

Efficacy and cost effectiveness of rapid on site examination (ROSE) in management of patients with mediastinal lymphadenopathies

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Abstract. – BACKGROUND: The diagnostic and staging approach for the mediastinal lymphadenopathies, with or without pulmonary lesions endoscopically visible, is based on transbronchial needle aspiration (TBNA) during fiberoptic bronchoscopy and on mediastinoscopy. One important factor impacting on TBNA sensitivity is the rapid on site cytological examination (ROSE).

AIM: The aim of this study was to evaluate the economic impact of TBNA and TBNA + ROSE, in the diagnosis of these lesions.

PATIENTS AND METHODS: 120 patients, affected by mediastinal lymphadenopathies suspected for lung cancer, underwent TBNA during fiberoptic bronchoscopy: 60 patients without ROSE (group A) and other 60 with ROSE (group B). Whenever needle aspirations failed to provide diagnosis, the patient underwent mediastinoscopy. The economic impact of the diagnostic process was performed.

RESULTS: In group A, 39 patients (65%) obtained a diagnosis with TBNA while 21 patients (35%) required mediastinoscopy. In group B, 48 patients (80%) obtained a diagnosis with TBNA + ROSE, while 12 patients (20%) required mediastinoscopy. With regards to the costs of the procedures performed in the diagnostic process, the use of TBNA with ROSE as first diagnostic approach has saved a considerable amount of euros (19,413) compared to the use of TBNA without ROSE and the combined procedure increased ($p < 0.02$; chi square test) the sensitivity of TBNA by 15%.

CONCLUSIONS: ROSE significantly impacts on the diagnostic yield, as well as on the overall management costs of patients with mediastinal lymphadenopathy, suspected for lung cancer.

Key Words:

Bronchoscopy, Cytology, Lung cancer, TBNA, Economic analysis.

Introduction

The mediastinal lymphadenopathy, with endoscopically not visible lung lesions, are frequently

encountered in clinical practice. It is not possible to give a unique interpretation of these x-ray/CT findings, because they are often linked to several diseases such as lung cancer, metastatic tumors, lymphomas, sarcoidosis, tuberculosis, etc.

Usually, the diagnostic and staging approach is based on the fiberoptic bronchoscopy with transbronchial needle aspiration (TBNA), with or without ultrasound guidance, and on the mediastinoscopy. In the last few years it has been demonstrated that the number of mediastinoscopies can be reduced by the use of TBNA during the fiberoptic bronchoscopy and that ultrasound guidance increases the sensitivity, but cost too, of this procedure¹⁻⁵. The sensitivity of TBNA, a quick and safe procedure, also depends on the presence of lymphadenopathies > 1 cm on the computed tomography (CT), the operator skills and experience, the type of needle used, the lymph nodes localization and diameter, the number of the performed aspirations, the extemporaneous cytological reading (rapid on site examination or ROSE), the nature of the lesion (lung cancer, metastases from other neoplasms, sarcoidosis, tuberculosis, etc.)^{2,6-11}.

Recent studies have shown the superiority of treatment with gefitinib or erlotinib in tumors with EGFR (epidermal growth factor receptor) mutation. As a consequence, the complete diagnosis and staging of lung cancer cannot be limited to histotype classification, but should include a series of molecular biology analyses (EGFR, K Ras, ALK fusion) that allow to single out the therapeutic target of the new drugs currently available and of those being presently developed²⁸⁻³¹.

The ROSE, added to TBNA, increases the sensitivity of the procedure and reduces costs, but also let to collect appropriate sample for molecular biology analyses^{12-14,31}.

The aim of this study was to evaluate the economic impact of TBNA combined with ROSE as primary procedure, vs TBNA in patient with hilar-mediastinal lymphadenopathies without or with endoscopically not visible lung lesions for a “complete” diagnosis and staging in two real groups of patients.

Patients and Methods

Patients

We revised 806 fiberoptic bronchoscopy performed between 2009 and 2010, among which 120 underwent TBNA. These patients (mean age 64.5 ± 11.9 years, range 36-80, 98 men and 22 women) were admitted in the Pneumology Unit of Sant’Andrea Hospital in Rome for cough and/or dyspnea and/or sputum. During the diagnostic process, the CT scan with contrast had put in evidence mediastinal lymphadenopathies without or with parenchymal lesions not visible endoscopically. In order to obtain the diagnosis and staging the disease, these patients underwent flexible fiberoptic bronchoscopy with transbronchial needle aspiration (TBNA) because there were not intra-bronchial abnormalities, and after, if the diagnosis was not performed, mediastinoscopy. The patients were divided in group A (TBNA without ROSE) and group B (TBNA with ROSE) because in the analyzed period the cytologist was not always in the bronchoscopic room. All patients signed informed consent.

