Review Article on Advance in Bronchoscopy for Peripheral Pulmonary Diseases

Diagnostic value of ultrathin bronchoscopy in peripheral pulmonary lesions: a narrative review

Masahide Oki[1], **Hideo Saka**[1,2]

[1]Department of Respiratory Medicine, National Hospital Organization Nagoya Medical Center, Nagoya, Japan; [2]Department of Respiratory Medicine, Matsunami General Hospital, Kasamatsu, Japan

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Correspondence to: Masahide Oki, MD. Department of Respiratory Medicine, National Hospital Organization Nagoya Medical Center, Nagoya, Japan. Email: masahideo@aol.com.

Abstract: Flexible bronchoscopes are being continuously improved, and an ultrathin bronchoscope with a working channel that allows the use of a radial-type endobronchial ultrasound (EBUS) probe is now available. The ultrathin bronchoscope has good maneuverability for passing through the small bronchi and good accessibility to peripheral lung lesions. This utility is particularly enhanced when it is used with other imaging devices, such as EBUS and navigation devices. Multimodality bronchoscopy using an ultrathin bronchoscope leads to enhanced diagnostic yield.

Keywords: Bronchoscopy; endobronchial ultrasound (EBUS); peripheral pulmonary lesions (PPLs); ultrathin bronchoscope; virtual bronchoscopic navigation (VBN)

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Introduction

Accurate diagnosis of small peripheral pulmonary lesions (PPLs) is still challenging (1). Bronchoscopy has been widely used for diagnosis, and instrumental and technical improvements have gradually enhanced diagnostic yield. As the bronchus branches peripherally, its diameter decreases; standard bronchoscopes with an external diameter of about 5 mm are too large to access the peripheral lung region. Thinner bronchoscopes have the advantage that they provide good accessibility to PPLs through small bronchi, so their use in diagnosing PPLs is reasonable. Although no formal definition has been widely accepted, we define an "ultrathin bronchoscope" as having an outer diameter ≤3.5 mm (2).

Most conventional ultrathin bronchoscopes are equipped with a working channel with an inner diameter of 1.2-mm, which allows the use of only mini-forceps <1.2 mm in diameter to obtain specimens of a limited size. Therefore, despite their potential high diagnostic yield, conventional ultrathin bronchoscopes with a 1.2-mm working channel have been regarded as an adjunct, rather than an alternative, to conventional bronchoscopes in PPL diagnosis (3,4). Conventional bronchoscopy for sampling PPLs has been performed only under fluoroscopic guidance. However, some ancillary techniques, such as navigation, computed tomography (CT), and endobronchial ultrasound (EBUS), have been developed and applied to bronchoscopy. Such guided methods have increased the diagnostic yield of bronchoscopy (5). An ultrathin bronchoscope has good maneuverability when passing it through the small-airway route and good accessibility to the peripheral lung, so its utility is enhanced when combined with confirmatory tools for use when in proximity to target lesions. Several studies have demonstrated the diagnostic utility of ultrathin bronchoscopes in combination with navigation devices (6-14), CT fluoroscopy (6,15,16), or cone-beam CT (CBCT) (17,18). Furthermore, a next-generation ultrathin

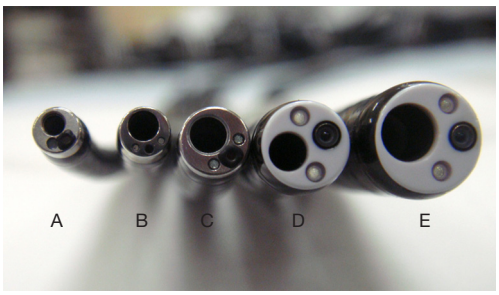

Figure 1 Flexible bronchoscopes. (A) A 2.8-mm ultrathin bronchoscope with a 1.2-mm channel; (B) a 3.0-mm ultrathin bronchoscope with a 1.7-mm channel; (C) a 4.0-mm-diameter thin bronchoscope with a 2.0-mm-diameter channel; (D) a 4.8-mm standard bronchoscope with a 2.0-mm-diameter channel; and (E) a 5.9-mm therapeutic bronchoscope with a 3.0-mm-diameter channel.

bronchoscope equipped with a 1.7-mm working channel, which allows the use of radial-probe EBUS (rEBUS), was developed and is now available for use in clinical practice (19-22). We present the following article in accordance with the narrative review checklist (available at http://dx.doi.org/10.21037/jtd-2020-abpd-001).

