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Effect of Different Bronchial Washing Sequences on Diagnostic Yield in Endoscopically Visible Lung Cancer

Alberto Fernández-Villar,[a] Ana González,[b] Virginia Leiro,[a] Cristina Represas,[a] María Isabel Botana,[a] Purificación Blanco,[a] Mar Mosteiro,[a] and Luis Piñeiro[a]

[a]Servicio de Neumología, Hospital Xeral-Cíes, Complexo Hospitalario Universitario de Vigo, Vigo, Pontevedra, Spain.
[b]Servicio de Anatomía Patológica, Hospital Xeral-Cíes, Complexo Hospitalario Universitario de Vigo, Vigo, Pontevedra, Spain.

OBJECTIVE: Aspiration of bronchial wash fluid is commonly used in conjunction with brushing and forceps biopsy to diagnose endoscopically visible lung cancer. However, the optimal sequence of these procedures is subject to debate. The objective of this study was to determine if the order in which bronchial washing is performed relative to bronchial brushing and forceps biopsy has any effect on the diagnostic yield.

PATIENTS AND METHODS: A prospective, cross-sectional study was carried out on patients with endoscopically visible lung cancer who underwent video-assisted fiberoptic bronchoscopy for diagnostic purposes. Aspiration of bronchial wash fluid was performed on all patients both before and after bronchial brushing and forceps biopsy. The results were analyzed separately for each type of endobronchial lesion and for both together.

RESULTS: The study included 75 patients, with a mean age of 63.3 years; 81% were men. Bronchoscopy was diagnostic in 71 (94.7%) cases. Findings from bronchial washing fluid were positive in 40 (53.3%) patients when washing was performed prior to brushing and forceps biopsy; when washing was performed after these procedures, findings were positive in 43 (57.3%) patients (*P*=.6). The combined diagnostic yield of washing before and after brushing and forceps biopsy was 69.3%, a significantly better result than either washing before (*P*=.001) or after (*P*=.004) the other sampling techniques. In cases where findings from washing done after brushing and forceps biopsy were negative (14 of 32, 43.7%), blood in the aspirated sample interfered with cytology. In comparison, when washing was performed prior to brushing and biopsy, that problem arose in only 3 of the 35 cases (8.5%) (*P*=.002).

CONCLUSIONS: The order in which bronchial washing is performed in relation to other sampling techniques for diagnosing bronchial tumors does not influence the diagnostic yield. This is probably because the aspirated fluid sample is more likely to contain excessive blood when washing is performed after brushing and forceps biopsy. However, the diagnostic yield can be significantly increased by combining the findings from bronchial washings performed both before and after other sample collection procedures.

Key words: *Fiberoptic bronchoscopy. Lung cancer. Endobronchial lesion. Bronchial lavage fluid. Cytology.*

Influencia en la rentabilidad diagnóstica del momento de realización del aspirado bronquial en los carcinomas broncogénicos endoscópicamente visibles

OBJETIVO: Además del cepillado y de la biopsia bronquiales, el aspirado bronquial (AB) es una técnica utilizada habitualmente en el diagnóstico del cáncer de pulmón endoscópicamente visible. Existe controversia sobre el momento adecuado para su realización. El objetivo del presente estudio ha sido evaluar si el momento de la realización del AB puede influir en el rendimiento diagnóstico.

PACIENTES Y MÉTODOS: Se ha llevado a cabo un estudio transversal prospectivo, en el que se incluyó a pacientes con carcinomas broncogénicos endoscópicamente visibles a los que se hizo una videofibrobroncoscopia con fines diagnósticos. A todos se les realizaba AB previo y tras el cepillado y la biopsia bronquiales. El resultado se analizó de forma global y para cada tipo de lesión endobronquial.

