

Difference in the Yields of Bronchial Washing Cytology before and after Forceps Biopsy for Lung Cancer Diagnosis

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Objectives: Fiberoptic bronchoscopy (FOB) has been one of the essential procedures used in the diagnosis of lung cancer. Diagnostic yields of FOB related procedures such as bronchial washing (BW), bronchial brushing (BB), bronchial biopsy (BBx), and transbronchial biopsy (TBBx) depend on the location and extent of the tumors. The yields of BW vary among different studies (39-79%). Some reported that the yield might increase in post-bronchoscopic sputum. Since samples from BW are obtained directly from the respiratory tract, we hypothesized that post bronchoscopic forceps biopsy BW might further increase the yield as well. The objective of this study was to compare the diagnostic yields of bronchial washing before and after forceps biopsy for lung cancer.

Material and Method: 114 patients, 70 with endobronchial lesions (42 exophytic lesions, 28 submucosal lesions) and 44 with non-endobronchial lesions, suspected to have lung cancers were evaluated at Siriraj Hospital between March and October 2000. All the patients underwent FOB with initial BW then forceps biopsy (BBx or TBBx) of the lesions followed by re-BW. The cytological specimens were blinded to the cytopathologists. Positive cytologic results of each procedural specimen were compared to final malignancy diagnosis (by positive specimens from FOB, transthoracic needle aspiration, surgery, clinical and radiological follow-up) to determine the sensitivity of each test.

Statistical analysis: Chi-square test comparing sensitivity of each test.

Results: 82 /114 patients (39 patients had exophytic lesions, 24 patients had submucosal lesions, and 19 patients had peripheral lung lesions) had a final diagnosis of malignancy. The sensitivity of initial BW before forceps biopsy was 37.8% (31/82), re-BW after forceps biopsy was 37.8% (31/82), both initial BW and re-BW was 46.3% (38/82), and forceps biopsy alone was 79.3% (65/82). There was no statistically significant difference ($p > 0.05$) in the sensitivity of initial BW, re-BW and combined initial BW and re-BW. No major complications such as massive hemorrhage, respiratory failure, or death occurred.

Conclusion: The diagnostic yields of BW before and after forceps biopsy for malignancy were not different in our study. However, the yield seemed to be higher when combined pre and post-forceps biopsy BW was used.

Keywords: Bronchial washing, Cytology, Forceps biopsy, Transbronchial biopsy, Bronchoscopy, Lung cancer, Diagnostic yields

J Med Assoc Thai 2006; 89 (Suppl 5): S37-45

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Fiberoptic bronchoscopy (FOB) is widely used to diagnose primary and metastatic lung cancers. Various bronchoscopic related procedures, including bronchial biopsy (BBx), transbronchial biopsy (TBBx), needle aspiration for cytology, bronchial washing (BW), or bronchial brushing (BB) aid in the diagnosis. How-

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ever, the sensitivity of these procedures varies, and depends primarily on the location and/or the extent of the tumor^(1,2). Overall, the cytological-based procedures seem to give lower sensitivity than histological-based procedures and they have been accepted for use in the diagnosis of lung cancer^(3,4).

There have been few reports showing improved yields of the cytological specimens such as sputum when collected post bronchoscopy^(5,6). These might be from the abrasion of the malignant bronchial surface after forceps biopsy. Based on this postulation, we hypothesized that examination of the bronchial washing fluid cytology, which can be collected directly from the bronchi after forceps biopsy, should increase the sensitivity as compared to using only bronchial washing fluid cytology before forceps biopsy.

