



# Differentiation between staple line granuloma and recurrence after sublobar resection for primary lung cancer

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**Background:** The use of sublobar resection for early-stage lung cancer or frail cases that cannot tolerate radical surgery for primary lung cancer has been increasing. This study aimed to identify the frequency, shape, and course of staple line thickening and granuloma formation after sublobar resection for primary lung cancer, and to identify factors that help distinguish them from recurrent cancer cases.

**Methods:** The medical records of 64 patients who underwent sublobar resection for primary lung cancer from January 2012 to December 2017 at our institution were retrospectively reviewed. Computed tomography (CT) images taken every 6 months for at least 3 years after surgery were reviewed, and the postoperative course was examined.

**Results:** Staple line thickening at the time of the first CT scan after surgery was observed in 43 cases (67.2%). Of them, linear thickening was seen in 31 cases (72.1%), and nodular thickening was seen in 12 cases (27.9%). Of these 43 cases, 25 cases were decreased, 8 cases were unchanged and 10 cases showed a tendency to progress during the follow-up period. Of the 64 cases, 7 (10.9%) had staple line recurrence. Staple line recurrence was significantly correlated with vascular invasion ( $P=0.015$ ), surgical margin ( $P=0.013$ ), nodular thickening ( $P<0.001$ ) and a tendency to show progressive thickening ( $P<0.001$ ).

**Conclusions:** Staple line thickening was observed in many cases of sublobar resection, and most of them were linear thickening. Staple line recurrence should be suspected if nodular thickening appears and shows a tendency to progress.

**Keywords:** Staple line thickening; sublobar resection; staple line recurrence; staple line granuloma

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## Introduction

The standard surgical procedure for early-stage non-small cell lung cancer (NSCLC) is lobectomy with systemic or selective lymph node dissection (1). However, in recent years, the use of sublobar resection such as wedge resection and segmentectomy for early-stage lung cancer with ground glass opacities and small nodules has been increasing (2,3). Sublobar resection is also an effective surgical procedure for frail cases that cannot tolerate radical surgery for primary

lung cancer. However, sublobar resection for primary lung cancer is always associated with the risk of local recurrence.

Automatic suturing devices are now widely used in thoracoscopic surgery. They are mainly made of titanium that shows good corrosion resistance in the human body and excellent compatibility with both hard and soft tissues. However, cases with staple line thickenings after lung parenchyma dissection with a stapler are often seen during postoperative follow-up. In those cases, it is very difficult to distinguish between benign granuloma and recurrence of

lung cancer only with imaging such as computed tomography (CT) or positron emission tomography (PET)-CT.

This study aimed to identify the frequency, shape, and course of staple line thickening and granuloma formation after sublobar resection for primary NSCLC, and to identify factors that help distinguish them from recurrent cancer cases. We present the following article in accordance with the STROBE reporting checklist (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-21-1626/rc>).

## Methods

The study was approved by the institutional ethics board of Japanese Red Cross Maebashi Hospital (No. 2021-5) and individual patient consent for this retrospective analysis was waived. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

### *Patient selection*

From January 2012 to December 2017, a total of 510 patients underwent lung resection for primary lung cancer at our hospital. Data were obtained from the medical records of 122 patients who underwent segmentectomy or wedge resection of lesions during the same period. Of them, cases in which CT scans were taken regularly for at least 3 years after surgery and the images could be verified were included in this study. Finally, 64 patients were enrolled. All patient data were analyzed retrospectively.

Preoperative evaluation consisted of physical examination, blood tests, chest radiography, CT of the chest and abdomen, CT or magnetic resonance imaging (MRI) of the brain, and PET-CT. In our department, the standard curative surgery for primary lung cancer is lobectomy with systemic lymph node dissection. In patients who underwent intentional sublobar resection for primary lung cancer, clinical stage 0-IA1 (Tis-1aN0M0) was confirmed by careful preoperative staging with CT and/or PET-CT. For patients who could not tolerate radical surgery due to complications and poor pulmonary function, sublobar resection was also performed as reduction surgery. Even in that case, only cases with cN0 were included. If necessary, we sampled hilar lymph nodes for pathological staging.