History

The idea of using a thinner bronchoscope is not novel. In the early development of flexible bronchoscopes, Shigeto Ikeda, the father of flexible bronchoscopy, manufactured several prototype bronchoscopes of different sizes, including a 3.3-mm thin bronchoscope (23). A few years later, the diameter of the thinnest prototype bronchoscope was reduced to 2.5 mm (24). In the 1980s, some thin bronchoscopes equipped with small working channels were developed, mainly for pediatric use. The first publication regarding the usefulness of a thin bronchoscope for PPLs in adult patients was reported by Prakash in 1985 (25). He reported three cases of PPLs in adult patients that could not be observed using a 4.9-mm bronchoscope but were successfully observed using a 3.6-mm thin bronchoscope. Various types of small-caliber bronchoscopes have since been developed, and several studies are available on their usefulness in diagnosing PPLs in adult patients (19,26-30). Bronchoscopes with a variety of external diameters and working-channel inner diameters are now available for clinical use (*Figure 1*).

Techniques

Although ultrathin bronchoscopes can be advanced close to PPLs, the localization of the target lesion is performed by fluoroscopy and rEBUS and not by direct bronchoscopic vision; thus, these imaging devices are necessary during ultrathin bronchoscopy.

The bronchial route is predicted before procedures by reading a preprocedural high-resolution chest CT scan (31). The anesthetic agents and techniques used are similar to those of standard bronchoscopy. Lidocaine is usually used for topical anesthesia and intravenous midazolam and fentanyl for conscious sedation. Ultrathin bronchoscopy can be performed through either the mouth or the nose. We usually insert a 5.0-mm-inner-diameter tracheal tube transnasally into the trachea. The airway established with the tracheal tube facilitates repeated insertion and removal of the ultrathin bronchoscope, reduces damage from rubbing of the nasal mucosa and vocal cords during bronchoscopy, and reduces deflection of the ultrathin bronchoscope.

After examining the endobronchial region, the ultrathin bronchoscope is advanced into the bronchial route, which is indicated by the navigation device on real-time fluoroscopy. The ultrathin bronchoscope approaches the target lesion and is then localized by rEBUS and fluoroscopy. If the tumor surrounding the EBUS probe is visualized on the EBUS image, the EBUS probe is removed and biopsy forceps are advanced through the same route. We usually perform biopsies under fluoroscopic guidance until 10 visible specimens have been obtained.

Direct observability

Small-caliber bronchoscopes can be advanced into deeper bronchi than large-caliber bronchoscopes (*Figure 2*) and, therefore, the possibility of direct observation of a peripheral endobronchial lesion increases with the use of a thin bronchoscope. Rooney *et al.* reported that 4 of 17 PPLs (24%) that could not be observed using a 6.3-mm bronchoscope could be observed directly using a 3.3-mm bronchoscope (3). Oki *et al.* reported that a 3.5-mm bronchoscope could reach two more distal generations of bronchi compared to a 5.9-mm bronchoscope, and 14 of 102 lesions (14%) were observed only using the 3.5-mm bronchoscope (28).

