway obstruction was released; then emergency extirpation of the tumor was performed.

PATIENT 4. A student with orthopnea was referred to our hospital, and our CT found a heterogeneous mediastinal tumor 17 cm in diameter (Figure 1, *D*). Squamous cell carcinoma and carcinoembryonic antigen levels were increased to 14 ng/mL (cutoff <2 ng/mL) and 6 ng/mL (cutoff <5 ng/mL), respectively. Chemotherapy was administered under the diagnosis of a malig-

TABLE 1. Patient data

Patient	Age (y)/ sex	Diagnosis	Operation mode	Outcome
1	19/male	Seminoma	Incisional biopsy Emergency PCPS Extirpation SVC reconstruction	7 y, alive Disease free
2	27/male	Yolk sac tumor Pulmonary metastasis	Extirpation Right lower lobectomy PCPS	3 y, alive Disease free
3	24/male	Yolk sac tumor	Incisional biopsy Emergency extirpation Right middle lobectomy	2 y, alive Disease free
4	15/male	Teratocarcinoma	Extirpation PCPS	1 y, alive Disease free

PCPS, Percutaneous cardiopulmonary support; *SVC*, superior vena cava.

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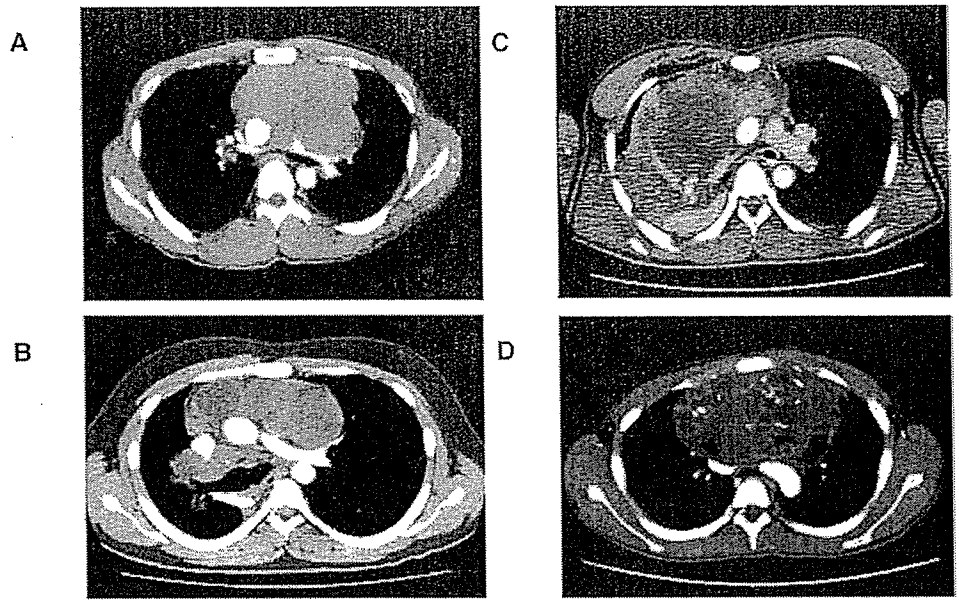

Figure 1. A, Patient 1: the right main PA and left main bronchus are seen compressed by an anterior mediastinal tumor. B, Patient 2: a metastatic tumor surrounding the great vessels is shown causing bronchial stenosis. C, Patient 3: emergency CT image taken after a needle biopsy revealing an intratumorous hemorrhage causing ventilation insufficiency. D, Patient 4: an anterior huge mass is seen compressing the left main bronchus and right main PA. The content was heterogeneous and consisted of cystic and calcified portions.

nant teratoma on the basis of the imaging and tumor marker results. The symptoms improved after 1 course; however, the tumor was not smaller and continued to compress the left main bronchus and right main PA. We performed tumor extirpation by using the assistance of PCPS with general anesthesia to prevent hypoxemia. PCPS was initiated with right femoral venous and arterial cannulation under infiltration anesthesia, with the patient in a semi-Fowler position. Cardiopulmonary support was sustained until the tumor was dissected from the neighboring mediastinal tissue, and complete resection was achieved without an intraoperative event.

Discussion

A huge anterior mediastinal tumor can obstruct the great vessels or respiratory tract during general anesthesia.[1-5] We documented the 4 patients with huge tumors to emphasize the usefulness of PCPS. According to our experience with patient 1, we used PCPS at the time of the induction of general anesthesia in patients 2 and 4, and the resections were performed uneventfully. As for patient 3, we did not use the assistance of PCPS for the biopsy under infiltration anesthesia. However, during the biopsy procedure, general anesthesia with tracheal intubation became required because intratumorous hemorrhage caused ventilatory insufficiency.

When acute ventilatory insufficiency occurs during an incisional biopsy of a huge mass, changing the position of the patient should be considered as an option to release mediastinal oppression caused by the tumor. We also recommend placing PCPS on standby, because general anesthesia with a muscle relaxant may be required and could make the airway obstruction worse. Further, PCPS should be indicated at the induction of general anesthesia for resection of a huge mediastinal tumor that causes airway compression. We consider that perioperative fatal complications can be avoided with the use of PCPS during surgical intervention for a huge anterior mediastinal tumor.

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Randomised study of adjuvant chemotherapy for completely resected p-stage I–IIIA non-small cell lung cancer

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We evaluated the therapeutic usefulness of adjuvant chemotherapy in patients with completely resected non-small cell lung cancer (NSCLC). We also examined the relation between DNA ploidy pattern and the response to chemotherapy. A total of 267 patients with NSCLC (pathologically documented stage I, II, or IIIA) underwent complete resection, and DNA ploidy pattern was analysed. Patients with stage I disease ($n = 172$) were randomly assigned to receive surgery alone (group A) or surgery followed by adjuvant chemotherapy (UFT (oral anti-cancer drug, a combination of Uracil and Tegaful) 400 mg day^{-1} for 1 year after surgery; group B). Stage II or IIIA disease patients ($n = 95$) were randomly assigned to surgery alone (group C) or surgery followed by chemotherapy (two 28-day courses of cisplatin 80 mg m^{-2} on day 1 plus vindesine 3 mg m^{-2} on days 1 and 8, followed by UFT 400 mg day^{-1} for at least 1 year; group D). Eight-year overall survival rate in patients with stage I disease was 74.2% (95% confidence interval (CI): 64.4–84.0%) in group B and 57.6% (95% CI: 46.4–68.8%) in group A ($P = 0.045$ by log-rank test). In patients with stage II and IIIA disease, no difference was found between groups C and D. Analysis according to DNA ploidy pattern revealed no difference between the groups. Postoperative chemotherapy with UFT was suggested to be useful in patients with completely resected stage I NSCLC. No difference was seen in relation to DNA pattern in any treatment group.

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A meta-analysis of postoperative chemotherapy in non-small cell lung cancer (NSCLC) reported by the British Medical Council in 1995 found that adjuvant chemotherapy did not adequately improve outcome in this condition (Non-small Cell Lung Cancer Collaborative Group, 1995). Despite a number of trials since, the value of postoperative chemotherapy for NSCLC remains controversial (Wada *et al*, 1996; Endo *et al*, 2003; Scagliotti *et al*, 2003). Beginning around 1990, considerable attention has been focused on DNA ploidy pattern as a possible new prognostic factor, with tumours showing aneuploidy, associated with a poor prognosis, reported to show a better response to chemotherapy than those showing diploidy (Granone *et al*, 1993; Salvati *et al*, 1994; Kim *et al*, 1996). However, these previous studies were based on retrospective data.

