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Rapid On-Site Evaluation Improves Needle Aspiration Sensitivity in the Diagnosis of Central Lung Cancers: A Randomized Trial

Michele Mondoni[a] Paolo Carlucci[a] Fabiano Di Marco[a] Stefania Rossi[b] Pierachille Santus[c] Alice D'Adda[d] Giuseppe Francesco Sferrazza Papa[a] Gaetano Bulfamante[b] Stefano Centanni[a]

[a]Respiratory Unit, [b]Unit of Pathological Anatomy, San Paolo Hospital, Dipartimento di Scienze della Salute, Università degli Studi di Milano, [c]Unit of Pulmonary Rehabilitation, Fondazione Salvatore Maugeri-Istituto Scientifico di Milano-IRCCS, Dipartimento di Scienze della Salute, Università degli Studi di Milano, [d]Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Università degli Studi di Milano, IRCCS Fondazione Ca' Granda, Milan, Italy

Key Words
Bronchoscopy · Lung cancer · Transbronchial needle aspiration · Cytopathology

Abstract
Background: Few prospective studies have evaluated the role of endobronchial needle aspiration in diagnosing central airways neoplasms. Rapid on-site evaluation has long been used in transbronchial needle aspiration of adenopathies and peripheral lesions, but its role in sampling central malignancies has not been substantiated yet. ***Objectives:*** In this study we evaluated if endobronchial needle aspiration may increase the sensitivity of bronchoscopy for diagnosing central airways neoplasms when added to conventional diagnostic methods (forceps biopsy, brushing and bronchial washing), and if rapid on-site evaluation may be beneficial in patients undergoing endobronchial needle aspiration. ***Methods:*** 125 patients (77% males, aged 70 ± 7 years; mean ± SD) with central lung cancers were randomized to undergo bronchoscopy including conventional diagnostic methods and needle aspiration, with or without rapid on-site evaluation, stratifying the patients on the basis of the neoplasm growth pattern (exophytic and submucosal/peribronchial disease). ***Results:*** Needle aspiration significantly increased the sensitivity of bronchoscopy when added to conventional methods (from 76 to 91%; $p < 0.001$), primarily resulting from differences in submucosal/peribronchial diseases (68 vs. 90%; $p < 0.001$) and independently from the presence of rapid on-site evaluation; needle aspiration guided by rapid on-site evaluation guaranteed a higher improvement in bronchoscopy sensitivity than conventional needle aspiration (98 vs. 84%, respectively; $p = 0.004$). Needle aspiration guided by rapid on-site evaluation showed a significantly higher sensitivity than the conventional method (97 vs. 76%, respectively; $p = 0.001$). ***Conclusions:*** Needle aspiration increases the sensitivity of bronchoscopy in diagnosing central airways malignancies when added to conventional diagnostic methods, with a further significant improvement when guided by rapid on-site evaluation.

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E-Mail karger@karger.com
www.karger.com/res

Michele Mondoni
Clinica di Malattie Respiratorie, Ospedale San Paolo
Via A. Di Rudinì 8
IT–20142 Milan (Italy)
E-Mail michele.mondoni@ao-sanpaolo.it

Introduction

Endobronchial lung cancer tends to show different growth patterns. It can present as an exophytic mass lesion, submucosal infiltration or extrinsic compression from peribronchial disease [1]. Bronchoscopy with forceps biopsy (FB), bronchial brushing (BB) and bronchial washing (BW) is the most used technique to diagnose central airways neoplasms. Some authors have suggested that the addition of endobronchial needle aspiration (EBNA) to these conventional diagnostic methods may increase the sensitivity of bronchoscopy in submucosal and peribronchial diseases, but few prospective studies have been performed and this procedure is still underutilized in many centers [1–10]. Rapid on-site evaluation (ROSE) has been shown to improve the sensitivity of transbronchial needle aspiration (TBNA) of mediastinal nodes and pulmonary peripheral lesions, reducing the number of inadequate specimens, costs and complications [11–15]. However, its utility during EBNA has not been substantiated yet. In this prospective trial we investigate whether ROSE may be beneficial in EBNA of central airways malignancies and evaluate the sensitivity of needle aspiration and its contribution to conventional diagnostic methods in the diagnosis of endobronchial neoplastic lesions.

