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Original Article

Role of bronchial washing in diagnostic accuracy for peripheral pulmonary lesions during transbronchial biopsy

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Abstract: Objectives: Bronchial washing has been frequently conducted during bronchoscopic examination. This study aimed to determine whether bronchial washing added additional diagnostic information for peripheral lung lesions. Methods: This retrospective study assessed the diagnostic sensitivity of bronchial washing. Lung tissue biopsy, brushing, and post biopsy washing were conducted sequentially in patients with peripheral lung lesions who underwent conventional transbronchial examinations. The samples from pre and post washing, brushing, and biopsy were collected separately for cytologic and culture examinations. Results: Between April 2015 and March 2017, a total of 122 patients with suspected lung cancer underwent conventional bronchoscopic examinations. Of these patients, 97 were diagnosed as having malignancy, 19 as having infection, and the remaining 8 patients were classified as having other diagnoses, such as organizing pneumonia, sarcoidosis, and scarring. The overall sensitivity of bronchoscopy was 80% for malignancy, 84% for infection, and 50% for other diagnoses in peripheral lung lesions. Although post-biopsy washing samples showed a better sensitivity than pre-biopsy washing samples in tumor lesions (59% vs. 29%, P<0.01), in transbronchial biopsy-negatives cases, there were 7 cases each that showed positive results with pre-biopsy and post-biopsy washing samples. Conclusion: Bronchial washing gave additional diagnostic information in the diagnosis of lung cancer. The timing of bronchial washing before or after biopsy did not affect the accuracy of bronchial examination.

Keywords: Bronchial washing, brushing, transbronchial biopsy, lung cancer, bronchoscopy

Introduction

According to estimates from the World Health Organization (WHO) in 2019, cancer was the first or second leading cause of death before the age of 70, in 112 of 183 countries and it ranks third or fourth as cause of death in another 23 countries, and lung cancer is the leading cause of cancer death (18.0% of the total cancer deaths) [1, 2]. Low-dose computed tomography (CT) has high sensitivity and reasonable specificity for the detection of lung cancer, with demonstrated benefit in screening persons at high risk [3]. For early diagnosis, different diagnostic modalities are available, including sputum, washing, brushing cytology, biopsy, and fine needle aspiration. Radial endobronchial ultrasound (EBUS) transbronchial biopsy (TBB) improves the diagnostic yield from peripheral pulmonary lesions (PPLs). However, the small specimens obtained using small forceps through a guide sheath may impede diagnosis and molecular analysis [4]. Flexible bronchoscopy is simple to learn and still provides many benefits as a key diagnostic procedure for patients with bronchopulmonary diseases [5].

The diagnostic sensitivity for PPLs depends on the lesion size, with a sensitivity of 63% for lesions ≥2 cm and 34% for lesions <2 cm [6, 7]. New endoscopes and technologically advanced navigational modalities have recently been introduced to the market and in clinical practice, mainly for the diagnosis of mediastinal

lymphadenopathy and PPLs [6]. The cytological specimens including sputum, bronchoalveolar lavage, bronchial washings, bronchial brushings, and percutaneous/endobronchial fine-needle aspiration have been widely used for the diagnosis of lung malignancy [8]. The mean sensitivities were 43% and 70% for bronchial washing alone and bronchial washing and brushing in PPLs, respectively [9, 10].

Bronchial washing is often combined with biopsy to increase the diagnostic yield of bronchoscopy. With the advantage of technology like EBUS in the diagnosis of PPLs, the value of bronchial washing for the diagnosis lung cancer is variable. Some studies reported that the diagnosis of pulmonary malignancy, made exclusively by washing specimens, was made in 0.2-1% of patients with PPLs [11, 12]. Due to its low sensitivity, some studies have suggested abandoning routine collection of bronchial cytology specimens during bronchoscopy [12], whereas other studies reported the sensitivity of bronchial wash/lavage cytology to vary, from 39.4% to 80.5% [13]. The present study was performed to determine whether bronchial washing added additional diagnostic information for PPLs. Washing samples were prospectively obtained after brushing in patients with PPLs during non-guided flexible bronchoscopy to investigate the diagnostic yield of these samples, and a retrospective review of the prospectively collected data was conducted.