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We dedicate this paper to the late Dr Takashi Mori, who died before completion of the study.
See Appendix.
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Here, we investigated the usefulness of postoperative adjuvant chemotherapy for the management of NSCLC patients prospectively assigned to treatment on the basis of DNA ploidy.

PATIENTS AND METHODS

Eligibility criteria

Eligibility criteria included an untreated primary lung cancer; histologically confirmed diagnosis of squamous cell carcinoma, adenocarcinoma, or large cell carcinoma; pathologically documented stage I, II, or IIIA disease; diploidy or aneuploidy on analysis of nuclear DNA of the primary tumour; age 75 years or younger in patients with stage I disease or 70 years or younger in those with stage II or IIIA disease; Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2; and adequate organ function as defined by a leucocyte count of at least 4000 mm^{-3}, platelet count of at least 100 000 mm^{-3}, serum haemoglobin level of at least 10 g dl^{-1}, serum aspartate aminotransferase (AST) level of not more than 100 U, alanine aminotransferase (ALT) level of at most 100 U, albumin/globulin ratio of at least 1.0, serum creatinine level of less than 1.5 mg dl^{-1}, and serum urea nitrogen level of not

more than 25 mg dl^{-1}. Further, patients with a serious concurrent condition were also excluded. All tumours were resected by pulmonary resection consisting of at least lobectomy and systematic hilar/mediastinal lymph node dissection. Cases of complete resection were defined as those without macroscopic residual tumour or microscopic positive margins. The study was reviewed and approved by the institutional review boards of each participating centre, and written informed consent was obtained from all patients.

Because stage I disease differs considerably from stage II and IIIA disease, assignment of similar treatments would have negatively affected outcome. Patients with stage II or IIIA disease were therefore assigned to receive different treatment from those with stage I disease.

Measurement of DNA ploidy

Samples were harvested and frozen immediately after tumour excision. Nuclear DNA content was measured by flow cytometry and evaluated by an independent flow cytometry evaluation committee who were blinded to patient data.

Treatment schedule

Patients were grouped according to stage as follows. For stage I patients, Group A (control) received no adjuvant chemotherapy but was followed after surgery, whereas Group B received single daily oral administration of UFT (oral anti-cancer drug, a combination of Uracil and Tegaful) at 400 mg day^{-1} for at least 1 year starting 3–6 weeks after surgery.

For stages II and IIIA, Group C (control) received no adjuvant chemotherapy but was followed after surgery, whereas Group D was given two 28-day courses of chemotherapy with cisplatin (80 mg m^{-2}) on day 1 and vindesine (3 mg m^{-2}) on days 1 and 8, starting 3–6 weeks after surgery, followed by single daily oral administration of UFT at 400 mg day^{-1} for at least 1 year.

Adverse effects of chemotherapy were evaluated using the National Cancer Institute Common Toxicity Criteria (version 2.0, Jan 30, 1998) and handled by appropriate treatment, discontinuation of UFT, or both. In Group D, chemotherapy after the administration of vindesine on day 8 of the first course was continued only after confirmation that white blood cell count was greater than 3000. Other anticancer drugs, immunomodulators, and radiotherapy were not used unless recurrence was confirmed.

Treatment assignment

Patients were stratified on the basis of pathological stage, histologic type, and ploidy pattern, and then randomly assigned to groups. Randomisation was performed centrally, with assignment for pathological T and N stage balanced using the minimisation method with probability and the method of Zelen (Yonekura *et al*, 1999; Tanaka *et al*, 2002).

Statistical analysis

The primary end point was overall survival, defined as the time from surgery until death from any cause. The secondary end point was disease-free survival, defined as the time from surgery until relapse or death from any cause, whichever occurred first.

Survival curves were calculated by the Kaplan–Meier method (Kaplan and Meier, 1958), and statistical significance of differences between groups was compared with the log-rank test (Peto *et al*, 1977). *P*-values of less than 0.05 were considered to indicate significance. Multivariable analysis to estimate the simultaneous effects of prognostic factors on survival was carried out with the Cox proportional-hazards model. Categorical variables were compared using the χ^2 test.

Target numbers of patients were calculated as follows. Based on previous studies (Kuwahara *et al*, 1989; The Study Group of Adjuvant Chemotherapy for Lung Cancer, 1995; Wada *et al*, 1996), the assumed 5-year survival in the control group was 75% in stage I patients and 40% in stage II or III patients. The expected survival improvement was 15% in stage I patients and 25% in stage II or III patients.

On the basis of Freedman's sample size table (Freedman, 1982), the sample size required to detect a significant difference between surgery alone and surgery plus chemotherapy at a power of 0.8 and a 5% level of significance was 169 patients with stage I disease and 102 with stage II, or III disease.

One goal of this study was to compare survival in patients with aneuploid tumours who received chemotherapy after surgery with that in patients who received surgery alone. Given an aneuploid to diploid tumour ratio of 8:2 (Yamaoka *et al*, 1991), 80% of stage I, II, and III cases were estimated to be aneuploid. The required number of cases was therefore estimated to be 212 cases of stage I disease and 128 cases of stage II or III disease. Allowing for 8% ineligibility and loss to follow-up, the target number was set at 230 patients with stage I and 140 with stage II or III disease.

All statistical analyses were carried out using the SAS software package ver. 7 (SAS Institute Inc, Cary, NC, USA).

RESULTS

A total of 287 patients were enrolled at 15 centres from April 1992 to March 1994. At this time, a number of new induction chemotherapy protocols for early stage lung cancer were introduced in Japan, hampering the further accrual of patients, and enrollment was therefore stopped in March 1994. This report evaluates cases followed until the end of November 2001.

Of the 287 patients enrolled, 20 were excluded because they did not meet the entry criteria, namely conditions other than cancer (inflammatory or benign tumours) or non-curative resection. Median follow-up time of the 267 patients studied was 7.4 years.

Clinical characteristics

Of 172 patients with stage I disease, 87 were assigned to group A and 85 to group B, with no significant difference between them in sex, mean age, performance status, T stage, histologic type, or tumour DNA pattern.

Of 95 patients with stage II ($n=33$) or IIIA ($n=62$) disease, 48 were assigned to group C and 47 to group D, with no significant difference between them in sex, mean age, performance status, T stage, N stage, pathologically determined disease stage, histologic type, or DNA pattern (Table 1).

Treatment rate

A 100% treatment rate was defined as at least 1 year of continuous treatment with 400 mg of UFT daily. From this, individual rates were calculated as (number of UFT administration days)/365 × (daily UFT dosage)/400 × 100. Mean treatment rates in groups B and D were estimated to be 76.7 and 48.6%, respectively. In group D, 39 patients were given one or more courses of cisplatin and vindesine (one course in three patients, two in 36). Treatment compliance was 83.0%. Treatment was not given to eight patients owing to patient refusal in two, postoperative complications in two, and poor general condition in four.

Survival rate

Eight-year overall survival rate in stage I patients was 57.6% (95% confidence interval (CI): 46.4–68.8%) in group A (control) and 74.2% (95% CI: 64.4–84.0%) in group B, with a significant

Table 1 Patient characteristics

	A	B	Total	C	D	Total
No. of eligible patients	87	85	172	48	47	95
Sex						
Male	49	49	98	35	35	70
Female	38	36	74	13	12	25
Age						
(Ave.)	60.9	60.2	60.6	59.3	60.5	59.9
PS						
0	66	66	132	36	35	71
1	19	19	38	12	10	22
2	2	0	2	0	2	2
pT						
1	41	45	86	12	13	25
2	46	40	86	24	24	48
3				12	10	22
pN						
0				6	1	7
1				18	19	37
2				24	27	51
Stage						
I	87	85	172			
II				16	17	33
IIIA				32	30	62
Histology						
Adenocarcinoma	67	68	135	29	27	56
Squamous cell carcinoma	17	15	32	17	17	34
Large cell carcinoma	3	2	5	2	3	5
DNA pattern						
Diploidy	18	17	35	10	8	18
Aneuploidy	69	68	137	38	39	77

Abbreviations: PS, performance status; pT, pathological tumour stage; pN, pathological lymph node stage.