Fiberoptic Bronchoscopy and TBNA

Patients were given premedication with midazolam, while local anesthesia was obtained with 1% lidocaine and the flexible bronchoscopy was introduced via transnasal.

The flexible videobronchoscopy used was an Olympus BF1T160 and the needle aspiration was performed with a 19 gauge needle without mandrel, type Wang MWF319 (ConMed via Figinio 39 A, Pero, Milan, Italy). If multiple lymph node stations were involved, the one with larger diameter was sampled firstly. The needle was introduced with the pushing method²⁷. In group A seven passes were made (“simple TBNA”), everyone followed by the preparation of two slides (fixed in ethanol 95°) for the final cytological examination. In group B each passage was followed by the preparation of two slides: one for a rapid on site examination was stained with the Hemacolor kit (Merck Frankfurter Str. 25, Darm-

stadt, Germany) and the other for the final cytological examination was fixed in ethanol (95°). In group B, the cytology slides were stained with Haemacolor kit and they were examined by the cytologist in order to evaluate the suitability of the samples (ROSE). The results were reported directly to the bronchoscopist as suitable or unsuitable for diagnostic purposes. If the cytopathologist considered the sample suitable, the procedure was terminated. The decision to make other aspirations was related to the necessity to obtain enough biological material for the subsequent molecular and immunocytochemical investigations. The procedure was interrupted when cytological material was considered suitable for the diagnosis. The highest total number of needle aspirations performed was 7, considering that it is reported in the literature that after seven passes the TBNA sensitivity reaches a plateau¹⁵. If all seven needle aspirations failed to provide suitable diagnostic material, the patient underwent mediastinoscopy for staging purpose.

Costs of the Procedures

In order to perform an economic analysis of the diagnostic process, costs were calculated in the following way¹⁶: the cost of the flexible bronchoscopy with TBNA was fixed equal to 477 euro (197 euro for instruments and 280 for personnel), the cost of ROSE equal to 48 euro (instruments and personnel) and that of mediastinoscopy equal to 2477 euro (1600 euro for hospitalization, 517 euro for instruments, 360 euro for personnel).

Statistical Analysis

Data for statistical analysis have been processed with SPSS software version 17.0 (SPSS, Chicago, IL, USA). Unpaired *t* Student test was used for comparing age and the average diameter of lymph nodes sampled of two groups while Chi square test was used for comparing sex, final diagnosis and results of TBNA vs TBNA + ROSE. A *p* value < 0.05 was considered significant.

Results

Diagnosis

The two groups of patients did not differ significantly from each other with regard to sex (chi square test: *p* > 0.05), final diagnosis (chi square test: *p* > 0.05), age and the average diameter of lymph nodes sampled (unpaired Student *t* test: *p* > 0.05).

The final diagnoses of the 120 patients were summarized in Table I. In group A, the 39 diagnoses obtained with “simple TBNA” included 32 malignancies and 7 non neoplastic lesions; of the 32 malignancies, 30 were non-small cell lung cancers (NSCLC) (18 adenocarcinomas, 8 squamous cell carcinomas, 4 large cell undifferentiated lung carcinomas), 2 small cell lung cancers (SCLC); the 21 additional diagnoses obtained with mediastinoscopy, revealed 5 NSCLC (3 adenocarcinomas, 2 squamous cell carcinomas), 4 SCLC, 10 lymphomas and 2 other not lung tumors.

In group B: the 48 diagnoses obtained with TBNA and ROSE included 37 malignancies and 11 non neoplastic lesions. Of the 37 malignancies, 28 were NSCLC (22 adenocarcinomas, 5 squamous cell carcinomas, 1 large cell undifferentiated lung carcinomas), 5 SCLC, 2 pleural mesothelioma, 1 seminoma, 1 metastases of extrathoracic disease; the 12 additional diagnoses obtained with mediastinoscopy, revealed 2 NSCLC (2 adenocarcinomas), 3 SCLC and 7 lymphoma.

The groups of patients did not differ significantly from each other with regard to sex (chi square test: $p > 0.05$), final diagnosis (chi square test: $p > 0.05$), age and the average diameter of lymph nodes sampled (unpaired Student’s t test: $p > 0.05$).

