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Original research

Balloon dilatation for bronchoscope delivery: first-in-human trial of a novel technique for peripheral lung field access

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► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/thorax-2025-223218).

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Received 21 February 2025
Accepted 6 October 2025

Linked

► https://doi.org/10.1136/thorax-2025-223940

Check for updates

To cite: Miyake K, Oki M, Suzuki H, *et al*. *Thorax* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/thorax-2025-223218

ABSTRACT

Background Bronchoscopic limitations in reaching peripheral pulmonary lesions (PPLs) can compromise biopsy sensitivity, especially for small PPLs. Therefore, we developed the balloon dilatation for bronchoscope delivery (BDBD) technique to dilate bronchial pathways and facilitate bronchoscope advancement into the periphery. This study evaluated the diagnostic performance and safety profile of transbronchial biopsy using this technique.

Methods This multicentre, single-arm, prospective study included patients with bronchus sign-positive PPLs measuring <20 mm. Bronchoscopy was performed using ultrathin or thin bronchoscopes under conscious sedation. When the bronchoscope could not advance further, the BDBD technique was used to approach closer to the target, followed by biopsies. The primary endpoint was the diagnostic sensitivity for malignancy in specimens obtained through the specified procedure, defined as bronchoscope advancement using balloon dilatation, direct biopsy site visualisation and absence of serious adverse events.

Results Eighteen of 22 patients who underwent bronchoscopy with the BDBD technique were ultimately diagnosed with cancer. BDBD enabled bronchoscope advancement in all 18 cases without serious complications, allowed direct biopsy site visualisation in 17 and detected cancer in 14. Thus, the diagnostic sensitivity for malignancy was 77.8% (14/18). Beyond these cases, one patient who met all procedural criteria was diagnosed with cryptococcosis. Another patient was diagnosed with cancer without direct visualisation. On average, BDBD enabled bronchoscope advancement by 2.3 bifurcations.

Conclusion In this small observational study, BDBD appeared to be a promising technique for improving the diagnostic sensitivity of bronchoscopy for small PPLs. Further validation is necessary in large cohorts.

Trial registration number jRCT2052220174

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ A biopsy of peripheral pulmonary lesions (PPLs) requires high sensitivity while maintaining procedural simplicity; however, conventional bronchoscopy is limited by airway narrowing, preventing access to peripheral lung fields. Therefore, successful biopsy of PPLs that cannot be directly visualised by the bronchoscope remains a major challenge in bronchoscopy.

WHAT THIS STUDY ADDS

⇒ This first-in-human trial demonstrated that the balloon dilatation for bronchoscope delivery (BDBD) technique enables bronchoscopic access to peripheral lung regions by expanding the airway, achieving a diagnostic sensitivity of 77.8% without severe complications for lesions <20 mm. Thus, in this small observational study, BDBD appeared safe and promising in improving the sensitivity of transbronchial biopsy.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ PPLs have traditionally been defined as lesions that cannot be directly visualised by bronchoscopy. Our findings suggest that this definition may warrant reconsideration in the context of BDBD-assisted bronchoscopy; confirmation in larger studies is required. BDBD may challenge the conventional belief that bronchoscopes cannot reach the peripheral lung field, introducing a new strategy to improve diagnostic yield.

INTRODUCTION

Accurate diagnosis of peripheral pulmonary lesions (PPLs) is a significant challenge in pulmonary medicine. Two primary methods are used for biopsy of suspected PPLs. Transthoracic needle aspiration is preferred because of high diagnostic sensitivity, although adverse outcomes, including pneumothorax and bleeding, are observed in up to 30% cases.[1 2] The second method is transbronchial biopsy (TBB). Robots have facilitated the use of TBB,[3 4] but the need for large, complex equipment and the associated high costs pose significant challenges. TBB using a flexible bronchoscope is less invasive and simple. However, the diagnostic sensitivity of TBB using bronchoscopy is often

insufficient, especially for lesions measuring ≤2 cm.[1 5] This emphasises the need for methods that improve its diagnostic sensitivity.

Endoscopic biopsy shows high sensitivity for detecting lesions in various organs. For example, endoscopy allows direct visualisation of gastric,[6] colorectal and[7] bladder cancer[8] lesions, making the biopsy procedure straightforward, minimally invasive and highly effective. Thus, endoscopic biopsy has become the standard for diagnosing these lesions. Endoscopic biopsy is also highly effective for pulmonary lesions exposed within the central airways (endobronchial biopsy). However, diagnosing PPLs is challenging; the bronchoscope cannot reach PPLs directly. In such cases, a significant distance remains between the bronchoscope and the lesion.[9]

To address this limitation, two distinct strategies were developed. The first focuses on improving the diagnostic sensitivity of biopsy performed from a distance using advanced technologies such as radial endobronchial ultrasound (r-EBUS),[10] electromagnetic navigation bronchoscopy,[11] cone-beam CT[12] and augmented fluoroscopy.[13] The second strategy aims to bring the bronchoscope closer to the target lesion to enhance diagnostic sensitivity.[14] This approach includes the use of ultrathin bronchoscopes, which offer improved diagnostic sensitivity compared with standard thin bronchoscopes.[15 16] However, even with ultrathin bronchoscopes, achieving sufficient proximity to PPLs is difficult.

We propose the balloon dilatation for bronchoscope delivery (BDBD) technique as a novel approach to improve TBB. This technique aims to enable direct visualisation and biopsy of peripheral lesions, similar to endobronchial biopsy for central airway lesions. TBB is generally performed by extending forceps from the point where the bronchoscope can no longer advance owing to bronchial narrowing. In contrast, BDBD dilates the bronchial pathway, enabling the bronchoscope to navigate closer to the target while visually selecting bronchial branches. The effectiveness of BDBD was recently demonstrated in a swine model,[17] where it enabled bronchoscopic advancement into peripheral airways without significant complications. However, its clinical feasibility in human subjects remains unclear.

This first-in-human trial of the BDBD technique aimed to evaluate the feasibility and safety of TBB with BDBD for patients with PPLs measuring<20 mm.