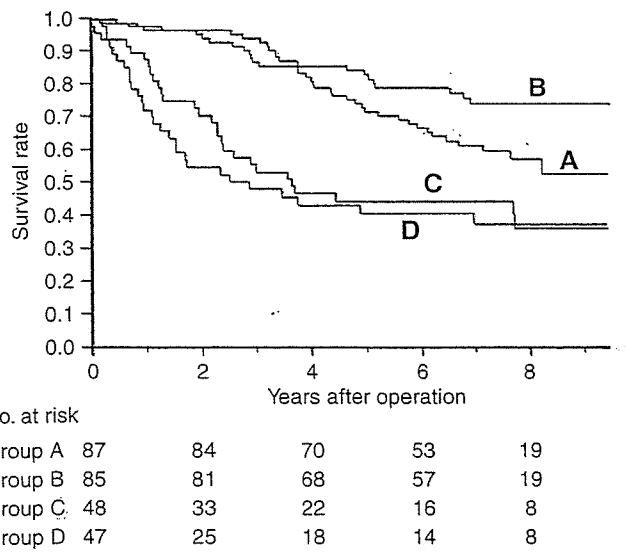

Figure 1 Overall survival of stage I control and UFT group patients. Eight-year survival rate was 57.6% for the control group **A** ($n=87$) and 74.2% for the UFT group **B** ($n=85$). A significant difference in survival curves for these groups is seen ($P=0.045$ by log-rank test).

Table 2 Overall survival in the control and UFT groups

	No. of cases		8-year survival rate (%)		
	A	B	A	B	*P*-value
Sex					
Female	38	36	74.7	78.0	0.850
Male	49	49	43.6	71.6	0.013
Age (years)					
<60	38	37	74.5	84.8	0.171
⩾60	49	48	45.9	65.4	0.153
PS					
0	66	66	62.0	78.3	0.055
1, 2	21	19	43.4	62.2	0.460
pT					
T1	41	44	56.4	87.7	0.014
T2	46	40	59.4	58.5	0.763
Histology					
Adeno carcinoma	67	68	60.2	75.6	0.065
Non-adeno carcinoma	20	17	51.7	69.3	0.503
DNA pattern					
Diploidy	18	17	53.5	86.7	0.078
Aneuploidy	69	68	59.0	71.3	0.158

Abbreviations: PS, performance status; pT, pathological tumour stage.

difference seen between the two survival curves ($P=0.045$; Figure 1). Respective rates in Groups C and D were 36.8% (95% CI: 21.3–52.3%) and 38.0% (95% CI: 23.5–52.5%), with no significant difference between these two overall survival curves ($P=0.52$). Moreover, no significant difference was seen in 8-year disease-free survival rate between groups A and B or C and D.

Subgroup analyses

When subgrouped by histology, the adenocarcinoma subgroup showed no significant difference in overall survival curves between groups A and B ($P=0.065$); or between patients in groups A and B with diploid tumours ($P=0.078$) or aneuploid tumours ($P=0.16$) (Table 2). Moreover, overall survival curves in this adenocarcinoma subgroup did not differ significantly between groups C and D (group C, $n=29$, 8-year survival rate 41.3%, 95% CI: 21.9–60.7%; group D, $n=27$, 8-year survival rate 40.0%, 95% CI: 19.9–60.0%; $P=0.98$).

When subgrouped by DNA pattern, no significant difference in overall survival curve was seen in diploid tumour patients in groups C and D (group C, $n=10$, 8-year survival rate 30.0%, 95% CI: 1.6–58.4%; group D, $n=8$, 8-year survival rate 37.5%, 95% CI: 4.0–71.0%; $P=0.92$); or between aneuploid patients in groups C and D (group C, $n=38$, 8-year survival rate 36.8%, 95% CI: 17.8–55.8%; group D, $n=39$, 8-year survival rate 38.1%, 95% CI: 21.8–54.4%; $P=0.44$).

Multivariate analysis

Multivariate analysis indicated that UFT treatment was a significant predictor of outcome in stage I patients, following age and sex (Table 3).

Adverse effects

Grade 3 anorexia occurred in one patient in group B. The incidence of grade 3 and 4 toxicity was only 1.2% in group B. In

group D, grade 3 or 4 leucopenia was seen in seven patients (14.6%), anorexia in three patients (6.3%), nausea/vomiting in two patients (4.2%), and hair loss in one patient (2.1%) (Table 4). No episode lasted more than 1 month.

There were no lethal adverse effects in either chemotherapy group.

Mortality

Twenty-six of 87 patients (29.9%) in group A and 14 of 85 (16.5%) in group B died of their tumours, with this difference being significant ($P=0.037$). Nine patients in group A and six in group B died of causes other than cancer, with this difference not significant ($P=0.45$).

The rate of mortality from cancer was 52.1% in group C and 42.6% in group D, with this difference not significant ($P=0.35$). The rate of mortality from other causes was 6.3% in group C and 17.0% in group D, again without significance ($P=0.10$).

DISCUSSION

UFT is an oral fluorinated dihydropyrimidine preparation which combines tegafur, a prodrug of 5-fluorouracil, with uracil, an inhibitor of dihydropyrimidine dehydrogenase, the enzyme which catalyses the metabolism of 5-fluorouracil. One reason for the effectiveness of postoperative adjuvant chemotherapy with UFT in patients with completely resected stage I lung cancer is the action of tegafur. The metabolism of tegafur results in prolongation of active levels of 5-fluorouracil, and its metabolites (GHB and GBL) promote angiogenesis (Yonekura *et al*, 1999; Basaki *et al*, 2001; Tanaka *et al*, 2002). Meta-analysis of several randomised controlled studies has confirmed that UFT is therapeutically useful. The Japan Lung Cancer Research Group (JLCRG) performed Phase III randomised controlled studies of post-operative adjuvant chemotherapy with UFT in patients with stage I adenocarcinoma of the lung, and showed significant improval in survival, with a hazard ratio of 0.71 (95% CI: 0.52–0.98) as compared with surgery alone in this subgroup ($P=0.04$) (Kato *et al*, 2004).

Our study enrolled a wider range of patients than the JLCRG study, including not only adenocarcinoma and completely resected stage I NSCLC, but also stage II and IIIA NSCLC. Survival in patients with stage I disease was significantly better in group B than in group A ($P=0.045$). On analysis by histologic tumour type, survival in patients with adenocarcinoma was slightly but not significantly better in group B ($P=0.065$). In contrast, survival in patients with diploid tumours did not differ between group A and B, probably because of the low patient numbers, which were insufficient for statistical analysis ($n=18$ and 17, respectively). The number of patients with diploid tumour was small as compared with that of patients with aneuploid tumour, and was insufficient for statistical analysis in the present study.

In stage II and III adenocarcinoma, in contrast, no difference in survival was seen either overall, or by ploidy. These results therefore suggest that UFT is effective for the management of stage I lung cancer, consistent with the findings of the WJSG 2nd study and the JLCRG study (Kato *et al*, 2004).

