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Tomosynthesis in Respiratory Medicine

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1. Introduction

In the field of respiratory medicine, chest radiography and chest CT have to date been the main modalities of imaging used in routine medical care. The word tomosynthesis is formed from tomography and synthesis, tomosynthesis is a kind of digital tomography which is an imaging modality capable of reconstructing a coronal plane section of arbitrary height from a single tomographic scan[1]. The principle of tomosynthesis was announced by Ziedes des Plantes in 1938, and the first application of tomosynthesis in medical science was reported by Miller et al in 1971[2) 3)]. In Japan, system developed at Shinshu University in 1989[4)] was subsequently refined and, in the middle of the 2000s, introduced by Shimadzu as a tomography system equipped with a direct-conversion flat panel detector (FPD) where the issue of distortion of the light receiving surface had been resolved[5)]. While it is mainly CT and MRI that are used in all fields including respiratory medicine, when used with a high-resolution FPD, tomosynthesis is also capable of high-definition tomographic images and as such has come to be used in orthopedics in particular. In the field of respiratory medicine that we are engaged in, recent research has shown these tomographic images are superior at showing nodules compared to chest radiography[6)]. The exposure dose of tomosynthesis is equivalent to performing several chest radiography scans or around one-tenth exposure dose of a chest CT scan, and system installation space is smaller than a chest CT system. In light of this, tomosynthesis can be described as positioned within the field of respiratory medicine in-between chest radiography and chest CT. **Table 1** shows the respective characteristics of chest radiography, chest tomosynthesis, and chest CT.

Shimadzu SONIALVISION safire series was introduced as one of the hospital's FPD-equipped R/F systems, and between June 2012 and October 2013, the SONIALVISION safire series was used for tomosynthesis in 540 cases of respiratory disorders (counting only cases of respiratory medicine). This article reviews tomosynthesis in the field of respiratory medicine based on experience and results obtained at the National Cancer Center Hospital.

	Chest Radiography	Chest Tomosynthesis (SONIALVISION safire series)	Chest CT
Examination Time	Several seconds	Several tens of seconds	Several minutes
Performance When Showing Lesions (sites that pose difficulties for visualization)	Difficulty showing nodules and ground glass opacity (lesions that overlap with mediastinum or diaphragm)	Capable of showing nodules and ground glass opacities (compares unfavorably to CT) (at edge of its field of view range)	Capable of showing nodules and ground glass opacities
System Cost	Low	Medium	High
System Installation Space Requirements	Small	Medium	Large
Image Reconstruction and Display	Only displayed in direction of radiography	Capable of reconstructing any coronal plane section	Capable of reconstructing along any plane
Dedicated System for Image Reconstruction (workstation)	None	Dedicated workstation	Dedicated (multi-functional) workstation
Exposure Dose	Low	Low to medium	Medium to high (low dose CT = medium)
Imaging Range	Medium	Medium (somewhat narrow)	Wide
Metal Artifacts	None	Few	Many
Use with Bronchoscopic Procedures	Only for display of mapping images	Capable of X-ray fluoroscopy (supports procedures in real time)	CT-guided bronchoscopy

Table 1 Characteristics of Each Modality

1. Chest Tomosynthesis of Ground Glass Opacities

The SOS study published in 2013 reported on the utility of using tomosynthesis to screen for lung cancer, stating the frequency of discovery of non-calcified nodules with tomosynthesis was equivalent to CT[6]. With the recent spread of CT, ground glass opacities, are now found frequently[7]. Chest radiography is known to be difficult to detect ground glass opacities. While there is a report that shows tomosynthesis is excellent at showing nodules[1], since no examination existed of using tomosynthesis to show ground glass opacities, our hospital performed a comparison of tomosynthesis against chest radiography. Subjects were 44 cases with a ground glass opacity identified using chest CT, with a definite pathological diagnosis provided by transbronchial lung biopsy or surgical biopsy. A respiratory physician and a radiological technologist interpreted images to decide (1) whether the lesion could be shown by chest radiography, (2) whether the legion could be shown by tomosynthesis, (3) finally, whether lesions shown in (1) and (2) were shown correctly on comparison with the lesion site as confirmed by chest CT. The results are shown in **Table 2**. We found that tomosynthesis was significantly more capable of showing ground glass opacities compared to chest radiography.