RESULTADOS: Se incluyó a 75 pacientes con una edad media de 63,3 años siendo el 81% varones. La broncoscopia fue diagnóstica en 71 (94,7%). El AB previo fue positivo en 40 pacientes (53,3%) y el posterior en 43 (57,3%) (p = 0,6). La rentabilidad conjunta de ambos fue del 69,3%, significativamente superior a la del AB previo (p = 0,001) y la del AB posterior (p = 0,004) por separado. En el 43,7% de los casos en que el AB posterior fue negativo, la valoración citológica se vio dificultada por ser muy hemática, frente al 8,5% de los AB previos negativos (p = 0,002).

CONCLUSIONES: El orden de la realización del AB en el diagnóstico de neoplasias bronquiales no influye en el rendimiento diagnóstico, probablemente por la mayor frecuencia de AB hemorrágicos que se producen cuando el AB se realiza tras el cepillado y la biopsia bronquiales. El estudio conjunto de ambos AB incrementa significativamente el rendimiento diagnóstico de la técnica.

Palabras clave: *Fibrobroncoscopia. Carcinoma broncogénico. Lesión endobronquial. Aspirado bronquial. Citología.*

Introduction

Fiberoptic bronchoscopy is the most commonly used method for diagnosing lung cancer.[1-5] In endoscopically visible tumors, the most common type, several techniques, such as biopsy, bronchial brushing, and

Correspondence: Dr. A. Fernández-Villar.
Joaquín Costa, 60, 6.° C. 36004 Pontevedra. España.
E-mail: jfv01po@saludalia.com

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bronchial washing are traditionally used together because their combined diagnostic yield is quite high, frequently greater than 90%.[1-12] Because complications are few, all 3 of these techniques should be performed whenever possible, as several scientific societies[6-8] and expert bronchoscopists recommend.[9-12]

No consensus currently exists as to the optimal sequence of these procedures—in particular, the best time to perform bronchial washing.[1,8,10,12] Collecting bronchial wash fluid before performing brushing and biopsy reduces the risk of blood contaminating the sample. This risk increases when washing is performed after other sampling procedures; however, in this case, the yield is likely to be higher since both biopsy and brushing promote desquamation of cells from the tumor surface.[1,8-15] After a comprehensive review of the literature, we located 2 articles[16,17] and several abstracts[18-21] reporting studies that evaluated the optimal sequence of bronchial washing; however, results from these studies varied. We carried out the present study to help clarify exactly how the diagnostic yield for endoscopically visible lung tumors is influenced by the sequencing of bronchial washing relative to other diagnostic techniques. In addition, we assessed the influence of the type of endobronchial neoplasm and blood in wash fluid samples on the diagnostic yield.

Patients and Methods

A prospective, cross-sectional study was carried out from January 2003 through December 2004 on patients with endoscopically visible primary or metastatic endobronchial neoplasms. All patients underwent video-assisted fiberoptic bronchoscopy for diagnostic purposes. Cases were excluded if the diagnosis was not carcinoma—as determined by video-assisted fiberoptic bronchoscopy or a surgical technique (video-assisted thoracoscopy or thoracotomy). The procedure was performed by 2 experienced bronchoscopists and 2 resident physicians under supervision of the bronchoscopists at the Hospital Xeral-Cíes in Vigo, a tertiary level referral hospital for a population of approximately 250 000 inhabitants. The patients were premedicated with 0.5 mg of intramuscular atropine and intravenous midazolam was used for conscious sedation. The bronchoscopy was transnasal, with the patient in dorsal decubitus; 2% lidocaine was used for local anesthesia. After the endobronchial tumor had been located, the following procedures were carried out in this order: aspiration of bronchial wash fluid, bronchial brushing, bronchial biopsy, and aspiration of bronchial wash fluid. The bronchial aspirates were obtained by instilling 20 mL to 30 mL of physiological saline solution perpendicular to the lesion and then aspirating the fluid into a container. The tumor surface was brushed twice and then the material collected was spread onto 2 slides and fixed immediately with 96% alcohol. The number of biopsies performed ranged from 4 to 6, at the discretion of the bronchoscopist in charge. If a diseased paratracheal lymph node greater than 10 mm in diameter had been detected by computed tomography prior to the endotracheal procedures, then a fine-needle transtracheal aspiration of the nodes was performed.