Early studies of DNA ploidy (Granone *et al*, 1993; Salvati *et al*, 1994; Kim *et al*, 1996) reported that aneuploidy is an independent predictor of poor outcome. In contrast, more recent investigations (Fujino *et al*, 1996; Bellotti *et al*, 1997; Reinmuth *et al*, 2000; Pelletier *et al*, 2001) have questioned the value of ploidy as a prognostic factor. Statistical analysis of the prognostic implications of diploidy was precluded in the present study owing to the low number of patients with diploid tumours (stage I, $n=35$; stage II and III, $n=18$).

With regard to the efficacy of the present therapeutic regimen, a meta-analysis of the usefulness of postoperative cisplatin-based adjuvant chemotherapy in NSCLC found good efficacy in stage II and III patients receiving cisplatin-based (320 mg m^{-2} or more) chemotherapy with vinorelbine (Pignon *et al*, 2006). In contrast, the dose of cisplatin in the present study was as low as 160 mg m^{-2} and vindesine was used as a combination drug. These differences

Table 3 Multivariate analysis of outcomes

Factor	Hazard ratio	95% CI	*P*-value
Sex			
Female	1		
Male	1.95	1.11–3.60	0.019
Age (years)			
<60	1		
⩾60	2.24	1.26–4.20	0.0053
Group			
Control	1		
UFT	0.57	0.32–0.97	0.039

Table 4 Toxicity

	UFT					CDDP+VDS+UFT				
	Grade					Grade				
Toxicity ($n=85$)	1	2	3	4	Frequency of G3 or G4 (%)	Toxicity ($n=47$)	1	2	3	4	Frequency of G3 or G4 (%)
Leucopenia	8	2	0	0		Leucopenia	8	11	5	2	14.6
Thrombocytopenia	2	0	0	0		Thrombocytopenia	3	2	0	0	
Anaemia	1	0	0	0		Anaemia	8	6	0	0	
AST	6	0	0	0		GOT	6	3	0	0	
ALT	5	2	0	0		GPT	9	4	0	0	
Anorexia	10	8	1	0	1.2	BUN	5	0	0	0	
Nausea/vomiting	8	1	0	0		Creatinine	2	0	0	0	
Diarrhoea	3	1	0	0		Anorexia	10	14	3	0	6.3
Stomatitis	4	0	0	0		Nausea/vomiting	12	4	2	0	4.2
Pigmentation	6	0	0	0		Diarrhoea	4	1	0	0	
Alopecia	0	1	0	0		Stomatitis	4	0	0	0	
						Alopecia	7	7	1	0	2.1

Abbreviations: BUN, blood urea nitrogen; CDDP, cisplatin; VDS, vindesine sulfate.

are likely associated with the insufficient efficacy seen here. Further, the response rate to UFT in unresectable NSCLC has been reported as only 8% (Keicho *et al*, 1986), and usefulness of postoperative adjuvant chemotherapy has been described for relatively early-stage NSCLC only. The possibility therefore exists that UFT may have insufficient efficacy in stage II/III disease with high malignancy.

In conclusion, although the relation between DNA ploidy pattern and the response to postoperative adjuvant chemotherapy remains unclear, our results suggest that postoperative adjuvant chemotherapy with UFT improves survival and is therapeutically useful in patients with completely resected stage I NSCLC.

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Appendix A

- Osaka University, Faculty of Medicine
- Osaka Medical Center for Cancer and Cardiovascular Diseases
- Osaka Prefectural Medical Center for Respiratory and Allergic Diseases
- Kansai Medical University
- Kansai Electric Power Hospital
- Kinki University School of Medicine
- Toneyama National Hospital
- National Kinki Central Hospital for Chest Diseases
- Sumitomo Hospital
- Takarazuka Municipal Hospital
- Kitano Hospital The Tazuke Kofukai Medical Research Institute
- Osaka City General Hospital
- Hyogo College of Medicine

Case Report

Surgically Removed Thoracolithiasis: Report of Two Cases

Teruo Iwasaki, MD, PhD,[1] Katsuhiro Nakagawa, MD, PhD,[1] Hiroshi Katsura, MD,[1] Naoko Ohse, MD,[1] Teruaki Nagano, MD,[2] and Kunimitsu Kawahara, MD, PhD[2]

Thoracolithiasis is a rare condition with only 12 cases of surgically removed nodules reported in the literature. We report 2 additional cases.

Case 1: A 19-year-old male admitted with an abnormal shadow on a chest X-ray. Computed tomography (CT) revealed a nodule in the right lower lung lobe. The material extirpated by thoracoscopy was milky white, glossy, and 1.6 cm in diameter. Histopathologically, it consisted of fatty necrotic tissue covered with hyalinized fibrous tissue.

Case 2: A 78-year-old female, with a past history of breast cancer, admitted with an abnormal shadow on chest X-ray. CT revealed a nodule in the left lung S^{1+2} segment, of which transbronchial biopsy findings indicated primary lung adenocarcinoma. Exploratory thoracoscopy incidentally revealed some pearly material, 0.4 cm in diameter, in the thoracic cavity. They were extirpated during left upper lobectomy for lung cancer; all of them demonstrated concentric hyalinized fibrous tissue. Thoracic surgeons should consider this condition in the differential diagnosis of a peripheral pulmonary nodule. (Ann Thorac Cardiovasc Surg 2006; 12: 279–82)

Key words: thoracolithiasis, pleural stone, thoracoscopy

Introduction

Thoracolithiasis, which is also described as pleural stone, intrathoracic calculus or pleurolith, is a rare condition and only 12 cases of surgically removed nodules have been reported in the literature.[1–11] We report 2 additional cases of surgically removed thoracolithiasis. Thoracic surgeons should bear in mind this condition in the differential diagnosis of a peripheral pulmonary nodule.

Cases

Case 1

A 19-year-old otherwise healthy male was admitted for further evaluation of an abnormal shadow found on chest X-ray. On admission, physical examination and laboratory data were unremarkable. A chest X-ray showed a well-defined oval nodule 1.5 cm in diameter in the right lower lung field (Fig. 1A). Computed tomography (CT) of the chest revealed a subpleural lesion, within which minute high density areas were detected in the lung window (Fig. 1B), but the nodule disappeared in the mediastinal window (Fig. 1C). A benign lung tumor such as a hamartoma was suspected.

Video-assisted thoracic surgery (VATS) was performed to examine the surface of S^9 segment of the lung with a scope from the 7th intercostal space (ICS) on the midaxillary line and to remove the material with a forceps from the 6th ICS on the posterior axillary line. The extirpated material was 1.6×1.5 cm in size and its surface was milky white and glossy (Fig. 2A); its cross-section was rough and yellowish brown (Fig. 2B). Histopathologically, it consisted of adipose and fatty necrotic tissue surrounded by hyalinized fibrous tissue (Figs. 2C and 2D). The patient's postoperative course was uneventful.