Material and Method

We enrolled 114 patients who were suspected of having lung cancer. They underwent FOB at the Division of Respiratory Disease and Tuberculosis, Siriraj Hospital between March 1 and October 31, 2000. We excluded patients with contraindications for FOB such as coagulopathy, uncooperativeness, or the patients who did not consent to participate in the study. All the patients underwent FOB (using 2% Lidocaine as a topical anesthetic agent) according to the following procedure: Initial BW pre-forceps biopsy followed by 2-4 times of bronchial biopsy for cases with visualized endobronchial lesions (both exophytic and submucosal infiltration) and transbronchial biopsy for cases with non-visualized lesions (non-endobronchial lesion) and then repeated BW post forceps-biopsy. The transbronchial biopsy was done without fluoroscopy. The amount of 0.9% saline instilled for BW was not limited each time but at least 15 milliliters (ml) of returned BW fluid was required for each specimen. The BW fluid was sent for cytological examination and microbial culture (aerobic bacteria, mycobacteria and fungus). The biopsy tissue was sent for histological examination. We recorded the amount of bleeding, color of returned BW fluid and complications of the procedures such as pneumothorax, hypoxemia, arrhythmia, etc.

Only two pathologists reviewed the cytological and histological specimens. They were both blinded to the pre and post-forceps biopsy BW specimens. The cytological results were classified as positive for malignancy only when the results were read as "suspicious for malignancy" or as "malignancy", the other readings were considered negative for malignancy.

From the 114 patients who participated in the study, the one who did not have a definite diagnosis from the procedures above went on to have transthoracic needle aspiration for cytology and/or surgery. Only a few patients had clinical evidence of metastatic diseases upon follow up.

The sensitivity of each BW procedure is the proportion of the number of specimens having malignant cytology diagnosis compared to the total number of specimens with a definite diagnosis of malignancy. The sensitivity of the biopsy procedure is the proportion of the number of malignant histology diagnosis specimens compared to the total number of specimens with definite diagnosis of malignancy.

Statistical analysis

Chi-square test and McNemar's test were used to compare the sensitivity of each procedure. A value of $p < 0.05$ was considered statistically significant.

Results

114 patients, 71 male and 43 female, aged 23-88 years old (mean \pm SD = 58 \pm 10.2) had final diagnoses from various procedures (FOB related procedures, open lung biopsy or lung resection, tissue biopsy of metastatic site). Of these 114 patients, 82 had diagnoses of malignancy, 22 had tuberculosis, one had aspergillosis, one had leiomyoma, and eight had benign conditions such as pneumonia, bronchiectasis or interstitial lung disease as shown in Table 1. The most common CXR findings were lung masses 52.6% (60/114). The rest were interstitial infiltration 16.7% (19/114), atelectasis 11.4% (13/114) and hilar mass 8.8% (10/114) respectively as shown in Table 2.

In the group of 82 patients with final diagnoses of malignancy, 39 patients had exophytic lesion, 24 patients had submucosal lesion and 19 patients had non-endobronchial lesion, see Fig. 1

These diagnoses were made from bronchial washing in nine patients, from forceps biopsy in 38

Table 1. Other diagnoses

Diagnosis	N
Mycobacterial infection	22
Aspergilloma	1
Bronchiectasis	4
Interstitial lung diseases	1
Pneumonia	3
Leiomyoma	1