METHODS

Patients

This prospective, multicentre, single-arm study was conducted in accordance with the standards for reporting diagnostic accuracy studies (STARD) guidelines (checklist provided as online supplemental material). We prospectively identified potentially eligible participants from patients considered for diagnostic bronchoscopy at three study centres. Written informed consent was obtained from all patients with localised PPLs between March and December 2023. Enrolment was prospective, but patients were included on an availability basis and were not strictly consecutive. The full inclusion and exclusion criteria are detailed in table 1. The bronchus sign was defined as a tubular area of hypoattenuation on CT that led directly to the target lesion.[18] The study was approved by the institutional review board of each participating institution (Identifier No. 2 21 005-A, Osaka University Hospital; Identifier No. S410-1, NHO Nagoya Medical Centre; Identifier No. 190–06_01, Osaka Habikino Medical Centre) and registered with the Japan Registry of Clinical Trials (identifier No. jRCT2052220174). The protocol complied with the amended Declaration of Helsinki.

Balloon device and BDBD technique

Figure 1A, B illustrates the newly developed balloon catheter for BDBD (SKD-001; Kaneka Corporation, Osaka, Japan). SKD-001 is a non-compliant balloon catheter, engineered so that its diameter remains essentially unchanged over the working-pressure range. The balloon expansion section is 10 mm long; the available balloon diameters range from 3.5 to 5.0 mm. A 1.2 mm working channel accommodates 3.5 and 4.0 mm balloons, whereas a 1.7 mm working channel allows 3.5, 4.0 and 4.5 mm balloons. The largest 5.0 mm balloon can be utilised for a 2.0 mm working channel. The catheter tip features a 10 mm X-ray opaque soft tip, which minimises the risk of lung parenchymal or pleural injury. Additionally, an X-ray opaque marker positioned on the proximal side allows precise balloon placement under fluoroscopy before inflation. The catheter is connected to a manually operated 5 mL syringe filled with a 1:1 mixture of iodinated contrast agent and saline for balloon inflation.

Figure 1C illustrates the procedure for the BDBD technique; it follows the same steps as the non-clinical trials involving swine.[17] When the bronchoscope reaches a narrowed bronchus and cannot advance further, the balloon catheter is inserted through the bronchoscope's working channel and guided into the target

Table 1 Inclusion and exclusion criteria for the study

Inclusion criteria	Exclusion criteria
Patients who have an abnormal chest shadow with a positive bronchus sign	Patients who are unable to undergo a bronchoscopy
Patients with an abnormal chest shadow less than 2 cm	Patients undergoing procedures for multiple target lesions
Patients with peripheral pulmonary lesions that cannot be visualised with a bronchoscopy	Patients with hypersensitivity to anaesthetics or other drugs used in bronchoscopy (excluding patients for whom another drug can be used)
Patients who are 20 years of age or older at the time of consent	Patients with serious circulatory, renal or hepatic dysfunction
Patients whose written consent to voluntarily participate in the clinical trial can be obtained from themselves	Patients with respiratory insufficiency or bleeding, coughing, etc. that make it difficult to perform or continue a bronchoscopy and prevent proper evaluation of this clinical trial
	Patients with hypersensitivity to ethylene oxide
	Patients who are pregnant, lactating or of childbearing potential
	Patients who have participated in other clinical trials within 3 months of obtaining consent
	Other patients deemed inappropriate by the investigator or subinvestigators