### *Surgical procedure*

All patients were operated under general anesthesia in the lateral decubitus position with differential lung ventilation.

All surgeries were performed under thoracoscopy with three or four ports. Specifically, XXS Alexis wound retractors (Applied Medical, Rancho Santa Margarita, CA, USA) were fitted to a 2.0-cm skin incision in the fourth intercostal space at the anterior axillary line and a 1.5-cm skin incision in the sixth intercostal at the anterior axillary line. A 10-mm flexible camera was inserted via the 1.5-cm skin incision in the sixth intercostal space in the mid axillary line. When four ports were used, an additional 15-mm skin incision was made in the seventh intercostal space below the scapula for use as the assistant's port.

In segmentectomy, the resection line was determined by preoperative three-dimensional computed tomography (3D-CT) angiography and bronchography. Segmentectomy was defined as resection of the targeted segment having all the dominant pulmonary vessels and bronchi divided. The inflation-deflation technique was used for segment identification. In almost all cases, intersegmental division was accomplished using only a stapler, but for some patients, cautery was used where necessary. Even in such cases, a stapler was used near the hilum.

### *Postoperative follow-up*

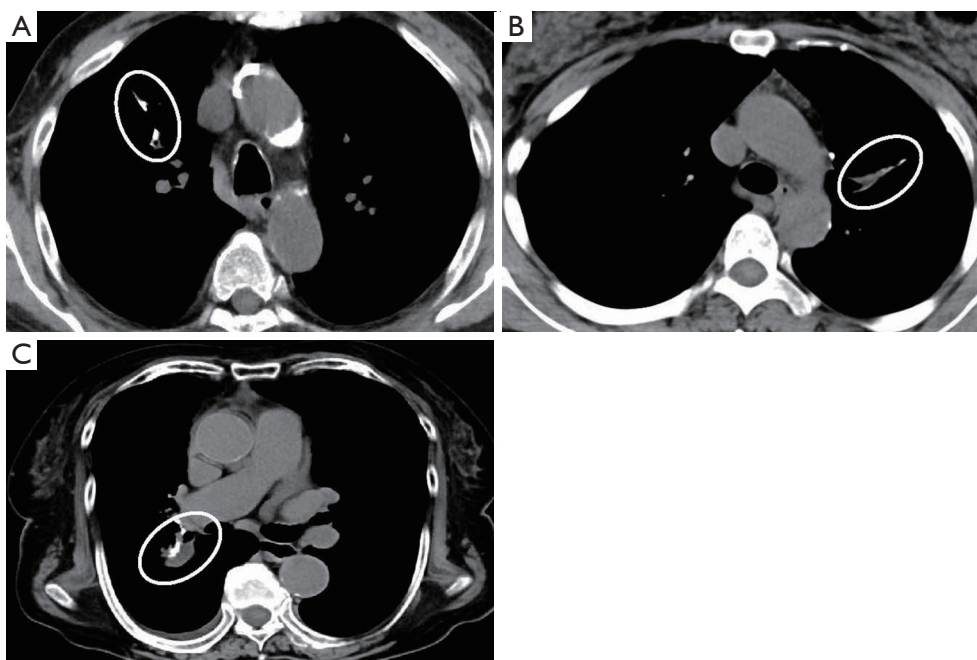
Postoperative follow-up was conducted at 6-month intervals for at least 5 years after surgery. Follow-up evaluations included physical examination, chest radiography, blood tests including tumor marker levels, CT of the chest and abdomen, and PET-CT if necessary. Chest CT was taken every 6 months in almost all cases with or without contrast agents. Postoperative recurrence was clinically diagnosed by these tests with or without a pathological diagnosis.

### *Morphology of staple line thickening*

The morphology of staple line thickening is defined as: no thickening, linear thickening or nodular thickening (*Figure 1*). Linear thickening is defined as uniformly thickening along the staple line, whereas nodular thickening is defined as a nodule that protrudes or surrounds the staple line. Thickening size was measured in the longest diameter perpendicular to the staple line in mediastinal view on CT; thickening was defined as a diameter greater than 3 mm.

### *Statistical analysis*

Categorical variables were compared using Fisher's exact test. Continuous variables were compared using the *t*-test.



