Endobronchial ultrasound-guided transbronchial needle aspiration is a sensitive method to evaluate patients who should not undergo pulmonary metastasectomy

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Received 12 September 2014; received in revised form 18 November 2014; accepted 26 November 2014

Abstract

OBJECTIVES: Pulmonary metastasectomy is considered an effective treatment in selected patients with extrapulmonary cancer and oligometastatic disease. We know that the presence of mediastinal node metastases reduces survival significantly, but the mediastinum is rarely evaluated before metastasectomy in these patients. We prospectively evaluated how endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) could identify metastases to the mediastinal lymph nodes in patients referred for pulmonary metastasectomy.

METHODS: All patients with extrapulmonary cancer and oligometastatic disease confined to the lungs on positron emission tomography–computed tomography, and who were considered eligible for pulmonary metastasectomy, routinely underwent EBUS-TBNA of the mediastinal lymph nodes. If EBUS-TBNA did not reveal malignant spread, the patient subsequently underwent pulmonary metastasectomy with systematic sampling of mediastinal lymph nodes for histological evaluation.

RESULTS: One hundred and three eligible patients were referred for EBUS-TBNA during a 4-year period. The primary cancers were located in the colon/rectum (n = 64), kidney (n = 16) and other sites (n = 23). EBUS-TBNA sampled 248 lymph nodes and adequate cytology was obtained in 93 patients (90%). EBUS-TBNA found lymph node metastases in 17 patients (16.5%) and during subsequent pulmonary metastasectomy in the remaining 86 patients 1 (1.0%) had a lymph node metastasis. The sensitivity, specificity, NPV and PPV of EBUS-TBNA for diagnosis of mediastinal lymph node metastasis were 94.4, 100, 98.8 and 100%, respectively.

CONCLUSIONS: EBUS-TBNA is a sensitive minimally invasive modality for evaluation of mediastinal lymph node metastases in patients with oligometastatic pulmonary disease. It allows surgeons to select patients who will not benefit from pulmonary metastasectomy.

Keywords: Pulmonary metastases • Lymph node metastases • Mediastinal lymph node staging

INTRODUCTION

Pulmonary metastasectomy is considered an effective treatment in selected patients with a primary extrapulmonary cancer and oligometastatic disease in the lung. The surgical approach and preoperative work-up varies from country-to-country and even hospital-to-hospital. We recently demonstrated that video-assisted thoracoscopic surgery (VATS) is an inferior approach for detection of all pulmonary metastases [1, 2] but whether or not this has any impact on survival remains unknown. Thus, it may be argued that nodules that are not detected by VATS during metastasectomy can be resected at a later stage when they present on computed tomography (CT) scan at follow-up. On the other hand, if metastases can metastasize, it is obvious that a surgical approach may influence survival when some metastases are left behind because mediastinal lymph node metastases in patients with pulmonary metastases has been shown to be one of the most important prognostic factors for reduced survival [3–5]. In contrast to patients who suffer from primary lung cancer, the importance of mediastinal spread is not always recognized in patients scheduled for pulmonary metastasectomy and, consequently, the mediastinum is rarely evaluated before this procedure. We therefore decided to prospectively evaluate the ability of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) to identify patients with mediastinal node metastases prior to pulmonary metastasectomy.

MATERIALS AND METHODS

This study was approved by the Regional Ethics Committee of Southern Denmark (approval number: S-20100033) and the Danish Data Protection Agency. Written informed consent was obtained...
from all patients. During a 45-month period (November 2010 to September 2014) 103 patients with a suspicion of limited pulmonary metastatic disease as seen on CT scan and considered eligible for therapeutic surgical resection were referred to our department. We considered patients eligible for resection if they had a history of completely resected extrathoracic cancer and any newly developed lesion(s) indicative of a metastasis on control CT scan. The maximum number of lesions that we considered eligible to qualify as oligometastatic disease was four metastases in one lung.

All patients underwent positron emission tomography (PET)—CT to exclude widespread disseminated disease and were routinely scheduled for endobronchial ultrasound-guided transbronchial fine-needle aspiration (EBUS-FNA) prior to metastasectomy to exclude metastatic disease in the mediastinal lymph nodes in which case they were considered inoperable and referred for oncological treatment.

