Role of Bronchial Washing in the Diagnosis of Endoscopically Visible Lung Cancer

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Objective : *To evaluate the usefulness of bronchial washings in addition to endobronchial biopsies and/or bronchial brushings for the pathological diagnosis of endoscopically visible lung cancer.*
Material and Method : *A retrospective study of patients diagnosed as lung cancer by bronchoscopy between January 1995 and December 1998. Patients were included in the study if they had 1) endoscopically visible tumors (exophytic mass or irregular mucosa) and 2) bronchial washings (BW_s) performed together with either endobronchial biopsies (EBB_s) or bronchial brushings (BR_s).*

Patients were classified into 3 groups according to the result of the histocytology as follows: A) positive in both BW_s and EBB_s / BR_s, B) positive in only EBB_s / BR_s and C) positive in only BW_s.

A number of patients in each group were analyzed to see the benefit of BW_s as an add-on diagnostic tool. The authors also evaluated the benefits of BW_s in the subgroup of patients who had necrotic and bleeding tumor. Statistical analysis of the data was performed by using the likelihood-ratio chi-square test.
Results : *Two hundred and twenty-two patients were included in the present study. The number of patients in group A, B and C was 108, 108, and 6, respectively. Therefore, BW_s was the only diagnostic procedure in 6 patients (2.7%). Those 6 patients all had incurable non-small cell lung cancer. The likelihood of a positive BW_s in an exophytic mass was no different from irregular mucosa. The likelihood of a positive BW_s in a tumor with necrosis was higher than in a tumor without necrosis. In contrast, tumors with active bleeding had a lower likelihood of positive BW_s when compared with those without bleeding. The likelihood ratio showed no statistical significance in any of the groups.*
Conclusion : *The addition of BW_s to either EBB_s or BR_s is beneficial, but it may not be cost-effective. This procedure may be useful in patients with an endoscopically visible necrotic tumor. In contrast, the bronchoscopic finding of a bleeding tumor may be a negative predictor. This procedure may be a suitable approach when performed only in selected cases, such as necrotic tumor or negative initial EBB_s / BR_s.*

Keywords : *Bronchial brushings (BR_s), bronchial washings (BW_s), endobronchial biopsies (EBB_s), endoscopically visible lung cancer*

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From bronchoscopic findings, lung cancer can be divided into central lesions that are endoscopically visible and peripherally non-visible[1]. The role of bronchoscopy in making a diagnosis of lung cancer and differentiating cell types is well established. The diagnostic yield of bronchoscopic procedures for a centrally-located tumor by using endobronchial biopsies is highest (80%), followed by bronchial brushings (72%)[2]. However, the benefit of bronchial washings, which provides the diagnostic yield for endoscopically visible tumors between 27% to 90%, is still controversial[2]. There have been many studies that support the use of bronchial washing (BW_s) in addition to endobronchial biopsies (EBB_s) and bronchial brushing (BR_s)[3,4], whereas other research has failed to show any benefit[5-9]. Therefore, the authors performed this retrospective study to see whether bronchial washing had any additional use for either endobronchial

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biopsies or bronchial brushing in the diagnosis of bronchoscopically visible lung cancer. The authors also tried to find the subtypes of endobronchial lesions that might predict the results of bronchial washing in this setting.

Material and Method

Patients

All the medical records of patients who underwent bronchoscopy at the authors' unit between January 1995 and December 1998 were reviewed. The patients, whose diagnosis of lung cancer was made by bronchoscopy, were included in the present study provided they met all of the following criteria: (1) endoscopically visible tumors in the airway that were either an exophytic mass or irregular mucosa due to tumor infiltration; and (2) BW_s that was performed together with either EBB_s or BR_s. Patients were excluded from the study if they had only one of the following: (1) extrinsic compression or submucosal infiltration by tumors without endobronchial component; (2) peripheral lesions that were invisible by the bronchoscope; (3) diagnosed lung cancer from histocytologic results that were suspicious or inconclusive; (4) known primary extrapulmonary site of cancer; and (5) other primary malignancies of the airway such as mucoepidermoid, adenoid cystic, or carcinoid tumors.

Procedures

Transnasal bronchoscopy was performed in every case. Premedications that included subcutaneous codeine, intramuscular injection of atropine and pethidine, and inhalation of 20 ml of 4% lidocaine through ultrasonic nebulization were administered unless there were any contraindications. Local administration of 3 ml of 2% lidocaine through the working channel of the fiberoptic bronchoscope at the vocal cord, subglottic area and carina was also carried out. After inspecting the airways and identifying the endobronchial tumors, endobronchial biopsies were performed. In cases where biopsies could not be carried out due to anatomical limitations, bronchial brushing was done instead. After the specimens were collected from either forceps biopsies or brushings, bronchial washing was performed.

Endobronchial biopsies (EBB_s)

Three to four specimens were taken from each lesion, if possible, by using standard cup forceps. Biopsy specimens were immediately fixed in 10% formalin solution before processing for histology.

Bronchial brushings (BR_s)

Brushings were done by using a standard brushing catheter. Two brushings were performed for each lesion. After the brushings, the specimens were smeared onto a glass slide in a circular motion. The slides were then immediately immersed into 95% alcohol solution before being sent to the Department of Pathology. The smears were finally stained by using hematoxylin and eosin (H&E) and Papanicolaou methods.

Bronchial washings (BW_s)

Washings were carried out by flushing the tumors with 20-40 ml of 0.9% NSS. The aspirated fluid was collected in a trap and transported to the laboratory for centrifugation. Direct smears were made from the sediment and stained by using H&E and Papanicolaou methods.