An example case is shown in **Fig. 1**. Chest radiography has trouble depicting the lesion, but tomosynthesis shows the lesion in the right lung apex (arrow). The pathological diagnosis was pulmonary adenocarcinoma. Tomosynthesis is not only capable of showing nodules, it may also be considered superior to chest radiography for the depiction of ground glass opacities.

2. Using Tomosynthesis for Mapping Images During Bronchoscopy

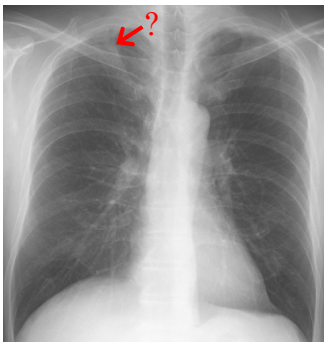
Bronchoscopy is an important examination approach for obtaining tissue from pulmonary lesions, then used as the basis of pathological diagnosis and decisions regarding treatment. In Japan, X-ray fluoroscopy-guided transbronchial lung biopsies are performed as bronchoscopy for peripheral pulmonary lesions. While the reported diagnostic yield of nodules under 20 mm in size is 34 %[8], in other countries, tissue is obtained from these lesions using CT-guided percutaneous needle lung biopsy or surgical biopsy.

So why is diagnosis of these small lesions difficult

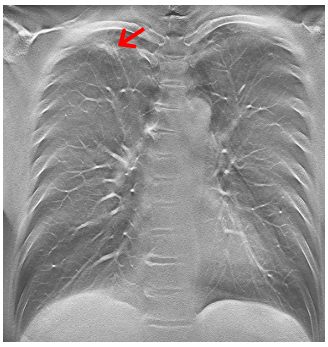
	Image Interpreter				Mean (%)	P value*	Kappa (κ) Value (95 % CI)
	A	B	C	D			
Chest Tomosynthesis	39/44 (88.6)	36/44 (81.8)	27/44 (61.4)	34/44 (77.3)	77.3	< 0.0001	0.56 (0.28-0.61)
Chest Radiography	20/44 (45.5)	26/44 (59.1)	16/44 (36.4)	19/44 (43.2)	46.0		0.60 (0.34-0.72)

*: Chest tomosynthesis vs. chest radiography; CI: confidence interval. Results are shown as number of cases where lesion was shown/total number of cases (%).

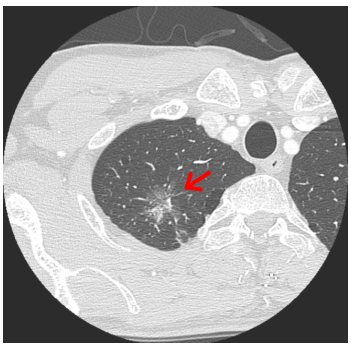
Table 2 Comparison of Ability to Show Ground Glass Opacity Using Chest Radiography and Chest Tomosynthesis by 4 Image Interpreters



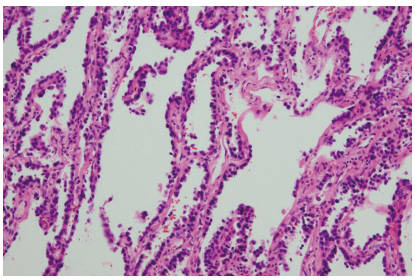
(a) Chest Radiography



(b) Chest Tomosynthesis



(c) Chest CT



(d) Pathology (adenocarcinoma, HE stain)

Fig. 1 **a, b)** Chest radiography has trouble showing the lesion, but chest tomosynthesis shows the lesion in the right lung apex (arrow).
c) Part-solid ground-glass opacity (GGO) found in right S^1 by CT
d) Pulmonary adenocarcinoma is shown at pathological specimen

when using bronchoscopy? One reason is that bronchoscopy is very rarely able to directly observe and biopsy peripheral pulmonary lesions. Another major reason is that X-ray fluoroscopy has trouble confirming the position of small lesions, and biopsy specimens are not obtained from the appropriate position.