All EBUS examinations were performed under general anaesthesia with a linear scanner (BF-UC160F, Olympus). All procedures were performed with laryngeal mask and intravenous propofol, fentanyl and local anaesthetic in the trachea. Paratracheal lymph node stations 2, 3, 4 and 7 according to Mountain et al. [6] were systematically identified and punctured. Fine needle aspiration was performed with a 22-G needle (NA-201SX-4022, Olympus) during real-time EBUS. Two aspirations or more were performed from each lesion to ensure that the biopsy contained sufficient material. Aspirated material was expelled onto glass slides and smeared for cytological examination and expelled into saline for preparation of cell blocks for histological examination. Rapid on-site evaluation was not performed. Instead, all biopsies were reviewed the following day by an experienced pathologist, and classified as ‘malignant’, ‘benign’ or ‘nondiagnostic’. In some patients with lymph nodes <5 mm in diameter it was not technically possible to perform a fine needle aspiration, but the evidence of a small diameter of the lymph node was interpreted as a low risk of metastasis in the actual lymph node and the patients proceeded to surgery without further reinvestigations if the biopsy was found non-diagnostic. Patients with malignant findings in the mediastinal lymph nodes were referred for oncological treatment and patients with benign findings—in the presence of lymphocytes indicating representative sampling—were referred for pulmonary metastasectomy with mediastinal lymph node sampling.

The patients included in the present study were also part of another study, which evaluated the efficacy of VATS versus open thoracotomy for pulmonary metastasectomy [1, 2]. Following resection of all palpable nodules in the lung complete mediastinal lymph node sampling was performed and specimens sent for histological evaluation. The pathology report from each resected lymph node was compared with the pathology report from the EBUS-TBNA, and the primary end point was any difference in the reported pathology from the EBUS-TBNA and the sampled lymph nodes from the thoracotomy.

The sample size calculation for our descriptive study was not based on a known prevalence of mediastinal lymph node spread because the prevalence of mediastinal lymph node metastases was not known for our population, which consisted of patients with extrathoracic cancer and a negative PET-CT to exclude widespread disseminated disease or local recurrence. Assuming that our prevalence was similar to the lowest known published in the literature, which was 14% [7], a 95% confidence interval for the true prevalence in our 100 patients was calculated as 7.2–20.8%. Increasing the number of patients to 150 in our study would only improve the prediction of prevalence to a range from 8.5 to 19.6%, which we did not consider.

Standard definitions of sensitivity, negative predictive value (NPV) and diagnostic accuracy were used. Positive malignant findings on EBUS-TBNA were not confirmed, and specificity was assumed to be 100%. Non-malignant findings at EBUS-TBNA were subject to surgical confirmation. This study conforms to the standards for the reporting of diagnostic accuracy studies.

RESULTS

In all 103 patients with oligometastatic pulmonary disease there were no surgical complications such as pneumothorax, pneumonia or bleeding related to the EBUS-TBNA procedure and all were discharged on the same day as the examination following an average operating time of 15–30 min. The primary cancers for the surgical patients were located in the colon/rectum (n = 64), kidney (n = 16) and others (n = 23). During EBUS-TBNA we sampled 248 lymph nodes and adequate cytology (presence of lymphocytes) was obtained in 93 patients (90%). Final cytology examination revealed that 17 of the 103 patients had metastatic mediastinal lymph node involvement: colon/rectum (n = 4), gynaecological (n = 1), breast (n = 2), malignant melanoma (n = 4), kidney (n = 4), bladder (n = 1), head/neck (n = 1) and were consequently excluded from pulmonary metastasectomy. The malignant cells discovered during EBUS-TBNA were always identified as metastases from the primary cancer.

During subsequent pulmonary metastasectomy we found spread to the mediastinal lymph nodes in one patient (1.0%) who had previously suffered from primary colorectal cancer. Histopathological examination of the pulmonary nodule and subcarinal lymph nodes (Station 7) demonstrated that the patient now suffered from small-cell lung cancer rather than metastatic colorectal cancer. Overall, 18 patients (17.5%) therefore had lymph node metastases and sensitivity, specificity, NPV and PPV of EBUS-TBNA for diagnosis of mediastinal lymph node metastasis in this cohort of patients were 94.4, 100, 98.8 and 100%, respectively.