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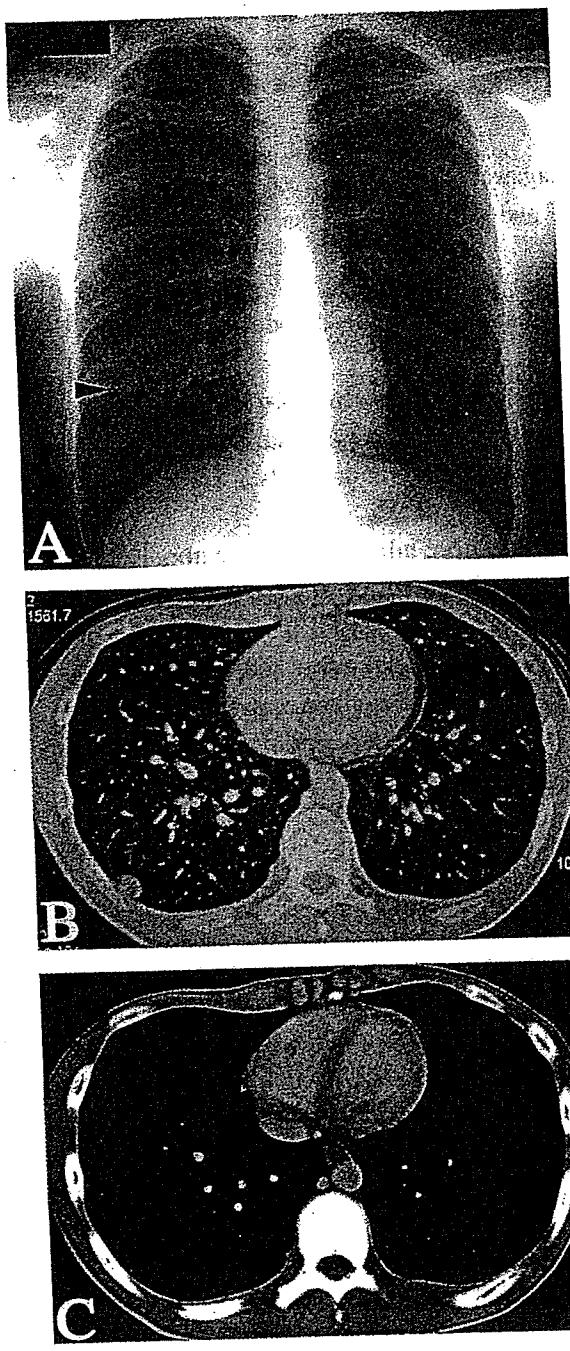

Fig. 1.
A: Chest X-ray showing a well-defined oval nodule (arrowhead) in the right lower lung field.
B: Minute high density areas were detected within the nodule in the lung window of chest CT.
C: The nodule disappeared in the mediastinal window.

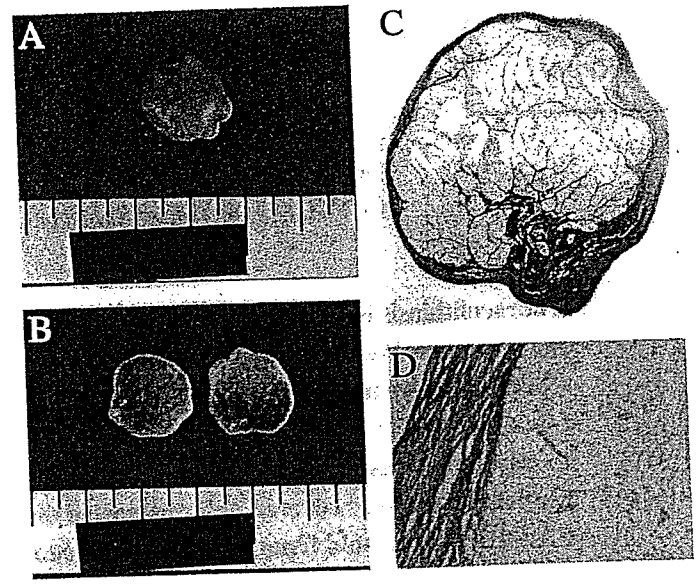

Fig. 2.
A: Photograph of the extirpated material. It was 1.6×1.5 cm in size and its surface was milky white and glossy.
B: The cross-section of the material was rough and yellowish brown, and the contents were covered with a milky white capsule.
C, D: Microscopic findings of the extirpated material under low (C; ×4.7) and high (D; ×40) power magnifications (HE stain) in case 1. The material consisted of adipose and fatty necrotic tissue surrounded by hyalinized fibrous tissue.

Case 2

A 78-year-old female was admitted to our hospital for further evaluation of an abnormal shadow detected by chest screening X-ray. She had undergone a left radical mastectomy for breast scirrhous carcinoma (pT2N3cM0 stage IIIc, estrogen- and progesterone-receptor negative) at the age of 70, followed by chemotherapy (cyclophosphamide plus methotrexate plus fluorouracil and doxifluridine plus medroxyprogesterone acetate) and radiotherapy (50 Gy) over the left supraclavicular and parasternal regions. A chest X-ray and CT demonstrated a nodule in the left lung S^{1+2} segment, and transbronchial biopsy findings of the lesion indicated primary lung adenocarcinoma.

An exploratory thoracoscopy was performed through the 7th ICS on the midaxillary line to incidentally find some pearly material on funicular and membranous adhesions between the parietal and visceral pleurae without disseminated lesions (Fig. 3). A left posterolateral incision and thoracotomy through the 4th ICS were done to carry out a complete left upper lobectomy for lung cancer. Histopathological examination revealed the lung cancer to be moderately differentiated adenocarcinoma (pT2N0M0 stage IB). Some pearly materials were extirpated and all of them were found to be concentric hyalinized fibrous tissue (Fig. 4). The postoperative course was uneventful.

Fig. 3. Exploratory thoracoscopy revealed the presence of pearly material (arrowhead) on funicular and membranous adhesions between the parietal (top) and visceral (bottom) pleurae.

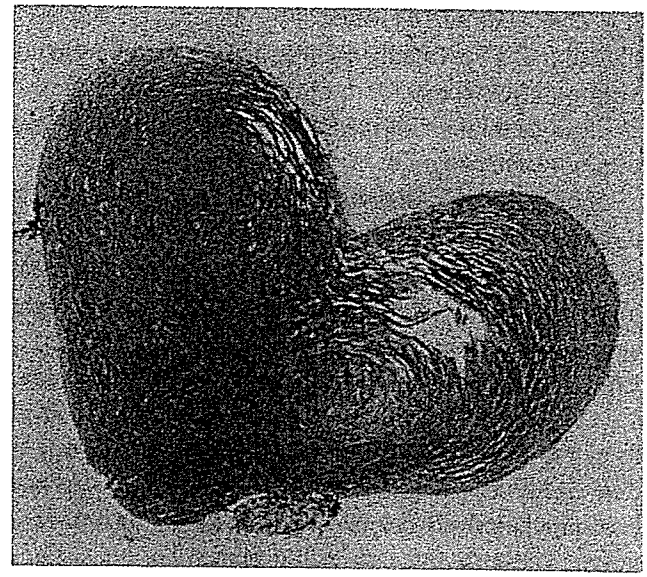

Fig. 4. Microscopic findings of one of the extirpated materials, 0.4 cm in diameter, in case 2. The material consisted of concentric hyalinized fibrous tissue. (HE stain: ×20)

Table 1. Reports of surgically removed thoracolithiasis in Japan

Case	Author/ref. no.	Year	Age (years)	Gender	Site	Preoperative detection	Mobility	Calcification	Size (cm)
1	Takiguchi et al.[2]	1987	71	M	L	+	+	+	1.5×1.2×0.8
2	Ishikawa et al.[3]	1988	57	M	L	−	nd	+	1×1×0.4
3	Kuwabara et al.[4]	1989	56	M	L	−	nd	−	0.6
4	Fujiwara et al.[5]	1992	53	F	R	+	+	−	1.5×1.2×0.7
5	Kuroya et al.[6]	1996	50	F	L	+	−	−	2×1×1
6	Kosaka et al.[7]	2000	76	M	L	+	−	−	1.5
7	Kosaka et al.[7]	2000	54	F	L	−	nd	−	0.5
8	Ando et al.[8]	2002	67	M	L	+	−	−	1.7×1.5×1.0
9	Takeichi et al.[9]	2004	72	M	L	+	−	+	2.5×2.0×1.8
10	Ito et al.[10]	2005	80	M	R	+	+	−	2.2×1.8
11	Our case	2006	19	M	R	+	−	−	1.6×1.5
12	Our case	2006	78	F	L	−	nd	−	0.4

M, male; F, female; L, left; R, right; nd, not determined.