Patients and methods

Ethics approval and consent to participate

In this retrospective cohort study, the medical records of patients with peripheral lung lesions admitted to a community-based hospital for bronchoscopic examination from April 2015 to March 2017 were reviewed. This study was approved by the institutional review boards of Shimada Municipal Hospital (reference numbers: R3-6) and conformed to the provisions of the Declaration of Helsinki (as revised in Brazil 2013). Written, informed consent was obtained from participants before starting the study.

Inclusion and exclusion criteria

All enrolled patients had been diagnosed with a peripheral lung lesion that was suspected as being malignant by CT or chest X-ray examinations.

Patients who fulfilled all of the following inclusion criteria were enrolled in the study

(1) A peripheral lung lesion was confirmed by chest X-ray or CT.

(2) No restriction to carrying out bronchoscopy.

(3) All specimens were collected.

(4) A definite pathological diagnosis was made based on cytology or histology findings. If the bronchoscopy did not yield a diagnosis, other techniques, such as surgery, lymph node biopsy, or CT-guided biopsy, were performed to pursue the definitive diagnosis.

Exclusion criteria

(1) Cases of endobronchial biopsy.

(2) Cases of EBUS biopsy for a peripheral lung lesion or biopsy of the mediastinum conducted simultaneously.

(3) Biopsy conducted from different lobes.

Procedures

Antiplatelet and anticoagulation treatment was routinely discontinued before, but was resumed after the procedure. After induction of moderate sedation by opium alkaloid hydrochlorides and local anesthesia by 2% lidocaine, conventional diagnostic flexible bronchoscopy was performed. Bronchoscopy procedures were performed in a dedicated bronchoscopy suite utilizing a 1T-160 or P-160 Olympus video bronchoscope (Olympus Canada, Markham, ON, Canada). Preliminary bronchial washing, using a total of 10 to 20 mL of saline solution according to the return volume after suctioning [14], was performed on the putative segmental bronchus and collected in a mucus trap (pre-biopsy washing). Brushing was conducted after pre-biopsy washing. TBB was then performed under real-time X-ray fluoroscopy guidance. A second washing was performed after biopsy (post-biopsy washing). During bronchoscopy, 0.01% adrenaline, carbazochrome sodium, and tranexamic acid were used for hemorrhage, as necessary.

Table 1. Characteristics of the patients, diagnoses, and complications

Age (y)	69.7 (63.2, 78)
Sex (M/F)	88/36
Fellow (Y/N)	44/80
Location	
Left upper lobe	31 (25.0%)
Left lower lobe	19 (15.3%)
Right upper lobe	35 (28.23%)
Right middle lobe	11 (8.9%)
Right lower lobe	28 (22.6%)
Diagnosis	
Tumor	97 (78.2%)
Infection	19 (15.3%)
Others	8 (6.5%)
Complication	
Hypoxemia	19 (15.3%)
Hypertension (>180 mmHg)	11 (8.8%)
Hemorrhage	1 (0.8%)

Outcomes

The primary outcome was whether bronchial washing provided additional information in the diagnosis of peripheral lung lesions. The secondary outcomes were diagnostic accuracy in different specimens. Hemorrhage was defined as blood coming out from the intubation tube. Hypertension was considered a systolic blood pressure above 180 mmHg. A need for oxygen was considered hypoxemia.

Statistical analyses

The results are presented as numbers and percentages or medians and interquartile ranges unless otherwise indicated. The significance of differences in the diagnostic yield of lung cancer between different specimens was determined using McNemar's test. In all instances, two-tailed values of $P<0.05$ were considered significant. Data analysis was performed using JMP software (version 15.0; SAS Institute, Cary, NC).