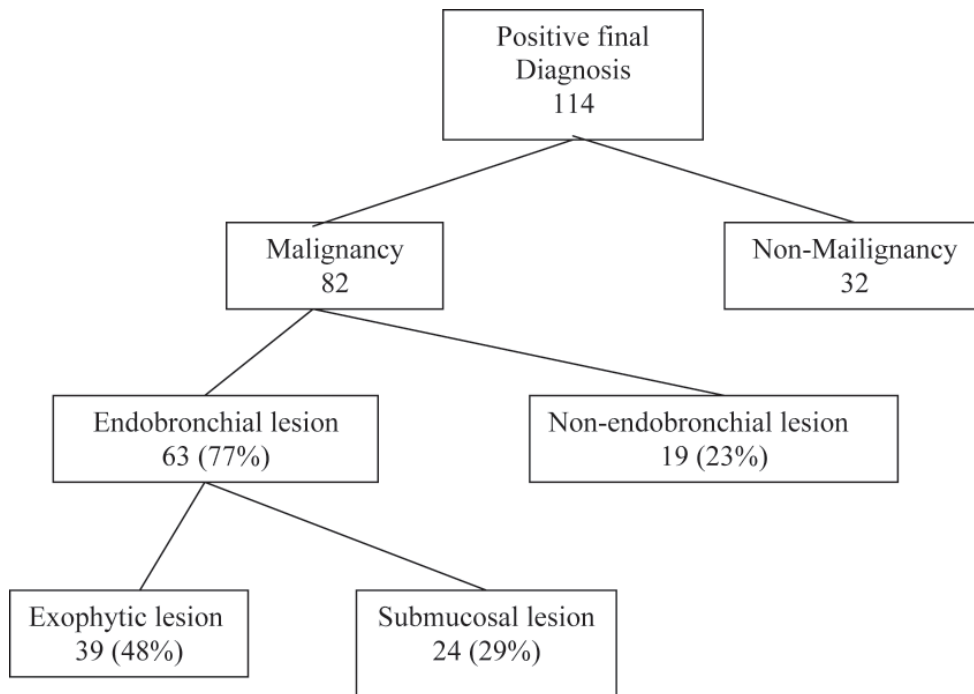


Fig. 1 Diagnoses and lesion characteristics

Table 2. Demographic data and CXR findings

Demographic data (N = 114)	
Male: Female	71:43
Age (years)	23-88 (Mean±SD = 58±10.2)
CXR findings	N (%)
Lung mass	60 (52.6)
Interstitial infiltrate	19 (16.7)
Atelectasis	13 (11.4)
Hilar mass	10 (8.8)
Lung nodule	6 (5.3)
Alveolar infiltration	2 (1.7)
Normal	2 (1.7)
Effusion	1 (0.9)
Bronchiectasis	1 (0.9)

patients, from both bronchial washing and forceps biopsy in 29 patients, from transthoracic needle biopsy in two patients, from surgery in three patients and by clinical evidence of malignancy upon follow up in only one patient. The overall sources of positive diagnosis of lung cancer are shown in Table 3.

The sensitivity of BW pre-forceps biopsy alone was 37.8% (31/82). The sensitivity of BW post-forceps biopsy was 37.8% (31/82); note that the members of this group were not all the same as the members of the pre-forceps biopsy group, Fig. 2. For the combined pre and post-forceps biopsy results, the sensitivity of BW was 46.3% (38/82). For the group that had only forceps biopsy, the sensitivity was up to 79.3% (65/82). When we combined the positive pre-forceps biopsy BW, positive post-forceps biopsy BW and the positive forceps biopsy groups together, the sensitivity increased to as high as 90.2% (74/82) as shown in Table 4.

We found no statistically significant difference ($p>0.05$) between the sensitivity of positive BW for pre and post-forceps biopsy (McNemar's test). This finding was also the same when the results were analyzed according to different lesion characteristics (exophytic ($p=0.08$), submucosal ($p=0.10$) or non-endobronchial ($p=0.25$)) as shown in Fig. 3.

We also analyzed the color of BW fluid post-forceps biopsy and the amount of instilled fluid for BW since these factors might have influenced the cytological results. The color of post-forceps biopsy BW fluid was divided into three groups: turbid, serosanguinous and bloody in color. In the turbid-colored

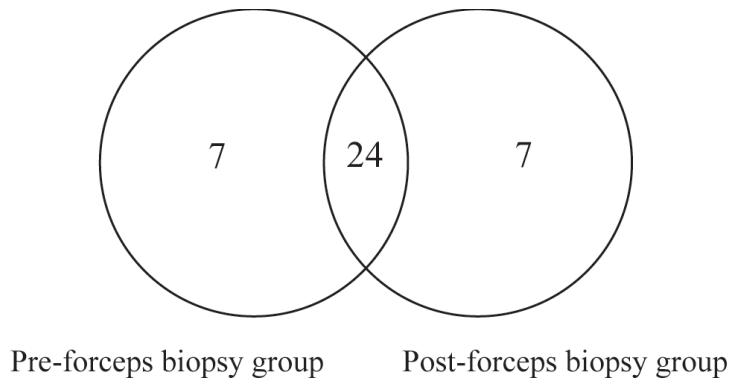


Fig. 2 Sensitivity of bronchial washing (BW)