The lesions were described as an endobronchial mass (vegetative endobronchial growth that is clearly distinguishable from the rest of the bronchial wall), mucosal infiltrate (irregular, friable, hypervascularized area with loss of cartilaginous folds), or submucosal lesion (thickening or loss of longitudinal folds or edema of the mucosa with thickened folds and stenosis).

All fiberoptic bronchoscopes used in the procedures were made by Olympus (Tokyo, Japan). A 20-mL Lukens specimen trap (Tyco Healthcare, Gosport, UK) with a 30-cm connection directly attached to the bronchoscope's aspiration valve was inserted to collect wash fluids. The Cellebrity Endoscopic Cytology Brush (Boston Scientific, Spencer, Indiana, USA) was used for bronchial brushing. The complete brush was 150 cm in length and 1.8 mm in diameter with brush fibers 12 mm in length and 3 mm in diameter. The biopsies were performed with model FB-21C-1 biopsy forceps (Olympus), which measured 100 cm in length by 1.8 mm in diameter.

The wash fluid samples were randomly labeled as A or B for blinded cytology. The samples were centrifuged at 1500 rpm for 10 minutes, the sedimented material was pipetted, and the supernatant was smeared on several slides and fixed in 96% alcohol. Samples obtained by forceps biopsy were fixed in a formaldehyde solution, bathed in paraffin, and cut. The cytological samples were routinely stained with the Papanicolaou stain and the histological samples were stained with hematoxylin and eosin.

The specimens were evaluated by a single pathologist who was unaware of the sequence in which the bronchial washings were performed. To assure that the cytohistologic results did not influence the diagnostic yield of bronchial washing, the wash fluid samples (both A and B) were evaluated prior to analysis of the brushing and biopsy specimens. Cases in which excessive amounts of blood in the wash fluid made it difficult or impossible to evaluate the sample were noted and any sample labeled suspicious or inconclusive was considered negative.

Patients were informed of the potential risks of the different endoscopic techniques and were made aware of the study objectives. All patients signed a general informed consent form and also verbally agreed to participate. The study was approved by the ethics committee at our hospital.

Statistical Analysis

Overall results are given as percentages and absolute frequency distributions for the qualitative variables and as a mean (SD) for the quantitative variables. The diagnostic value of the procedures was evaluated with the 2-tailed McNemar exact test, with a level of significance of P=.05. Statistical analysis was performed with the SPSS 9.0 Statistical Software Package (SPSS; Chicago, Illinois, USA).

Results

The study included 78 patients with endobronchial lesions and suspected primary or metastatic lung tumors. After definitive diagnosis of a benign process (n=2) and a primary lung lymphoma (n=1), 3 patients were excluded from the study. The general clinical data for the final population is given in Table 1. Histologic cell types were as follows: 54 (72%) nonsmall cell lung cancers (28 squamous cell carcinomas, 20 adenocarcinomas, and 6 undifferentiated large cell carcinomas), 19 (25.3%) small cell carcinomas, and 2 (2.7%) metastatic endobronchial carcinomas originating from renal-cell carcinomas.

Table 2 shows the overall diagnostic yield of the different endoscopic techniques and for each type of

endobronchial lesion. Bronchoscopy yielded a diagnosis in 71 cases (94.7%). In the other 4 patients, diagnosis was made through surgical techniques (n=2), pleural biopsy (n=1), and transbronchial needle aspiration (n=1). The diagnostic yield for submucosal lesions was significantly lower compared to other types (11 of 14 [78.6%] submucosal lesions and 60 of 61 [98.3%] masses and infiltrates; *P*=.002).

The combined yield of bronchial washing performed before and after bronchial brushing and biopsy was 69.3%, a significantly higher percentage than that of washing performed either before (*P*=.001) or after (*P*=.004) the other sampling procedures. In 18 cases (24%), cytological findings from wash fluids collected before and after brushing and biopsy did not agree: in 11 of these cases, washing was diagnostic when performed after but not before brushing and biopsy; in the other 7 cases, just the opposite occurred. In 14 of the 32 cases (43.7%) where findings from washing done after brushing and forceps biopsy were negative, blood in the aspirated sample interfered with cytology. In comparison, when washing was performed prior to brushing and biopsy, that problem arose in only 3 of the 35 cases (8.5%) (*P*=.002).