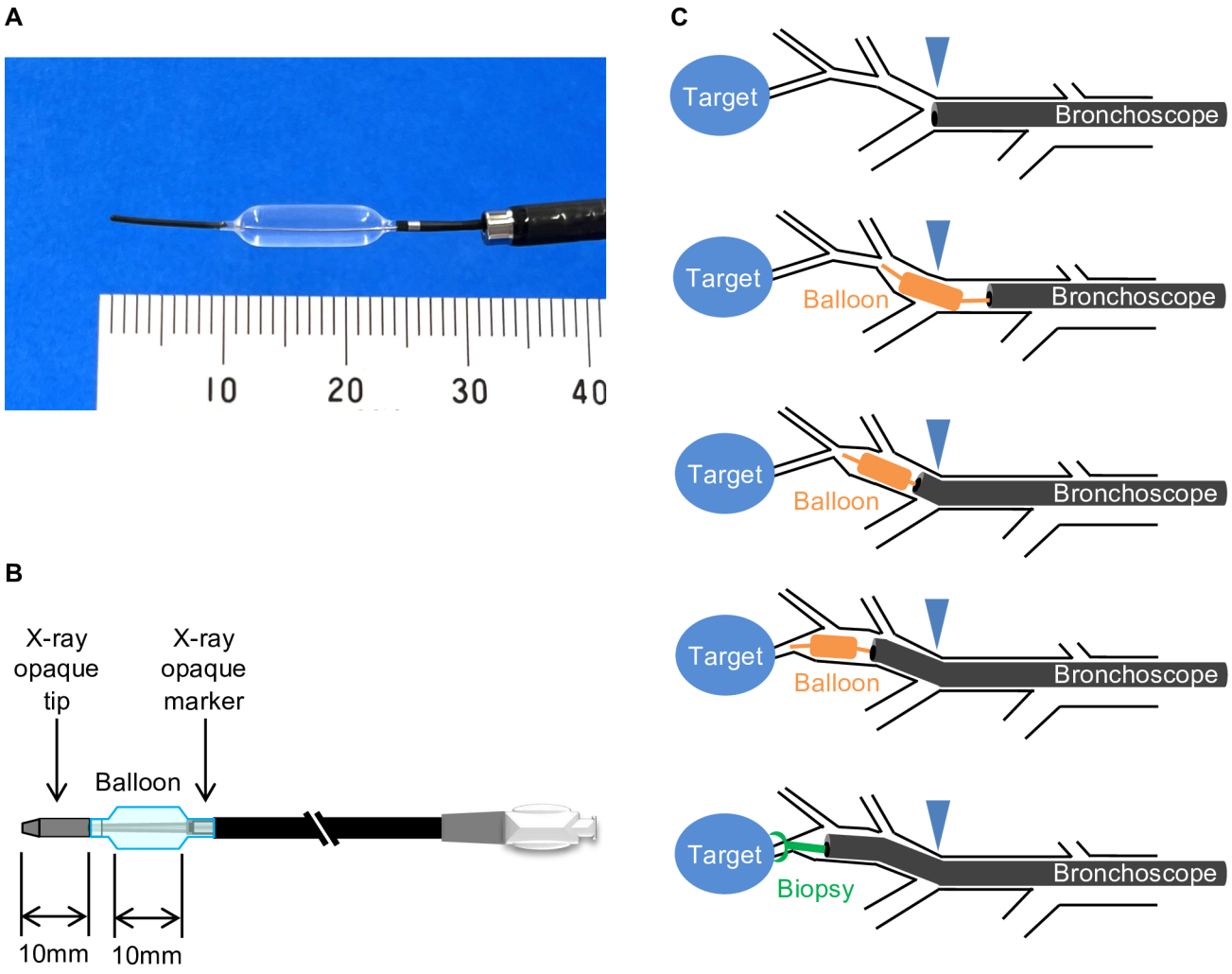

Figure 1 Dedicated balloon catheter for the balloon dilatation for bronchoscope delivery (BDBD) technique. (A) The balloon catheter used in the BDBD technique. A 3.5 mm balloon is inserted into the bronchoscope (BF-MP290F, outer diameter 3.0 mm, working channel 1.7 mm; Olympus, Tokyo). The scale is in millimetres. (B) Schematic diagram of the balloon catheter. The balloon diameter is 3.5–5 mm. The X-ray opaque tip is made of a very soft material. (C) Procedure for the BDBD technique. First, the bronchoscope was advanced distally until it could no longer proceed because of bronchial narrowing. Second, the balloon catheter was inserted through the bronchoscope's forceps channel. Third, the balloon was positioned in the bronchus leading to the target, and the bronchus was dilated. Fourth, postdilatation, the bronchoscope was advanced distally. The balloon dilatation was repeated if necessary, and the biopsy was performed. BDBD, balloon dilatation for bronchoscope delivery.

bronchus. The balloon is inflated using the syringe, after which it is deflated, and the catheter is removed from the bronchoscope. The bronchial changes are observed, and the bronchoscope is further advanced into the lung periphery, if feasible. Additional balloon dilatations are performed as needed.

Balloon dilatation near the pleura (within 20 mm) was avoided to prevent pneumothorax. The balloon position was carefully confirmed under fluoroscopy before inflation. Air or liquid introduction through the bronchoscope's working channel was avoided when positioned close to the pleura to prevent pleural injury. No further balloon inflation was performed if significant bronchial wall damage (ie, macroscopic bronchial laceration or perforation) was observed through the bronchoscope after balloon dilatation.

Bronchoscopy with BDBD

Prior to bronchoscopy, a pathway to the bronchus-sign–positive target was planned using thin-section CT data (0.5–0.625 mm slice thickness) in accordance with each institution's routine practice. Osaka University and Habikino Medical Centre used the oblique method with SYNAPSE VINCENT (Fujifilm Medical, Tokyo, Japan) or OsiriX MD (Pixmeo, Geneva, Switzerland) without virtual bronchoscopy,[19–23] whereas Nagoya Medical Centre used the virtual-bronchoscopy navigation software DirectPath (Olympus, Tokyo, Japan).

An ultrathin (BF-MP290F; outer diameter 3.0 mm, working channel 1.7 mm; Olympus, Tokyo) or a thin (BF-P290; outer diameter 4.2 mm, working channel 2.0 mm; Olympus) bronchoscope was chosen at the operator's discretion, based on the anticipated balance between distal airway reach and the ability to use larger biopsy instruments. Bronchoscopy was initiated under conscious sedation with local anaesthesia using lidocaine combined with intravenous midazolam and fentanyl, without mechanical ventilation. The bronchoscope was advanced towards the target based on the planned pathway. When the bronchoscope could not be advanced, the BDBD technique was used to go closer to the target. Fluoroscopy-guided forceps biopsy was subsequently performed, primarily to monitor the distance to the pleurae, with occasional brushing or washing. R-EBUS was used without a guide sheath as necessary. We ensured that the

bronchoscope was as peripheral as possible before using the BDBD technique to minimise the balloon dilatations. To facilitate this, patients were sometimes positioned laterally.[17 24 25]

Measurements and study endpoints

Patients' background information was collected after obtaining consent (visit 1), and blood tests, X-rays and CT scans were performed. During visit 2, bronchoscopy was performed and recorded on video. Additionally, we recorded balloon use, including expansion locations, time at each location and number. Approximately 2 weeks after bronchoscopy (visit 3), blood tests and chest X-rays were repeated. Vital signs were recorded during all visits and before and after bronchoscopy. Three experienced pulmonologists assessed effectiveness and safety by independently reviewing the X-ray and CT images and bronchoscopy video recordings. Serious adverse events were defined as those requiring hospitalisation or extended hospital stay for treatment.

This study was designed as a first-in-human feasibility and safety study of the BDBD technique. The reported diagnostic sensitivity of conventional bronchoscopic biopsy for PPLs <2 cm is approximately 34%.[26] Based on this background, we aimed to explore whether the BDBD technique could improve diagnostic sensitivity in a small cohort. The planned enrolment number was set at 22 patients to provide preliminary data on feasibility and safety. No formal superiority testing was performed; instead, sensitivity with corresponding 95% CIs was descriptively reported.

The primary endpoint was the diagnostic sensitivity for malignancy (described in the trial registry as 'diagnostic rate of specimens') in samples obtained through the specified procedure. This was defined as the proportion of cases with a biopsy-based positive cancer diagnosis among all cases that underwent bronchoscopy with SKD-001 and had a final cancer diagnosis confirmed by either biopsy or final histopathological diagnosis. The specified procedure was defined as bronchoscope advancement beyond a bronchial bifurcation unpassable without balloon dilatation, direct biopsy site visualisation and absence of serious adverse events related to balloon dilatation. Cases not meeting the specified procedure criteria were not considered successful in primary endpoint analysis, despite accurate histopathological diagnosis. The postbronchoscopy follow-up period was 3 months. Secondary endpoints were the overall diagnostic yield, including benign diseases and the number of additional bronchial branches accessed beyond the initially impassable bifurcation. The overall diagnostic yield was defined as the proportion of all cases in which the BDBD technique was performed, for cases that fully met the specified procedure's criteria and were assessed as cancerous based on histopathological evaluation or non-cancerous based on bronchoscopy with subsequent confirmation as non-cancerous by final histopathological diagnosis. Sensitivity and specificity were calculated with 95% CIs using the Clopper-Pearson method. No subgroup analyses were prespecified for the primary or secondary endpoints. The number of additional bronchial branches accessed equalled the number of branches beyond the initial bifurcation that were reachable using the BDBD technique. For describing bronchial levels, segmental bronchi were considered the second generation. Means with SD or percentages are presented as appropriate. Exploratory comparisons (eg, vital signs and laboratory values) were performed using paired t-tests, with $p<0.05$ considered statistically significant. All statistical analyses were performed using Microsoft Excel V.16.88 (Microsoft Corporation; Redmond, Washington). Continuous variables are expressed as mean±SD.