Table 3. Final diagnosis of malignancy by procedures

Procedure	Exophytic Lesion N=39		Submucosa lesion N=24		Non-endobronchial lesion N=19		Total N=82	
	No	%	No	%	No	%	No	%
-BW pre-forceps biopsy	17	43.6	7	29.2	7	36.8	31	37.8
-BW post-forceps biopsy	14	35.9	9	37.5	8	42.1	31	37.8
-BW pre+post-forceps biopsy	20	51.3	10	41.7	8	42.1	38	46.3
-Forceps biopsy	35	89.7	21	87.5	9	47.4	65	79.3
-BW pre+post-forceps biopsy + forceps biopsy	38	97.4	23	95.8	13	68.4	74	90.2

Table 4. Sensitivity of each procedure among different types of lesions

Procedures	N
BW only	9
BX only (TBBx, BBx)	38
BW + BX	29
FNA	2
Surgery	3
Clinical evidence of metastasis disease	1

group, 6.4% (2/31) of these specimens had positive cytology for malignancy and 15.6% (13/83) were negative for malignancy. In the serosanguinous group, 83.9% (26/31) were positive for malignancy and 69.9% (58/83) were negative for malignancy. In the bloody group, 9.7% (3/31) were positive for malignancy and

14.5% (12/83) were negative for malignancy. There was no statistically significant difference between the groups ($p > 0.05$) as shown in Fig. 4. The amount of instilled fluid for BW was also analyzed as shown in Fig. 5. There was no significant difference in positive or negative cytology for malignancy among the groups that used small (21-44 ml) ($p = 0.11$), moderate (41-60 ml) ($p = 0.13$) or large (>60 ml) ($p = 0.11$) amount of instilled fluid either.

The use of different bronchoscopists may have played a role in the different sensitivity of each procedure⁽⁷⁾. There were seven bronchoscopists involved in this study, and there was no significant difference in the yield of positive cytology results (using Chi-square test) between the samples obtained by the broncho-scopists as shown in Table 5.

In our study, no severe complications such as severe hypoxemia, respiratory failure, massive bleed-