Results

This study included a total of 80 men and 36 women, with a median age of 69.7 years (63.2-78 years) (**Table 1**). Fellows of the Japan Gastroenterological Endoscopy Society conducted the examinations in 44 cases, and the remaining 80 cases were conducted by medical interns. Most cases, 97 (78%), were diagnosed as tumors, and 19 cases were diagnosed as pulmonary infection, including 7 cases of nontuberculous mycobacterial infection. The remaining 8 cases were classified as other diagnoses, including 4 cases of organizing pneumonia and 2 cases of sarcoidosis and scarring, respectively. The most common procedural complications were hypoxia, hypertension, and hemorrhage in 19 (15.3%), 11 (8.8%), and 1 (0.8%), respectively. The characteristics of patients with tumors are shown in **Table 2**, including a total of 73 men and 24 women, with a median age of 70.6 years (66.5-78 years). The median diameter was 38.2 cm (22, 45 cm), and most were adenocarcinomas. Three cases were diagnosed as non-small cell lung cancer, and one case was metastatic thyroid carcinoma. A total of 80 (75%) cases were smokers.

Table 2. Characteristics and diagnoses of peripheral tumors

Age (y)	70.6 (66.5, 78)
Sex (M/F)	73/24
Tumor diameter (cm)	38.2 (22, 45)
Tumor types	
Adenocarcinoma	64 (65.98%)
Squamous carcinoma	19 (19.59%)
Small cell lung cancer	7 (7.22%)
None-small cell lung cancer	3 (3.09%)
Metastatic lesion	1 (1.03%)
Smoker	
Current (pack-years)	24 (47.9)
Former (pack-years)	46 (41.2)
Non-smoker	27

The overall sensitivity of bronchoscopy for all peripheral lung lesions was 79% (98/124). The overall sensitivities for peripheral lung tumor, infective lesion, and other diagnoses were 80% (78/97), 84% (16/19), and 50% (4/8), respectively (**Figure 1**). In peripheral lung cancer cases, sensitivities were 29% (28/97) by pre-biopsy washing, 59% (57/97) by post-biopsy washing, 69% (67/97) by brushing, 68% (66/97) by TBB, and 80% (78/97) by all specimens. The sensitivity for malignancy was higher in post-biopsy washing than pre-biopsy washing (59% vs. 29%; $P<0.01$). Pre-biopsy washing and post-biopsy washing showed the same sensitivity at 47% (9/10) for infective

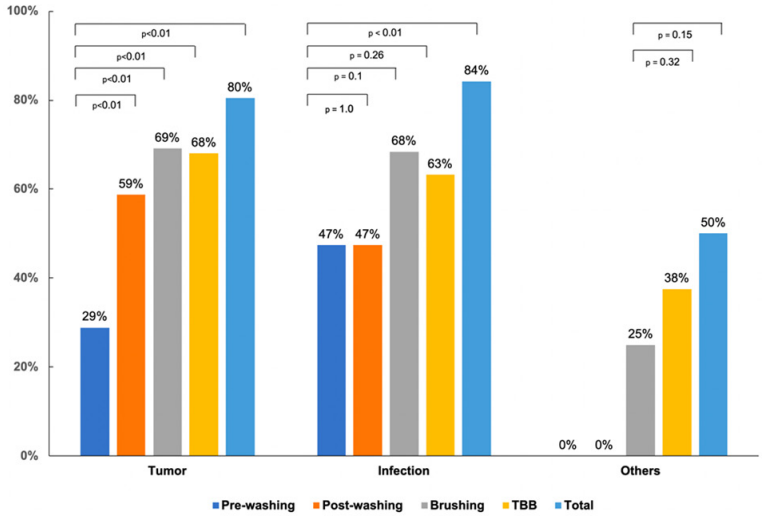

Figure 1. Sensitivity of different specimens collected by bronchoscopy.