Discussion

Dias et al.[1] reported the first case of pleural stone in 1968 and noted that no similar cases had been found in the literature until then. Takiguchi et al.[2] termed an unusual isolated calcified lesion in the intrathoracic space "thoracolithiasis", and Kosaka et al.[7] defined thoracolithiasis as a condition in which 1 or more free bodies with or without calcification exist in the thoracic cavity without any previous trauma, intervention, or pleurisy. To the best of our knowledge, only 12 cases of surgically removed nodules have been reported in the literature: 10 in Japan,[2–10] 1 in America[1] and 1 in Germany.[10] In 3 cases,[3,9,11] the patients had a previous history of pleurisy and 1 of them had also undergone an artificial pneumothorax for pulmonary tuberculosis.[3] Here we consider the above-mentioned condition as thoracolithiasis regardless of pleurisy.

The characteristics of the 12 Japanese cases, including our 2 cases, are summarized in Table 1. Two thirds were men (67%; 8 cases). The patients' age ranged from 19 years to 80 years (mean: 61 years): our case 1 was the youngest. Nine cases (75%) occurred in the left hemitho-

rax. The maximum diameter of the material ranged from 0.4 cm to 2.5 cm (median: 1.5 cm). All patients were asymptomatic except for 1 case in which the material shadow gradually enlarged and the patient complained of productive cough.[7]

Four cases, including our case 2, had no imaging evidence before extirpation, the nodules were discovered incidentally during surgery for lung cancer, and were no more than 1 cm in diameter (median: 0.6 cm).[3,4,7] Eight cases were detected on chest X-ray and/or CT before extirpation and were at least 1.5 cm in diameter (median: 1.6 cm). In 3 of these 8 cases, thoracolithiasis was noted to be mobile during the course of their evaluation.[2,5,10] Five cases, including our case 1, were immobile and had been preoperatively diagnosed as a peripheral pulmonary tumor. These findings showed that thoracolithiasis was difficult to diagnose correctly when they were small (<1 cm) or immobile. Thoracoscopy was reported to be useful for the diagnosis and treatment of thoracolithiasis, and the same was true in our cases.

Histopathological findings of the extirpated materials were as follows: fibrous tissue with fatty necrosis at the core in 7 cases (including our case 1); calcification covered with fibrous tissue in 1 case;[9] fatty tissue with calcificasion in 1 case;[2] fibrous tissue with caseous necrosis at the core in 1 case;[3] fibrous tissue with dust, containing calcium compounds, at the core in 1 case;[6] and hyalinized fibrous tissue in 1 case (our case 2). Thus, thoracolithiasis usually consisted of fatty tissue with or without necrosis (8 cases; 67%) and/or calcification or calcium compounds (4 cases; 33%). Magnetic resonance imaging (MRI) of the chest was done only in 1 surgical case.[10] Both T1- and T2-weighted MRI revealed a central area of high intensity corresponding to fatty necrotic tissue. The histological characteristics of the thoracolithiasis described above suggest the diagnostic usefulness of MRI.

The etiology remains to be clarified. However, some explanations for the core formation in thoracolithiasis have been proposed: (1) pleural or pericardial fat dropping into the intrathoracic space;[7–10] (2) pleural or peripheral pulmonary lipoma tearing off;[2,4] (3) focus of old pulmonary tuberculosis;[3,9] and (4) aggregation of macrophages phagocytosing dust.[6] The relationship between pericardial fat and thoracolithiasis is supported by a predominant (75%) left hemithorax occurrence. Inflammation may also facilitate the fibrosis and development of thoracolithiasis, as in our case 2. Its association with chemotherapy, radiotherapy or concomitant lung cancer is unknown. The elucidation of its etiology requires the accumulation of additional cases.

Conclusion

We report 2 additional cases of surgically removed thoracolithiasis. This condition is difficult to diagnose correctly in immobile cases even if detectable. Since it usually consists of fatty tissue or calcification at the core, MRI is useful for its diagnosis, in addition to thoracoscopy. Thoracic surgeons should consider this condition in the differential diagnosis of a peripheral pulmonary nodule.

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CASE REPORT

Pulmonary suture abscess with false-positive ^{18}F-fluorodeoxyglucose positron emission scan mimicking lung cancer recurrence

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Abstract We present the case of a 57-year-old woman with pulmonary suture abscess. She had undergone right S3 segmentectomy for early lung adenocarcinoma 7 years before and right breast-conserving surgery for invasive ductal carcinoma 5 months previously, followed by irradiation plus endocrine therapy. Chest radiography and computed tomography revealed an irregular mass (3.5 cm in diameter) between the residual S1 segment and the middle lobe, neighboring the staple line of the segmentectomy. ^{18}F-fluorodeoxyglucose uptake into the mass increased, seen by positron emission scans. Therefore, we could not rule out the possibility of local recurrence of lung cancer and resected it. Pathologically and microbiologically, the mass was a suture abscess arising around the nylon suture of the previous segmentectomy. This lesion was the result of a foreign-body reaction, as confirmed by polarized microscopy. Moreover, titanium staples at the segmentectomy and breast-conserving surgery may also have contributed to this condition.

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Key words Positron emission tomography · Lung cancer · Pulmonary suture abscess · Foreign body granuloma · Breast-conserving surgery

Introduction

Pulmonary suture abscess or granuloma rarely requires surgical procedures. We present the fifth case reported in the literature of surgically resected pulmonary suture abscess arising around the nylon suture 7 years after segmentectomy for early lung cancer. We performed ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) for the first time for a pulmonary suture abscess according to our review of the literature. Based on the computed tomography (CT) scan of the chest and FDG-PET, we could not rule out the possibility of local recurrence of the lung cancer. Possible contributing factors to pulmonary suture abscess are reviewed.

Case

A 57-year-old woman was admitted to our hospital for further evaluation of an abnormal shadow on a chest radiograph in June 2005. She had undergone right S3 segmentectomy (ND2a) for a well-differentiated adenocarcinoma of the lung (1.3 cm in diameter, pT1N0M0P0, stage IA) in our hospital in February 1998 and right breast-conserving surgery for invasive ductal carcinoma (pT1N0M0, stage I) in another hospital in January 2005, followed by tangential irradiation of 50 Gy to the remaining breast and oral administration of anastrozole (an aromatase inhibitor). In May 2005, a routine radiograph revealed an irregular mass (3.5 × 1.8 cm) in the right-middle lung field, overlapping a staple line of the segmentectomy (Fig. 1).

She had never smoked and was asymptomatic on her second admission. Laboratory data, including a white blood cell count, C-reactive protein, blood glucose, carcinoembryoric antigen, and CYFRA (a tumor marker) were all within normal limits. Microbiological and cytological examinations of sputum showed nothing of particular significance. Chest CT showed a mass with a spiculated margin located between the residual S1 segment and the middle lobe, which neighbored the staple line of the S3 segmentectomy (Fig. 2). No calcification or lymph node swelling was detected. FDG-PET and fused PET/CT images demonstrated abnormally intense uptake (maximum standardized uptake value, or SUVmax, was 4.9) in a right pulmonary lesion (Fig. 3). No evidence of another metastatic disease was detected.