Many new methods have been devised for confirming the position of lesions. The utility of radial endobronchial ultrasonography (R-EBUS) that uses a small-diameter radial ultrasound probe and ultrasonic waves to confirm lesion position in addition to X-ray fluoroscopy, and of EBUS used with a guide sheath (EBUS-GS) have been evaluated **(Fig. 2)**, and brought into use at over 300 facilities in Japan[9) 10)]. Virtual bronchoscopic navigation has also been commercialized that automatically creates a route to a lesion based on chest CT data, which is used to diagnose peripheral lesions by bronchoscopy **(Fig. 3)**. At the National Cancer Center Hospital, we have been using the ziostation2 3D medical image processing workstation to generate virtual bronchoscopy, and are examining whether they are useful for selecting the bronchial tubes involved in peripheral lesions for subsequent bronchoscopic examination **(Fig. 4)**. The rate of diagnostic yield of small peripheral pulmonary lesions is reported to increase dramatically when using EBUS-GS, from 40 % to 90 %[10)], showing the importance of a correct lesion biopsy. However, how effectively R-EBUS shows ground glass opacities has yet to be determined, and the need remains for new tools that confirm the position of ground glass opacities.

We have been using tomosynthesis as just such a tool. For ground glass opacities that cannot be shown with X-ray fluoroscopy, we have used chest tomosynthesis to capture images and use these images to anticipate the lesion position prior to bronchoscopy. A view of an actual examination setup is shown in **Fig. 5**. The position of the lesion is anticipated based on chest CT, tomosynthesis (arrow), and X-ray fluoroscopy and used during bronchoscopic examination[11)]. An example case is shown. Chest radiography and X-ray fluoroscopy have trouble showing the lesion while tomosynthesis is able to show the lesion, and the transbronchial lung biopsy was performed based on that positional information. The case was diagnosed as pulmonary adenocarcinoma **(Fig. 6)**.

To date, we have performed transbronchial lung biopsies of ground glass opacities using tomosynthesis images as reference in 40 cases, with a diagnostic yield of around 65 %.

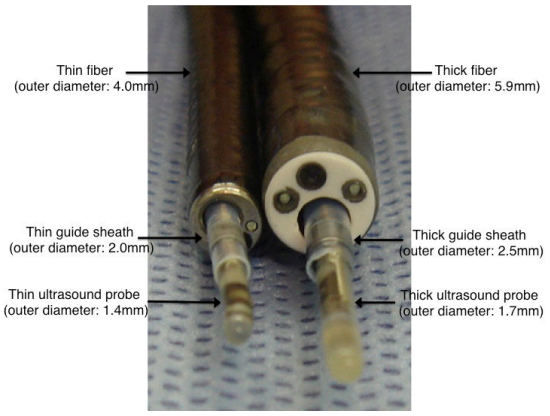
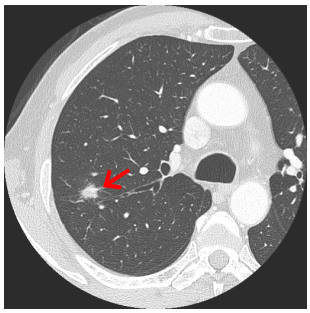
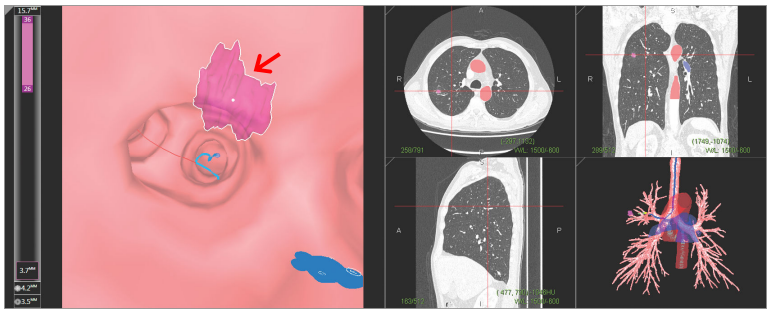


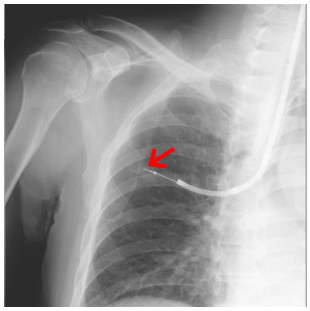
Fig. 2 Using endobronchial ultrasonography with a guide sheath (EBUS-GS), the guide sheath and ultrasound probe are inserted from the forceps port of the bronchoscope.