**Figure 1** Definition of the morphology of staple line thickening. (A) No thickening, (B) linear thickening, and (C) nodular thickening.

Results were considered significant for values of  $P < 0.05$ . All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics.

## Results

### *Patients' characteristics and staple line thickening*

The characteristics and clinicopathological features of all patients [38 male, 59.4%; 26 female, 40.6%; mean age 75 years (range, 38–91 years)] are shown in *Table 1*. The surgical procedure was segmentectomy in 31 patients (48.4%) and wedge resection in 33 patients (51.6%), including 26 intentional sublobar resections. The histopathological type was adenocarcinoma in 50 patients (78.1%), squamous cell carcinoma in 11 patients (17.2%) and other types in 3 patients (4.7%), including large cell neuroendocrine carcinoma in 2 patients, and pleomorphic carcinoma in 1 patient. Mean tumor size was 1.9 cm (range, 0.2–4.5 cm) and mean invasive component size was 1.1 cm (range, 0.2–4.1 cm). Almost all cases underwent PET-CT before surgery and the mean maximum standardized uptake value

(SUV-max) was 2.7 (range, 0–15.5). Comparison of patient characteristics and perioperative outcomes between the segmentectomy and wedge resection groups are shown in *Table S1*. Nodular thickening was significantly more in wedge resection group (*Table S1*).

Staple line thickening at the time of the first CT scan after surgery (typically performed 6 months after surgery) was observed in 43 cases (67.2%). Of them, linear thickening was seen in 31 cases (72.1%) and nodular thickening was seen in 12 cases (27.9%). The mean size of thickening was 10.3 mm (range, 4–26 mm). Of these 43 cases, 25 were decreased and 8 were unchanged in shape and size during the course. On the other hand, 10 cases showed a tendency to progress during the follow-up period, of which three cases were linear but increased partially to nodules (*Figure 2*).

PET-CT was taken in 17 cases during postoperative follow-up. Of them, 10 cases, 9 with linear thickening and 1 with nodular thickening, showed no accumulation on the staple line. The remaining 7 cases were 6 cases with staple line recurrence and 1 case with staple line granuloma.

### *Comparison between patients with and without staple line recurrence*

Comparison of patient characteristics and clinicopathological differences between patients with and without staple line

**Table 1** Characteristics of all patients

Characteristic	Frequency
Age, years	75±9.6
Sex	
Female	26 (40.6)
Male	38 (59.4)
Tumor location	
Right upper lobe	21 (32.8)
Right lower lobe	10 (15.6)
Left upper lobe	24 (37.5)
Left lower lobe	9 (14.1)
Surgical procedure	
Segmentectomy	31 (48.4)
Wedge resection	33 (51.6)
Reason for sublobar resection	
Intentional	26 (40.6)
Unintentional	38 (59.4)
Histology	
Adenocarcinoma	50 (78.1)
Squamous cell carcinoma	11 (17.2)
Others	3 (4.7)
Tumor size, cm	1.9±1.0
Invasive component size, cm	1.1±1.1
PET-CT, SUV-max	2.7 (0–15.5)
Surgical margin, mm	18±14
Staple line thickening	
Yes	43 (67.2)
Linear	31 (72.1)
Nodular	12 (27.9)
No	21 (32.8)

Data are shown as mean ± standard deviation or number (%). PET-CT, positron emission tomography-computed tomography; SUV-max, the mean maximum standardized uptake value.

recurrence are shown in *Table 2*. Staple line recurrence was observed in 7 patients (10.9%) during the observation period. All were not intentional limited resection. There were no significant differences between the groups in patient characteristics including age, sex, SUV-max on PET-CT, tumor size, surgical procedure and histology. There was no

significant difference in lymphatic invasion, but vascular invasion was significantly more common in the staple line recurrence group ( $P=0.027$ ). There was significantly less surgical margin in the staple line recurrence group ( $P=0.018$ ). Staple line thickening was observed in all cases of the staple line recurrence group, but it was not significant ( $P=0.085$ ).

