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Restaging of Mediastinal Nodes with Transbronchial Needle Aspiration after Induction Chemoradiation for Locally Advanced Non-small Cell Lung Cancer

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Introduction: Selecting the appropriate treatment strategy for patients with locally advanced non-small cell carcinoma (NSCLC) is of utmost importance to determine patient outcome. Previous studies have shown that nodal down-staging after induction therapy and definitive local irradiation in these patients better predict survival when combined with surgery. However, nodal restaging can be technically difficult. We investigated the role of transbronchial needle aspiration (TBNA) in mediastinal restaging of patients who had completed induction cytotoxic therapy.

Methods: A total of 14 patients with proven stage IIIa-N2 NSCLC who received chemotherapy or chemo-radiotherapy as induction regimen between 2005 and 2006 were studied. Outpatient flexible bronchoscopy with TBNA was performed in all patients under local anesthesia, and 17 TBNA procedures were performed. TBNA results were matched against the histopathology of surgical specimens.

Results: Seventeen lymph nodes in 14 patients who had undergone induction therapy were sampled. Positron emission tomography (PET) scan results of 11 patients were also available for comparison. All positive TBNA procedures had positive PET scans. However, for five patients with lymph nodes measuring 9 to 17 mm, the PET scans were falsely positive, as mediastinoscopy and subsequent surgically resected lymph nodes revealed no tumor. TBNA achieved a correct diagnosis in 71% of patients who underwent mediastinal restaging and obviated further need for invasive procedures in 35%.

Conclusion: For patients presenting with locally advanced NSCLC who are surgical candidates after induction chemo- and/or radiotherapy, TBNA should be considered as the initial procedure of choice for restaging of the mediastinum.

Key Words: Transbronchial needle aspiration, Induction therapy, Mediastinum, Nodal restaging.

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In recent years, progress has been made in the management of lung cancer because of improvement in staging techniques. Selecting the appropriate treatment strategy for a patient is of utmost importance for patient outcome. It has been shown that mediastinal nodal down-staging in patients with locally advanced non-small cell lung cancer (NSCLC) predicts survival after induction chemo-radiotherapy.[1–4] Patients who have down-staged N2 disease may benefit from surgical resection, although up to 33% of resected patients might experience subsequent disease relapse.[1–5] The use of concurrent chemo-radiotherapy has been shown to be a very effective approach for nodal down-staging and lung cancer treatment.[5] The radiation dose to the mediastinum must be greater than 66 Gy to be curative, but the main disadvantage of high-dose radiotherapy is the development of local fibrosis and adhesions, which makes it technically difficult to perform subsequent surgery.[6,7] Therefore, nodal down-staging has been performed at a lower radiation dose (45 Gy), but the window among neo-adjuvant therapy, mediastinal restaging, and definitive treatment should be as short as possible to prevent repopulation of cancer cells.[8,9]

Currently, a number of different techniques are available for investigating the initial pathological status of the mediastinal lymph nodes or for restaging. Computed tomography (CT) and positron emission tomography (PET) are not sufficient, as histological confirmation is required.[5,10] Annema et al. reported the use of endoscopic ultrasound (EUS) for restaging in 19 patients, but not all nodal stations were accessible, and no data on EUS after chemo-radiotherapy were available.[11–13] Bronchoscopy with transbronchial needle aspiration (TBNA) is an established technique to sample nodes in the mediastinum, but the reported diagnostic yield is highly variable, with a meta-analysis reporting the pooled sensitivity and specificity to be only 39% (95% CI, 17–61) and 99% (95% CI, 96–100), respectively.[14] The yield of conventional TBNA has been higher for bulky lymph nodes.[14] In recent years, many investigators have evaluated the mediastinum with endobronchial ultrasound (EBUS) and have reported excellent results, but these procedures are performed in patients who had no prior treatment.[14] The notable advantage of TBNA with or without EBUS is that it is a rapid, feasible technique by which an immediate pathological diagnosis can be made on-site.[15] We report the yield of TBNA procedure in patients

who received chemotherapy and radiation therapy for locally advanced pathological Stage IIIA NSCLC.