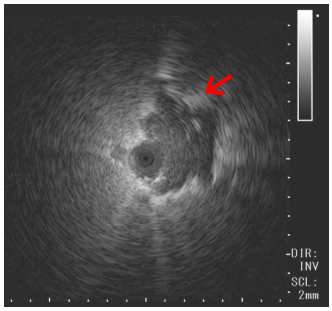
(a) Chest CT



(b) Virtual Bronchoscopy



(c) EBUS-GS



(d) EBUS

Fig. 3 **a)** A small nodule found in right S^2 by chest CT (arrow)
b) Virtual bronchoscopy (LungPoint, Broncus Technologies, Inc., USA) used to automatically show route to lesion from the CT data. Lesion is indicated by arrow.
c) Using EBUS-GS under X-ray fluoroscopy to perform transbronchial lung biopsy. X-ray fluoroscopy has some difficulties in showing the lesion.
d) The lesion is heterogeneous as depicted by EBUS, with the ultrasound probe shown inside the lesion (arrow).

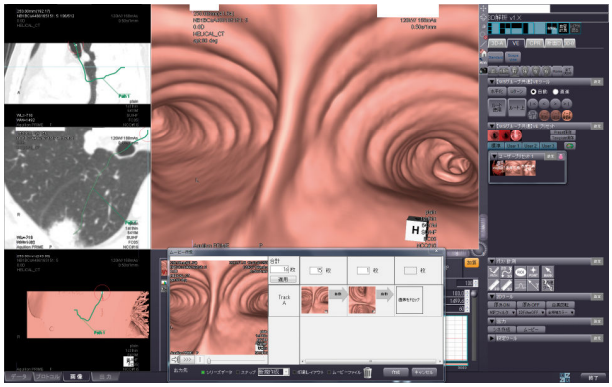


Fig. 4 Generating Virtual Bronchoscopic Simulation Using ziostation2 (Ziosoft, Inc., Japan)

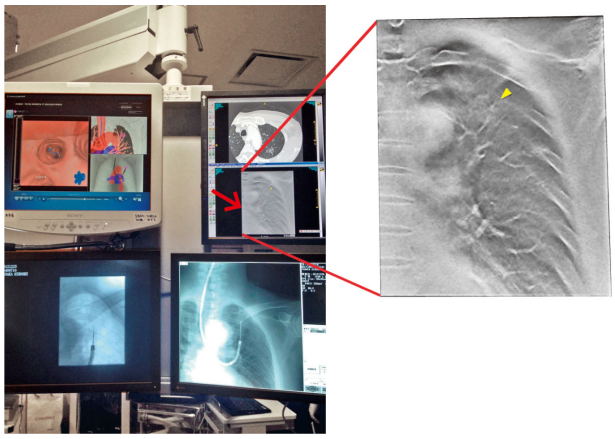
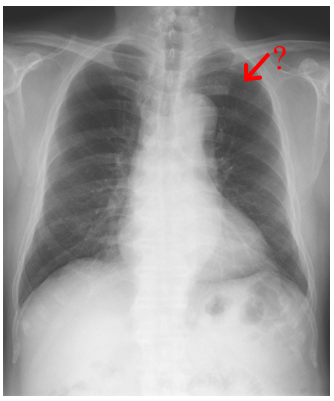
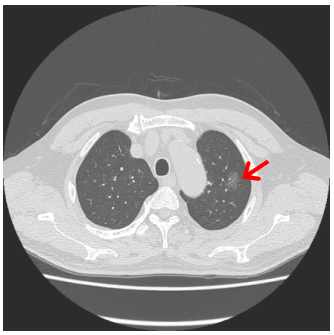