Materials and Methods

Study Design

This is a prospective, randomized and controlled trial. The study was approved by the local ethical committee (protocol No. 108/2011 CE) and registered at ClinicalTrials.gov with the number NCT01456741. Written informed consent was subscribed by all the patients.

Patients and Interventions

Consecutive adult patients with a suspected central lung cancer on a chest computed tomography (CT) scan between August 2011 and March 2012 were judged eligible for the study. Exclusion criteria included the presence of uncontrolled coagulopathy, preexisting known lung malignancies, and the refusal to sign an informed consent. All the study bronchoscopies were performed under topical anesthesia (lidocaine 1%) and conscious sedation (midazolam 2–5 mg i.v.) at the Respiratory Unit of San Paolo Hospital (Milan, Italy). During bronchoscopy, submucosal and peribronchial diseases were defined as previously described in the literature [1]. All patients underwent EBNA with a 21-gauge needle (Excelon, Boston Scientific, USA), and at least three FBs, BB and BW in this procedural sequence [5, 7, 8, 16]. Consecutive patients were randomized, at the time of bronchoscopy, to undergo EBNA with or without ROSE (fig. 1). ROSE was performed by a pathologist. In the group that underwent EBNA without ROSE (conventional EBNA, cEBNA), 3 passes were performed as suggested by literature [17]. The material obtained was smeared on clean glass slides, spray-fixed by pulmonologists trained by the pathologist in the handling of specimens and subsequently sent to laboratory for Papanicolaou staining without immediate adequacy evaluation. In the ROSE-EBNA group, slides were immediately evaluated by the pathologist. For each pair of smeared slides, one was spray-fixed and stored for laboratory Papanicolaou staining, one was air-dried for immediate rapid May-Grünwald-Giemsa staining. Cell blocks and/or subsequent immunocytochemistry were performed when desired. The pathologist on site reported in real-time the findings and informed the operator when sufficient material had been obtained for provisional diagnosis and for all ancillary tests required for its confirmation. The number of needle passes sufficient to obtain the diagnosis was registered. If ROSE did not provide a specific diagnosis after three passes, the procedure ended and sampling continued with the conventional diagnostic methods. In cytologic samples, cellular atypia and abnormal cells suggestive of malignancy were considered as nondiagnostic evidence for malignancy. The patients with inconclusive bronchoscopic procedures underwent CT-guided transthoracic needle aspiration or were operated if considered candidates for surgery with curative intent. Patients who had a diagnosis of benign disease were excluded. No patients refused further testing after inconclusive bronchoscopy.

Outcome Measures

This study has two primary aims: to investigate the sensitivity for malignancy comparing conventional diagnostic methods (association of FB, BB and BW) with conventional diagnostic methods + EBNA (with and without ROSE) and to compare the sensitivity of ROSE-EBNA with that of cEBNA.

In the secondary analysis, we evaluated the sensitivity of each of the individual procedures, stratifying the patient population on the basis of the endoscopic patterns, exophytic mass lesions and submucosal/peribronchial diseases.

Any procedure-related complications and damages to the bronchoscope were documented as well.

Randomization and Statistical Analysis

The randomization list was produced by a computer-generated sequence (www.randomization.com). The present study was powered to detect an increase in sensitivity of EBNA with ROSE of 17%, and an increase in sensitivity of 6–7% by adding EBNA to conventional diagnostic methods. All data are reported as mean ± standard deviation (SD), if not otherwise stated. Normally distributed continuous variables were analyzed using Student's t test and analysis of variance (ANOVA) and, if positive, post hoc comparisons were carried out by t test with Bonferroni adjustment with a parametric test (t test). Fisher's test and McNemar's test were used for categorical data. p values <0.05 were considered statistically significant. Data were analyzed using the Statistical Package for the Social Sciences (version 19.0; SPSS, Chicago, Ill., USA).