Diagnostic Accuracy

In the group A the average diameter of the lymph nodes underwent biopsy and detected by chest CT, was 2 cm ± 0.8, in the group B 2.2 cm ± 0.7 ($p > 0.05$).

The sampled lymph node stations were, in order of frequency: lower right paratracheal (30%), subcarinal (21%), left hilar (14%), right hilar (10%), front carinal (9%), left paratracheal (4%), left main bronchus (4%), right main bronchus (3%), retrocarinal (3%), upper right paratracheal (2%).

All 120 patients were subjected to fiberoptic bronchoscopy with sampling of biological material from their mediastinal lymphadenopathies by transbronchial needle aspiration (TBNA), with ROSE only in group B.

In group A, TBNA reached the diagnosis in 39/60 patients (65%). In group B, TBNA+ROSE reached diagnosis in 48/60 patients (80%); ROSE increased significantly diagnostic accuracy (Chi-square test, $p < 0.02$). The sampling during bronchoscopy in the remaining cases (21 in group A and 12 in group B) were “unsuitable for diagnosis” and consequently the mediastinoscopy was performed. No significant complications arose during these procedures (Table I). The diagnostic yield of TBNA was evaluated based on the sampled lymph node station; the best diagnostic yield was observed

Table I. Characteristics of the study population and diagnoses obtained with each procedure.

Number of patients	Group A TBNA = 60	Group B TBNA + ROSE = 60
Sex	47M (78%)/13F (22%)	49M (81.7%)/11F(18.3%)
Age (years ± SD)	61.3 ± 9.2	64.5 ± 11.9
Mean Lymph node diameter (cm ± SD)	2 ± 0.8	2.2 ± 0.7
Diagnosis and staging	39/60 (65%)	48/60* (80%)
Malignant neoplasia	32	37
• NSCLC	30	28
• SCLC	2	5
• Pleural mesothelioma	–	2
• Mediastinal seminoma	–	1
• Metastases from extrathoracic neoplasiae	–	1
• Not malignant	7	11
• Reactive lymphnode (not metastatic)	21	12
• Not diagnostic		
Diagnosis and staging with mediastinoscopy:	21/21 (100%)	12/12 (100%)
NSCLC	5	2
SCLC	4	3
Lymphoma	10	7
Other neoplasie	2	–
Complications	None	None

The two groups of patients did not differ significantly from each other with regard to sex (chi square test: $p > 0.05$), final diagnosis (chi square test: $p > 0.05$), age and the average diameter of lymph nodes sampled (unpaired Student t test: $p > 0.05$); *Chi square test: TBNA vs TBNA + ROSE $p < 0.02$.

Table II. Sensitivity of the procedures in 120 patients affected with hilar/mediastinal lymphadenopathies.

Procedures	TP	FP	TN	FN	PPV	NPV	Sensitivity %
TBNA (60 pts)	39	0	0	21	1	0	65
TBNA + ROSE (60 pts)	48	0	0	12	1	0	80*
Mediastinoscopy (33 pts)	33	0	–	0	1	1	100

TP: True Positive; FN: False Negative; TN: True Negative; FN: False Negative; PPV: Positive Predictive Value; NPV: Negative Predictive value. *Chi square test: TBNA vs TBNA + ROSE $p < 0.02$.

with the sampling of the lower right paratracheal (4R ATS classification)²⁷ and subcarinal stations (7 ATS classification)²⁷ according to previous reports¹⁰.

Economic Evaluation

The costs of the diagnostic procedures carried out for the evaluation of hilar-mediastinal lymphadenopathies in the 120 patients have been calculated and summarized in Table III.

A total of 80,637 Euro were spent for the diagnostic procedures (60 bronchoscopy with TBNA, 21 mediastinoscopy) in group A.

A total of 61,224 Euro were spent for the diagnostic procedures (60 bronchoscopy with TBNA + ROSE, 12 mediastinoscopy) in group B.

ROSE produced a saving of 19,413 Euro (Table III), because the rapid on-site cytological examination allowed to increase the sensitivity of TBNA by 15%, thus preventing the recourse to other more invasive and expensive procedures such as mediastinoscopy (Table III).

