MEDICAL INSIGHTS ePaper

Cryobiopsy vs forceps for bronchoscopic lung biopsy

The FROSTBITE-2 randomized clinical trial

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Background

Transbronchial biopsy is a cornerstone procedure in interventional pulmonology and is routinely used for the evaluation of pulmonary nodules or masses, evaluation of lung transplant rejection, and diffuse parenchymal lung disease. Despite major advances in bronchoscopic navigation technologies, the diagnostic yield of conventional forceps biopsy remains limited and specimen quality may be compromised by small sample size and crush artifact, potentially restricting histopathologic interpretation and downstream molecular analysis.

Cryobiopsy has emerged as a promising alternative because tissue acquisition through localized freezing can provide larger and more intact specimens with improved preservation of tissue architecture. However, earlier cryobiopsy approaches using larger cryoprobes (1.9 mm and 2.4 mm) raised important safety concerns, particularly related to bleeding and pneumothorax, because the bronchoscope and cryoprobe had to be removed en bloc during specimen retrieval. These limitations restricted broader adoption in routine bronchoscopic practice.

To overcome these challenges, an Erbe flexible single-use 1.1-mm cryoprobe was developed that permits tissue retrieval through the bronchoscope working channel while maintaining continuous airway visualization. Earlier studies, including the FROSTBITE trial, demonstrated feasibility and an acceptable safety profile of this approach. However, randomized clinical data comparing diagnostic performance with standard forceps biopsy had not previously been available.

The FROSTBITE-2 trial therefore aimed to determine whether transbronchial biopsy with an Erbe 1.1-mm cryoprobe improves diagnostic yield and histologic specimen quality compared with conventional forceps biopsy while maintaining procedural safety across multiple bronchoscopic indications.

Methods

FROSTBITE-2 was an investigator-initiated, multicenter, open-label randomized clinical trial conducted at 9 US medical centers. According to the authors, this was the first randomized clinical trial comparing an Erbe 1.1-mm cryoprobe with forceps for transbronchial biopsy.

The study enrolled 500 patients aged ≥18 years who were scheduled to undergo transbronchial biopsy for pulmonary nodules or masses, lung transplant evaluation, or diffuse parenchymal lung disease. Participants were randomized 1:1 to undergo transbronchial biopsy using either an Erbe 1.1-mm cryoprobe (n=250) or conventional forceps biopsy (n=250).

Bronchoscopic procedures were otherwise performed according to institutional standard practice. Localization modalities including fluoroscopy and advanced bronchoscopic navigation techniques could be used at the discretion of the treating bronchoscopist. Outcome assessors and centralized pathology reviewers were masked to treatment allocation to reduce interobserver variability.

In the cryoprobe group, tissue samples were retrieved through the bronchoscope working channel while the bronchoscope remained in the airway throughout the procedure, allowing continuous airway visualization.

The primary endpoint was diagnostic yield, defined as the percentage of patients in whom transbronchial biopsy established a specific histopathologic diagnosis. Secondary analyses included subgroup diagnostic yield, histologic specimen quality, specimen size, crush artifact proportion, artifact-free tissue proportion, and safety outcomes.

Results

Diagnostic yield

The overall diagnostic yield was significantly higher with cryobiopsy compared with forceps biopsy:

Diagnostic Yield	Erbe cryoprobe	Forceps	Absolute difference (95% CI)	P value
Overall	88.6% (217/245)	78.8% (193/245)	9.8% (3.3–16.3%)	.003

Subgroup analyses

Subgroup	Erbe cryoprobe	Forceps	P value
Lung nodules/masses	83.2%	70.1%	.04
Lung transplant	96.0%	88.7%	.03
Diffuse parenchymal lung disease	72.0%	62.5%	.55

Cryobiopsy demonstrated significantly higher diagnostic yield in patients with pulmonary nodules/masses and lung transplant evaluation. No statistically significant difference was observed in diffuse parenchymal lung disease, however, interpretation is limited by the relatively small subgroup size.

Histologic specimen quality

Cryobiopsy produced significantly larger specimens with less crush artifact compared with forceps biopsy.

Histologic Parameter	Erbe cryoprobe	Forceps	P value
Median total specimen area	16.7 mm^2	9.6 mm^2	<.001
Median alveolated area	13.1 mm^2	6.4 mm^2	<.001
Median crush artifact	0 %	5 %	<.001
Median artifact-free tissue	100 %	95 %	<.001

Safety

Unlike larger conventional cryoprobes, the Erbe 1.1-mm cryoprobe allowed specimen retrieval through the bronchoscope working channel while maintaining continuous airway visualization throughout the procedure. Only 0.6% of procedures required rigid bronchoscopy and 0.4% used prophylactic bronchial blockers, suggesting compatibility with routine flexible bronchoscopic workflows.

The predefined composite safety endpoint included pneumothorax requiring drainage, significant bleeding, and respiratory failure. No composite safety endpoint events occurred in the cryoprobe group, whereas four events occurred in the forceps group*.

No pneumothoraces were observed in the cryoprobe group, while six pneumothoraces occurred in the forceps group, including four requiring chest tube placement. No grade ≥3 bleeding events, respiratory failure events, or deaths were reported in either study arm.

Safety Outcome	Erbe cryoprobe	Forceps
Composite safety endpoint events*	0	4
Pneumothoraces	0	6
Pneumothoraces requiring chest tube placement	0	4
Grade ≥3 bleeding events	0	0
Respiratory failure events	0	0
Deaths	0	0

Implications and recommendations

The FROSTBITE-2 trial demonstrated that transbronchial biopsy with an Erbe 1.1-mm cryoprobe achieved significantly higher overall diagnostic yield compared with forceps biopsy, without an increase in major procedural complications. No grade ≥3 bleeding events, respiratory failure events, or deaths were observed in the cryoprobe group.

Cryobiopsy also produced larger tissue specimens with less crush artifact and a higher proportion of artifact-free lung parenchyma, which may facilitate histopathologic interpretation through improved preservation of tissue architecture.

Overall, the trial provides randomized evidence supporting the use of an Erbe 1.1-mm cryoprobe as an effective transbronchial biopsy modality with improved specimen quality and preserved procedural safety.

Products

For FROSTBITE-2 the Erbe flexible single-use 1.1-mm cryoprobe was used in combination with the ERBECRYO® 2.

Erbe flexible cryoprobe for single use, 1.1 mm

References

1 Thiboutot J, Kapp CM, Illei P et al. Cryobiopsy vs Forceps for Bronchoscopic Lung Biopsy: The FROSTBITE-2 Randomized Clinical Trial. JAMA. Published online May 18, 2026; doi.org/10.1001/jama.2026.7908