Results

During the study period 134 patients were enrolled and 133 were randomized. Eight patients were eventually excluded because of benign lesions (fig. 1). Of the

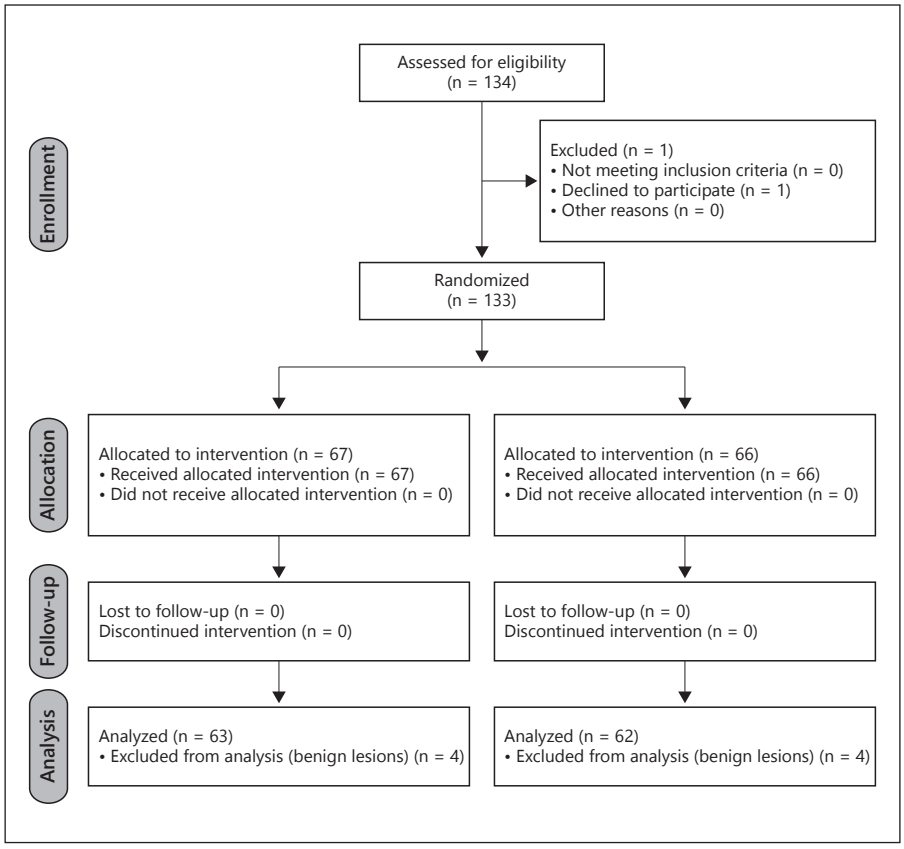

Fig. 1. Study flowchart.

125 diagnosed malignant neoplasms, 52 (42%) were exophytic mass lesions and 73 (58%) were submucosal/peribronchial diseases. As listed in table 1, age, sex, lesion types and sensitivities of conventional diagnostic methods were similarly distributed among patients who underwent bronchoscopy with and without ROSE.

