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BEYOND THE PRIMARY TARGET: THE SAFETY PROFILE OF SAMPLING SYNCHRONOUS PULMONARY NODULES

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The clinical question

Does sampling multiple peripheral pulmonary nodules (PPNs) during a single robotic-assisted bronchoscopy (RAB) session provide clinically meaningful diagnostic and staging information, and what procedural factors predict benefit?

Take Home Message

Targeting multiple synchronous PPNs during the same RAB session is safe and clinically impactful, altering the final diagnosis in 38% of cases. Procedural factors, including effective lesion localization and sampling tool diversification, predict the likelihood of benefit, and the authors conclude that same session multinodule sampling should be routinely incorporated into RAB practice.

Background

The increasing use of chest CT and lung cancer screening programs has led to more frequent detection of synchronous multiple peripheral pulmonary nodules (mPPNs). When present, these nodules may represent a range of diagnoses, including synchronous multiple primary lung cancers (sMPLCs), metastatic disease, or coexisting infection, each with distinct staging, prognostic, and therapeutic implications. Tissue sampling of multiple nodules is therefore often necessary, yet conventional biopsy techniques typically require sequential procedures. CT-guided transthoracic needle biopsy carries a meaningful risk of pneumothorax, making same-session sampling of multinodules impractical, while prior bronchoscopic platforms lacked the reach and stability needed for smaller or more peripheral lesions...

... Robotic-assisted bronchoscopy (RAB) represents the next evolution in advanced diagnostic bronchoscopy (ADB), offering improved catheter stability, maneuverability, and peripheral access. While RAB has demonstrated diagnostic yields approaching those of CT-guided biopsy with a superior safety profile, its application has largely been limited to single-nodule procedures in published literature, with same-session multinodule sampling representing 0–19% of reported cases, and with no data on outcomes in that context. No formal guidelines exist for the bronchoscopic management of synchronous multiple PPNs. Current standard practice typically involves sequential procedures to characterize each lesion individually, using either CT-guided transthoracic biopsy or ADB. RAB is increasingly used as a first-line modality for peripheral pulmonary lesion biopsy given its favorable diagnostic yield and safety profile, however, routine same-session multinodule sampling has not been formally recommended or systematically evaluated prior to this study. The authors hypothesized that targeting mPPNs during a single RAB session would be clinically meaningful and undertook this study to evaluate the clinical impact, safety, and procedural predictors of benefit in the setting of multinodule RAB.

Study design

- **Study type:** Single-center retrospective analysis of a prospectively maintained QI registry.
- **Primary Outcome:** Proportion of multinodule RAB procedures in which sampling secondary PPNs clinically benefited the patient.
- **Secondary Outcomes:**
  - Predictors (patient, procedural, nodule) of diagnostic benefit from secondary nodule sampling
  - Per-nodule and per-procedure diagnostic yield
  - Procedure duration
  - Complications (with focus on pneumothorax)
  - Radiation exposure
- Definition of clinical benefit: Secondary PPN sampling was considered beneficial if it: (1) established a second, distinct diagnosis in addition to the primary nodule result; (2) provided the exclusive diagnosis when the primary target was non-diagnostic; or (3) delivered clinically meaningful upstaging information impacting therapeutic management.

Population

- **Inclusion criteria:**
  - All consecutive RABs performed by 2 interventional pulmonologists from January 2022 to June 2024
  - Procedures intended for diagnostic sampling
- **Exclusion criteria:**
  - RABs performed solely for fiducial marking or other non-diagnostic purposes
- **Baseline characteristics:**
  - 341 total RABs targeting 503 PPNs; 125 RABs (37%) sampled multiple nodules (range 2–5)
  - Mean age 66.9 years (± 12.3); 55% female; 88% outpatient
  - Among multinodule cases: 55% bilateral, 26% targeted >2 nodules
  - No significant between-group differences in patient comorbidities, immunosuppression, or operator
  - Nodule characteristics:
    - 503 total PPNs: 216 primary targets from single-nodule RABs, 125 primary targets, and 162 secondary targets from multinodule RABs
    - Secondary nodules were smaller (median 15 mm) than primary targets (median 18–21 mm; p=0.003), more frequently ≤10 mm (31.5% vs. 16–21%), and less often solid or bronchus-sign positive (p=0.001)

Outcomes

- **Primary Outcome** – Clinical Benefit of Secondary Nodule Sampling:
  - Secondary PPN sampling impacted the final clinical diagnosis in 48 of 125 multinodule RABs (38.4%; 95% CI: 30.3%–47.2%)
  - Second, distinct diagnosis established: 24 cases (19.2%), including 14 sMPLCs, 7 mixed malignant–infectious, and 2 dual infections
  - Lung cancer upstaged (M1a or T4): 12 cases (9.6%), half with unrevealing convex EBUS lymph node survey
  - Exclusive diagnosis from secondary nodule: 12 cases (9.6%), increasing per-procedure yield by 9.6% over primary-nodule-only strategy (95% CI: 5.6%–16.0%)
  - Among 59 multinodule cases with primary lung cancer, 33 (56%) derived meaningful information from secondary sampling...