PATIENTS AND METHODS

Patients with pathologically proven stage IIIA-N2 NSCLC who had received induction chemotherapy and/or radiotherapy as part of their standard of care from 2005 to 2006 were included. Initial staging was performed with PET and CT scanning within a month for treatment, according to the Dutch guidelines for NSCLC. All patients had pathologically proven stage IIIa-N2 NSCLC by TBNA. Treatment consisted of either chemo-radiotherapy or chemotherapy alone. Combined chemo-radiotherapy was routinely used at our hospital, and patients referred from other hospitals had received induction chemotherapy. In the combination arm, the chemotherapy consisted of cisplatin 20 mg/m^2 and docetaxel 20 mg/m^2 weekly for 6 consecutive weeks and radiotherapy starting from day 8 up to 60 Gy. The induction treatment with chemotherapy alone consisted cisplatin 80 mg/m^2 (day 1) and gemcitabine 1250 mg/m^2 (day 8) repeated every 3 weeks for three cycles.

Restaging procedures were performed 2 weeks after the third cycle of cisplatin and gemcitabine, at radiation dose of 45 Gy. These consisted of PET scanning and flexible bronchoscopy with TBNA performed under local anesthesia. When the TBNA results of the mediastinal nodes sampled were reported as negative, a cervical mediastinoscopy was performed within a week of discontinuation of radiotherapy. If nodal metastases persisted, radiotherapy was restarted within 5 working days to a dose greater than 60 Gy. If mediastinoscopy confirmed the absence of nodal metastasis, a thoracotomy with the aim of a radical resection including mediastinal lymph node dissection was performed within 2 weeks. All patients gave informed consent for staging procedures, and the study protocol was approved by local ethics committee.

Before TBNA, all patients had chest CT with contrast enhancement at 5-mm cuts from the thoracic inlet to carina and from inferior pulmonary veins to the diaphragm. TBNA was performed using a 19-gauge cytology needle (Boston Scientific Benelux, Maastricht, the Netherlands). Four TBNA passes were performed at each site, and selection of the lymph node for TBNA was left to the discretion of an experienced bronchoscopist after review of imaging studies and previous TBNA results. No rapid on-site cytological evaluation was used, and all specimens were submitted as dry smears.

Clinical characteristics, lymph node stations according to American Thoracic Society (ATS) classification, size of lymph node measured by its short-axis diameter on CT, final surgical pathological diagnosis after mediastinoscopy and/or thoracotomy, and PET scan results were recorded.

Statistical Analysis

Data were entered onto a spreadsheet. Values were expressed as frequency and percentages.

RESULTS

Seventeen lymph nodes from 14 patients who had undergone induction therapy for stage IIIa-N2 NSCLC were sampled. Table 1 shows the characteristics of the patients. All but two patients received chemoradiation as the induction regimen. No complications resulting from the bronchoscopy and TBNA procedure were recorded. Mediastinoscopy was

TABLE 1. Patient Characteristics and Transbronchial Needle Aspiration, Positron Emission Tomography, and Surgical Histopathology Results

Patient	Age (yr)	Sex	Initial N2 Metastasis (Naruke station)	TBNA Result (adeno/SCC)	Definitive Diagnosis (adeno/SCC)	FDG-PET Result	Nodal Diameter (short axis, mm)
1	55	F	7	Not representative	Negative	Positive	17
2	58	M	4R	Atypia	NA	Positive	9
3	73	M	7	Negative	Negative	NA	14
4	57	F	4R	Negative	NA	NA	18
5	58	F	3	Negative	Negative	NA	5
6	57	M	4R	Negative	NA	NA	32
7	68	M	4R	Negative	Negative	Positive	11
7	68	M	7	NSCLC	NSCLC	Positive	14
8	56	F	4R	Negative	Negative	Negative	12
8	56	F	7	Negative	Negative	Positive	20
9	61	F	7	Negative	Negative	Negative	16
10	51	M	4R	NSCLC	—	Positive	18
10	51	M	7	NSCLC	—	Positive	12
11	66	F	4L	NSCLC	—	Positive	40
12	66	F	4R	NSCLC	—	NA	8
13	43	M	7	NSCLC	—	NA	25
14	49	M	4R	NSCLC	—	Positive	20

TBNA, transbronchial needle aspiration; adeno, adenocarcinoma; SCC, small cell carcinoma; FDG-PET, positron emission tomography; NSCLC, non-small cell lung cancer; NA, not applicable.

not performed in three patients: patient 6 experienced arterial thrombosis after chemotherapy, and it was therefore decided to continue treatment with radiotherapy. Although the cytological result of patient 2 showed atypia, radial endobronchial ultrasound demonstrated tracheal invasion, and the patient was continued on radiotherapy. In patient 1, the TBNA aspirate was considered non-representative and thus regarded as a procedure failure. Because of the clinician's doubt regarding the TBNA result, although patient 7 had a positive result at lnn 7, the patient underwent mediastinoscopy as lnn 4R (initially proven to be positive) showed a negative result.

