Title

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CLINICAL VIGNETTE

Endobronchial Ultrasound in the Diagnosis and Staging of Lung Cancer

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Case 1

A 69-year-old woman with a history of COPD and breast cancer presented with a mild cough was found to have an 18 x 30 mm right upper lobe lesion on chest X-ray. A chest CT confirmed the presence of a 29 x 23 mm mass (figure 1) and a 10 x 14 mm right paratracheal (station 4R) lymph node (figure 2). No other mediastinal or hilar adenopathy was identified. A subsequent PET-CT scan (figure 3) found both the right upper lobe lesion and the paratracheal lymph node to be hypermetabolic. Bronchoscopy with endobronchial ultrasound transbronchial needle aspiration (EBUS-TBNA) of the paratracheal lymph node revealed squamous cell carcinoma. She received four cycles of neoadjuvant cisplatin/gemcitabine with radiographic improvement. The SUV of the right upper lobe lesion was previously 28.8 and decreased to 3.6. The paratracheal lymph node was no longer hypermetabolic. She underwent thoracoscopy with resection of the right upper lobe and lymph node dissection. All hilar and six of seven mediastinal lymph nodes were negative for metastatic carcinoma. Postoperatively, she received three cycles of carboplatin/paclitaxel and mediastinal radiation. Twelve months after completing all treatment she is doing well with no evidence of recurrent cancer.

Case 2

A 55-year-old previously healthy woman with a 20-year history of smoking developed a cough for 3 months. She presented to the emergency department with hemoptysis. A chest CT revealed a 4.1 x 2.1 cm mass adjacent to right hilum (figure 4). There was no identifiable mediastinal adenopathy. A subsequent PET-CT scan confirmed hypermetabolic activity in the mass with an SUV 4.7 (figure 5) with no other areas of hypermetabolism. Electromagnetic navigation bronchoscopy (ENB) with transbronchial biopsy diagnosed adenocarcinoma consistent with primary lung cancer. Bronchoscopy with EBUS was then performed for staging of the mediastinum. All lymph nodes $\geq$8 mm were sampled and cytology from a subcarinal lymph node (station 7) was consistent with metastatic adenocarcinoma.

Lung cancer remains the leading cause of cancer death in the United States and the developed world.[1] Accurate staging is paramount in the diagnosis and treatment of lung cancer for two reasons. First, prognosis is highly dependent upon stage. Second, appropriate treatment can only be provided with accurate staging. Staging of the mediastinum is particularly important because surgical intervention is dependent upon the absence of mediastinal metastases.

Staging with noninvasive imaging techniques such as CT or PET scans is suboptimal due to relatively low sensitivity and specificity. Although various size criteria have been used to define an abnormal mediastinal lymph node on chest CT, the most commonly used criterion is a lymph node >1 cm in the short axis. Using this size cutoff, the median sensitivity and specificity for CT scans in detecting mediastinal metastases was only 55% and 81%, respectively.[2] PET scans are more accurate than CT scans in diagnosing mediastinal lymph node involvement with a sensitivity and specificity of 80% and 88%, respectively.[2] However even with the higher accuracy, there is still a significant false positive and false negative rate with PET scanning. Errors from overstaging the mediastinum by PET scan can prevent a patient from receiving a potentially curative surgery. On the other hand, understaging the mediastinum by PET scan subjects the patient to unnecessary surgery without improvement in survival. Thus, pathologic confirmation is usually required when there is suspicion for mediastinal involvement.

Invasive staging of the mediastinum is recommended in the third edition of the ACCP guidelines for the Diagnosis and Management of Lung Cancer in: 1) Patients with "discrete mediastinal lymph node enlargement, with or without PET uptake in mediastinal nodes" and 2) Patients with PET avid mediastinal lymph nodes with normal appearance on CT.[2] However even when CT or PET scans do not suggest mediastinal involvement, invasive staging is also recommended in the following situations given the significant incidence of occult metastases: 1) The primary tumor is >3 cm;[3] 2) There is suspicion of N1 disease;[2, 3,4] 3) Central tumors, within the proximal one-third of the hemithorax.[2, 3, 4] The patient in case 1 required invasive mediastinal staging because she not only had discrete mediastinal lymph node enlargement but also had evidence of increased metabolic activity by PET. The patient in case 2 also required invasive staging for two reasons. First, tumor was > 3 cm, and second, the primary cancer was located proximally, near the hilum.

