A needle in the haystack - looking for occult N2 disease. What is the diagnostic performance of EBUS-TBNA for mediastinal staging of centrally located T1N0M0 NSCLC clinical staged with PET/CT

Hypothesis

Evaluate the clinical utility and diagnostic accuracy of EBUS-TBNA for centrally located T1N0M0 NSCLC clinically staged with PET/CT

Conclusion

EBUS-TBNA shows a good diagnostic performance for centrally located T1N0M0 staged with PET-CT and should be considered to evaluate for occult N2 disease prior to lung resection.

Study Background

- The incidence of early stage NSCLC is likely to increase with the introduction of lung cancer screening programs
- Proceeding for surgical resection after a normal appearing mediastinum/hilum on PET/CT may be satisfactory in some cases, however in selected patients, invasive mediastinal staging may be indicated to detect occult N2 disease
- The overall prevalence of occult N2 disease in clinical stage 1 NSCLC (cT1N0) after a normal appearing mediastinum on PET-CT ranges from 4.6% to 8% in different case series. It is higher for N1 on PET-CT (26% to 41%), tumors >= 3cm (11%-22%) and central T1N0 tumors (4.6% to 6.4%)
- With the promising results of the latest randomized controlled trials on neoadjuvant chemo immunotherapy for patients with resectable NSCLC in stages IB-IIIA, the selection of patients with nodal disease before surgery has become even more crucial.

Current Practice

- As per current practice guidelines, invasive mediastinal staging is indicated even in cases of normal appearing mediastinum on PET-CT for clinical stage I disease in the following scenarios; cN1 disease, >= T2 lesions and central T1N0 lesions (inner 2/3rd of hemithorax - ESTS definition)
- While guidelines recommend EBUS-TBNA as the first choice for invasive mediastinal staging, the reported sensitivity of EBUS-TBNA to detect occult N2 disease for normal appearing mediastinum on PET-CT can be as low as 49%.
- This study attempts to provide more information on diagnostic accuracy and clinical utility (in terms of NNT) of EBUS-TBNA in central T1N0M0 disease.

Study Design

- **Type of trial:** Retrospective analysis of prospectively collected data
- **N:** 118 patients
- **Study population:** Adult patients with pure solid cT1N0M0 NSCLC
- **Setting:** Two centers in Barcelona, Spain
- **Enrollment:** Patients with pure solid, centrally located cT1N0M0 NSCLC staged with PET-CT who underwent EBUS TBNA and then complete surgical staging.
- **Assessment period:** January 2020 to June 2022
- **Primary outcome:** Sensitivity, specificity, NPV, PPV and accuracy of EBUS for mediastinal staging
- **Secondary outcome:** Number needed to undergo EBUS-TBNA to avoid a case of pathologic N2 disease after resection.

Population

Inclusion criteria

- Patients with pure solid, cT1N0M0 NSCLC staged with PET-CT and EBUS-TBNA who underwent surgical staging with lung resection and systematic node dissection and/or mediastinoscopic lymphadenectomy

Exclusion criteria

- Prior lung resection or mediastinoscopy
- Ground glass nodules, mixed solid/sub-solid nodules
- Patient who could not undergo surgical staging

Baseline Characteristics

- Age in years, mean (SD) 68.0 (+- 8.1)
- Gender: 84% male
- Tobacco status: Never smoker (13.6%), Current smoker (38.1%), Former smoker (48.3%)
- Tumor size (mm), mean (SD): 21.3 (+- 6.0)
- Location: Right upper lobe (35.6%), Middle lobe (5.9%), Right lower lobe (17.8%), Left upper lobe (30.5%), Left lower lobe (12%)
- Histologic type: Adenocarcinoma (64.5%), Squamous cell cancer (24.6%)
- T1 category: T1a 9.3%, T1b 38.1%, T1c 52.6%
- Number of lymph nodes sampled by EBUS-TBNA, number (SD): 8.8 (+- 3.3)
- Number of nodal stations sampled through EBUS-TBNA, number (SD): 5.1 (+-1.2)