Target conditions, index test and reference standard

The target condition was malignancy for the primary endpoint. The index test was the histopathological diagnosis obtained from a specimen collected after the specified procedure including the BDBD technique. The reference standard was a definitive histopathological diagnosis obtained via the index bronchoscopy or, if that sample was non-diagnostic, any subsequent tissue-acquisition procedure (repeat bronchoscopy or surgical resection) performed within 3 months of the index bronchoscopy. When tissue was still unavailable, chest CT performed within the same 3-month window served as the reference.

RESULTS

Patients and lesions

We obtained written consent from 25 patients (figure 2). In two cases, the bronchoscope reached the target without balloon dilatation. One case was excluded because the target lesion exceeded the size criterion on CT scans. Thus, the BDBD technique was performed for 22 patients at three clinical trial sites, namely Osaka University (n=14), Nagoya Medical Centre (n=7) and Osaka Habikino Medical Centre (n=1), by a total of 13 pulmonologists. Table 2 presents the background characteristics of these 22 patients. The mean lesion size was 15.3±3.3 mm (mean±SD).

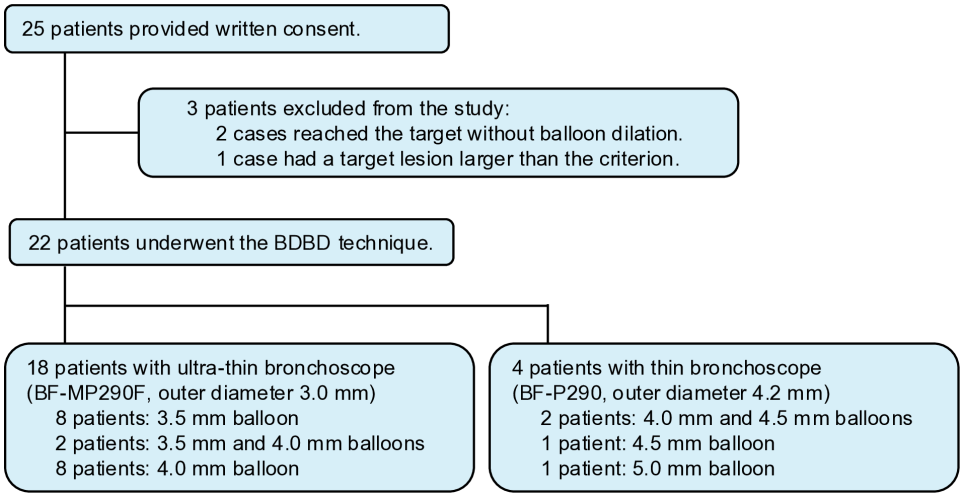

Figure 2 Flowchart of patients enrolled in the study. BDBD, balloon dilatation for bronchoscope delivery.

Table 2 Patients' demographic and lesion characteristics

	Total (n=22)
Sex	
Male, n (%)	12 (54)
Female, n (%)	10 (46)
Type of care	
Inpatient, n (%)	15 (68)
Outpatient, n (%)	7 (31)
Median age (SD), years	73.5 (8.7)
Tobacco-use history	
Never, n (%)	8 (36)
Previous, n (%)	10 (45)
Current, n (%)	4 (18)
Self-reported comorbidities	
COPD, n (%)	2 (9)
ILD, n (%)	0 (0)
Prior thoracic radiotherapy	0 (0)
CT slice thickness	
0.5 mm, n (%)	21 (95)
0.6 mm, n (%)	1 (5)
Lesion size in the largest diameter on CT scan	
10 mm<15 mm, n (%)	8 (36)
15 mm≤20 mm, n (%)	14 (64)
Pulmonary segments	
Right upper lobe, n (%)	7 (31)
Right middle lobe, n (%)	2 (9)
Right lower lobe, n (%)	8 (36)
Left upper lobe, n (%)	4 (18)
Left lower lobe, n (%)	1 (4)
Bronchus generation levels on CT, mean (SD)	7.8 (2.1)
Lesion location relative to the hilum	
Intermediate, n (%)	8 (36)
Peripheral, n (%)	14 (64)
Type of internal opacity	
Solid, n (%)	19 (86)
Part-solid, n (%)	3 (14)

COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease.

For preprocedural planning and bronchus sign detection, thin-section CT with a 0.5 mm slice thickness was used in most cases. Axial CT images of all target lesions, together with their anatomical locations, are provided in online supplemental e-Figure 1.

Procedures and complications

An ultrathin bronchoscope was used for 18 (81%) cases (table 3); it could reach 5.7±2.0 bronchial generations. The BDBD technique using 3.5 and 4.0 mm balloons (figure 2) accessed 2.3±1.0 additional branches. A thin bronchoscope was used for four cases (19%), reaching 4.0±1.4 bronchial generations. The BDBD technique using 4.0 to 5.0 mm balloons (figure 2) accessed 2.2±0.5 additional branches. In all cases, the BDBD technique allowed the bronchoscope to advance by at least one additional bronchial bifurcation. All balloons were manually inflated using a syringe, with a mean inflation duration of 21.1±7.6 s. The number of balloon inflations averaged 3.1±2.3 per case. The mean bronchoscopy duration was 56±17 min. The midazolam and fentanyl doses were 4.5±2.2 and 0.066±0.017 mg, respectively. A mean of 9.6±2.4 forceps biopsy samples was obtained per case.

Table 3 Procedural details

	Ultrathin bronchoscope (n=18)	Thin bronchoscope (n=4)	Total (n=22)
Bronchus levels with bronchoscope only	5.7±2.0	4.0±1.4	5.7±1.9
Additional bronchial levels reached with BDBD	2.3±1.0	2.2±0.5	2.3±0.9
Bronchoscopy duration (min)	57±17	49±22	56±17

Values are presented as mean±SD.
BDBD, balloon dilatation for bronchoscope delivery.