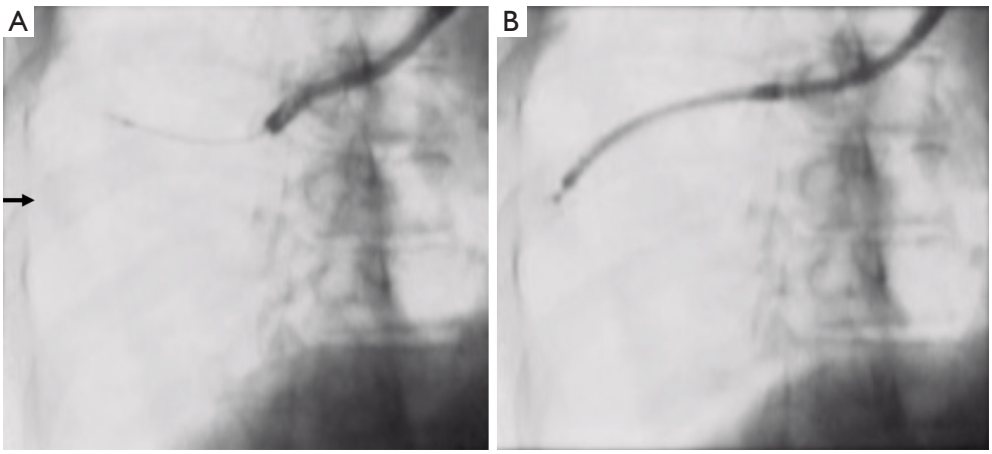

Figure 2 Fluoroscopic images showing the accessibility of a PPL using a 3.0-mm ultrathin bronchoscope and a 4.0-mm bronchoscope. (A) The EBUS probe could not be advanced towards the target lesion (arrow) using a 4.0-mm bronchoscope. (B) The 3.0-mm ultrathin bronchoscope approached the lesion and provided a diagnosis of adenocarcinoma. PPL, peripheral pulmonary lesion; EBUS, endobronchial ultrasound.

Diagnostic yields

The study results on bronchoscopy using ultrathin bronchoscopes for PPLs are summarized in *Table 1*. The overall diagnostic yield of ultrathin bronchoscopy is 66%, with a yield of 59% for lesions <2 cm. These yields seem comparable to those of other guided bronchoscopy procedures (5,33). As shown in *Table 1*, ultrathin bronchoscopes have been used with various guiding methods, including rEBUS, navigation devices, fluoroscopy, and CT fluoroscopy. The diagnostic utility of ultrathin bronchoscopes can be enhanced by combining them with other guiding methods.

Randomized trials among bronchoscopes of different sizes

Several randomized studies comparing diagnostic yields among bronchoscopes of different sizes have been published. Franzen *et al.* conducted a small pilot study comparing bronchoscopy using a conventional 2.8-mm ultrathin bronchoscope with a 1.2-mm working channel to standard-size bronchoscopes with external diameters of 5.0–6.0 mm for diagnosing PPLs in a region endemic for tuberculosis (32). Forty patients were enrolled and assigned to either ultrathin or standard-size bronchoscope groups, of whom 28% were ultimately diagnosed with tuberculosis. The diagnostic yields in the ultrathin bronchoscope group and standard-size bronchoscope group were 55% and 80% (P=0.95), respectively. Adverse events, including extensive coughing, a blocked working channel, and arterial hypertension were more frequent in the ultrathin bronchoscope group. Bronchoscopy times in the ultrathin bronchoscope group and the standard-size bronchoscope group were 31 and 26 min, respectively (P=0.15). These results fail to show the superiority of fluoroscopy-guided bronchoscopy with a conventional ultrathin bronchoscope over a standard-size bronchoscope. Oki *et al.* conducted a randomized non-inferiority study of rEBUS-guided bronchoscopy using a 3.4-mm bronchoscope compared to rEBUS with a guide sheath (GS)-guided bronchoscopy using a 4.0-mm bronchoscope (30). In total, 203 patients with PPLs with a median diameter of 26 mm, were analyzed. The diagnostic yields of bronchoscopy using the 3.4-mm and 4.0-mm bronchoscopes were 65% and 62%, respectively. The difference in diagnostic yield was 3.6%, with a 90% confidence interval from –7.5% to 14.7%. The lower limit of the confidence interval was higher than the predetermined margin of –10%, thus confirming the non-inferiority of the procedure with the 3.4-mm bronchoscope. Later, Oki *et al.* conducted a multicenter randomized study comparing rEBUS, fluoroscopy, and virtual bronchoscopic navigation (VBN)-guided bronchoscopy using a 3.0-mm ultrathin bronchoscope to rEBUS-GS, fluoroscopy, and VBN-guided bronchoscopy using a 4.0-mm bronchoscope (19). The results in 305 patients with PPLs with a median diameter of 19 mm were analyzed. The histological