Traditionally, mediastinoscopy has been the primary method for staging the mediastinum. However, the development of needle-based endoscopic techniques, both endobronchial ultrasound (EBUS) and endoscopic ultrasound (EUS), has

changed the way in which the mediastinum is staged. Accuracy of video-assisted mediastinoscopy in a pooled analysis of 995 patients demonstrated a sensitivity of 89% and a false negative rate of 8%.[2] Accuracy of EBUS-TBNA in a pooled analysis of 2,756 patients had similar results with a sensitivity of 89% and a false negative rate of 9%.[2] When directly compared, EBUS-TBNA performs as well or better than mediastinoscopy. In a study that evaluated patients with suspected lung cancer and enlarged mediastinal lymph nodes, EBUS-TBNA had a sensitivity of 87% and a negative predictive value (NPV) of 78% versus mediastinoscopy with a sensitivity of 68% and NPV of 59%.[5] Another prospective comparison study found similar sensitivities and NPVs for EBUS-TBNA (81% and 93%, respectively) and mediastinoscopy (79% and 93%, respectively).[6]

Given the similar operating characteristics of EBUS-TBNA and mediastinoscopy, what is the preferred test for initial staging of the mediastinum in suspected lung cancer? The safety of the procedures is an important consideration. Mediastinoscopy is relatively safe with morbidity and mortality rate of 2% and 0.08%, respectively.[2] However, EBUS-TBNA had a complication rate of only 0.15% in a meta-analysis of 11 studies that included 1,299 patients.[7] EBUS and EUS also have the advantage of being less invasive and can be performed with conscious sedation rather than general anesthesia. A prospective trial randomized 241 patients to mediastinoscopy or combined EBUS/EUS needle aspiration (endoscopy group).[8] Thoracoscopy was performed in both groups if nodal metastases were not identified. The sensitivities for mediastinoscopy, endoscopy, and combined endoscopy followed by surgical staging were 79%, 85% and 95% respectively. Although complication rates were similar in the two arms (6% vs. 7%), 12 of 13 complications occurred in patients who underwent surgical staging. Because of these considerations, the American College of Chest Physicians has recommended needle-based techniques over surgery as the best first test in staging patients with suspected N2/N3 disease (Grade 1B).[2]

The patient in case 1 also illustrates another important principle in the evaluation of patients with possible lung cancer. Whenever possible, diagnostic procedures that will provide the most information with the least risk to the patient should be performed first. Although a diagnosis of lung cancer could have been made with a biopsy of the right upper lobe lesion, by sampling the mediastinal lymph node the patient was simultaneously diagnosed and staged with one minimally invasive, low-risk procedure. A study by Almeida et al[9] highlights the importance of adhering to this strategy. In this retrospective study of 137 patients with lung cancer and mediastinal adenopathy and no evidence of distant metastases, only 22% of patients had sampling of the mediastinal lymph nodes (guideline-consistent care) as part of the first invasive procedure. Patients who had guideline-consistent care had fewer invasive tests (1.3 vs. 2.3, P<0.001) and fewer complications (0 of 30, 0% vs. 18 of 108, 17%, P=0.01).

In summary, EBUS-TBNA plays an important role in the diagnosis and staging of lung cancer and should be considered in the initial evaluation of patients with suspected lung cancer.

Figures

Figure 1. A chest CT confirmed the presence of a 29 x 23 mm mass.

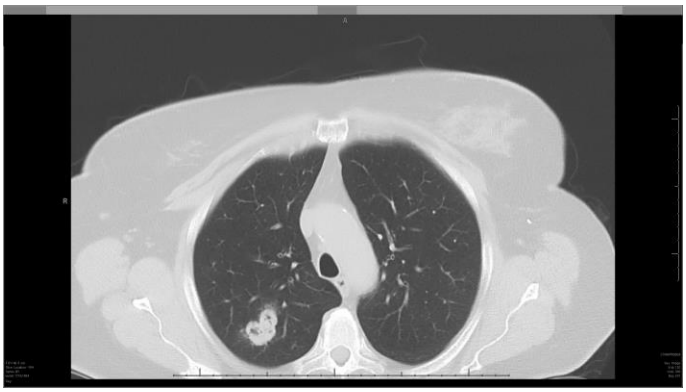


Figure 2. A chest CT confirmed the presence of a 10 x 14 mm right paratracheal (station 4R) lymph node.