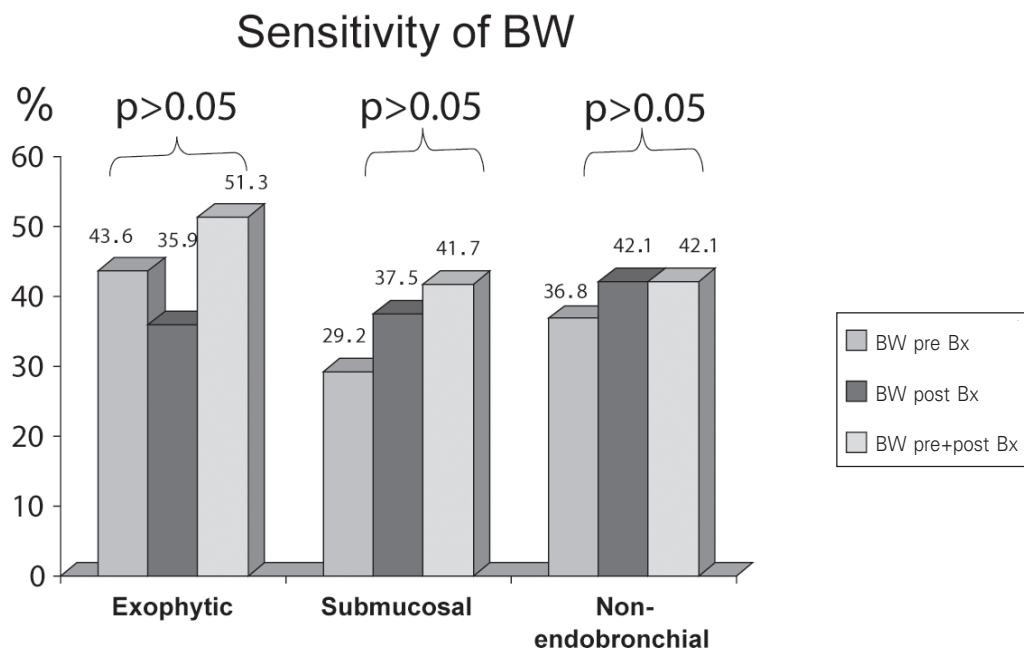


Fig. 3 Sensitivity of pre and post-biopsy bronchial washing (BW) per lesion characteristics