Discussion

The aim of this study was to determine the overall cost of the procedures and the economic

impact of ROSE, for the evaluation of hilar-mediastinal lymphadenopathies suspected for lung cancer, in two real cohort of 60 patients each. In particular, we have calculated the impact of TBNA and ROSE on the expenses of the diagnostic and staging process, demonstrating that TBNA without ultrasound guidance but with ROSE, obtained a considerable economic saving.

In the diagnostic and staging process of hilar-mediastinal lymphadenopathies with/without parenchymal lesions fiberoptic bronchoscopy with TBNA should become the first diagnostic approach, based on the evidence of several studies that have shown the high specificity of this method – with values ranging from 96% to 100% –, the very small prevalence of false positives^{2,17-19} and a sensitivity ranging from 15% to 85%¹⁻⁵, due to the influence of many factors such as the site and size of the lymph node, the nature of the lymphadenopathy, the presence of a guiding system²⁻¹⁰ and the possibility to perform a rapid on-site cytological examination (ROSE)²⁰.

The main difference with previous papers²¹ is that in this study we performed ROSE and analyzed its economic impact on diagnostic and staging process of two groups of patients and not only on cost evaluation of fiber bronchoscopy procedure¹⁴.

In our survey fiberoptic bronchoscopy with TB-

Table III. Economic evaluation.

Total expenses incurred for the diagnostic procedures in the 60 patients with ROSE (group B)	
60 bronchoscopies + TBNA + ROSE	31,500 Euro
12 mediastinoscopies	29,724 Euro
Total	61,224 Euro
Total expenses incurred for the diagnostic procedures in the 60 patients without ROSE (group A)	
60 bronchoscopies + TBNA	28,620 Euro
21 mediastinoscopies	52,017 Euro
TOTAL	80,637 Euro
SAVING achieved through use of ROSE	
Total costs in patients approached without ROSE	80,637 Euro
Total costs in patients approached with ROSE	61,224 Euro
SAVING obtained with ROSE	19,413 Euro

Table IV. Patient's risk according to the diagnostic method used and the literature.

Diagnostic method	Mortality	Major complications
Fiber bronchoscopy (TBNA) ¹⁹⁻²¹	0.02%	0.12%
Mediastinoscopy ¹⁸	0.8%	2%

NA, without and with rapid on-site cytological examination, respectively showed a sensitivity of 65% and 80%. ROSE improved, significantly, the sensitivity of TBNA ($p < 0.02$) because the bronchoscopist might change the needle insertion point guided by previous ROSE results; these results are according with previous studies^{25,26}. Furthermore, ROSE increased diagnostic accuracy because guided the bronchoscopist to obtain enough cytological material for molecular biology and immunochemistry for a "complete" diagnosis of NSCLC (EGFR, K Ras, ALK fusion) that allowed to single out the therapeutic target of the new drugs currently available and of those being presently developed²⁸⁻³¹.

In 35% of cases in group A and in 20% of group B it was impossible to formulate a diagnosis with transbronchial needle aspiration and, therefore, it was necessary to resort to mediastinoscopy.

The combination of ROSE and TBNA not only increases the percentage of positive diagnoses, but also allows to significantly reduce expenses and time; this is an important factor, because hospital managers have to respond not only for the efficacy, but also for the cost of their work. The technological progress of the last 30 years has provided a great number of increasingly sophisticated and expensive tools. The task of the modern physician is to adopt equipment suitable for the patient's needs, based on a careful evaluation of costs and benefits.

In addition to the cost-benefit ratio, it is important to consider also the risk-benefit ratio, i.e. the risks and complications a patient when undergoing the above described diagnostic procedures.

The mediastinoscopy (a surgical diagnostic-staging method), on the other hand, albeit characterized by excellent sensitivity (100%) with a low percentage of false positives, has a 2% prevalence of major complications and a mortality occurrence of 0.8%²⁶; these disadvantages are due to the fact that the method is a "surgical" procedure (Table IV).

Conclusions

The flexible bronchoscopy with transbronchial needle aspiration is a safe procedure with high specificity and sensitivity for the diagnosis of hilar and mediastinal lymphadenopathies; besides, this technique has a very low percent prevalence of mortality (0.02%) and of major complications (0.12%) for the patient²²⁻²⁴. Furthermore, ROSE applied on TBNA offers a good degree of sensitivity and significantly it impacts on the diagnostic yield, as well as on the overall management costs of patients with mediastinal lymphadenopathy with or without parenchymal lesions, also allowing to obtain samples suitable for biomolecular analysis.

Conflict of Interest

None to declare.

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