Malignancy was diagnosed by bronchoscopy in 114 patients (91%), by transthoracic needle aspiration in 9 (7%) and surgery in 2 (2%). Pathological analysis revealed 9 non-small cell lung cancers (NSCLC) not otherwise classified, 54 adenocarcinomas, 44 squamous carcinomas, 17 small cell lung cancers and 1 carcinoid. We found 58 neoplasms in the upper lobes, 38 in the lower lobes, 13 in the middle lobe, 15 in the main bronchi and 1 in the trachea. Malignancy was detected at on-site evaluation in 60 out of 63 patients with cancer yielding a 95% accuracy rate. In these patients we had 3 false negatives (5% of malignancies missed by ROSE but diagnosed at the definitive examination). In the overall analysis the addition of needle aspiration to conventional methods increased the sensitivity of bronchoscopy from 76 to 91% ($p < 0.001$), primarily resulting from differences in the submucosal/peribronchial diseases group (table 2; fig. 2). Although no statistical differences were observed in exophytic mass lesions, EBNA identified 3 additional patients with lung cancer. In submucosal/peribronchial diseases, the addition of needle aspiration to conventional methods sig-

Table 1. Demographics and baseline data of all patients and according to ROSE randomization

Characteristics	All patients (n = 125)	cEBNA (n = 62)	ROSE-EBNA (n = 63)	p value
Age, year	70±7	71±7	69±6	0.142
Male sex	96 (77)	47 (76)	49 (78)	0.835
Type of lesion				
EML	52 (42)	25 (40)	27 (43)	0.857
SPD	73 (58)	37 (60)	36 (57)	
CDM sensitivity	95 (76)	45 (73)	50 (79)	0.408

Values are given as mean ± SD or n (%). p value: cEBNA vs. ROSE-EBNA. CDM = Conventional diagnostic methods; EML = exophytic mass lesion; SPD = submucosal/peribronchial disease.

Table 2. Sensitivity from CDM versus CDM + EBNA according to neoplasm growth pattern

Neoplasms	CDM n (%)	CDM + EBNA n (%)	p value
Total (n = 125)	95 (76)	114 (91)	<0.001
EML (n = 52)	45 (87)	48 (92)	0.250
SPD (n = 73)	50 (68)	66 (90)	<0.001

CDM = Conventional diagnostic methods; EML = exophytic mass lesion; SPD = submucosal/peribronchial disease.

Table 3. Sensitivity comparing CDM versus CDM + EBNA, with and without ROSE

Procedures	Total	p value
CDM CDM + cEBNA	45/62 (73%) 52/62 (84%)	0.016
CDM CDM + ROSE-EBNA	50/63 (79%) 62/63 (98%)	<0.001
CDM + cEBNA CDM + ROSE-EBNA	52/62 (84%) 62/63 (98%)	0.004

CDM = Conventional diagnostic methods.

Table 4. Sensitivity of cEBNA versus ROSE-EBNA according to neoplasm growth pattern

Neoplasms	cEBNA	ROSE-EBNA	p value
Total	47/62 (76%)	61/63 (97%)	0.001
EML	18/25 (72%)	26/27 (96%)	0.022
SPD	29/37 (78%)	35/36 (97%)	0.028

EML = Exophytic mass lesion; SPD = submucosal/peribronchial diseases.

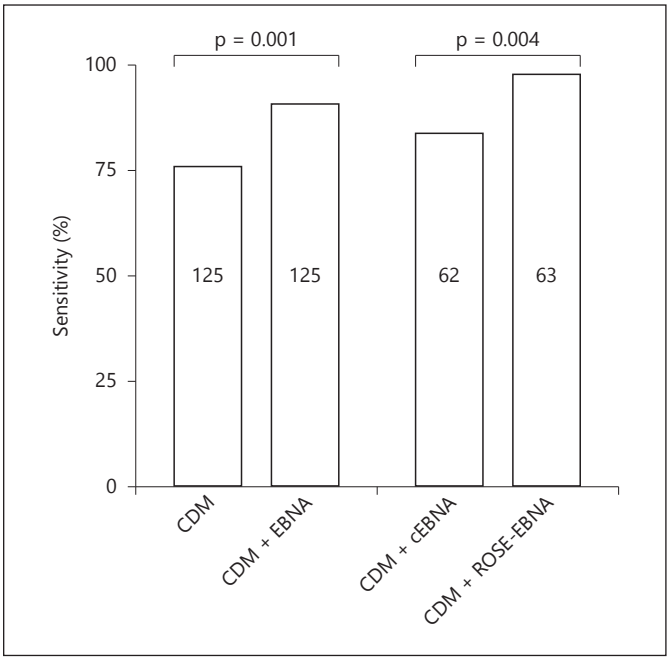

Fig. 2. Sensitivity of CDM and CDM + EBNA in the overall analysis, with and without ROSE. The numbers in the histograms refer to the number of patients studied. CDM = Conventional diagnostic methods.

nificantly improved the sensitivity of bronchoscopy ($p < 0.001$).