DISCUSSION

The preoperative work-up for patients with oligometastatic pulmonary disease before pulmonary metastasectomy is different from hospital-to-hospital. As recommended by the European Society of Thoracic Surgeons working group [8], we routinely perform a PET-CT to exclude patients with disseminated disease and locoregional recurrence because these factors lead to very poor survival [9]. Mediastinal lymph node involvement is known as a poor prognostic factor [3, 6, 10] with a 5-year survival for patients who have positive lymph nodes ranging from 0 to 33.5% compared with 38.7 to 71% for patients without mediastinal lymph node metastases [11]. Previous retrospective studies reported a prevalence of lymph node involvement from 14 to 50% [6] and we found that 17.5% of the patients had mediastinal lymph node involvement. Prior to routine use of EBUS-TBNA these patients would all have been offered pulmonary metastasectomy, which may very well have influenced survival in the whole cohort and one can only speculate that better mediastinal staging in patients who are offered metastasectomy will improve survival in the future because these patients with the poorest survival rate are not operated, but this needs to be investigated in future research.
We know that EBUS-TBNA is a procedure without complications and with a high yield and in patients with undiagnosed mediastinal lesions [12, 13] which also applies for mediastinal staging of patients with NSCLC [14]. In the present study, we have demonstrated that EBUS-TBNA is also a valuable diagnostic tool to identify mediastinal lymph node metastases in patients considered for pulmonary metastasectomy from an extrathoracic cancer. EBUS-TBNA was able to identify all patients with metastases to the mediastinal lymph node and only 1 patient who unsuspected had a primary small-cell lung cancer with a metastasis in a subcarinal lymph node was not identified by EBUS-TBNA.

EBUS-TBNA for diagnosis of mediastinal lymph node metastases in patients with extrathoracic disease has been published before but these studies were all retrospective, had different inclusion criteria and investigated a population where the prevalence was likely different from ours, i.e. they only investigated patients by EBUS-TBNA if they had enlarged lymph nodes in the mediastinum. In addition, previous studies did not validate a negative EBUS-TBNA by systematic lymph node sampling during subsequent metastasectomy. Comparing NPV and PPV between studies of different patient populations therefore may not be relevant because NPV and PPV depend on the prevalence. One must assume that EBUS-TBNA has a false-positive rate of 0% in all studies leaving specificity at 100% and we can only calculate the sensitivity, which was 94.3% and therefore similar to previous studies that ranged from 86.4 to 96.3% [15–18].

One would assume that the sensitivity was different in studies where the populations investigated were different and we have no obvious explanation for this except that that they did not investigate patients under general anaesthesia. It is our impression that general anaesthesia improves the investigation because we have better time to investigate all lymph node stations more thoroughly and we can therefore target each lymph node station better to ensure adequate biopsies (presence of lymphocytes). Although there is no evidence that EBUS-TBNA in general anaesthesia have a higher yield than EBUS-TBNA in local anaesthesia, it was recently demonstrated that deep sedation is superior to moderate sedation in patients undergoing EBUS-TBNA [19].

Given our results, we now believe that it is important to investigate the mediastinum invasively in all patients considered for pulmonary metastasectomy regardless of findings on preoperative imaging. We also recommend EBUS-TBNA over mediastinoscopy because the sensitivity is high, as demonstrated in the present study, and because EBUS-TBNA is much less invasive as stated in previous studies [12–14]. Thus, we did not experience any complications during the EBUS-TBNA. In contrast, although rare, mediastinoscopy is associated with serious complications in up to 1% of the procedures [20]. We therefore challenge the general concept that mediastinoscopy is considered the gold standard for mediastinal staging in patients with extrathoracic disease [21].

Even though we consider patients with pulmonary metastasis who have mediastinal lymph node involvement ineligible for further pulmonary resection, this is also controversial [6, 9, 22]. Current recommendations state that these patients should not be operated [21] because there is a significant difference in survival in patients with pulmonary metastases who have lymph node involvement and those who do not. Thus, large case series have been published where the median survival was only 20 months in patients with mediastinal spread compared with 63.9 months, and the subgroup of patients who had isolated metastasis in the hilar lymph nodes had a median survival of 32.7 months [10, 23].