- **Secondary Outcomes**
  - Multivariate Predictors of Diagnostic Benefit:
    - Older patient age (aOR 1.11, 95% CI: 1.05–1.17; p<0.001)
    - ROSE unavailability (aOR 5.96, 95% CI: 1.53–23.26; p=0.010)
    - Only a single biopsy tool was used for the primary nodule (aOR 5.84, 95% CI: 1.44–23.75; p=0.014)
    - Concentric radial EBUS image obtained from any secondary nodule (aOR 3.68, 95% CI: 1.17–11.62; p=0.026)
    - Multiple tools used to biopsy any secondary nodule (aOR 3.18, 95% CI: 1.05–9.65; p=0.041)
    - No nodule feature (size, location, border, attenuation) predicted benefit
  - Diagnostic Yield:
    - Per-procedure yield: 89.6% (multinodule) vs. 83.3% (single-nodule); p=0.11
    - Secondary nodules had lower per-nodule yield than primary targets (61.7% vs. 80.0%)

- **Safety**
  - Pneumothorax requiring chest tube: 2.4% (multinodule) vs. 0.5% (single-nodule); p=0.11
  - Any major complication: 5.6% vs. 3.7%; p=0.41

- **Operational Metrics**
  - Median RAB duration: 76 min (multinodule) vs. 45 min (single-nodule); p<0.001
  - +20.8 minutes per additional nodule targeted (95% CI: 17.5–24.1)
  - Radiation exposure: 4.6 Gy-cm^2 (multinodule) vs. 2.4 Gy-cm^2 (single-nodule); p<0.001

Commentary

Study Strengths:

This study addresses a previously unexplored clinical question. Despite the growing use of RAB and the high prevalence of synchronous PPNs in screened populations, no prior publication had rigorously evaluated the multinodule RAB setting. The analysis draws from a prospectively maintained, consecutively enrolled registry, substantially reducing ascertainment bias compared to purely retrospective chart reviews. The classification of "clinical benefit" is well-constructed and clinically meaningful, requiring either a distinct second diagnosis, exclusive diagnosis, or actionable staging change. The use of a multidisciplinary thoracic tumor board for adjudicating all multifocal malignancy cases strengthens the validity of the staging and sMPLC classifications, which are difficult to standardize. The study also provides practical procedural guidance, showing that using multimodal biopsy tools and confirming localization with concentric rEBUS independently predicted benefit, reinforcing ADB principles already embedded in training.

Study Limitations:
The retrospective, single-center design is the primary limitation. Although the registry was prospective, the decision to target multiple nodules, and which nodules to target, was at the bronchoscopist's discretion, introducing selection bias. Clinicians may preferentially pursue secondary targets when they appear technically accessible or diagnostically likely, inflating apparent benefit rates. The absence of cone-beam CT (CBCT) during the study period is notable given its growing adoption. However, CBCT may have improved secondary nodule yield, suggesting the 38% benefit rate could be an underestimate. Cryobiopsy was used in only 16.6% of cases and may further enhance yield for smaller secondary lesions. Although current data is inconclusive on the clinical significance of the practice, the study does not mention whether new biopsy tools were used to target separate lesions. Only four patients required chest tube placement for a pneumothorax; three of them were in the multiple nodule cohort. Radiation exposure in multinodule cases was nearly double that of single-nodule procedures, and while the absolute values remain modest, cumulative exposure across repeat procedures warrants consideration, particularly in younger or immunosuppressed patients. Finally, generalizability is uncertain as the study was conducted at a high-volume academic RAB center, and the observed mix of infectious and oncologic diagnoses may not reflect practice elsewhere.

For the practicing interventional pulmonologist, this paper makes a compelling case for routine multinodule sampling during RAB. The 38% clinical impact rate, particularly the 56% meaningful information rate among patients ultimately found to have lung cancer, justifies the additional procedure time and modest radiation cost. The finding that nodule characteristics do not predict benefit is particularly actionable as it removes a common decision heuristic and argues for defaulting to biopsying all accessible synchronous nodules. As RAB technology matures with improved imaging integration and cryobiopsy protocols, the utility of this strategy is likely to grow.

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Suggested Reading

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