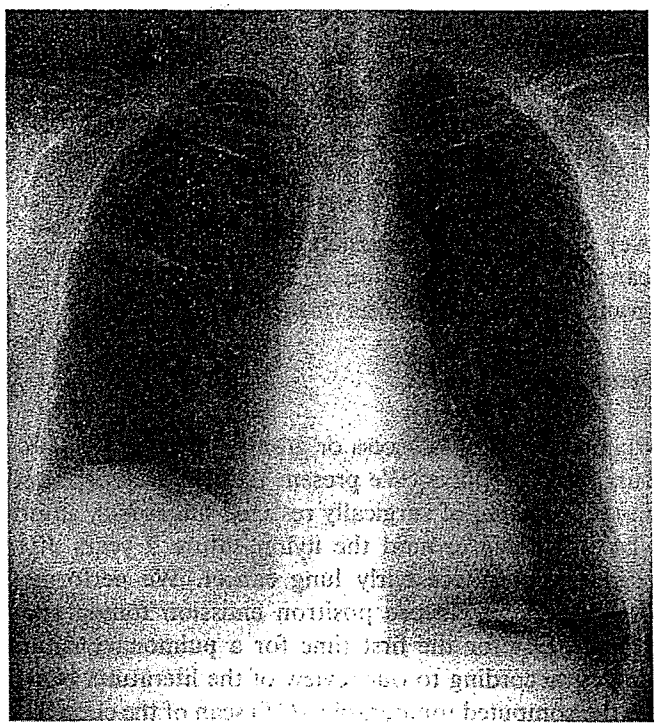

Fig. 1 Chest radiograph showing an irregular mass along the minor fissure in the right middle lung field. The mass shadow overlapped with a staple line at the S3 segmentectomy

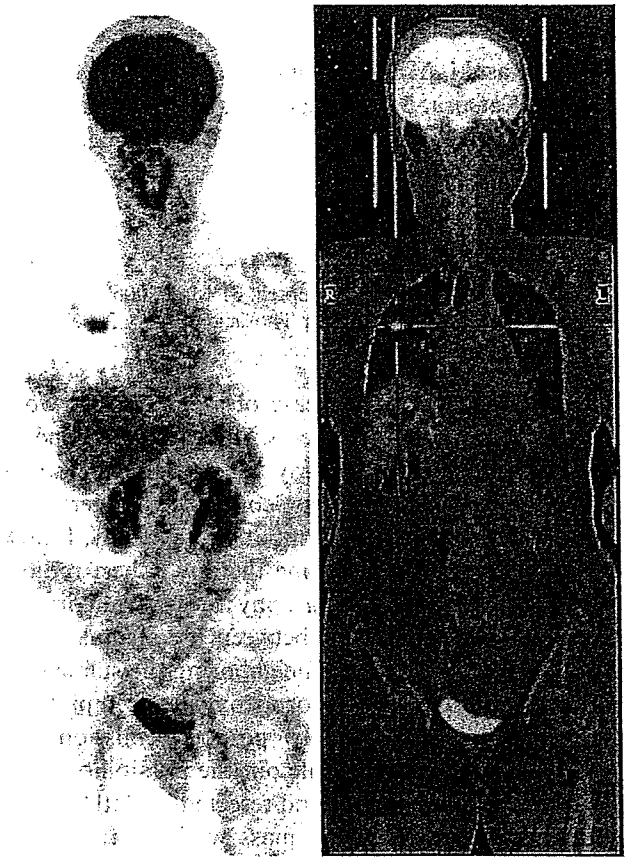

Fig. 3 Initial images on ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) scan (maximum intensity projection) (*left*) and coronal fused PET/CT (*right*) demonstrating abnormally intense uptake in the mass in the right lung

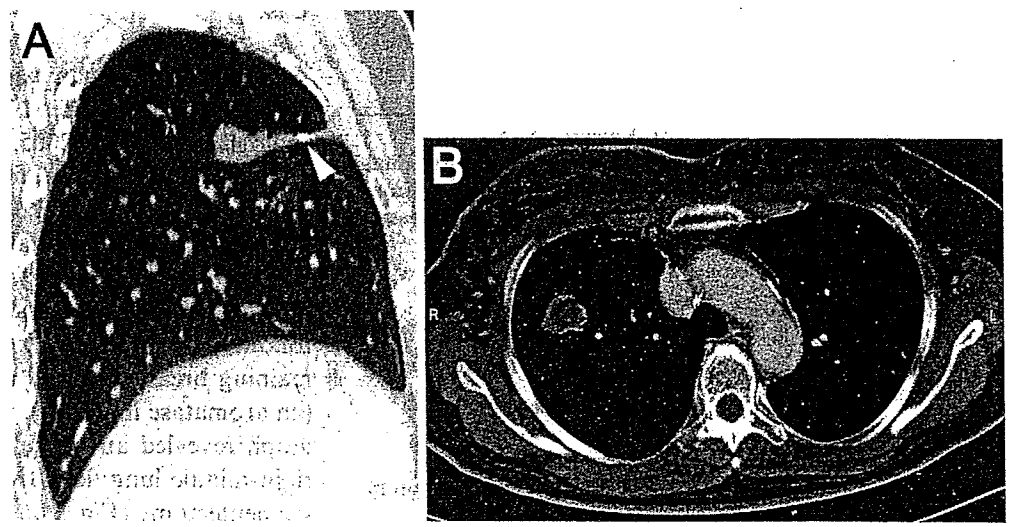

Fig. 2 **A** Sagittal multiplanar reconstruction computed tomography scan (CT) showing an irregular mass between the residual S1 segment and the middle lobe. The mass was adjacent to the staple line (*arrowhead*) at the S3 segmentectomy. **B** A mass with low density was weakly and heterogeneously enhanced by contrast medium

The mass could not be definitively diagnosed by bronchoscopic examination, and so we could not rule out the possibility of local recurrence of lung cancer.

In July 2005, we performed a second right posterolateral thoracotomy along the previous incision through the fifth rib bed. Extensive adhesions were divided with care to find the mass, which was on the resected surface of the residual S1 segment adjacent to the staple line of the S3 segmentectomy. On fine-needle aspiration, viscous whitish-yellow pus was obtained in which no malignant cells or bacteria were detected during the operation. The residual firm mass corresponding to the abscess wall was then excised. Pathological findings were consistent with the diagnosis of inflammatory granuloma around the abscess (Fig. 4). The granuloma contained both degraded suture (probably the nylon suture used to control air leaks at the time of the previous segmentectomy) and many multinuclear giant cells phagocytosing a foreign body with findings similar to that of a nylon suture under polarized microscopy. Bacteriological cultures and polymerase chain reaction for *Mycobacterium* species of the pus and tissue were all negative. Taken together, we thought that this suture abscess would not have been caused by transbronchial infection but by a foreign-body reaction. The postoperative course was uneventful.

Discussion

Cases of a surgically resected pulmonary suture abscess or granuloma are rare. According to our review of the literature, only four surgically resected cases[1–4] have been reported up to the present, as summarized in Table 1. Among them, two cases manifested as hemoptysis after a surgical procedure for pneumothorax, and they were preoperatively diagnosed as benign granuloma: tuberculoma in case 1 and suture granuloma in case 3. In three patients with a history of lung cancer, the spiculated margin of the nodule on the chest CT led to the preoperative diagnosis of recurrence of the lung cancer.