#### *Comparison between with and without staple line recurrence among the cases with staple line thickening*

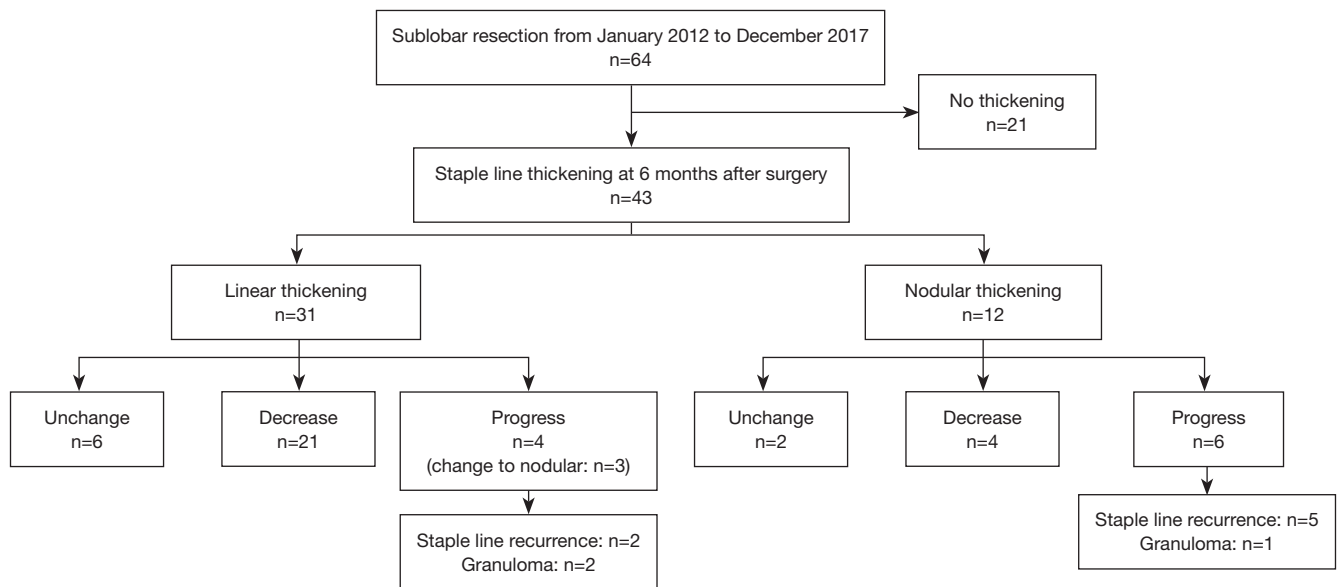
Comparisons of patients' characteristics and clinicopathological differences between patients with and without staple line recurrence among the cases with staple line thickening are shown in *Table 3*. There were no significant differences between the groups in patients' characteristics including age, sex, SUV-max of PET-CT, tumor size, surgical procedure, and histology. There were significant differences between the groups in vascular invasion ( $P=0.015$ ) and surgical margin ( $P=0.013$ ). The thickening type in the staple line recurrence group was all nodular ( $P<0.001$ ). All cases in the staple line recurrence group showed a tendency to progress ( $P<0.001$ ). Non-staple line recurrence group also had 9 cases showing nodular thickening. Any of the 9 cases finally revealed decreasing of the thickening nodular shadow in the follow-up CT, which allowed us to diagnose the nodular shadow as granuloma.

#### *Details of the staple line recurrence cases*

*Table 4* shows the details of the staple line recurrence cases. The mean disease-free interval was 24.4 months (range, 11.9–32.3 months). After 3 to 6 months of follow-up after showing a tendency to progress, all cases were diagnosed as suspected recurrence. Three of them were diagnosed as recurrence by surgery (wedge resection in 2 cases and completion lobectomy in 1 case). In a case which completion lobectomy was performed, intentional sublobar resection had been performed because the tumor had been diagnosed with non-invasive preoperatively. The remaining 4 cases were clinically diagnosed without a biopsy because it was difficult to diagnose the tumor pathologically due to the tumor location. *Figure 3* shows an example of a staple line recurrence case (case 2).