Biopsy yielded the only positive result in 9 patients (12%; 3 masses, 4 mucosal infiltrates, and 2 submucosal lesions), bronchial brushing in 1 case (1.3%; mucosal infiltrate), and bronchial washing after brushing and biopsy in 2 cases (2.7%; 1 mass and 1 submucosal lesion).

TABLE 1
Clinical Data of Patients with Endobronchial Neoplasms*

Variable	
Number of patients	75
Men	61 (81.3%)
Women	14 (18.7%)
Age, mean (SD), years	66.3±10.5
Type of tumor	
Primary, nonsmall cell	54 (72.0%)
Primary, small cell	19 (25.3%)
Metastatic	2 (2.7%)
Location of tumor	
Main bronchi and lobes	53 (70.7%)
Distal bronchi	22 (29.3%)
Type of lesion	
Endobronchial mass	32 (42.7%)
Mucosal infiltrate	29 (38.7%)
Submucosal lesion	14 (18.6%)

*SD indicates standard desviation.

Needle aspiration was performed in 17 cases of diseased paratracheal or subcarinal lymph nodes and in 13 (76.4%) of these cytology was positive.

No noteworthy complications related to the endoscopic procedures were described.

Discussion

Bronchial secretions may be aspirated either directly or after physiological saline solution has been instilled.[9-11] The resulting sample is the mixture, in unknown proportions, of bronchial and upper airway secretions with saline solution and the anesthetic agent.[9-11] The most common reason for bronchial washing is the need for cytology to diagnose lung cancer.[1-12] Several scientific societies[6-8] and expert working groups[9-11,14] recommend that all 3 techniques be routinely performed whenever possible despite evidence from some studies that washing fails to improve–or increases only slightly—the diagnostic sensitivity of other bronchoscopic techniques.[1,4,5,10,12] In 4% of the cases included in our study, the only techniques that yielded a diagnosis were the cytological procedures (washing and brushing). However, bronchial washing has proven to be an economical, safe, and cost-effective technique, particularly in cases with highly vascularized lesions or small cell carcinomas in which crush artifacts are relatively common.[1,4,10,14,16] In addition, cell samples obtained via bronchial washing can be cultivated for microbiological analysis.[9,10,14]

The optimal sequence for performing these 3 techniques is highly controversial.[1,8,12] The British Thoracic Society[8] guidelines on diagnostic flexible bronchoscopy, published in 2001, indicate that the optimal sequence for performing endoscopic techniques for visible endobronchial neoplasms is unclear and that further studies are needed. Lee and Metha,[11] in a reference manual, recommend that washing be performed before brushing and biopsy to prevent blood from contaminating the sample and making it more difficult to perform cytology. The authors say that an exception to this recommendation may be lesions with submucosal involvement, in which alterations to the integrity of the mucosa may actually increase the yield of bronchial washing performed afterwards.

Castella,[9] in the manual *Medicina Respiratoria,* recently published by the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR), recommend collecting wash fluid samples both before and after bronchial

TABLE 2
Diagnostic Yield of the Different Bronchoscopic Techniques by Type of Endobronchial Lesion*

	Endobronchial Mass (n=32)	Mucosal Infiltrate (n=29)	Submucosal Lesions (n=14)	Total (n=75)
BW-pre	16 (50%)	19 (65.5%)	5 (35.7%)	40 (53.3%)
BW-post	17 (53%)	19 (65.5%)	7 (50%)	43 (57.3%)
Combined BW-pre and BW-post	23 (71.9%)	22 (75.9%)	7 (50%)	52 (69.3%)
Brushing	25 (78.1%)	20 (69%)	7 (50%)	52 (69.3%)
Biopsy	30 (93.8%)	28 (96.6%)	10 (71.4%)	68 (90.7%)
All	32 (100%)	28 (96.6%)	11 (78.6%)	71 (94.7%)

*BW-pre indicates bronchial washing performed before biopsy and brushing; BW-post, bronchial washing performed after biopsy and brushing.

brushing and biopsy because the second specimen may be more sensitive given that any cells dislodged by the other techniques will be included in the wash fluid. Nevertheless, any bleeding may render the second wash fluid useless. However, according to the author, if no hemorrhaging has occurred, then the 2 flasks should be mixed together and evaluated as a single sample.