Table 1 Studies on ultrathin bronchoscopy of PPLs

Study	Year	Study design	Bronchoscope diameter (mm)	Guidance method	Mean lesion diameter (mm)	No. lesions	No. diagnosed	Yield (%)	No. lesions <2 cm	No. lesions <2 cm diagnosed	Yield for lesions <2 cm (%)	Prevalence of malignancy (%)	Complications
Shinagawa (6)	2004	Pro	2.8	CT, VBN	13	26	17	65	26	17	65	69	0
Yamamoto (4)	2004	Pro	2.8	Flu	ND	67	40	60	ND	ND	ND	76	ND
Asano (7)	2006	Pro	2.8	Flu, CT, VBN	19	38	31	82	26	21	81	55	ND
Shinagawa (8)	2007	Pro	2.8	CT, VBN	14	71	50	70	71	50	70	72	1 PTX
Tachihara (9)	2007	Pro	2.8	Flu, VBN	16	58	33	57	46	21	46	ND	0
Oki (28)	2008	Pro	3.5	Flu	34	98	68	69	23	13	57	69	0
Oki (29)	2009	Pro	3.4	Flu, rEBUS	31	71	49	69	14	5	36	62	0
Eberhardt (10)	2010	Pro	2.8	VBN	28	25	20	80	ND	ND	ND	84	1 PTX
Matsuno (16)	2011	Retro	2.8	Flu, CT	ND	166	113	68	ND	ND	ND	58	1 PTX
Oki (30)	2012	RCT	3.4	Flu, rEBUS	26	101	66	65	25	10	40	75	3 PTX, 1 PNA, 1 bleeding
Asano (12)	2013	RCT	2.8	Flu	17	167	100	60	110	62	56	90	1 PTX, 1 lidocaine intoxication, 1 PNA
		RCT	2.8	Flu, VBN	18	167	112	67	114	74	65	86	1 PTX, 2 bleeding, 1 bradycardia
Oki (19)	2015	RCT	3.0	Flu, rEBUS, VBN	19	150	111	74	80	52	65	82	3 PTX, 1 PNA, 1 chest pain
Franzen (32)	2016	RCT	2.8	Flu	20	20	11	55	6	ND	ND	40	2 extensive coughing, 3 blocked working channel, 1 hypertension
Diez-Ferrer (14)	2019	Pro	2.8/3.1	Flu, VBN	23	55	26	47	26	11	42	60	ND
		Retro	2.8/3.1	Flu	25	110	44	40	46	11	24	78	ND
Ali (18)	2019	Pro	2.8	Flu, VBN, CBCT	20	40	36	90	ND	ND	ND	63	1 PTX, 1 lung abscess
Sehgal (20)	2019	Retro	3.0	rEBUS	16	34	19	56	ND	ND	ND	ND	1 PTX, 1 bleeding
Oki (21)	2019	RCT	3.0	Flu, rEBUS, VBN	19	177	124	70	102	64	63	80	2 PTX, 2 PNA, 1 bleeding
Sumi (22)	2020	Retro	3.0	Flu, rEBUS	20	102	77	75	65	46	71	ND	1 PTX, 2 PNA, 1 bleeding
Summary						1,717	1,130	66%	780	458	59%	76%	Overall 3%, PTX 1%

PPL, peripheral pulmonary lesion; CBCT, cone-beam computed tomography; Flu, fluoroscopy; ND, no data; PNA, pneumonia; Pro, prospective study; PTX, pneumothorax; RCT, randomized controlled trial; rEBUS, radial-probe endobronchial ultrasound; Retro, retrospective study, VBN, virtual bronchoscopic navigation.

diagnostic yield of multimodality bronchoscopy using the 3.0-mm ultrathin bronchoscope was significantly higher than that with the 4.0-mm bronchoscope (74% *vs.* 59%, respectively, P=0.04). The median bronchus level attained using the 3.0-mm-diameter ultrathin bronchoscope was the fifth-generation level, thus more distal than that achieved by the 4.0-mm-diameter bronchoscope (median fourth-generation) and comparable to that of a conventional 2.8-mm ultrathin bronchoscope [median fifth-generation (12)]. Complications, including pneumothorax, bleeding, chest pain, and pneumonia occurred in 3% and 5% of cases in the respective groups (P=0.6). Oki *et al.* further performed a randomized study comparing the 3.0-mm ultrathin bronchoscopic method to the 4.0-mm bronchoscopic method, which was modified by adding transbronchial needle aspiration (TBNA) and standard-size biopsy forceps (21). In the 4.0-mm bronchoscope group, TBNA was performed for patients in whom the radial EBUS probe could not be inserted into the target lesion. In addition, the use of 1.5-mm forceps with a GS, standard forceps without a GS, or a combination of the two was permitted in the 4.0-mm bronchoscope group. The results in 356 patients with PPLs with a median diameter of 19 mm were analyzed. The diagnostic superiority of the 3.0-mm ultrathin bronchoscopic method over the 4.0-mm bronchoscopic method was demonstrated again (70% *vs.* 59%, respectively, P=0.03). The incidence of complications did not differ between the two groups (3% *vs.* 5%, respectively, P=0.57).