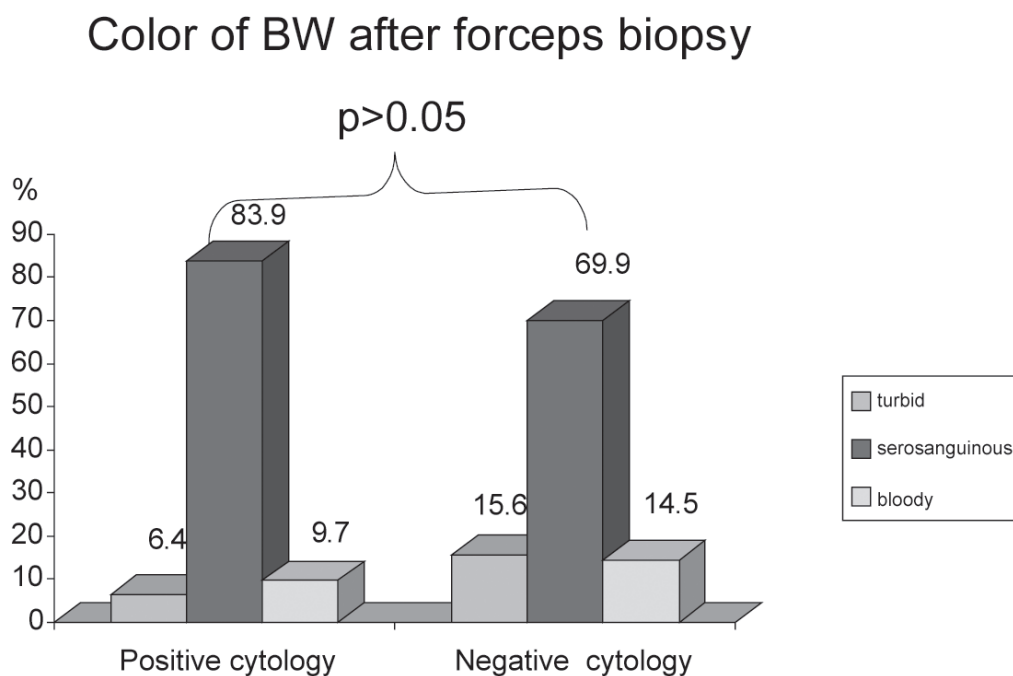


Fig. 4 Color of BW fluid after forceps biopsy VS cytologic result

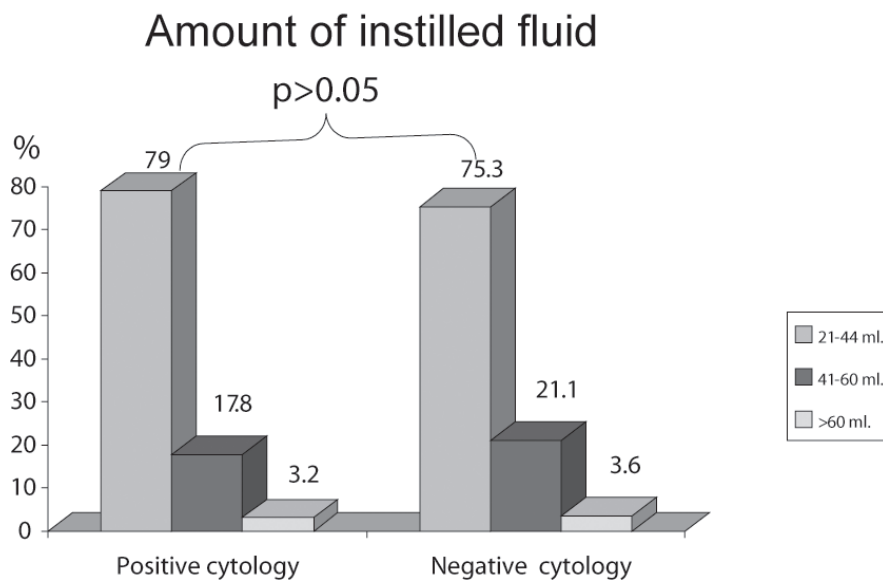


Fig. 5 Amount of instilled fluid for BW VS cytologic result

Table 5. Different bronchoscopists and Cytologic yields

Bronchoscopists	Positive Cytology		Negative Cytology		Total
	N	%	N	%	N
1	12	(46.2)	14	(53.8)	26
2	2	(18.2)	9	(81.8)	11
3	7	(41.2)	10	(58.8)	17
4	8	(66.7)	4	(33.3)	12
5	4	(57.1)	3	(42.8)	7
6	0	(0)	3	(100.0)	3
7	4	(66.7)	2	(33.3)	6

Table 6. Sensitivity of BW and Bx among different studies

Studies	Endobronchial			Non-endobronchial			Total		
	N	Bx (%)	BW (%)	N	Bx (%)	BW (%)	N	Bx (%)	BW (%)
Chaudhary 1978 ⁽⁸⁾	95	78.8	77.9	13	15.4	46.1	60	67	47
Lundgren 1983 ⁽⁹⁾	47	80.9	46.8	87	80.5				
Popp 1991 ⁽¹⁰⁾	99	92.9		63	36.5	38.1			
Mak 1996 ⁽¹¹⁾	125	76	49.6						
Govert 1996 ⁽¹²⁾	177	80.8	42.9						
Rosell 1998 ⁽¹³⁾	82	58.5	39.2						
The present study (pre)	63	88.9	38.0	19	47.4	36.8	82	79.3	37.8
(post)			36.5			42.1			37.8

ing or death occurred. Only one patient in our study who had a peripheral non-endobronchial lesion had pneumothorax post transbronchial lung biopsy.

Discussion

The sensitivity of BW for diagnosis of malignancy varied from 39-79%^(5,8-14) as shown in Table 6. Most of the malignancies were from endobronchial lesions. Only a few studies have been done to test the sensitivity of BW from non-endobronchial lesions. None of the studies has explored the sensitivity of pre and post-forceps biopsy BW. Very few studies reported a sensitivity increase in post bronchoscopy sputum^(5,6) and one reported an increased yield in bronchial biopsy rinsed fluid cytology⁽¹³⁾.

The sensitivity of BW (either pre or post-forceps biopsy) in our study was 37.8%, which was not much different from the results of previous studies. The wide range of the sensitivity might be from the use of different techniques, different study populations, and different criteria for the cytological diagnosis of malignancy (some studies included "atypia" as part of malignancy).

In our study, we could not demonstrate a statistically significant difference in the sensitivity between pre and post-forceps biopsy BW regardless of the lesion characteristics (endobronchial or non-endobronchial lesions). This may be due to the small sample size used in this study. Nevertheless, we found a higher sensitivity for malignancy diagnosis when combined pre and post-forceps biopsy BW (46.3%) was used than when each of these procedures was used exclusively, though it was not statistically different. We also found that there were a few cases where the malignancy diagnosis could be demonstrated only from BW, either pre or post-forceps biopsy, but not from biopsy alone. This suggests that BW is helpful and should not be disregarded in assisting the diagnosis of malignancy using FOB.