Fig. 5 Using Tomosynthesis to Anticipate the Position of the Lesion (arrow), Then Performing Transbronchial Lung Biopsy

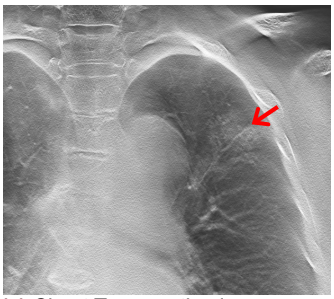
Excluding reports of pathological examinations of ground glass opacities where the biopsy is performed surgically, there are occasional reports on CT-guided percutaneous needle lung biopsies mainly from the U.S. and Europe, with no published reports to date of such examinations performed by bronchoscopy. We investigated the utility of using EBUS-GS for ground glass opacities and published the first ever report on the topic[12]. Our investigation showed that the diagnostic yield did not vary by size of target lesion. While univariate analysis showed that whether the lesion could be shown by ultrasound images obtained from the previously-mentioned R-EBUS (in some cases a part-solid GGO lesion could be shown by R-EBUS) and whether the lesion could be shown by tomosynthesis were both significant factors that affected diagnostic yield, multivariate analysis showed that the only factor that significantly affected whether diagnosis was possible or not was the ability of R-EBUS to show the lesion and identify its position **(Table 3)**. In other words, an important factor for diagnostic yield was whether lesion position could be confirmed in real time during the ongoing examination, and at present R-EBUS is the only means capable of confirming lesion position in real time. Nevertheless, on many occasions we have found ground glass opacities that R-EBUS is unable to depict (difficulty in determining position), and while improving R-EBUS itself is a valid approach, other methods of recognizing lesions in real time need to be developed to improve diagnostic yields.



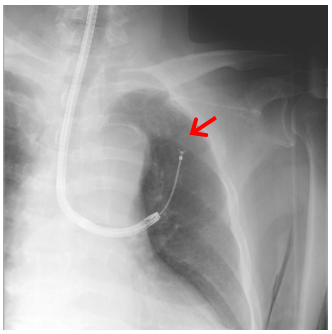
(a) Chest Radiography



(b) Chest CT



(c) Chest Tomosynthesis



(d) Transbronchial Lung Biopsy Under X-Ray Fluoroscopy

Fig. 6 Transbronchial Lung Biopsy of a Pure GGO Under X-Ray Fluoroscopy

- **a)** Chest radiography has trouble showing the lesion.
- **b)** Pure GGO found in left S^{1+2} by chest CT
- **c)** Pure GGO is shown clearly by tomosynthesis.
- **d)** X-ray fluoroscopy-guided transbronchial lung biopsy was performed based on tomosynthesis images, with the lesion diagnosed as pulmonary adenocarcinoma. Edited excerpt from reference 11

Univariate Analysis		
Variable	No./Total No. (%)	P Value
All	26/40 (65.0)	
Lesion size		
< 20 mm	13/21 (61.9)	0.75
≥ 20 mm	13/19 (68.4)	
Ground Glass Opacity		
Pure GGO	2/4 (50.0)	0.47
GGO-dominant lesions	8/14 (57.1)	
Lesions with GGO < 50%	16/22 (72.7)	
X-ray fluoroscopy		
Visible	14/18 (77.8)	0.18
Invisible	12/22 (54.5)	
Tomosynthesis Image		
Visible	26/36 (72.2)	0.01
Invisible	0/4 (0)	
R-EBUS Image		
Visible	19/24 (79.2)	0.04
Invisible	7/16 (43.8)	
	Multivariate Analysis	
	Odds Ratio (95% CI)	P Value
EBUS Image	16.2 (1.65-160.0)	0.017

GGO, Ground glass opacity
R-EBUS, Radial Endobronchial ultrasonography

Table 3 Logistic Regression Analysis of the Factors Affecting Diagnostic Yield of EBUS-GS-Guided Bronchoscopy for Peripheral Pulmonary Lesions with GGO

3. Real Time Tomosynthesis-Guided Bronchoscopy

So since tomosynthesis is excellent at depicting ground glass opacities, can it replace a chest CT? We believe the answer is no. Tomosynthesis is a low dose modality compared to chest CT, but with further and impending developments in chest CT systems, it is thought that the exposure dose of a chest CT scan will be reduced to a level equivalent to that of chest radiography.