In six lymph nodes samples, no malignant cells were found on both TBNA aspirates and biopsies by mediastinoscopy, and these patients subsequently underwent thoracotomy, which confirmed the negative findings. For the remaining seven lymph node samples with persistent tumor on TBNA, the corresponding patients were treated with a radical dose of radiotherapy. Therefore, true negative results and positive results of lymph nodes samples were found in 14 of 17 lymph nodes (81%). TBNA correctly diagnosed the state of mediastinal nodes for 10 patients (71%), and 5 patients (35.7%) did not require further exploration.

PET scan results were available for 11 patients. All positive TBNA procedures in these patients had positive PET scans. However, five patients with lymph nodes measuring 9 to 17 mm had false-positive PET scans, as mediastinoscopy-guided lymph node biopsies and later examination of surgically resected lymph nodes revealed no tumor.

DISCUSSION

Simple and quick techniques that facilitate tissue biopsy from the mediastinum are necessary for optimal treatment planning in patients with stage IIIa-N2 NSCLC. A number of techniques, including FDG- PET, integrated PET-CT, and endoscopic techniques (i.e., EBUS), have recently been developed to investigate the mediastinum.[16–20] Selection of patients after induction therapy for surgical therapy is still a moving field. Because it is generally accepted that mediastinal down-staging is important, the question is how to assess this in the most reliable way. Response evaluation after chemo-radiotherapy by serial CT scans can be difficult, as significant gross residual tumor may be present at thoracotomy in up to 40% of patients with radiological stable disease and in 27% of the patients with a partial response.[5] Recent studies have shown that integrated PET-CT improves sensitivity without compromising specificity compared with standalone PET.[16] However, reliance on imaging alone is unacceptable, and a tissue diagnosis is still required to guide management.[10] A single-center study reported that after a thorough staging mediastinoscopy, remediastinoscopy after induction therapy had a disappointingly low sensitivity because of adhesions and fibrosis.[10]

However, the impact of tumor necrosis on the diagnostic yield with different staging techniques is not known.

In this study, TBNA (in experienced hands) was found to be an easy and rapid technique with good results after chemoradiation, and it resulted in a reduction in surgical staging procedures. TBNA can access stations Naruke 4R, 7, 4L, 2L, and 2R. It is not possible to reach 5, 6, 8, and 9 endobronchially,[21–23] but they can be reached by endo-esophageal ultrasound with reportedly good results after chemotherapy.[11] Whether the yield in this study can be increased by performing EBUS[13,23,24] is doubtful given the results of the surgical staging procedure in our patients. Larger series with EBUS real-time punctures have already proven to have a superior yield compared with TBNA,[13] but this remains to be proven for restaging. Because equipment for EBUS real-time TBNA is costly and is therefore not available in every hospital, the present results indicate a need to use TBNA more widely. That this still is not the case may be the result of a lack of experience, bronchoscopic damage, or failure to reproduce results in the literature.[25,26] The low yields mentioned for TBNA in the literature[14] may also be improved upon with training and experience.[25] Furthermore, the training could help to make this technique more widespread. In this study, four TBNA passes were used for restaging, as the superior amount of passes in normal staging is four to five.[27] Considering the results of this study, we also recommend four passes, although this was not thoroughly investigated.

As mentioned by Rami-Porta recently,[4] in clinical practice, the staging and restaging of tumors should be performed using techniques that can provide high clinical certainty of nodal down-staging, as these are the only parameters associated with prolonged survival. TBNA procedure is one such procedure, as may be concluded from our experience. It is easy to perform and provides rapid results so that it does not cause delay in the institution of further treatment. The study has three limitations. First, the sample size is small. Second, the lymph nodes sampled were also initially pathological proven stage IIIa-N2 by TBNA. Third, although patients with positive TBNA for residual tumor were not subjected to mediastinoscopy (and the false-positive rate therefore could not be accurately determined), we believe our findings are of clinical relevance for pulmonologists managing patients with stage IIIA NSCLC. This is the first study to demonstrate a role for TBNA in the restaging of the mediastinum after induction cytotoxic therapy.

CONCLUSION

Our experience suggests that TBNA should be the initial procedure of choice in the restaging of the mediastinum for patients with stage IIIA NSCLC who may be considered surgical candidates after induction chemo- and/or radiotherapy.

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