Interestingly, in the non-endobronchial lesion subgroup analysis, we found higher sensitivity from post-forceps biopsy BW (42.1%), which was very close to the sensitivity of biopsies (47.4%), as compared to a lower sensitivity from pre-forceps biopsy BW (36.8%). This data may suggest that post-forceps biopsy BW may give a higher sensitivity than pre-forceps biopsy BW even though we could not demonstrate that there was a statistically significant difference.

Other factors that may influence the cytological results such as the color of BW fluid, the amount of instilled fluid in each washing and the use of different

bronchoscopists was analyzed in this study. For the BW fluid color, most of the specimens were serosanguinous, the rest were turbid or bloody. The number of specimens with positive cytology for malignancy was not different from the number with negative cytology disregarding the color of the BW. The amount of blood in the BW fluid did not seem to interfere with the cytological readings. As for the fluid instilled for each BW, we found that the numbers of specimens with positive cytology were not different from the ones with negative cytology among the groups that used a small, moderate or large amount of instilled fluid. We did not find there was a statistically significant difference in the sensitivity of BW as performed by different bronchoscopists either.

We had no serious complications such as massive hemoptysis, respiratory failure, and severe hypoxemia in our study despite the longer duration of procedures using two BW. The only complication we had was pneumothorax from TBBx in a non-endobronchial case.

The advantages of our study were that both pre and post-forceps biopsy BW were from the same location, from the same patient, performed by the same bronchoscopist, on the same day. This reduced subject variability. However, a limitation of this study was the use of a small sample size.

From our study results, we found increased sensitivity of combined pre and post-forceps biopsy BW cytology compared to using either one exclusively. This may be a useful guide for improving the sensitivity of bronchoscopic methods for use in the diagnosis of lung cancer. Our future study plan is to evaluate the sensitivity of the combined pre and post-forceps biopsy BW fluid for diagnosis of lung cancer in a larger population.

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ความแตกต่างของผลการวินิจฉัยมะเร็งปอดโดยการตรวจเซลล์จากน้ำล้างหลอดลมก่อนและหลังการตัดชิ้นเนื้อปอดผ่านทางกล้องส่องหลอดลม

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วัตถุประสงค์: การส่องกล้องหลอดลมร่วมกับหัตถการต่างๆ เช่น การตรวจเซลล์น้ำล้างหลอดลม การตัดชิ้นเนื้อเยื่อปอดหลอดลม การตัดชิ้นเนื้อปอด การแปรงลอกเซลล์บุผิวหลอดลม เป็นต้น ช่วยในการวินิจฉัยมะเร็งปอดได้ดี การตรวจ เซลล์น้ำล้างหลอดลม ให้ผลการตรวจวินิจฉัยแตกต่างกันตั้งแต่ร้อยละ 39 ถึง 79 ขึ้นกับตำแหน่งและจำนวนพยาธิสภาพในปอด การตรวจเสมหะผู้ป่วยหลังการส่องกล้องหลอดลมมีรายงานว่าอาจเพิ่มอัตราการตรวจวินิจฉัยมะเร็งปอดได้ น้ำล้างหลอดลมซึ่งเก็บได้โดยตรงจากการส่องกล้องเข้าไปยังบริเวณหลอดลมที่มีความผิดปกติน่าจะให้ผลการตรวจเพิ่มขึ้นโดยเฉพาะหลังการทำหัตถการซึ่งอาจทำให้มีการหลุดลอกของเซลล์ผิดปกติมากขึ้น เป็นที่มาของการศึกษานี้ซึ่งเปรียบเทียบอัตราการวินิจฉัยมะเร็งปอดโดยการตรวจเซลล์น้ำล้างหลอดลมก่อนและหลัง การตัดชิ้นเนื้อปอด