Three pulmonologists reviewed the video recordings of all balloon dilatations; no serious complications were associated with the procedure (table 4). Minor bleeding occurred immediately following balloon dilatation in one case, while two cases showed minor haemoptysis postbronchoscopy, likely related to the biopsy procedure. Minor epistaxis, attributed to transnasal bronchoscope use, occurred in one case. Comparisons of vital signs before and after bronchoscopy during visit 2 revealed slightly decreased diastolic blood pressure and pulse rate (online supplemental e-Table 1). Comparisons of blood tests and vital signs prebronchoscopy (visit 1) and approximately 2 weeks post-procedure (visit 3) showed significant differences in white blood cell counts; haemoglobin, albumin, total protein and potassium levels; and diastolic blood pressure (online supplemental e-Table 2). No case showed abnormalities on chest X-rays at visit 3.

Diagnostic yield and sensitivity

Table 5 presents the bronchoscopy findings and final diagnoses. Fifteen of the 22 cases were diagnosed with cancer and one was diagnosed with cryptococcosis through bronchoscopy. Thus, 72.7% (16/22; 95% CI 49.8% to 89.3%) lesions were successfully diagnosed. In an exploratory size-stratified analysis, the proportion successfully diagnosed was 88% (7/8; 95% CI 49.3% to 99.7%) for <15 mm lesions and 64% (9/14; 95% CI 35.1% to 87.2%) for 15–20 mm lesions. Three of the six non-diagnostic cases were subsequently diagnosed with lung cancer (two by surgical resection and one by repeat bronchoscopy). One case showed lesion resolution during imaging follow-up, and the remaining two were not definitively diagnosed within the planned 3-month follow-up period. Eighteen patients were ultimately diagnosed with cancer. No anticancer therapy or radiotherapy was performed between the index test and the reference standard assessment in any case.

Table 4 Complications

	Total (n=22)
Related to the BDBD technique	
Bleeding, minor, n (%)	1 (5)
Related to the forceps	
Haemoptysis, minor, n (%)	2 (9)
Related to the bronchoscope	
Nose bleeding, minor, n (%)	1 (5)

BDBD, balloon dilatation for bronchoscope delivery.

Table 5 Bronchoscopy findings and final diagnoses

Bronchoscopy findings	Total (n=22)	Final diagnosis and outcomes
Diagnostic	16	
Malignant		
Lung cancer		
Adenocarcinoma	9	
Squamous cell carcinoma	5	
Metastatic carcinoma		
Adenocarcinoma	1	
Benign		
Fungal infection	1	
Non-diagnostic	6	Malignant, 3
		Lung cancer, 3
		Benign, 3
		Disappeared, 1
		Suspected to be benign, diagnosis not confirmed during the follow-up period, 2

Among 15 patients diagnosed with cancer via bronchoscopy, 14 underwent the specified procedure that included advancing the bronchoscope beyond a bronchial bifurcation that was otherwise unpassable without balloon dilatation, direct visualisation of the biopsy site and absence of severe adverse events related to balloon dilatation. For one patient, the biopsy site could not be directly visualised, necessitating conventional fluoroscopy-guided indirect biopsy. Therefore, the study's primary endpoint, that is, the diagnostic sensitivity of histopathological diagnosis obtained from a specimen collected through the specified procedure including the BDBD technique, was 77.8% (14/18; 95% CI 52.4% to 93.6%). This exploratory result suggests that the BDBD technique may be promising, although the wide CI reflects the small sample size. The corresponding specificity was 100% (4/4; 95% CI 60.2% to 100%). A complete 2×2 contingency table is provided as online supplemental e-Table 3. The patient diagnosed with cryptococcosis met the specified procedure criteria. Thus, the secondary outcome, the overall diagnostic yield using the specified procedure, was 68.2% (15/22; 95% CI 45.1% to 86.1%), including benign diseases.

Case presentations

An example of the BDBD technique applied to a bronchial bifurcation is shown (figure 3). A 3.0-mm-diameter ultrathin bronchoscope (BF-MP290F) and 4 mm balloon were used.

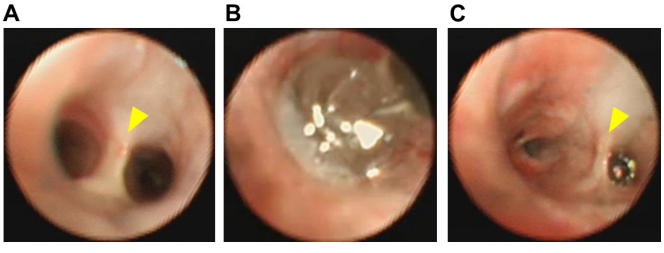

Figure 3 Balloon dilatation for bronchoscope delivery (BDBD) technique: step-by-step in humans. (A) Bronchus before performing the BDBD technique. (B) Balloon dilatation. (C) Bronchus after performing the BDBD technique. The yellow arrowheads indicate the same bronchial bifurcation.

Figure 4 presents a case involving a 10 mm nodule in the right middle lobe (figure 4A). An oblique CT image revealed that the bronchus bifurcated just before reaching the target, with two bronchi (right B4aiiβYYX and right B4aiiβYYY) leading to the lesion (figure 4B). Bronchoscopy was performed using the BF-MP290F; two 4.0 mm balloon dilatations were performed, allowing the bronchoscope to further approach the target (figure 4C). Direct bronchoscopic visualisation revealed black spots, likely from anthracotic pigmentation, and white mucosal changes in the right B4aiiβYYX lumen (figure 4D). Similar black spots were also evident in the right B4aiiβYYY (figure 4E). Forceps biopsy was performed from the right B4aiiβYYY, with direct biopsy site visualisation through the bronchoscope (figure 4F). During the procedure, we observed the forceps biopsy damage the bronchial wall and form a cavity within the lung parenchyma visible through the bronchoscope (figure 4F). The biopsy specimen confirmed adenocarcinoma.