To the best of our knowledge, ours is the first operative case of pulmonary suture granuloma evaluated by FDG-PET or combined PET/CT. On FDG-PET imaging, the most common semiquantitative measurement is the SUV calculation.[5] Because an SUV greater than 2.5 is usually considered suggestive of malignancy, our case with an SUVmax of 4.9 was suspected of having lung cancer recurrence. FDG uptake, however, is not specific for cancer, and various inflammatory lesions have been discovered to exhibit a high SUV.[5–7] FDG uptake in inflammation is attributed mainly to the presence of metabolically active macrophages and young granulation tissue. Therefore, inflammatory lesions such as ab-

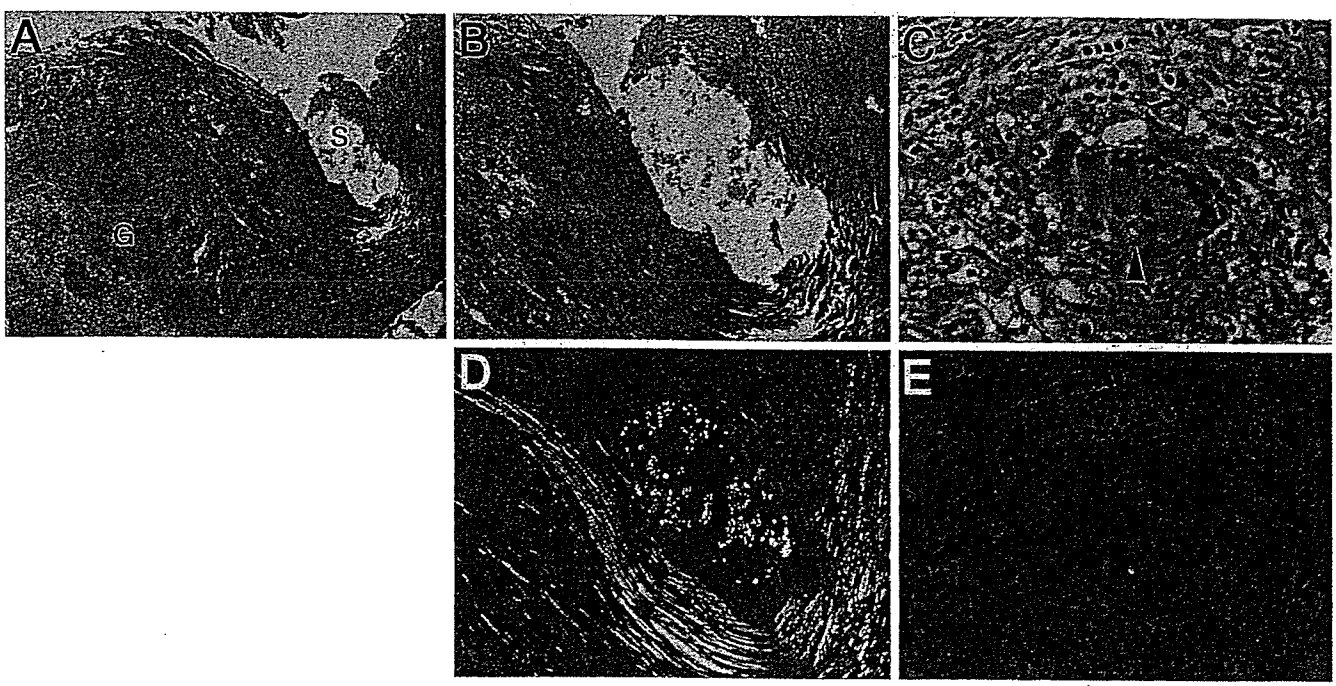

Fig. 4 Histological findings of the abscess wall. **A** Abscess cavity (top) and degraded suture (*S*) were surrounded by a fibrous capsule. An inflammatory granuloma (*G*) was confirmed. **B** Degraded suture under high-power magnification. **C** In the granuloma, many multinuclear giant cells phagocytosing a foreign body (*arrowhead*) were present. The degraded suture (**D**) and the foreign body phagocytosed by a giant cell (**E**) were reflected similarly under polarized microscopy. (A–E H&E. A ×40; B, D ×100; C, E ×200)

Table 1 Surgically resected cases of pulmonary suture granuloma

Case	Author	Year	Age	Sex	Underlying disease	Previous surgery	Interval	Symptoms	Preoperative diagnosis	Operation	Suture	Abscess formation/infection	Size (cm)
1	Nonaka[1]	1991	53	M	Pneumothorax	LU-PR	5 Years	Hemoptysis	Tuberculoma	LU-LY	Braided polyester	+/*Pseudomonas aeruginosa*	2.0
2	Fink[2]	1993	65	M	LC (Sq) ⇒ 2nd LC (Sq)	RU-LY ⇒ Rt S^6-SY	3 Months	–	Recurrence	Resection	Silk	–/–	2.0
3	Baba[3]	1996	29	M	Pneumothorax	Bullectomy	10 Years	Hemoptysis	Suture granuloma	RU-LY	Braided silk	–/–	2.3
4	Katsura[4]	2005	76	F	LC (Sq)	Lt S^{1+2} + S^6-PR	2 Years	Cough	Recurrence	Lt S^{1+2} + S^6-PR	Nylon	+/*Aspergillus fumigatus*	3.0
5	Our case	2006	57	F	LC (Ad)	Rt S^3-SY	7 Years	–	Recurrence	Rt S^1-PR	Nylon	+/–	3.5

Ad, adenocarcinoma; LC, lung cancer; Lt, left; LU, left upper lobe; LY, lobectomy; PR, partial resection; Rt, right; RU, right upper lobe; Sq, squamous cell carcinoma; SY, segmentectomy

scess and granuloma may also show false-positive FDG accumulation. Dual-time-point FDG-PET has been reported to be useful for differentiating malignant lesions from benign nongranulomatous lesions but not from granulomatous diseases.[7] Further investigation on FDG-PET is necessary regarding the differential diagnosis between lung cancer and pulmonary granulomatous diseases.

Suture abscess or granuloma is usually caused by a foreign-body reaction to nonabsorbable yarn-like suture materials. In these five cases, the suture materials were polyester in one, silk in two, and nylon in two cases (Table 1). Among them, two cases of suture granuloma around silk suture were not accompanied by abscess formation or infection. Cases 1 and 4 were associated with transbronchial infection by *Pseudomonas aeruginosa* and *Aspergillus fumigatus*, respectively. Our case, however, would not have been caused by transbronchial infection but by a foreign-body reaction, which was supported by the polarized microscopic findings. Cases of pulmonary foreign body granuloma[8] and pseudotumor[9] possibly due to surgical titanium staples have been reported. Because the suture abscess was located adjacent to titanium staples in our case, a foreign-body reaction to titanium staples may also have contributed to subsequent abscess formation around the nylon suture.

Approximately 50 cases of bronchiolitis obliterans organizing pneumonia (BOOP) induced by radiation therapy after breast-conserving surgery have been reported, 70% of which also underwent endocrine therapy.[10] Our case was not complicated with BOOP, but irradiation to the residual breast plus endocrine therapy might have contributed to severe inflammation through a foreign-body reaction leading to suture abscess formation.

Conclusions

We present the fifth case reported in the literature of surgically resected pulmonary suture abscess arising around nylon suture 7 years after segmentectomy for early lung cancer. Using chest CT and, for the first time in surgically resected cases, FDG-PET, we could not preoperatively distinguish this condition from local recurrence of lung cancer. By pathological and microbiological examinations including polarized microscopy, it was concluded that this suture abscess would not have been caused by transbronchial infection but by a foreign-body reaction. Moreover, titanium staples at the segmentectomy and breast-conserving surgery followed by irradiation plus endocrine therapy may also have contributed to this condition through a foreign-body