In the cEBNA group, the addition of needle aspiration to conventional diagnostic methods significantly increased the sensitivity of bronchoscopy from 73 to 84% ($p = 0.016$) and in the ROSE-EBNA group, by adding needle aspiration to conventional diagnostic methods, we found a significant improvement in sensitivity of bronchoscopy from 79 to 98% ($p < 0.001$). Comparing the two groups, ROSE-EBNA revealed a greater improvement in sensitivity than cEBNA when added to conventional diagnostic methods ($p = 0.004$) (table 3; fig. 2).

The sensitivities of cEBNA and ROSE-EBNA are listed in table 4. In the overall analysis, ROSE significantly increased the sensitivity of EBNA ($p = 0.001$). In the subgroup analysis, ROSE-EBNA was significantly better than cEBNA in both exophytic mass lesions ($p = 0.022$) and submucosal/peribronchial diseases ($p = 0.028$).

In the cEBNA group the pathologist never pointed out mistakes in handling of specimens responsible for incorrect or misleading diagnosis. The number of passes with ROSE-EBNA required to obtain the diagnosis was 1.6 ± 0.756.

In the overall analysis EBNA diagnosed 94 NSCLC (55 ROSE-EBNA and 39 cEBNA): 87 were histologically typified (47 adenocarcinomas, 40 squamous carcinomas) while 7 were not otherwise classified. ROSE-EBNA guaranteed a better histological classification of NSCLC (sensitivity of 96%) than cEBNA (87%) without reaching statistical significance.

The different sensitivities from each procedure and their combination are shown in table 5. EBNA demonstrated the best sensitivity, significantly higher than ev-

Table 5. Sensitivity of individual procedures and their combination according to neoplasm grow patterns

Procedures	Total (n = 125)	EML (n = 52)	SPD (n = 73)	Exclusively diagnostic
EBNA	108 (86)	44 (85)	64 (88)	19 (15)
FB	88 (70)	43 (83)	45 (62)	6 (5)
BB	69 (55)	34 (65)	35 (48)	0 (0)
BW	36 (29)	18 (35)	18 (25)	0 (0)
EBNA + FB	114 (91)	48 (92)	66 (90)	

Values are given as n (%). EML = Exophytic mass lesion; SPD = submucosal/peribronchial disease.

ery other individual sampling method (EBNA vs. FB, $p = 0.001$; EBNA vs. BB, $p < 0.001$; EBNA vs. BW, $p < 0.001$). In exophytic lesions EBNA did not reveal to be statistically better than FB although superior to BB and BW ($p < 0.05$). In submucosal/peribronchial malignancies, EBNA revealed a significantly higher sensitivity than every other conventional sampling method ($p < 0.001$). EBNA was exclusively diagnostic in 19 patients (15% of the patients): 16 patients with peribronchial/submucosal diseases and 3 with exophytic mass lesions (one of these with a largely necrotic neoplasm). Twelve patients were diagnosed by ROSE-EBNA and 7 patients by the conventional method. FB was exclusively diagnostic in 6 patients (5%), 4 patients with exophytic lesions and 2 patients with submucosal/peribronchial neoplasms. BB and BW never resulted positive in lesions in which the other procedures were negative. Minor bleeding was observed in 8 patients, 4 after FB, 2 after BB and 2 after EBNA. One patient experienced atrial fibrillation after the bronchoscopic examination. No damage occurred to the bronchoscope.