Figure 5 shows another case with a 15 mm nodule in the right upper lobe (figure 5A). An oblique CT image showed a bronchus leading to the target and running adjacent to it (figure 5B). A small bronchial depression was also identified, which corresponded to the right B3biiαXYXYXXX (figure 5B), red arrowhead). Bronchoscopy was performed using the BF-MP290F, and balloon dilatation (3.5 mm) allowed bronchoscope advancement closer to the target (figure 5C). Obstruction with a yellow-white substance was observed at the right B3biiαXYXYXXX entrance (figure 5D), red arrowhead). r-EBUS was performed for the right B3biiαXYXYXXX to confirm that the probe was within the lesion (figure 5E), and biopsy revealed cryptococcosis.

DISCUSSION

This first-in-human feasibility study evaluated the feasibility and safety of the BDBD technique. For small lesions <20 mm, with an average size of 15.3 mm, diagnostic results showed 77.8% sensitivity for malignancy detection. This technique enabled bronchoscope advancement for an average of 2.3 additional bifurcations without any significant adverse events in 22 patients. Therefore, in this small observational study, the BDBD technique appeared to augment the diagnostic performance of bronchoscopy for small PPLs while maintaining an acceptable safety profile. The chief advantage is that it requires only a small, simple, disposable balloon catheter, unlike cost-intensive systems such as robotic bronchoscopy.

The BDBD technique may significantly shift bronchoscopy strategies. Bronchoscopy has been limited by the assumption that it cannot reach the lung periphery. Thus, most studies have focused on improving the diagnostic yield of indirect biopsy for targets beyond bronchoscopic reach. The BDBD technique refutes this assumption by demonstrating that bronchoscopy can reach further into the lung periphery than previously thought. Nevertheless, further investigation should optimise its indications and applications. For instance, bronchoscope advancement using the BDBD technique may offer little additional benefit when r-EBUS confirms that the probe is within the target and a guide sheath can be utilised. Conversely, the ability of the BDBD technique to facilitate bronchoscope advancement deeper into the lung periphery may be of significant value if r-EBUS indicates that the probe is adjacent to or outside the target. Procedures performed with the ultrathin scope were particularly lengthy, averaging 57 min. Although no clinically relevant vital sign changes were observed after bronchoscopy, relative to those before bronchoscopy (online supplemental e-Table 1), the prolonged procedure may have required higher-than-usual

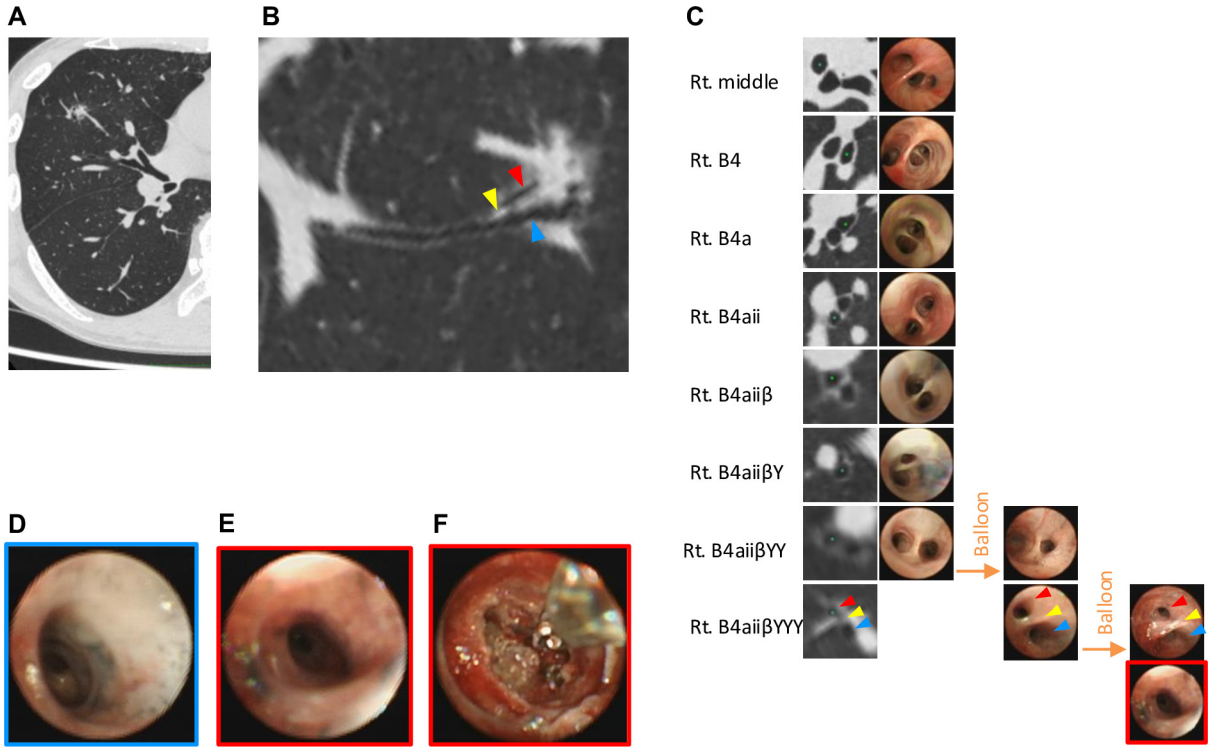

Figure 4 A case of direct visual biopsy using the balloon dilatation for bronchoscope delivery technique (adenocarcinoma). (A) An axial CT image shows the target (10 mm) located in the right middle lobe. (B) An oblique CT image displays the target and the two bronchial paths leading to the target. (C) A detailed schematic shows the bronchial pathway to the target. The left column lists the names of the bronchi (eg, Rt. middle, Rt. B4, Rt. B4a); the corresponding bronchoscopy view-like oblique CT and bronchoscopy images are shown on the right. Green dots indicate the planned pathway to the target in the oblique CT images. The 'Balloon' labels indicate where balloon dilatation is performed to proceed further into the bronchi. (D) Bronchoscopy view in the Rt. B4aiiβYYX bronchus. (E) Bronchoscopy view in the Rt. B4aiiβYYY bronchus before forceps biopsy. (F) Bronchoscopy view in the Rt. B4aiiβYYY bronchus during forceps biopsy. In all panels, blue arrowheads indicate the Rt. B4aiiβYYX bronchus; a blue border surrounds the bronchoscopy view. Red arrowheads indicate the Rt. B4aiiβYYY bronchus, with a red border surrounding the bronchoscopy view. A yellow arrowhead indicates the bifurcation between the Rt. B4aiiβYYX and B4aiiβYYY. Rt, right.

sedative doses. Further investigation should determine the precise extent to which the BDBD technique itself contributes to prolonged procedures. Moreover, preprocedural CT analysis plays a crucial role in effective use of the BDBD technique. This study used the oblique method and DirectPath system for analysis, and all observed bronchial bifurcations during bronchoscopy matched the preprocedural CT findings. However, further research is warranted to refine procedural strategies and maximise the effectiveness of the BDBD technique.