So what is the biggest advantage of tomosynthesis (SONIALVISION safire series)? We consider it to be the advantages offered from making best use of tomosynthesis integrated into a fluoroscopy system. Real time image capture by tomosynthesis is important whatever the procedure (endoscopy, angiography, gastrointestinal fluoroscopy, surgery) we perform as it makes the procedure easier to perform and improves precision. We have investigated real time tomosynthesis-guided bronchoscopy, a new bronchoscopic technique utilizing the real time capabilities of tomosynthesis.

To date, tomosynthesis has required around 10 minutes from image data capture to display of the image. This time lag has precluded use of tomosynthesis for obtaining images in real time, but in collaboration with Shimadzu Corporation we have substantially reduced the time required to perform image reconstruction and made it possible to show lesions in real time by tomosynthesis during an ongoing procedure.

Real time tomosynthesis-guided bronchoscopy involves a bronchoscopic examination with the added advantage that tomosynthesis enables confirmation of whether the tool being used to obtain tissue, such as biopsy forceps or needle, are positioned inside the lesion not only along a transverse direction, but also on the anteroposterior direction that shows whether a tool is positioned anteriorly towards patient's chest, or posteriorly towards their back. Normal fluoroscopy is quite capable of confirming positions in a transverse direction, but has trouble confirming positions in this anteroposterior (chest–back) direction. Confirming the position of tools in an anteroposterior direction has to date required a patient be placed in a lateral recumbent position during the examination, or required the tube be swung left and right if the fluoroscopy system is equipped with a C-arm. Confirming the position of a lesion was not easy due to the mediastinum organs. However, using tomosynthesis to capture images will make it very easy to ascertain the positional relationship between lesion and tool. Knowing in what way a tool is out of alignment with respect to a lesion makes it very easy to correct the orientation of the tool. A view of an actual examination setup is shown in **Fig. 7**. Whether the tool is inside the lesion can be confirmed on the tomosynthesis screen by reconstructing contiguous cross-sections in the anteroposterior direction from the back through to the chest **(Fig. 8 and Fig. 9)**.

At the National Cancer Center Hospital, we have conducted real time tomosynthesis-guided bronchoscopic examinations for nodules and ground glass opacities in 12 patients to date, of which diagnosis was possible in 11 patients (11/12 patients, 91.7 %). Even though this is still a small number of case series, considering the diagnostic yield of normal bronchoscopy (for nodules and the like) is around 60 % to 70 %, it seems likely that real time tomosynthesis-guided bronchoscopy is a useful procedure, and one deserving further investigation.

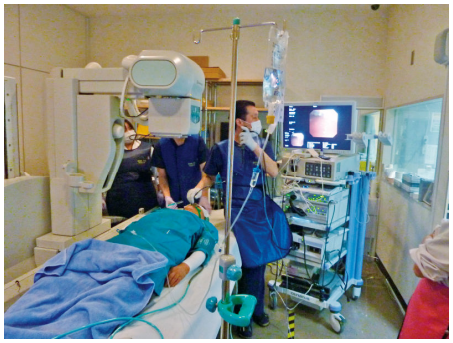
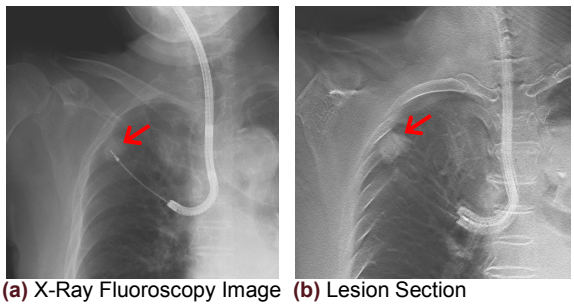