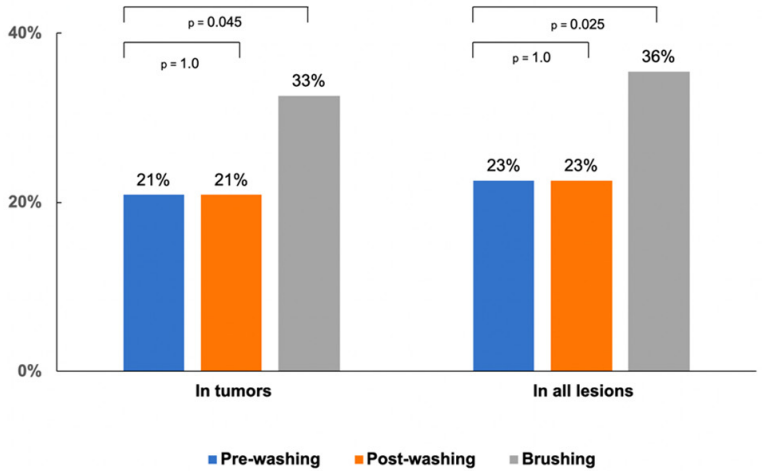

Figure 2. Test accuracy of bronchial washing and brushing in biopsy negative specimens.

lesions and yielded little information in other diagnoses due to their lesion characteristics. Although post-biopsy washing showed a better sensitivity than pre-biopsy washing, both of them showed the same sensitivity (21% vs. 21%, P=1) in all TBB-negative lesion samples in the subgroup analysis (**Figure 2**). The same finding was confirmed in TBB-negative tumor lesions, and the sensitivities of pre-biopsy and post-biopsy washing were 22.6% and 22.6%, respectively (P=1).

In cases of bronchoscopic examinations in different sizes of peripheral tumor lesions, the sensitivity for lesions of diameter more than 2 cm was better than that for lesions below 2 cm (80% (61/76) vs. 76% (16/21); P<0.01) (**Figure 3**). Post-biopsy washing showed a better sensitivity than pre-biopsy washing in both <2 cm and ≥2 cm lesions (62% (13/21) vs. 24% (5/21), P<0.001; 58% (44/76) vs. 30% (23/76), P<0.01). For tumor lesions of diameter <2 cm, although brushing had a good result of sensitivity, there was no antistatic difference (71% (15/21) vs. 57% (12/21); P=0.18).

Discussion

This study analyzed 97 cases of peripheral pulmonary tumors and 19 cases of pulmonary infections, and total sensitivities were 80% and 84%, respectively, which was consistent with the values reported in other studies [15]. Bronchial washing added diagnostic information in TBB-negative cases, and the sensitivities were 21% and 23% for tumor and infective lesions, respectively. Although post-biopsy bronchial washing showed better sensitivity, the sequence of bronchial washing showed no differences in sensitivity in TBB-negative cases after subgroup analysis. Hypoxemia (15.3%) was the most frequently observed complication in this study, and this was likely due to the use of opium alkaloid hydrochlorides in sedation.

With bronchoscopy, central lesions have the highest diagnostic yield, whereas small peripheral lesions often prove more elusive, unless more demanding and time-consuming techniques are used. Biopsy of PPLs using EBUS with a GS has been shown to be effective and safe and has enabled visualization of some peripheral lung nodules to increase the diagnostic yield (58% to 79%) [16]. The specific combination of cytologic and histologic proce-