#### *Granuloma cases showing a tendency to progress*

Three of benign granuloma cases showed a tendency to progress, of which 2 cases were at 24 months after



**Figure 2** Flow diagram of all patients' results.

**Table 2** Characteristics and clinicopathological differences between patients with and without staple line recurrence

Variables	Staple line recurrence (+), n=7	Staple line recurrence (-), n=57	P
Age, years	79±10	74±10	0.187
Sex, male	5 (71.4)	33 (57.9)	0.691
Side, right	2 (28.6)	29 (50.9)	0.428
Lobe, upper	5 (71.4)	40 (71.2)	1
Surgical procedure			0.428
Segmentectomy	2 (28.6)	29 (50.9)	
Wedge resection	5 (71.4)	28 (49.1)	
Histology			0.531
Adenocarcinoma	7 (100.0)	43 (75.4)	
Squamous	0	11 (19.3)	
Others	0	3 (5.3)	
Tumor size, cm	2.0±1.3	1.9±1.4	0.897
Invasive size, cm	1.8±1.4	1.0±1.0	0.084
PET-CT, SUV-max	3.6±3.8	2.5±3.5	0.452
Surgical margin, mm	10±2.9	19±9.8	0.018
Staple line thickening			
Yes	7 (100.0)	36 (63.2)	0.085
Lymphatic invasion	3 (42.8)	11 (19.3)	0.171
Vascular invasion	4 (57.2)	9 (15.8)	0.027

Data are shown as mean ± standard deviation or number (%). PET-CT, positron emission tomography-computed tomography; SUV-max, the mean maximum standardized uptake value.

**Table 3** Characteristics and clinicopathological differences between patients with and without staple line recurrence among the cases with staple line thickening

Variables	Staple line thickening + recurrence, n=7	Staple line thickening, n=36	P
Sex, male	5 (71.4)	19 (52.8)	0.437
Age, years	79±10	74±10	0.238
Side, right	2 (28.6)	19 (52.8)	0.412
Lobe, upper	5 (71.4)	27 (75.0)	1
Surgical procedure			0.211
Segmentectomy	2 (28.6)	22 (61.1)	
Wedge resection	5 (71.4)	14 (38.9)	
Histology			0.45
Adenocarcinoma	7 (100.0)	25 (69.5)	
Squamous	0	8 (22.2)	
Others	0	3 (8.3)	
Tumor size, cm	1.8±0.9	2.0±1.3	0.705
Invasive size, cm	1.0±1.1	1.8±1.4	0.126
PET-CT, SUV-max	2.9±3.7	3.6±3.8	0.651
Surgical margin, mm	10±2.9	21±11.1	0.013
Thickening size, mm	10±4.5	12±7.3	0.387
Thickening type			<0.001
Linear	0	27 (75.0)	
Nodular	4 (57.2)	6 (16.7)	
Linear→nodular	3 (42.8)	3 (8.3)	
Increase in dimension			
Yes	7 (100.0)	3 (8.3)	<0.001
Lymphatic invasion	3 (42.8)	7 (19.4)	0.325
Vascular invasion	4 (57.2)	4 (11.1)	0.013

Data are shown as mean ± standard deviation or number (%). PET-CT, positron emission tomography-computed tomography; SUV-max, the mean maximum standardized uptake value.

surgery and 1 case was at 30 months after surgery. All cases were decreased on the subsequent CT. *Figure 4* shows an example of a staple line granuloma case. In this case, a linear thickening had been observed on CT from 6 months after surgery (*Figure 4A*). A nodular thickening was seen on CT 24 months after the surgery (*Figure 4B*), and abnormal accumulation was observed on PET-CT (*Figure 4C*), but it decreased on CT 2 months later (*Figure 4D*).

## Discussion

It is common to use a stapler to dissect the lung parenchyma during wedge resection and segmentectomy, and now that the number of sublobar resection cases is increasing, the chances of seeing postoperative stapler line thickening are increasing. In the present study, staple line thickening at the time of the first CT scan after surgery (typically performed 6 months after surgery) was observed in 67.2% of cases.

