Lung Cancer 76 (2012) 46–50

Contents lists available at SciVerse ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Are EUS–FNA and EBUS–TBNA specimens reliable for subtyping non-small cell lung cancer?

K.G. Tournoy[a,b,*], M. Carprieaux[b,c], E. Deschepper[d], J.P. van Meerbeeck[a,b], M. Praet[b,c]

[a] Department of Respiratory Medicine and Thoracic Oncology, Ghent University Hospital, Belgium
[b] Lung Oncology Network Ghent, Ghent University Hospital, Belgium
[c] Department of Pathology, Ghent University Hospital, Belgium
[d] Biostatistics Unit, Ghent University Hospital, Belgium

ARTICLE INFO

Article history:
Received 21 July 2011
Received in revised form 1 September 2011
Accepted 3 September 2011

Keywords:
Endoscopic ultrasound
Fine needle aspirates
Histology
Non-small cell lung carcinoma
Subtyping

ABSTRACT

With endosonography, the diagnosis and staging of non-small cell lung cancer (NSCLC) increasingly relies on small samples. The discrimination between squamous and non-squamous subtypes is now important for therapy tailoring. We analyzed the agreement between fine needle aspirates obtained by endosonography and matched biopsy samples for subtyping NSCLC. Patients with a positive endoscopic fine needle aspirate and a matched biopsy were identified. The level of diagnostic agreement was estimated with biopsy samples as golden standard.

In 951 patients investigated with endosonography, we identified 92 with NSCLC on the positive fine needle aspirate and on the matched biopsy. Squamous cell carcinoma was diagnosed in 34 (37%) and 44 (48%) of fine needle aspirate and biopsy samples; while non-squamous carcinoma was diagnosed in 58 (63%) and 48 (52%) respectively. The agreement between needle aspirate and biopsy for the subtyping of NSCLC was 76% (kappa = 0.52). In cases with cell block preparation, the agreement for subtyping was 96% (kappa = 0.91) vs 69% (kappa = 0.39) in cases without cell blocks.

Therefore, the diagnostic agreement between endosonographic fine needle aspirates and biopsy specimens for subtyping NSCLC is moderate with a disagreement in 1 out of 4 patients. However, cell block preparation increased the agreement and thus the reliability of the fine needle specimens obtained during endosonography, for subtyping NSCLC considerably.

In conclusion, for patients with NSCLC in whom subtyping is relevant, a diagnostic technique yielding larger samples (FNA with cell block preparation or biopsies) should be preferred.

1. Introduction

Endosonography has profoundly changed the diagnosis and staging of patients with (presumed) lung cancer over the past five years [1,2]. Endosonography includes both transoesophageal endoscopic ultrasound with real time guided fine needle aspirates (EUS–FNA) and endobronchial ultrasound with real time guided transbronchial fine needle aspirates (EBUS–TBNA). These techniques are minimally invasive and can be performed under mild sedation, enabling the demonstration of mediastinal nodal metastasis [2]. They avoid a more invasive staging with mediastinoscopy or video-assisted thoracoscopy in 47–70% of the patients with non-small cell lung cancer (NSCLC) [3–7].

Since both EUS–FNA and EBUS–TBNA are becoming widely available, a foreseeable evolution is that these techniques will be often deployed not only for mediastinal staging in patients with known NSCLC, but also to obtain a pathological diagnosis. Examples are patients with a peripheral lung lesion or with metastatic disease presenting with enlarged mediastinal or hilar lymph nodes. Endoscopic fine needle techniques have already shown to contribute to the diagnosis of centrally located lung lesions [8–12]. Thus, in daily practice the diagnosis of lung lesions will increasingly result from fine needle aspirates (FNA) (smears and cell blocks) obtained with endosonography rather than on biopsy samples obtained by bronchoscopy, transthoracic tru-cuts or surgical techniques.

Abbreviations: EUS–FNA, transoesophageal endoscopic ultrasound with real time guided fine needle aspirates; EBUS–TBNA, endobronchial ultrasound with real time guided transbronchial needle aspiration; FNA, fine needle aspirate obtained either by EUS–FNA or EBUS–TBNA; H&E, hematoxylin and eosin stain; IHC, immunohistochemistry; LAG, left adrenal gland; LLL, left lower lobe; LUL, left upper lobe; ML, middle lobe; NSCLC, non-small cell lung cancer; RLL, right lower lobe; RUL, right upper lobe; TTF-1, thyroid transcription factor one.

* Corresponding author at: Ghent University Hospital, Department of Respiratory Medicine, Building 7K12 I.E., De Pintelaan 185, 9000 Ghent, Belgium.
Tel.: +32 9 3322611; fax: +32 9 3322341.
E-mail address: kurt.tournoy@UGent.be (K.G. Tournoy).