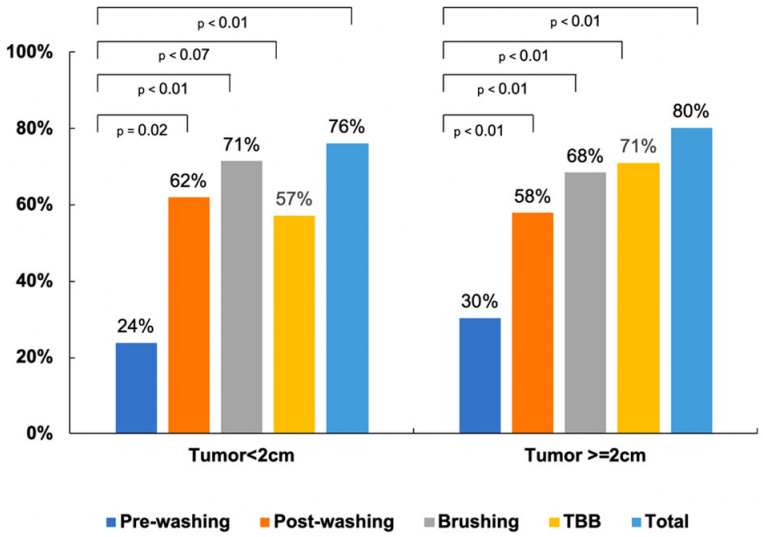

Figure 3. Sensitivity of bronchoscopic examination for peripheral lung cancers of different sizes.

dures that provides the optimum diagnostic yield has not been conclusively identified and may depend on the available institutional expertise. Bronchial washing may remain a valuable method that can provide significant information for the evaluation of lung pathology. Especially for situations in which transbronchial biopsies cannot be obtained, examination of bronchial washings may yield useful and complementary information [17].

Bronchial brushing is often used to obtain supplementary samples for diagnosing lung cancer. In this study, in cases of peripheral tumors <2 cm in size, although brushing had good sensitivity, there was no significant antistatic difference. Cytology samples obtained by bronchial brushing were suitable for next-generation sequencing analysis [18, 19]. Personalized treatment generally requires the outcomes of multiple gene analyses and needs a rapid and accurate result from various materials including cytology samples [20]. Considering the equivalent sensitivity of TBB, bronchial brushing might be useful in PPLs, especially in cases <2 cm in size.

Limitations

The present study has several limitations. First, this study was limited by its single-center design. Bias might have been introduced by the facility and the medical staff. Second, this study did not include cases that underwent EBUS with a GS; therefore, the diagnostic value of bronchial washing in such cases remains unclear. Third, for tumors >30 mm in size, including peripheral lesions, EBUS staging and simultaneous biopsy of the mediastinum are needed and have been recommended by guidelines [21]; cases of biopsy of the mediastinum were excluded due to the time-consuming nature of completing all procedures.

Conclusions

Bronchial washing did not have a high sensitivity for the diagnosis of PPLs, but added diagnostic information. The timing of bronchial washing did not improve diagnostic accuracy. Bronchial brushing might be useful in PPLs, especially in cases of tumors <2 cm in size.

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Disclosure of conflict of interest

None.

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References

[1] (WHO). WHO. Global Health Estimates 2020: deaths by cause, age, sex, by country and by region, 2000-2019. WHO; 2020. Accessed December 11, 2020. who.int/data/gho/data/themes/mortality-and-global-health-estimates/ghe-leading-causes-of-death.

[2] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F. Global cancer statistics 2020: GLOBOCAN estimates of

incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021; 71: 209-249.
[3] Krist AH, Davidson KW, Mangione CM, Barry MJ, Cabana M, Caughey AB, Davis EM, Donahue KE, Doubeni CA, Kubik M, Landefeld CS, Li L, Ogedegbe G, Owens DK, Pbert L, Silverstein M, Stevermer J, Tseng CW and Wong JB. Screening for lung cancer: US preventive services task force recommendation statement. JAMA 2021; 325: 962-970.
[4] Park S, Yoon HY, Han Y, Wang KS, Park SY, Ryu YJ, Lee JH and Chang JH. Diagnostic yield of additional conventional transbronchial lung biopsy following radial endobronchial ultrasound lung biopsy for peripheral pulmonary lesions. Thorac Cancer 2020; 11: 1639-1646.
[5] Paradis TJ, Dixon J and Tieu BH. The role of bronchoscopy in the diagnosis of airway disease. J Thorac Dis 2016; 8: 3826-3837.
[6] Shinagawa N. A review of existing and new methods of bronchoscopic diagnosis of lung cancer. Respir Investig 2019; 57: 3-8.
[7] Dhillon SS and Harris K. Bronchoscopy for the diagnosis of peripheral lung lesions. J Thorac Dis 2017; 9: S1047-S1058.
[8] Rao S, Rao S, Lal A, Barathi G, Dhanasekar T and Duvuru P. Bronchial wash cytology: a study on morphology and morphometry. J Cytol 2014; 31: 63-67.
[9] Rivera MP, Mehta AC and Wahidi MM. Establishing the diagnosis of lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013; 143: e142S-e165S.
[10] Giti R and Hosseinzadeh M. Efficacy of bronchial washing and brushing cytology in the diagnosis of non-neoplastic lung diseases. Acta Med Iran 2017; 55: 636-641.
[11] van der Drift MA, van der Wilt GJ, Thunnissen FB and Janssen JP. A prospective study of the timing and cost-effectiveness of bronchial washing during bronchoscopy for pulmonary malignant tumors. Chest 2005; 128: 394-400.
[12] Girard P, Caliandro R, Seguin-Givelet A, Lenoir S, Gossot D, Validire P and Stern JB. Sensitivity of cytology specimens from bronchial aspirate or washing during bronchoscopy in the diagnosis of lung malignancies: an update. Clin Lung Cancer 2017; 18: 512-518.
[13] Thakur A, Bakshi P, Kaur G and Verma K. Liquid-based and conventional cytology for bronchial washings/bronchoalveolar lavages in the diagnosis of malignancy - an institutional experience. J Cytol 2017; 34: 127-132.
[14] Sompradeekul S, Chinvetkitvanich U, Suthinon P and Wongbunnate S. Difference in the yields of bronchial washing cytology before and after forceps biopsy for lung cancer diagnosis. J Med Assoc Thai 2006; 89 Suppl 5: S37-45.
[15] Han Y, Kim HJ, Kong KA, Kim SJ, Lee SH, Ryu YJ, Lee JH, Kim Y, Shim SS and Chang JH. Diagnosis of small pulmonary lesions by transbronchial lung biopsy with radial endobronchial ultrasound and virtual bronchoscopic navigation versus CT-guided transthoracic needle biopsy: a systematic review and meta-analysis. PLoS One 2018; 13: e0191590.
[16] Minami D, Takigawa N, Morichika D, Kubo T, Ohashi K, Sato A, Hotta K, Tabata M, Tanimoto M and Kiura K. Endobronchial ultrasound-guided transbronchial biopsy with or without a guide sheath for diagnosis of lung cancer. Respir Investig 2015; 53: 93-97.
[17] Schreiber G and McCrory DC. Performance characteristics of different modalities for diagnosis of suspected lung cancer: summary of published evidence. Chest 2003; 123: 115s-128s.
[18] Furuya N, Matsumoto S, Kakinuma K, Morikawa K, Inoue T, Saji H, Goto K and Mineshita M. Suitability of transbronchial brushing cytology specimens for next-generation sequencing in peripheral lung cancer. Cancer Sci 2021; 112: 380-387.
[19] Wang Q, Wu B, Yang D, Yang C, Jin Z, Cao J and Feng J. Optimal specimen type for accurate diagnosis of infectious peripheral pulmonary lesions by mNGS. BMC Pulm Med 2020; 20: 268.
[20] Koo JY, Kim NI, Lee T and Choi YD. Bronchial brushing cytology is comparable to bronchial biopsy for epidermal growth factor receptor mutation test in non-small cell lung cancer. Cytojournal 2020; 17: 16.
[21] De Leyn P, Dooms C, Kuzdzal J, Lardinois D, Passlick B, Rami-Porta R, Turna A, Van Schil P, Venuta F, Waller D, Weder W and Zielinski M. Revised ESTS guidelines for preoperative mediastinal lymph node staging for non-small-cell lung cancer. Eur J Cardiothorac Surg 2014; 45: 787-798.