Discussion

This is, to our knowledge, the first randomized controlled trial specifically designed to evaluate the usefulness of ROSE of endobronchial needle aspirates in the diagnosis of central lung malignancies; this is also the largest prospective study conducted to examine whether needle aspiration may increase the sensitivity of bronchoscopy in sampling these neoplasms when added to conventional methods. We demonstrated that EBNA increases the sensitivity of bronchoscopy in sampling central airway cancers when added to conventional diagnostic methods, independently from the presence of ROSE; moreover, ROSE guaranteed a further significant improvement in sensitivity.

Only few prospective trials have evaluated the role of needle aspiration in diagnosing central airways malignancies, directly comparing this technique with the other conventional diagnostic methods in the same patients [1, 3–9]. Lundgren et al. [4] did not report an increase in sensitivity of bronchoscopy by adding EBNA to conventional diagnostic methods, but their results were later reversed in other studies. Shure and Fedullo [5] showed that the addition of needle aspiration to FB raised the diagnostic yield from 55 to 87%, and this increase was statistically significant. Moreover, two other trials demonstrated that the combination of EBNA and conventional diagnostic methods increased the sensitivity compared to conventional methods alone [1, 8].

In our series, the addition of EBNA to conventional methods significantly augmented the sensitivity of bronchoscopy, resulting from differences in the submucosal/peribronchial disease group. Conventional procedures such as FB tend to sample mainly the surface rather than deep within the lesion. Therefore the ability of the needle to penetrate the mucosal surface and sample the outer bronchial layers, may explain these results [5]. Only a part of the patients enrolled in the study underwent EBNA with ROSE. In our opinion this situation may be common in many institutions where a cytopathologist may not always be available. In order to limit the occurrence of possible selection biases we employed a randomized design. Govert et al. [8] firstly described the utilization of ROSE-EBNA in sampling central neoplasms; however, this study was not randomized.

In both randomization groups, by adding needle aspiration to conventional methods we observed an increase in the sensitivity of bronchoscopy. Moreover, the rate of improvement in sensitivity was significantly higher in the ROSE-EBNA arm, suggesting the importance of ROSE in elevating the sensitivity of EBNA.

Furthermore, in our study needle aspiration with immediate cytological assessment clearly demonstrated a better sensitivity than conventional needle aspiration. cEBNA revealed an overall diagnostic sensitivity of 76%, a value consistent with that reported by other authors, while ROSE-EBNA showed a sensitivity of 97%, higher than that described by Govert et al. [3, 8, 9]. However, analyzing the sensitivity of the technique by the different lesion types in both studies, we may observe a comparable sensitivity of ROSE-EBNA in exophytic lesions but a very

different sensitivity in the submucosal/peribronchial diseases group [8]. In these neoplasms we found a sensitivity of 97%, which is similar to that obtained by other authors with the conventional technique [1]. On the contrary in these lesion types, Govert et al. [8] reported the lowest sensitivity described in the literature (64%). The sensitivity of conventional needle aspiration described in our study in both exophytic and submucosal/peribronchial malignancies was comparable with the literature as well [1, 5, 9, 18].

The subgroup analysis showed a significantly higher sensitivity of EBNA guided by ROSE in both lesion types. The role of ROSE in needle aspiration is still partly controversial. Two different uncontrolled studies demonstrated a higher yield of TBNA of peripheral lesions and mediastinal adenopathies when ROSE was present than in the absence of ROSE [11, 12]. Other authors described a significant reduction in the utilization of consumables, laboratory and radiographic resources and a cost-effectiveness associated with immediate cytological assessment [13, 14]. More recently Trisolini et al. [15], in a randomized and controlled trial, failed to demonstrate a significant increase in sensitivity of ROSE-TBNA in hilomediastinal nodes but reported a significant reduction in the complication rate of bronchoscopy in these patients.