วัสดุและวิธีการ: ผู้ป่วยกลุ่มเสี่ยงต่อการเป็นมะเร็งปอดที่พบมีพยาธิสภาพในปอดจำนวน 114 คนได้รับการตรวจส่องกล้องหลอดลม ณ โรงพยาบาลศิริราช ระหว่างเดือนมีนาคมถึงตุลาคม พ.ศ. 2543 ในจำนวนนี้ผู้ป่วย 70 คนพบมีความผิดปกติในหลอดลม โดยเป็นก้อนนูน 42 คน และมีผิวเยื่อหลอดลมหนา 28 คน ผู้ป่วย 44 คนมีก้อนในเนื้อปอด ผู้ป่วยเหล่านี้ได้รับการตรวจส่องกล้องหลอดลมและเก็บตัวอย่างน้ำล้างหลอดลม ตามด้วยการตัดเนื้อเยื่อปอดหลอดลมหรือการตัดเนื้อปอด แล้วจึงใช้น้ำเกลือล้างหลอดลมตามหลังอีกครั้ง การตรวจเซลล์จากน้ำล้างหลอดลมทั้งก่อนและหลังการตัดชิ้นเนื้อปอดเพื่อวินิจฉัยมะเร็งปอดทำโดยพยาธิแพทย์ซึ่งไม่ทราบลำดับการเก็บสิ่งส่งตรวจ อัตราการตรวจวินิจฉัยมะเร็งปอดของสิ่งส่งตรวจแต่ละกลุ่มนี้คำนวณได้จากการเปรียบเทียบกับผลการวินิจฉัยมะเร็งปอดขั้นสุดท้ายด้วยวิธีต่าง ๆ เช่น การตรวจชิ้นเนื้อจากการส่องกล้องหลอดลม การใช้เข็มดูดเนื้อเยื่อปอดผ่านผนังทรวงอก การผ่าตัดก้อนออกตรวจการติดตามอาการแสดง เช่น มีการกระจายของก้อนไปที่อื่น เป็นต้น

การวิเคราะห์ทางสถิติ: ใช้ Chi-square test

ผลการศึกษา: ผู้ป่วย 82 คนจาก 114 คนได้รับการวินิจฉัยมะเร็งปอด โดยมีก้อนนูนในหลอดลม 39 คน มีผิวเยื่อหลอดลมหนา 24 คน มีก้อนในเนื้อปอด 19 คน การตรวจเซลล์จากน้ำล้างหลอดลมก่อนการตัดชิ้นเนื้อปอดมีความไวร้อยละ 37.8 การตรวจเซลล์จากน้ำล้างหลอดลมหลังการตัดชิ้นเนื้อปอดมีความไวร้อยละ 37.8 การตรวจเซลล์จากน้ำล้างหลอดลมทั้งก่อนและหลังการตัดชิ้นเนื้อปอดรวมกันมีความไวร้อยละ 46.3 การตัดชิ้นเนื้อจากเยื่อหลอดลมและเนื้อปอดมีความไวร้อยละ 79.3 อัตราการตรวจวินิจฉัยมะเร็งปอดจากการตรวจเซลล์น้ำล้างหลอดลมทั้งก่อนหรือหลังหรือผลรวมทั้งก่อนและหลังการตัดชิ้นเนื้อปอดไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ ไม่พบปัญหาแทรกซ้อนร้ายแรง เช่น เลือดออกมาก ภาวะหายใจวายหรือเสียชีวิตในการศึกษานี้

สรุป: การตรวจเซลล์น้ำล้างหลอดลมก่อนหรือหลังการตัดชิ้นเนื้อปอดให้อัตราการวินิจฉัยมะเร็งปอดไม่แตกต่างกัน แต่ผลรวมของการตรวจเซลล์น้ำล้างหลอดลมก่อนและหลังการตัดชิ้นเนื้อปอดให้อัตราการวินิจฉัยมะเร็งปอดเพิ่มขึ้น