The BDBD technique does not guarantee that the bronchoscope can reach all areas of the lung periphery. In one case, the bronchoscope could not reach the right B1 bronchus periphery, even with the BDBD technique. Despite applying torque to the bronchoscope, further advancement failed. This case demonstrates that some cancer targets cannot be accessed even with the BDBD technique. In addition, the bronchus quickly returned to its original size after balloon dilatation in some cases, requiring multiple dilatations for successful advancement. This phenomenon was more common in central than peripheral bronchi, possibly because of smooth bronchial muscle.

No severe adverse events occurred with balloon dilatation. However, we propose recommendations for safe implementation of the BDBD technique. X-ray fluoroscopy is crucial to confirm balloon positioning and prevent pneumothorax. In addition, we recommend avoiding air or water introduction through the bronchoscope near the pleura. No severe bronchial injuries, such as macroscopic laceration or perforation, were observed in this study, but additional dilatation should be avoided if severe damage is suspected. Minimising invasiveness is also critical, and an ultrathin scope should be used when feasible. The recent development of cancer gene panel testing for cytology specimens has decreased the necessity for large histology samples, increasing the practicality of thinner bronchoscopes.[27 28]

One significant study limitation is its single-arm design without a control group. This limited direct assessment of the effect of the BDBD technique on diagnostic sensitivity. Additionally, the small sample size restricts the generalisability of the findings, necessitating larger studies to confirm our results for diverse patient populations. The experience of the operator may have also influenced the outcomes of the BDBD technique; the learning curve associated with this new technique was not assessed, potentially affecting the reproducibility of the results in other settings. Furthermore, the follow-up duration was only 3 months, and late complications and long-term effectiveness remain unknown. Clarification of both late adverse events, such as airway remodelling or fibrosis after balloon dilatation, and true long-term diagnostic performance will require studies with substantially longer follow-ups. Two patients without a definitive diagnosis declined repeat biopsy or surgery; their lesions remained stable on CT even 1 year later. However, indolent malignancy cannot be entirely excluded and may have inflated our sensitivity estimate. Finally, including only patients with bronchus sign-positive lesions and candidates for the BDBD procedure may have introduced selection bias, leaving the