Some considerations should be pointed out to explain our results and to better understand the importance of ROSE in sampling central malignancies. In the absence of immediate cytological evaluation the operator performs three needle passes in the site thought to be the most promising for a diagnosis, without obtaining immediate confirmation of the adequacy of the sample and any information regarding the diagnosis itself. With a pathologist on site, after the first pass, the operator can immediately know the quality of the sample. In case of a nondiagnostic sample the operator may thus perform other needle passes, modifying the technique or the site of puncture. On the contrary, in case of diagnostic material, the bronchoscopist can decide to keep on sampling with needle biopsy in the same site to obtain more material, change the sampling modality or stop the procedure if sufficient material has been harvested for diagnosis. Hence, by avoiding further needle passes or the use of other sampling methods, he can reduce costs and complications [13, 19]. In our opinion this is particularly noticeable in diagnosing central malignancies where large pathological areas may be suitable for sampling and where different diagnostic techniques are available. This aspect might also explain why a lower rate of biopsies performed with ROSE may lead to a higher diagnostic sensitivity in comparison with three blind needle aspirations. The experience of the pathologist also guarantees that samples are handled and processed in the best way; however, in the present study the operators were trained by the cytologist to smear and fix the specimens and no mistakes in handling responsible for incorrect or misleading diagnosis emerged. In our study ROSE-needle aspiration also showed a higher sensitivity in histological tumor typing as compared to the conventional technique; although this result failed to reach statistical significance, probably because of the small population studied, it may suggest a better quality of the material sampled with ROSE-needle aspiration. Indeed, the presence of an immediate cytological assessment of the aspirated specimens provides the possibility to address the sampling to the most diagnostic sites, thus obtaining good quality material. This aspect is of great importance in the era of targeted oncologic treatments, since ROSE might help identify the best site for obtaining the proper amount of tissue for molecular studies. Nevertheless, some pathologists are reluctant to join the operator in bronchoscopy suite, considering ROSE not to be cost-effective. It should be underlined that in order to overcome this obstacle, some pulmonologists are training to evaluate themselves the adequacy of the aspirates, obviously leaving the final diagnosis to the pathologist [15, 19].

In our series EBNA proved to be the most sensitive sampling technique, significantly higher than each single conventional diagnostic method. The best sensitivity of FB was registered in exophytic lesions and this finding is consistent with the literature [1, 9]. In all the lesion types EBNA showed a better sensitivity than FB but reached statistical significance only in submucosal/peribronchial diseases where needle aspiration was far superior to any other individual procedure. These findings are consistent with those reported by other authors [1, 8, 9]. As stated before, the ability of the needle to provide adequate sampling by penetrating either the submucosa or directly through the bronchial wall into the neoplasm may explain these results [5]. Unlike previously reported by other authors, in our study BB alone never proved to be exclusively diagnostic [1].

Some limitations of the present study need to be discussed. Firstly, the results should not be generalized since this trial was performed in a single institution and involved a close working relationship with a pathologist who is very skilled in lung cytology. Secondly, we postulated that the presence of ROSE may avoid aimless needle passes or the use of other sampling methods, thereby re-

ducing costs; nevertheless, we did not make any cost analysis and therefore we cannot clearly establish if it is also cost-effective.

In conclusion this study suggests that EBNA significantly increases the sensitivity of bronchoscopy in diagnosing central airway neoplasms when added to FB, and mainly when guided by ROSE. EBNA is the most sensitive procedure in all lesion types and the technique of choice in submucosal/peribronchial diseases. ROSE promotes an increase in sensitivity of EBNA and allows ending a diagnostic bronchoscopy after 1 or 2 needle passes in the majority of patients.

Financial Disclosure and Conflicts of Interest

None of the authors has a financial interest to declare.

References

1 Dasgupta A, Jain P, Minai OA, Sandur S, Meli Y, Arroliga AC, Mehta AC: Utility of transbronchial needle aspiration in the diagnosis of endobronchial lesions. Chest 1999;115:1237–1241.