Fig. 7 Performing Real Time Tomosynthesis-Guided Bronchoscopy

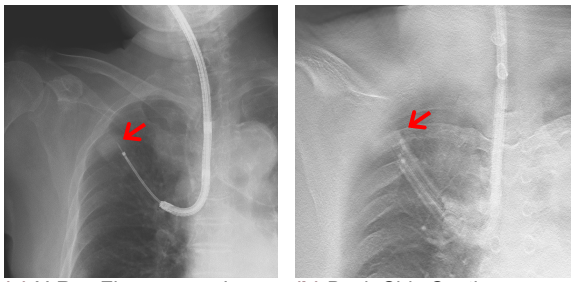


(a) X-Ray Fluoroscopy Image **(b)** Lesion Section

(c) Tool Section **(d)** Chest-Side Section

Fig. 8 Real Time Tomosynthesis-Guided Bronchoscopy (example showing tool and lesion out of alignment)

- **a)** Tool looks to be positioned entirely within the lesion on the X-ray fluoroscopy image.
- **b)** Tomosynthesis section shows the lesion clearly but does not show the tool inside the lesion.
- **c)** Tomosynthesis section shows the tool clearly, but no longer shows the lesion clearly. (The tool is positioned on the edge on the chest side of (anterior to) the lesion).
- **d)** Tool is even observed in a section that does not show the lesion, which easily confirms the tool is present on the chest side of (anterior to) the lesion.

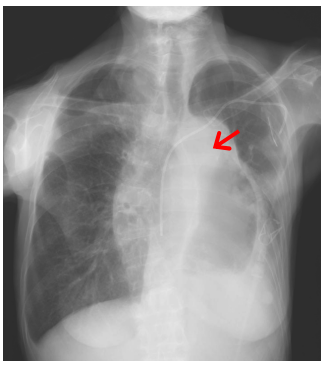


(a) X-Ray Fluoroscopy Image **(b)** Back-Side Section

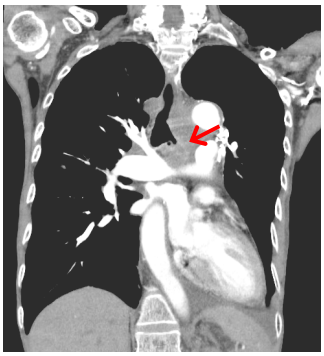
(c) Lesion Section **(d)** Chest-Side Section

Fig. 9 Real Time Tomosynthesis-Guided Bronchoscopy (example showing lesion and tool positions in alignment)

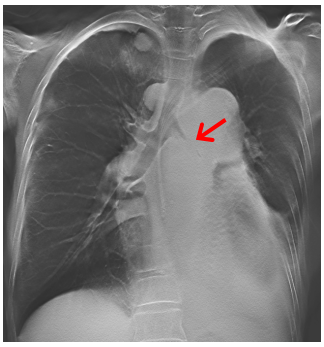
- **a)** Tool looks to be positioned entirely within the lesion on the X-ray fluoroscopy image.
- **b)** Tomosynthesis back-side (posterior) section showing the lesion and tool similarly
- **c)** Tomosynthesis section in which the lesion is shown most clearly, where the tool is also shown clearly inside the lesion (shows the tool is positioned in alignment with the lesion in an anteroposterior direction).
- **d)** Tomosynthesis chest-side section depicts the lesion and tool similar to how they are shown in the back-side section, showing the tool and lesion are present in the same section.