Safety

As shown in *Table 1*, the complication rate related to ultrathin bronchoscopy is approximately 3%, and the occurrence of pneumothorax is 1%, which are rates comparable to those of bronchoscopy using larger bronchoscopes (5). Ultrathin bronchoscopes can reach the visceral pleura in certain cases, so they can damage the visceral pleura directly, which causes pneumothorax. Oki *et al.* reported that pneumothorax occurred in 6 of 410 patients (1.5%) who underwent transbronchial forceps biopsy using a 2.8-mm ultrathin bronchoscope under fluoroscopy; four cases were related to the forceps biopsy, and the remaining two were caused by the ultrathin bronchoscope itself (34).

Limitations of ultrathin bronchoscopes

The obvious disadvantage of a thinner bronchoscope is the limitation of available biopsy instruments. The diagnosis of lung cancer includes genotype as well as subtype classifications, so it is necessary to obtain a sufficient amount of tumor tissue for molecular and morphological analyses. Relatively small 1.5-mm forceps must be used when performing bronchoscopic sampling using an ultrathin bronchoscope with a 1.7-mm working channel. The size of the specimens obtained using 1.5-mm forceps is smaller than those obtained with 1.8- or 1.9-mm standard forceps. This issue notwithstanding, the 1.5-mm forceps have been widely used not only during ultrathin bronchoscopy but also for bronchoscopy with EBUS-GS, and many investigators have reported a high diagnostic yield of bronchoscopic biopsy using 1.5-mm forceps (19-22,28-30,35-43). Indeed, one study suggested that the size of the biopsy forceps did not affect the diagnostic yield of bronchoscopy (44). In addition, high degrees of concordance of results of genotyping (45), subtyping (46), and programmed death-ligand (47) between specimens obtained with 1.5-mm forceps and surgical specimens have been reported.

Future perspectives

Some promising instruments that can be used during ultrathin bronchoscopy have been developed. Bronchoscopic aspiration needles have recently undergone improvement, and thinner and more flexible needles compared to conventional needles are now available for use in clinical practice (48). A new 21-gauge needle can be used through a 1.7-mm working channel of an ultrathin bronchoscope. Conventional bronchoscopic aspiration needles are stiff, and their steerability and accessibility in the peripheral lung are quite limited (21), while the flexibility of the new needle facilitates TBNA procedures for PPLs (49). The use of TBNA seems to be reasonable in certain cases (e.g., lesions into which rEBUS cannot be inserted), as TBNA can be used to gain access and obtain specimens from peribronchial lesions. The utility of TBNA should be evaluated in terms of efficacy, safety, and cost-effectiveness. Further studies are needed to determine the indications for TBNA.

Another promising instrument is the cryoprobe. Cryobiopsy is an effective diagnostic method for PPLs because it provides larger and better-quality specimens (50). An ultrathin 1.1-mm cryoprobe, which is used through the working channel of an ultrathin bronchoscope, has already been adopted in clinics worldwide. The ultrathin cryoprobe is flexible enough to access PPLs located past the deep-curved bronchus (51). The use of an ultrathin cryoprobe during ultrathin bronchoscopy may overcome the limitation

of a small sample size.

Bronchoscope manufacturers have continued efforts to develop thinner bronchoscopes with larger working channels and better visibility. In addition, sampling instruments that can be used through the small working channel of an ultrathin bronchoscope have been developed and improved. These efforts will continue in the future and will enhance the diagnostic yield of ultrathin bronchoscopy for PPLs.

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Footnote

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