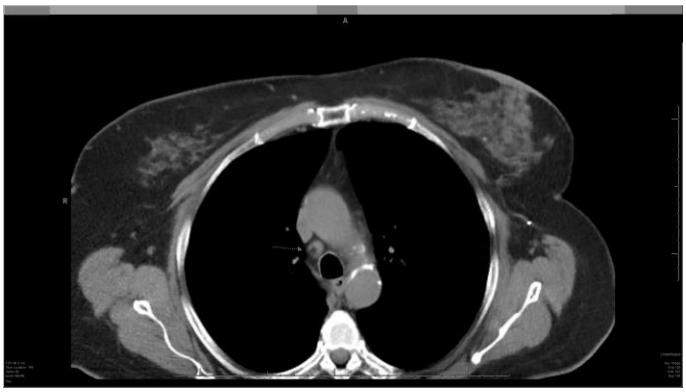


Figure 3. A subsequent PET-CT scan found both the right upper lobe lesion and the paratracheal lymph node to be hypermetabolic.

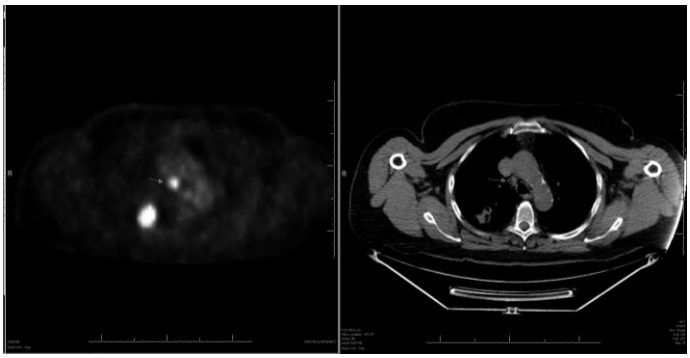


Figure 4. A chest CT revealed a 4.1 x 2.1 cm mass adjacent to right hilum.

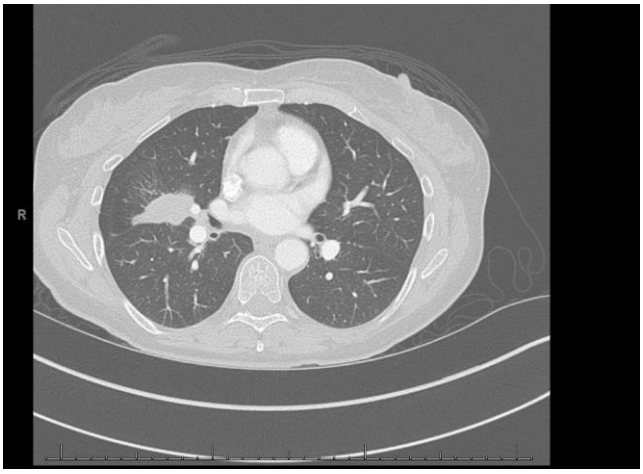
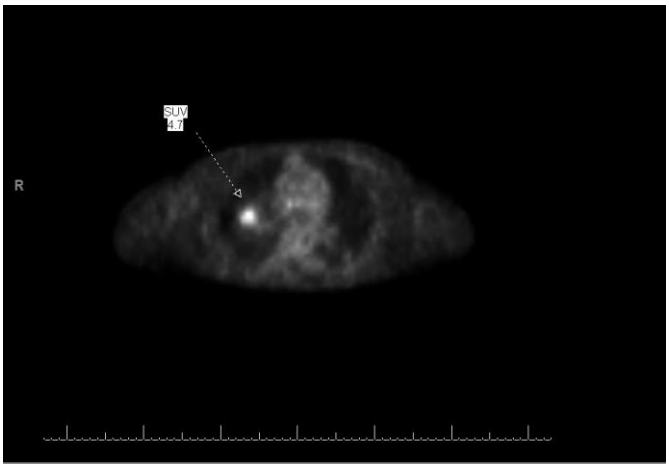


Figure 5. A subsequent PET-CT scan confirmed hypermetabolic activity in the mass with an SUV 4.7 with no other areas of hypermetabolism.



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