**Table 4** Details of cases with staple line recurrence

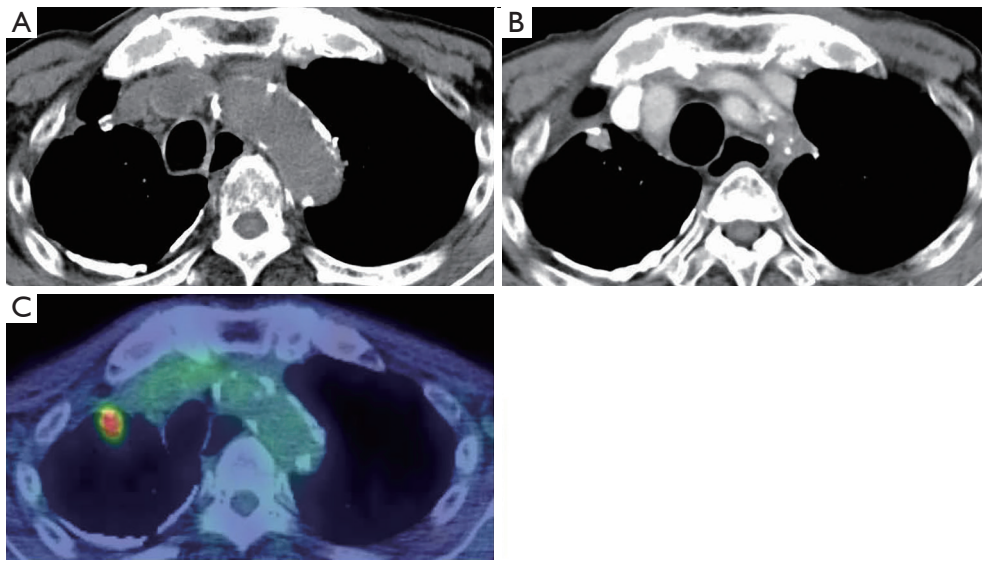
Case	Sex	Age	Tumor location	Surgical procedure	Histology	PET-CT SUV-max (primary)	Tumor size (cm)	Invasive size (cm)	DFI (months)	Thickening size (cm)	Thickening type/tendency to progress	PET-CT SUV-max	Therapy	Prognosis
1	M	72	L S1+2	W	AD	2.1	1.2	1.2	28	1.6	Nodular/yes	6.8	Surgery	Dead
2	M	91	R S1	W	AD	0	0.8	0.2	31.2	1.2	Nodular/yes	6.26	Surgery	Dead
3	M	73	L S10	W	AD	0	1.0	1.0	32.3	3.2	Nodular/yes	-	Chemotherapy	Dead
4	F	83	L S3	W	AD	5.5	1.8	0.6	23.1	1.6	Nodular/yes	7	SBRT	Alive
5	F	85	L S1+2+3	S	AD	5.7	2.8	2.8	29.7	1.8	Nodular/yes	10.5	Chemotherapy (osimertinib)	Alive
6	M	88	L S1+2	S	AD	10.41	4.2	4.2	14.8	2.9	Nodular/yes	12.3	SBRT	Alive
7	M	64	R S10	W	AD	1.5	2.5	2.5	11.9	3.2	Nodular/yes	1.7	Surgery	Alive

PET-CT, positron emission tomography-computed tomography; SUV-max, the mean maximum standardized uptake value; DFI, disease free interval; M, male; F, female; L, left; R, right; W, wedge resection; S, segmentectomy; AD, adenocarcinoma; SBRT, stereotactic body radiotherapy.