The present study has limitations and may theoretically overestimate the sensitivity of EBUS-TBNA. We could have missed detection of some positive lymph nodes in the mediastinum during metastasectomy because we did not perform complete and systematic mediastinal lymph node dissection as our reference. Instead, we performed the same routine lymph node evaluation as we do in patients who are operated for non-small-cell lung cancer, namely systematic lymph node sampling, which is in accordance with Danish guidelines for surgical treatment of lung cancer. Although not documented, it is generally assumed that thoracic surgeons clear visible lymph node tissue in the lymph node stations targeted.

In conclusion, and in accordance with current guidelines, we strongly recommend that patients with oligometastatic pulmonary disease should have a routine PET-CT to exclude widespread disseminated disease or locoregional recurrences. If so, and provided that patients are considered for pulmonary metastasectomy, we recommend that everyone should first undergo EBUS-TBNA to exclude mediastinal lymph node metastasis.

ACKNOWLEDGEMENTS

We greatly appreciate the efforts and interest to participate in the surgical procedures by Lars Ladegaard, Ole Dan Jørgensen, Kirsten Neckelmann and Erik Jakobsen, Department of Cardiothoracic Surgery, Odense University Hospital.

Conflict of interest: none declared.

REFERENCES


APPENDIX. CONFERENCE DISCUSSION

Dr Eckardt: Your question is if some of the cancers have a greater risk for precipitating lymph node metastasis than others? Dr Shiono: Yes.

Dr Eckardt: I do not think that I understand your question.

Dr Shiono: If there are mediastinal lymph nodes involved, we know that your chances of influencing survival with subsequent metastasectomy are small, so I would support you in your efforts to make the diagnosis before a thoracotomy.

Dr Eckardt: That is a very good point. Our experience was that the lymph nodes that we were puncturing during the procedures were very small, and I think that it has been demonstrated in multiple papers that if you have small targets, the PET-CT does not lighten this area. This is actually following the recommendations from a working group from ESTS, which stated that if you use PET-CT, you can use it to exclude patients with a disseminated disease. You can see if they are spread to other parts of the body, but you cannot use PET-CT to exclude metastases in the mediastinum, because that is not what PET-CT is good at, locating metastasis, to locate the metastasis in the mediastinal lymph nodes.

Dr Eckardt: I think it is a very interesting point because we know that in the thoracic departments in Denmark, we are performing the procedures under general anaesthesia. If we heard the discussion yesterday, we could hear that it was not thought for certain that the EBUS-TBNA and the high yield of EBUS-TBNA was as good as it was described, because now the procedure is spread out to more hands, and it means that it is not in all departments that the patients are under general anaesthesia. If they are not under general anaesthesia, you are not able to have as much time to explore the lymph nodes. Maybe, to explain some of the higher yields that we have, but I think that some of it is also that we have had some experience, we have done more than 1000 EBUS-TBNA procedures in our department, and there are only 3 persons doing these procedures. So of course, we have some experience with the procedure.

Dr Kocher: Yes, exactly.

Dr Eckardt: I have one last question heading sort of in that direction. You mentioned that you did a PET-CT scan in all the patients before metastasectomy. Where do you see the role of PET in identifying patients with mediastinal lymph node metastasis? Are there some patients, in whom you do not even need to do an EBUS-TBNA because PET already identifies them, or what is your experience in your subset of patients?

Dr Eckardt: That is a very good point. Our experience was that the lymph nodes that we were puncturing during the procedures were very small, and I think that it has been demonstrated in multiple papers that if you have small targets, the PET-CT does not lighten this area. This is actually following the recommendation from a working group from ESTS, which stated that if you use PET-CT, you can use it to exclude patients with a disseminated disease. You can see if they are spread to other parts of the body, but you cannot use PET-CT to exclude metastases in the mediastinum, because that is not what PET-CT is good at, locating metastasis, to locate the metastasis in the mediastinal lymph nodes.

Dr Kocher: So your final conclusion is that all of those patients should receive the same examinations, which should be PET-CT and EBUS-TBNA before undergoing metastasectomy, right?