0169-5002/$ – see front matter © 2011 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.lungcan.2011.09.004

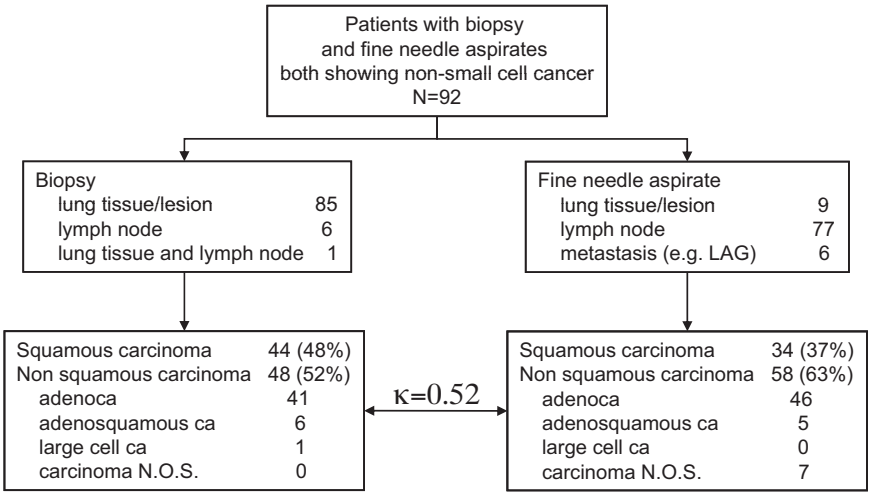

Fig. 1. Subtyping non-small cell lung cancer in biopsies ves EUS/EBUS fine needle aspirates.

A differentiation between non-small cell and small cell carcinoma was until recently sufficient to tailor the patient's therapy, with an excellent discriminatory accuracy for fine needle aspirates [13,14]. More recently however, subtyping NSCLC has become an important issue [15,16]. Although histologic subtyping has not been consistently associated with clinical outcome in advanced NSCLC, it has recently emerged as a predictive marker for therapy response to both epidermal growth factor receptor tyrosine kinase inhibitors and anti-folate therapy (pemetrexed) [15–18]. In addition, knowledge about the subtype of NSCLC is for safety reasons also important in the selection of patients for therapy with bevacizumab [19].

Whereas the accuracy in subtyping of exfoliative pulmonary specimens (bronchial brush and lavage) and transthoracic fine needle aspirates has been reported [20–24], this has not been done for FNA-cytology obtained with endosonography (EUS–FNA and EBUS–TBNA) in NSCLC subtyping.

In this manuscript, we analyzed the level of agreement for subtyping NSCLC in a large cohort of NSCLC patients in whom both FNA (obtained by endosonography) and matched biopsies of the tumor were available. We report on the reliability of FNA specimens for the histopathology subtyping of NSCLC. We also report on the added value of cell block analysis in this respect.

2. Materials and methods

2.1. Patient selection

The medical records of all patients referred to the Ghent University Hospital for thoracic endosonography (either EUS–FNA or EBUS–TBNA) between June 2004 and July 2010 were reviewed. For patients to be eligible, the FNA needed to show NSCLC, in the presence of a pulmonary or nodal biopsy sample that matched the same clinical episode (Fig. 1). Approval of the medical ethics committee for this study is available (EC-Ghent University Hospital 2009/492; local registration number B6702009047).

2.2. Sample processing and analysis

The biopsy samples were obtained either by surgery (mediastinoscopy, lobectomy or pneumectomy), bronchoscopy or transthoracic trucut biopsy. The FNA's were obtained with 21 (EUS–FNA) or 22 (EBUS–TBNA) Gauge needles from Olympus (Aartselaar, Belgium). The fine needle aspirates were all processed following a standard protocol: (i) smears were always immediately made followed by (ii) cell block preparations if enough material was available. All material (biopsies and fine needle samples) was routinely processed for a haematoxylin–eosin staining. Immunohistochemistry was performed on formalin fixed samples with TTF-1(also NKX2-1 or TITF-1; 8G7G3/1;1:50;Dako) and P63(4A4;1:200;Dako). Positive and negative controls were thyroid and appendix for TTF1, and skin/tonsil and liver for P63 respectively. The subtyping of NSCLC followed the standard cytomorphological criteria [24,25]. The biopsies were classified and graded according to the 2004 World Health Organization (WHO) classification of tumors [26]. All samples (fine needle aspirates and biopsies) were classified dichotomously (squamous vs non-squamous carcinoma) and categorically (squamous carcinoma, adenocarcinoma, adenosquamous carcinoma, large cell carcinoma or carcinoma not otherwise specified—N.O.S.). Two illustrative cases are shown in Fig. 2.

After the samples (biopsies and FNA's) were selected, they were blinded and re-evaluated by a team of two cytopathologists (MC; MP) with expertise in FNA cytopathology and thoracic malignancies.

2.3. Data analysis

For the analysis of agreement, we assumed that the FNA and the biopsy specimens represented a sample from a single tumor tissue that was analyzed twice, with the biopsy sample result being considered the gold standard. Agreement was hence estimated as the rate of the sum of the FNA-samples showing a similar subtype as the matched biopsy over the total number of patients with an interobservation level of agreement expressed as a κ-value with 95% confidence intervals. Kappa values less than 0.40 suggest a low agreement; values between 0.40 and 0.75 indicate medium agreement; and values greater than 0.75 indicate high agreement between both observations [27]. Categorical variables were compared with the Fishers' exact test. The significance level was set at $p = 0.05$. The analysis was done using SPSS 17.0 (SPSS Inc., Chicago, IL).

3. Results

3.1. Study population

In 951 consecutive patients who underwent endosonography, we identified 92 (10%) in whom both a fine needle aspirate and a matched biopsy sample showed NSCLC (Fig. 1). The majority of the biopsy samples were obtained from a primary lung lesion (86/92;