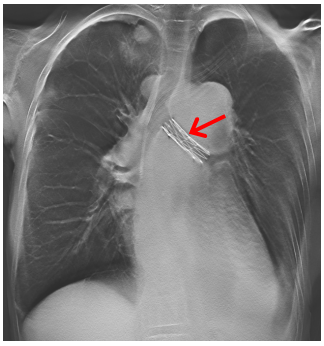
(a) Chest Radiography



(b) Chest CT



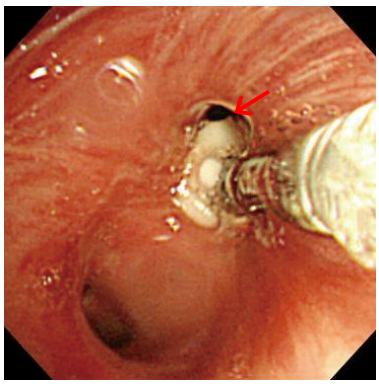
(c) Tomosynthesis



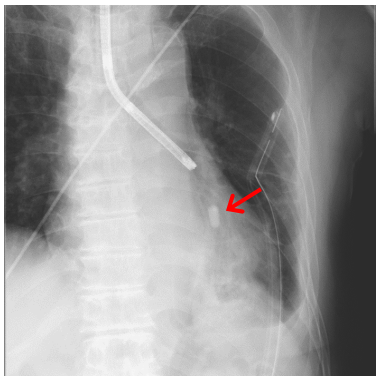
(d) Tomosynthesis After Stenting

Fig. 10 Example of Stenting Metal Stent for Stenosis of Left Main Bronchus

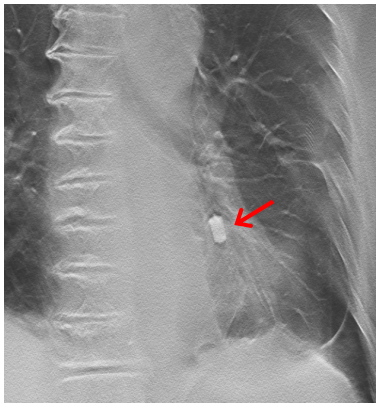
- **a)** Severity of stenosis in left main bronchus is unclear using chest radiography.
- **b)** Chest CT. Shows stenosis from inlet of left main bronchus caused by tumor.
- **c)** Because tomosynthesis is capable of reconstructing an arbitrary coronal section, it is able to confirm the severity of stenosis in the left main bronchus. Air is confirmed inside the left main bronchus, showing the occlusion is not complete.
- **d)** After stenting metal stent. Metal stent position can be confirmed with ease due to the presence of few metal artifacts.



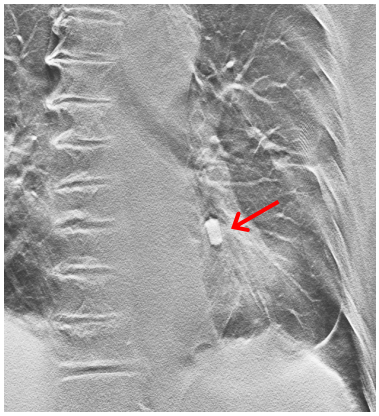
(a) Bronchoscopy



(b) X-Ray Fluoroscopy



(c) Chest Radiography After EWS Placement



(d) Tomosynthesis After EWS Placement

Fig. 11 Bronchial Occlusion
- **a)** Insertion of endobronchial Watanabe spigot (EWS, arrow) by bronchoscopy
- **b)** X-ray fluoroscopy image during procedure
- **c)** Chest radiography after EWS insertion. EWS is just identifiable (arrow).
- **d)** Using tomosynthesis, the EWS position is clearly identifiable, and the center of the EWS is also identifiable (arrow).

However, movement of the gantry in a longitudinal direction along the body for tomosynthesis prevents the operator from standing at the head of the patient as normal during bronchoscopy, and forces the operator to stand to the side of the patient as shown in **Fig. 7**. This makes control of the bronchoscope somewhat difficult. Techniques that have real time imaging capabilities need further development, and making the capture of tomosynthesis images possible by gantry movement in a transverse direction, not only a lateral direction, will certainly increase the amount of freedom allowed to the operator during procedures.

4. Tomosynthesis Before and After Bronchoscopic Therapy

Tomosynthesis is also being used to evaluate the severity of respiratory stenosis, to confirm positioning after respiratory stenting **(Fig. 10)**, and to confirm the position of EWS used during bronchial occlusion **(Fig. 11)**. Regarding metal stents in particular, CT is strongly affected by metal artifacts while tomosynthesis is not substantially affected by metal artifacts and capable of obtaining very clear images. Further investigation is required into the use of tomosynthesis for image evaluation before and after bronchoscopic therapy.

Conclusion

We have reviewed the use of tomosynthesis in respiratory medicine based on experiences and results at the National Cancer Center Hospital. Making further improvements to the real time capabilities of tomosynthesis (SONIALVISION safire series), which integrates digital tomography with a fluoroscopy system, is required for its use in the field of respiratory medicine. We expect further development and applications of procedures using tomosynthesis.

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