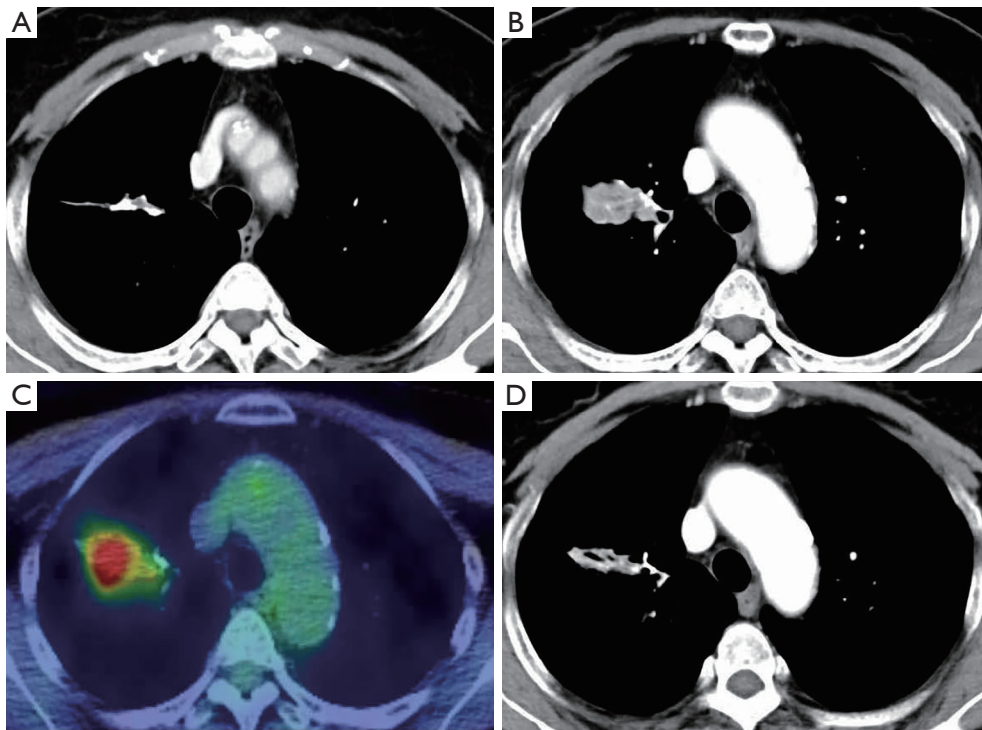
Sun *et al.* (4) also reported that 78.2% of staple lines of patients who underwent limited resection for NSCLC showed thickening of 2 mm or greater on initial postoperative scans. This indicates that staple line thickening is often observed on postoperative CT and is usually followed up as a normal biological reaction. However, when it shows a tendency to progress over time, local recurrence is suspected.

Granulation after sublobar resection has been reported (5-9), but the reason why granulation is more common in wedge resection or segmentectomy rather than after lobectomy is considered to be the atelectasis causing an imbalance of blood flow and ventilation or poor wound healing associated with dissection of relatively thick lung parenchyma. The titanium used in staples has excellent safety and biocompatibility, therefore, the reports of foreign body reactions to titanium are extremely rare. There have also been some reports that infection involving the staple line was a factor in the formation of granuloma (10,11).

When the staple line has been thickened and shows a tendency to progress, it is very difficult to distinguish between a benign granuloma and recurrence of lung cancer (11). In the present study, staple line recurrence was significantly correlated with vascular invasion, surgical margin, nodular thickening, and a tendency for thickening to progress. Although it is essential to secure a sufficient margin as far as possible in sublobar resection, it can be difficult when passive limited resection is performed. In the present study, although the positive predictive value for cancer recurrence at the site of staple line thickening was only 16.3%, it included recurrent cases that certainly required examination. Based on the results of this study, patients with staple line thickening and predisposing factors for recurrence (such as vascular invasion and inadequate surgical margin) should be actively followed up for further scrutiny. When cancer recurrence is suspected, PET-CT is one of the useful and non-invasive imaging modalities. The sensitivity of PET-CT for lung cancer is reported to be 83–96% and the specificity is reported to be 78–91% (12,13). However, inflammatory diseases and infectious diseases may also show relatively high abnormal accumulation (14), so it is reported that PET-CT cannot differentiate a granuloma from staple line recurrence (6,9,11). In the present study, the SUV-max values on PET-CT in cancer recurrent cases were 1.7 to 12.3; in particular, 5 of the cases had a high accumulation of 5 or more. The cut-off value of SUV-max when distinguishing between benign and malignant is usually 2.5 (15), which can be an important clue for further examination and biopsy. However, one of the recurrent



**Figure 3** Staple line recurrence. (A) Twenty-four months after surgery. (B) Thirty months after surgery. CT shows a nodule along the staple line (12 mm in diameter). (C) PET-CT shows abnormal accumulation. SUV-max is 6.26. CT, computed tomography; PET, positron emission tomography; SUV-max, the maximum standardized uptake value.