Interventions

- Adult patients with cT1N0M0 NSCLC staged by PET-CT with centrally located tumors underwent mediastinal staging by EBUS-TBNA. Endobronchial ultrasound TBNA staging included sampling of every lymph node measuring more than 5 mm starting from contralateral hilar and mediastinal lymph node stations and proceeding to the subcarinal, ipsilateral mediastinal and hilar lymph node stations. Rapid on-site cytologic examination was done for every station. Benign lymph nodes were defined by detection of normal lymph node tissue, lymphocytes and absence of cancer cells. If malignancy was detected, the needle was changed to avoid contamination, and examination was continued.
- Every patient with N0/N1 tumors were discussed in a multidisciplinary tumor conference. In one of the institutions, all the patients underwent surgical exploration of the mediastinum for VAMLA or video-mediastinoscopy (sampling of the right and left inferior paratracheal and subcarinal lymph node stations regardless of nodal size) prior to lung resection. In the other institution, only patients with N1 disease after EBUS-TBNA, co-morbidities and /or high surgical risk underwent mediastinoscopy to gain confidence prior to lung resection
- Systematic lymph node dissection (SND) with lung resection was performed as per the recommendations of The Bronchogenic Carcinoma Cooperative Group of the Spanish Society of Pneumology and Thoracic Surgery

Outcomes

- 118 patients with centrally located cT1N1M0 with negative mediastinum on PET-CT were studied.
- During EBUS TBNA, a mean of 5.1 nodal stations and 8.8 lymph nodes were sampled.
- Endobronchial ultrasound-TBNA proved N2 disease in four out of 118 patients. In the remaining 114 patients who went for surgery, two patients had N2 disease detected during surgery (one in 4L and the other at station 5). The overall prevalence of N2 disease in this series was 6/118 (5.1%).
- For detecting mediastinal metastases (N2 disease), EBUS-TBNA had a sensitivity of 66% (4/6), specificity of 100%(112/112), NPV of 98%(112/114), PPV of 100% (4/4), and diagnostic accuracy of 98% (116/118)
- Thirty-one EBUS-TBNA procedures would be needed to diagnose one case of occult N2 disease in central cT1N0M0 tumors (normal mediastinum on PET-CT). This number was 21 for upper lobe tumors, 24 for T1c tumors, and 26 for adenocarcinoma.
- VAMLA or video-mediastinoscopy did not identify any additional lymph node involvement after EBUS-TBNA.

Study Strengths

- First study to describe the diagnostic features of EBUS-TBNA in patients specifically with centrally located stage 1A NSCLC (cT1N0M0), not those with the overall stage one NSCLC.
- The prevalence of occult N2 disease in cT1N0 tumors (5.1%) is consistent with other larger case series.
- The mediastinal and hilar sampling by EBUS-TBNA was very thorough with a high median number of lymph nodes sampled (8.8 lymph nodes, 5.1 lymph node stations). Out of the false negative EBUS for N2 disease, one was a 4 mm focus in station 4L and the other was at station 5 was not sampled by EBUS.
- The NNT calculation provides a useful context to determine the utility of EBUS-TBNA to identify mediastinal nodal mets for patients who may benefit from Neoadjuvant cancer directed therapies, including immunotherapy.

Study limitations and potential for bias

- One of the major limitations of the study is the small sample size and even smaller event rate, which means that the diagnostic performance and NNT calculation should be interpreted with caution.
- These results may not be generalized to other institutions, where the median number of lymph node stations or lymph nodes may be lower than in this study.
- More studies may be needed to further characterize the diagnostic performance of EBUS in patients of the normal mediastinum on PET/CT with high risk of occult N2 disease.

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Research Question

What is the diagnostic performance of EBUS-TBNA for mediastinal staging of centrally located T1N0M0 NSCLC clinically staged with PET/CT?

AABIP Take Home Message

Endobronchial ultrasound TBNA shows a good diagnostic performance for centrally located T1N0M0 staged with PET-CT and should be considered to evaluate for occult N2 disease prior to lung resection in certain patients who are known to have high risk of occult N2 disease: such as cN1, tumor >= 3 cm or centrally located tumors. The EBUS approach for these patients should be systematic and thorough, sample all lymph nodes > 5mm starting from contralateral hilar and mediastinal lymph nodes. More studies are needed to fully characterize the diagnostic performance of EBUS in the normal appearing mediastinum by PET-CT.

Suggested Reading

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