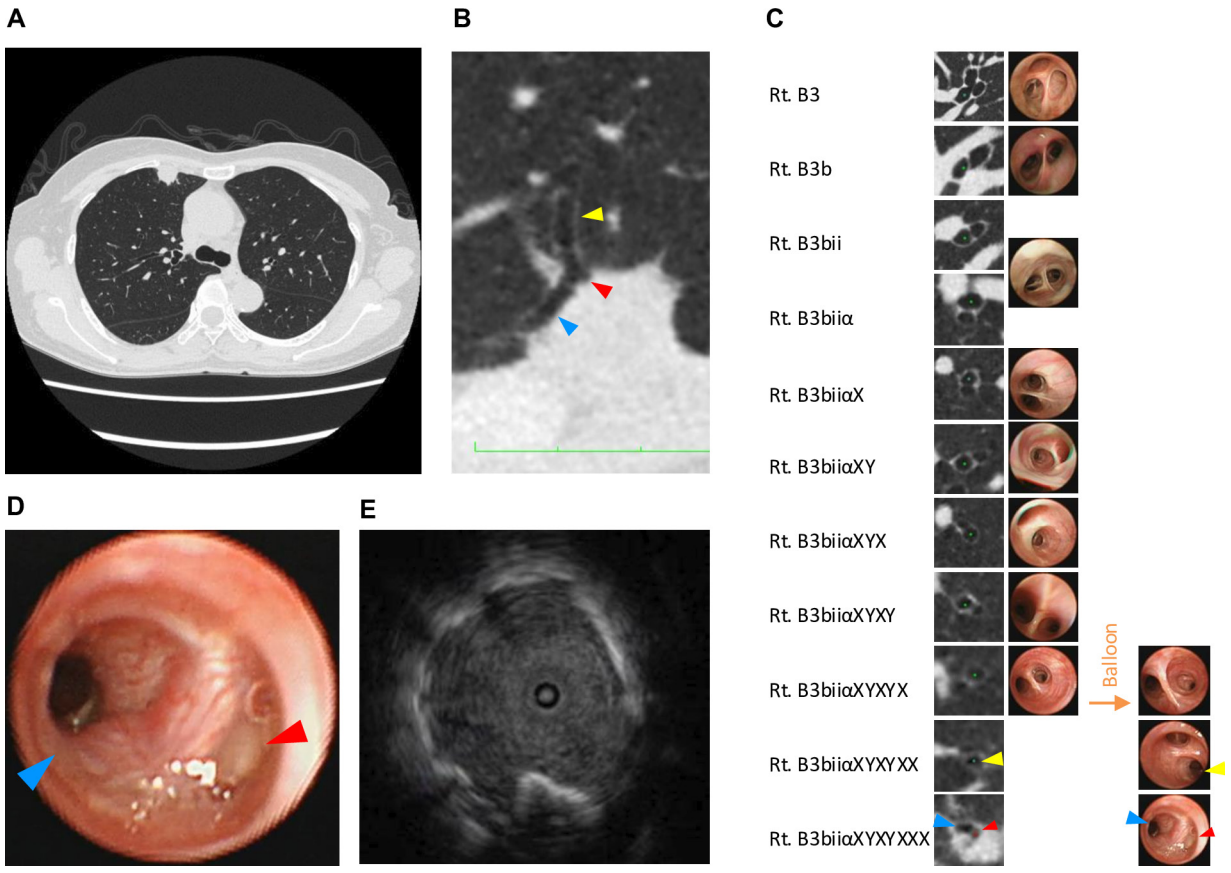

Figure 5 A case of direct visual biopsy using the balloon dilatation for bronchoscope delivery technique (cryptococcosis). (A) An axial CT image shows the target (15 mm) located in the right upper lobe. (B) A magnified oblique CT image shows the target area. A bronchus leads directly to the target and runs adjacent to it. Each increment of the green scale represents 10 mm. (C) A detailed schematic shows the bronchial pathway to the target. The left column lists the bronchi names (eg, Rt. B3, Rt. B3b, Rt. B3bii); the corresponding CT and bronchoscopy images are shown on the right. Green dots indicate the planned pathway to the target in the bronchoscopy view-like oblique CT images. The 'Balloon' label indicates where balloon dilatation is performed to proceed further into the bronchi. (D) Magnified bronchoscopy view shows the Rt. B3biiαXYXYXXX, which is the same as the last image in (C). (E) Radial EBUS image obtained for the Rt. B3biiαXYXYXXX to confirm that the probe is within the lesion (marked by the red arrowhead in D). In all panels, the Rt. B3biiαXYXYXX, Rt. B3biiαXYXYXXX and Rt. B3biiαXYXYXXY bronchi are indicated by yellow, red and blue arrowheads, respectively. EBUS, radial endobronchial ultrasound; Rt, right.

applicability of the technique to a broader patient population uncertain. In particular, the potential role of BDBD for bronchus sign-negative lesions remains an important topic that warrants future investigation.

In conclusion, the BDBD technique shows promise for enhancing the bronchoscopic diagnosis of small PPLs by facilitating bronchoscope advancement into the lung periphery with an acceptable risk level in this small observational study. Compared with robotic bronchoscopy or cone-beam CT-guided systems, BDBD is a simpler and more affordable approach, and its ability to allow direct visualisation might also facilitate future local ablative treatments. However, large-scale, controlled studies are needed to confirm the effectiveness of the BDBD technique, refine the procedure and establish its role in routine clinical practice.

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Acknowledgements This study has been submitted for presentation at the ATS 2025 International Conference to be held in San Francisco, CA on May 17–21, 2025.

Contributors KM had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis, and serves as the guarantor of the work. MO, HSuz, HSak, SS, NO, TI, YK, TS, HH, IN, YT and AK contributed substantially to the study design, data analysis and interpretation and the writing of the manuscript.

Funding Kaneka Corporation supplied the SKD-001 catheters and provided unrestricted funding. Kaneka collaborated with the academic investigators on the study design but had no role in the subsequent trial conduct, site operations, patient management, data collection, data monitoring, statistical analysis, data interpretation or manuscript drafting and preparation, nor in the decision to submit it for publication; all of these activities were undertaken independently by the authors. This study was also supported by the Osaka City Innovation Support Grant 2022 (no grant number).

Competing interests KM: Kaneka—Research (institutional) and honouraria (personal) related to this research; Chugai, Takeda, MSD, Nippon Kayaku, Ziosoft, AstraZeneca, Novartis—Speaker (unrelated to this study); Mitsubishi Tanabe, Ziosoft—Collaborative research (unrelated to this study). MO: Kaneka—Research

(institutional) related to this research; AstraZeneca, AMCO, Novartis, Canon Medical Systems, Eli Lilly, MSD, Merit Medical, Olympus, Fujifilm, Kaneka Medix—Speaker (unrelated to this study); AbbVie, GlaxoSmithKline, MSD, Parexel, Sanofi, AstraZeneca, Janssen, Ono Pharmaceutical, Gilead Sciences, ArriVent Biopharma—Research funding (institutional, unrelated to this study). HSu: Kaneka—Research (institutional) related to this research; Chugai, AstraZeneca, MSD, Takeda, Eli Lilly—Speaker (unrelated to this study). HSa: Kaneka—Honoraria (personal) related to this research. SS: Kaneka—Honoraria (personal) related to this research; Pentax—Consultant (unrelated to this study); AstraZeneca, Canon Medical Systems, Chugai, Eli Lilly, GlaxoSmithKline, Bristol-Myers Squibb, Novartis, Sanofi, Kyorin, Boehringer, Olympus, Teijin—Speaker (unrelated to this study). NO: Kaneka—Honoraria (personal) related to this research; Chugai, AstraZeneca, Ono Pharmaceutical, Takeda, MSD, Daiichi Sankyo, Eli Lilly—Speaker (unrelated to this study). TI: Kaneka—Honoraria (personal) related to this research; AstraZeneca, Amco, Chugai, COOK, Daiichi Sankyo, Eli Lilly, Fujifilm, GlaxoSmithKline, Merck, Novartis, Olympus—Speaker (unrelated to this study); Hitachi, Hitachi High-Tech—Collaborative research (unrelated to this study). YK: Kaneka—Research (institutional) related to this research; AstraZeneca, MSD, Taiho Pharmaceutical, Chugai Pharmaceutical, Ono Pharmaceutical, Boehringer, Eli Lilly, Kyowa Kirin, Nippon Kayaku, GSK, Takeda, Daiichi Sankyo—Speaker (unrelated to this study). TS: Kaneka—Research (institutional) related to this research; Chugai, AstraZeneca, MSD, Ono Pharmaceutical, Eli Lilly—Speaker (unrelated to this study). HH: Kaneka—Research (institutional) related to this research; AstraZeneca, Boehringer, GSK, Kyorin, Taiho Pharmaceutical, Chugai Pharmaceutical, Sanofi—Speaker (unrelated to this study). IN: Chugai—Speaker (unrelated to this study); PITTAN—Collaborative research (unrelated to this study). YT: Kaneka—Research (institutional) related to this research; GSK, Sanofi, AstraZeneca, Boehringer, Chugai, Kyorin—Speaker (unrelated to this study). AK: Kaneka—Research (institutional) related to this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by The study was approved by the institutional review board of each participating institution (Identifier No. 221005-A, Osaka University Hospital; Identifier No. S410-1, NHO Nagoya Medical Centre; Identifier No. 190-06_01, Osaka Habikino Medical Centre) and registered with the Japan Registry of Clinical Trials (identifier No. jRCT2052220174). This study was conducted in accordance with the amended Declaration of Helsinki. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The data that support the findings of this study and the original study protocol are available from the corresponding author (KM) on reasonable request.

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