2 Rivera MP, Mehta AC: Initial diagnosis of lung cancer. ACCP evidence-based clinical practice guidelines (2nd edition). Chest 2007; 132:131S–148S.

3 Buirski G, Calverley PMA, Douglas NJ, Lamb D, McIntyre M, Sudlow MF, White H: Bronchial needle aspiration in the diagnosis of bronchial carcinoma. Thorax 1981;36:508–511.

4 Lundgren R, Bergman F, Angstrom T: Comparison of transbronchial fine needle aspiration biopsy, aspiration of bronchial secretions, bronchial washing, brush biopsy and forceps biopsy in the diagnosis of lung cancer. Eur J Respir Dis 1983;64:378–385.

5 Shure D, Fedullo PF: Transbronchial needle aspiration in the diagnosis of submucosal and peribronchial bronchogenic carcinoma. Chest 1985;88:49–51.

6 Castella J, Buj J, Puzo C, Anton PA, Burgués C: Diagnosis and staging of bronchogenic carcinoma by transtracheal and transbronchial needle aspiration. Ann Oncol 1995;6:S21–S24.

7 Bilaçeroğlu S, Günel Ö, Çağirici U, Perim K: Comparison of endobronchial needle aspiration with forceps and brush biopsies in the diagnosis of endobronchial lung cancer. Monaldi Arch Chest Dis 1997;52:13–17.

8 Govert JA, Dodd LG, Kussin PS, Samuelson WM: A prospective comparison of fiberoptic transbronchial needle aspiration and bronchial biopsy for bronchoscopically visible lung cancer. Cancer 1999;87:129–134.

9 Kaçar N, Tuksavul F, Edipoğlu Ö, Ermete S, Güçlü SH: Effectiveness of transbronchial needle aspiration in the diagnosis of exophytic endobronchial lesions and submucosal/peribronchial diseases of the lung. Lung Cancer 2005;50:221–226.

10 Medford ARL, Agrawal S, Free CM, Bennett JA: A prospective study of conventional transbronchial needle aspiration: performance and cost utility. Respiration 2010;79:482–489.

11 Davenport RD: Rapid on-site evaluation of transbronchial aspirates. Chest 1990;98:59–61.

12 Diette GB, White P, Terry P, Jenckes M, Rosenthal D, Rubin HR: Utility of on-site cytopathology assessment for bronchoscopic evaluation of lung masses and adenopathy. Chest 2000;117:1186–1190.

13 Diacon AH, Schuurmans MM, Theron J, Louw M, Wright CA, Brundyn K, Bolliger CT: Utility of rapid on-site evaluation of transbronchial needle aspirates. Respiration 2005; 72:182–188.

14 Baram D, Garcia RB, Richman PS: Impact of rapid on-site cytologic evaluation during transbronchial needle aspiration. Chest 2005; 128:869–875.

15 Trisolini R, Cancellieri A, Tinelli C, Paioli D, Scudeller L, Casadei GP, Forti Parri S, Livi V, Bondi A, Boaron M, Patelli M: Rapid on-site evaluation of transbronchial aspirates in the diagnosis of hilar and mediastinal adenopathy: a randomized trial. Chest 2011;139:395–401.

16 Shure D, Astarita RW: Bronchogenic carcinoma presenting as an endobronchial mass. Chest 1983;83:865–867.

17 Diacon AH, Schuurmans MM, Theron J, Brundyn K, Louw M, Wright CA, Bolliger CT: Transbronchial needle aspirates: how many passes per target sites? Eur Respir J 2007;29: 112–116.

18 Karahalli E, Yilmaz A, Türker H, Özvaran K: Usefulness of various diagnostic techniques during fiberoptic bronchoscopy for endoscopically visible lung cancer: should cytologic examinations be performed routinely? Respiration 2001;68:611–614.

19 Gasparini S: It is time for this 'ROSE' to flower. Respiration 2005;72:129–131.