Despite the controversy regarding the optimal sequence for bronchial washing, little research has been carried out in this area until the recent publication of 2 research articles[16,17] and 4 abstracts[18-21] of prospective studies that have tried to clarify the question.

Raymond et al[18] found no significant differences in diagnostic yield for central tumors regardless of the timing of wash fluid collection, although differences were found for tumors not visible on endoscopy (positive results were found in 25% of wash fluids collected before other sampling procedures compared to 45% for samples collected afterwards). Scriven et al,[19] in series of 36 patients, reported that the sensitivity of washing performed before and after other sampling techniques was 65% and 85% (*P*=.01), respectively, compared to brushing at 43% and biopsy at 86%. Findings from 2 more recent studies found no differences in diagnostic yield after varying the sequence of bronchial washing, brushing, and biopsy.[20,21] However, because only the abstracts for these 4 studies were published and it is impossible to analyze either the methods or results, it is difficult to reach any definitive conclusions.

Yigla et al,[6] in a sample of 54 patients, found that washing was positive for malignancy in 33% of cases when performed prior to brushing and biopsy, compared to 48% when performed afterwards; this difference, however, was not statistically significant, although in our opinion it may have clinical relevance.

Van der Drift et al[17] very recently reported a diagnostic yield of 72% and 74% from aspirated wash fluids collected before and after biopsy and brushing in a series of 137 patients with endoscopically visible tumors (*P*=.85).

Similarly, in our study, we found no differences in yield between samples collected before or after other sampling techniques (53.7% compared to 57.7%; *P*=.6). The largest differences have been observed in submucosal tumors, in which brushing and biopsy alter the integrity of the mucosa, thereby potentially producing more cell desquamation in these types of tumors than generally occurs after brushing and biopsy in other types of endobronchial lesions[1,11,17,21]; the differences were not statistically significant, however, perhaps due to the small sample sizes of the subgroups. The overall diagnostic yield of all bronchoscopic techniques for submucosal neoplasms was significantly lower than that found when the neoplasm presented as a mass or infiltrating lesion; as a result, needle aspiration of submucosal endobronchial lesions is indicated.[1,9,11,16,22,23]

Perhaps the reason that the timing of bronchial washing does not affect the yield may be the excessive amounts of blood contained in a high percentage of wash fluid samples collected after brushing and biopsy, although some authors disagree.[17] This excess blood makes processing and obtaining high quality cytological specimens difficult and probably affects the number of cells considered in reaching the diagnosis.[15,24]

We should point out that it is quite common to encounter discrepancies in diagnostic yield between wash fluid samples collected before and after biopsy and brushing; this explains why the combined yield is significantly higher than for each separately. Although no study has evaluated the usefulness of this technique, our results seem to confirm the recommendation made by Castella,[9] who suggests processing both wash fluid samples together to maximize the yield; however, because the influence of bronchial brushing on wash fluids collected after brushing has not yet been evaluated, we do not yet know if this strategy could replace the routine performance of bronchial brushing.

In conclusion, the sequence in which bronchial washing is performed relative to other techniques used to diagnose endoscopically visible bronchial neoplasms does not appear to affect the diagnostic yield, most likely because samples collected after brushing and biopsy are likely to contain excessive amounts of blood. Due to the high degree of diagnostic discrepancies between wash fluid samples collected before and after brushing and biopsy, combining both samples increases the diagnostic yield of the technique significantly. More studies are necessary to determine whether this strategy might be sufficiently effective to eliminate the need to perform other cytological procedures such as bronchial brushing.

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