**Figure 4** Staple line granuloma. (A) Six months after surgery. (B) Twenty-four months after surgery. CT shows a nodule along the staple line (22 mm in diameter). (C) PET-CT shows abnormal accumulation. SUV-max is 6.80. (D) Two months later. The size of thickening has decreased. CT, computed tomography; PET, positron emission tomography; SUV-max, the maximum standardized uptake value.



cases had a low SUV-max value of 1.7, which indicates that recurrence cannot be distinguished only by SUV-max value.

Usuda *et al.* (16) reported the usefulness of diffusion-weighted magnetic resonance imaging (DWI) for differentiation of suture recurrence and suture granuloma after resection for lung cancer. Mizukami *et al.* (6) and Mizuno *et al.* (17) reported differences in morphology. Staple line granuloma shows a smooth marginated mass in contact with the staple line. On the other hand, staple recurrence grows concentrically or radially from the staple line and the edges are irregular. In the present cases, for example, staple recurrence was formed on the edge of the staple line (Figure 2). It is still difficult to distinguish by morphology alone, but in most of the present cases, the granuloma had a smooth margin (Figure 1), which may help in the differentiation.

There are some reports of cases diagnosed by CT-guided fine needle aspiration biopsy (FNAB) (6,8), but it is often difficult in cases deep in the lung or near the hilum, and there also may be differences between institutions. In the present cases, none underwent biopsy. However, completion surgery is often technically difficult and with various risks, so caution should be exercised in the indications for surgery. Moreover, there is a need to avoid unnecessarily lengthening the follow-up period and causing systemic disease in recurrent cancer cases. Biopsy is a useful diagnostic method in some cases.

This study has some limitations. First, this was a retrospective and single-institution study. Second, the total number of cases was relatively small; in particular, there were only 7 cases of recurrence. Thus, multivariate analysis could not be performed to identify factors associated with recurrence. A prospective, multicenter study is required.

In conclusion, staple line thickening is observed in many cases of sublobar resection, most of which are linear. Recurrence should be suspected if nodular thickening appears and shows a tendency to progress. More cases need to be examined to find out how to distinguish benign granuloma from cancer recurrence.

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## Footnote

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*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 institutional ethics board of Japanese Red Cross Maebashi Hospital (No. 2021-5) and individual patient consent for this retrospective analysis was waived.

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**Table S1** Characteristics and clinicopathological differences between the segmentectomy group and the wedge resection group

Variables	Segmentectomy, n=31	Wedge resection, n=33	P
Sex, male	16 (51.6)	22 (66.7)	0.309
Age, years	73±11	76±8	0.417
Side, right	12	19 (52.8)	0.144
Lobe, upper	24 (77.4)	21 (63.6)	0.28
Histology			0.557
Adenocarcinoma	26 (83.9)	24 (72.7)	
Squamous	4 (12.9)	2 (6.1)	
Others	1 (3.2)	7 (21.2)	
Tumor size, cm	1.8±1.0	1.9±1.8	0.82
Invasive size, cm	1.1±1.3	1.1±0.8	0.866
PET, SUV-max	2.7±3.6	2.6±3.5	0.921
Pathological stage			0.012
0	10 (32.3)	3 (9.1)	
IA	17 (54.8)	29 (87.9)	
IB	1 (3.2)	1 (3.0)	
≥2	3 (9.7)	0	
Surgical margin, mm	18±10.6	7.7±4.9	<0.001
Staple line thickening			0.114
Yes	24 (77.4)	19 (57.6)	
Thickening type			0.012
Linear	19 (61.3)	8 (24.2)	
Nodular	5 (16.1)	11 (33.3)	
Staple line recurrence			
Yes	2 (6.5)	5 (15.2)	0.428
Lymphatic invasion	9 (29.0)	5 (15.2)	0.232
Vascular invasion	4 (12.9)	6 (18.2)	0.734

Data are shown as mean ± standard deviation or number (%). PET-CT, positron emission tomography-computed tomography; SUV-max, the mean maximum standardized uptake value.