Histologic and cytologic results

Histocytology of the tumor was classified as small cell lung cancer, squamous cell carcinoma, adenocarcinoma, large cell carcinoma and unclassified non-small cell lung cancer (when subclassification could not be made or a discrepancy between the histologic and cytologic results was found).

Bronchoscopic findings

The gross appearance of the tumor was reported as either an exophytic mass or nodularly irregular mucosa. The associated necrotic materials on top of the tumor surface and associated active bleeding that might affect the diagnostic role of BW_s were also recorded.

Data collection

All of the following data were collected for analysis: (1) demographic data (age, sex); (2) bronchoscopic findings; and (3) cell types of the tumor from histocytologic results.

The patients were classified into 3 groups according to the result of histocytology as follows: Group A, positive in both EBB_s /BR_s and BW_s; Group B, positive in only EBB_s /BR_s and; Group C, positive in only BW_s. The number of patients in each group was recorded in order to see the benefit of add-on BW_s in the diagnosis of endoscopically visible lung cancer.

The authors also looked for the association of bronchoscopic findings (exophytic mass vs irregular mucosa, tumor with necrosis vs tumor without necrosis, and tumor with active bleeding vs tumor without bleeding) and the cytologic results from BW_s

Statistical analysis

The likelihood-ratio chi-square test was used to compare the likelihood of positive BW_s between exophytic mass and irregular mucosa, necrotic and non-necrotic tumors, and bleeding and non-bleeding tumors.

Results

A total of 1,406 bronchoscopies were performed at our division between January 1995 and December 1998. Three hundred and fifty-six patients were definitely diagnosed as lung cancer. Two hundred and twenty-two of them (male: female 156:66; aged 60.5 + 9.81 years) fulfilled the authors' inclusion criteria. Histologic subtypes of lung cancer were non-small cell lung cancer in 211 patients (105 squamous cell carcinomas, 62 adenocarcinomas, 6 large cell carcinomas, and 38 unclassified non-small cell carcinomas) and small cell lung cancer in 11 patients. The number of patients in groups A, B and C were 108 (48.65%), 108 (48.65%) and 6 (2.7%), respectively. Therefore, EBB_s/BR_s were positive in 216 patients (97.3%), BW_s were positive in 114 patients (51.4%), and BW_s were the only diagnostic procedures in 6 (2.7%) patients. All patients in group C were male and had non-small cell carcinoma (squamous cell carcinoma:adenocarcinoma: unclassified non-small cell carcinoma 3:1:2). Five patients were in stage IV and the other one was in stage III B.

The results of BW_s and the likelihood of positive BW_s in different kinds of bronchoscopic findings are displayed in Table 1. The likelihood of positive BW_s in exophytic mass and irregular mucosa was not different. When comparing necrotic with non-necrotic tumors, the likelihood of positive BW_s in the necrotic group was slightly higher than in the non-necrotic group. However, there was no statistical significance ($p = 0.468$). In addition, the likelihood of positive BW_s in bleeding tumors was lower than in non-bleeding tumors without statistical significance ($p = 0.268$).

Table1. Results of BW_s and likelihood of positive BW_s in association with various bronchoscopic findings

Bronchoscopic findings	BW +	BW -	Likelihood of positive BW_s	Likelihood ratio
Exophytic mass (n = 152)	78	74	0.51	0
Irregular mucosa (n = 70)	36	34	0.51	(p = 0.988)
Necrosis (n=24)	14	10	0.58	0.528
Non-necrosis (n = 198)	100	98	0.50	(p = 0.468)
Bleeding (n = 18)	7	11	0.38	1.225
Non-bleeding (n = 204)	107	97	0.52	(p = 0.268)

Discussion

There is still no clear-cut agreement on the addition of BW_s to the EBB_s/BR_s for the diagnosis of centrally located lung cancer. Many studies showed that BW_s did not increase diagnostic yield for endoscopically visible lung cancer when compared with EBB_s and BR_s[5-9]. In contrast to those studies, Mak et al found that BW_s was the only diagnostic tool for lung cancer in 2.2% of the patients when the results of other procedures were all negative[4].One reason that might explain this different result is seen from the study by Chaudhary et al, who performed BW_s after EBB_s. They found that BW_s alone had the highest diagnostic yield of 77.9%, which could be increased to 95.8% when combined with EBB_s. They concluded that BW_s should be done after EBB_s to increase the malignant cells within the washing specimens[3]. The present procedures followed the suggestion of Chuadhary et al and the authors were able to make additional diagnoses of lung cancer from BW_s in 2.7% of the patients. Although BW_s in the present study was positive in only 51.4%, which was quite different from Chaudhary's study, an additional 2.7% of lung cancer diagnoses by this procedure might be useful in terms of clinical diagnosis. However, in terms of cost-effectiveness, the benefit of this procedure has to be reconsidered.

The cost of each bronchoscopy, histology (from EBB_s) and cytology (from BR_s or BW_s) at our center was $ 30, $ 7.5 and $ 7.5, respectively. From the present study, the authors had to perform 222 additional BW_s to diagnose 6 patients. Therefore, the authors had to pay $ 1,665 more to diagnose 6 endoscopically visible lung cancer patients, or $ 277.5 per patient which was 37 times the cost of one BW. Not only the higher cost, but the addition of BW_s to

EBB_s/BR_s also increased the time and work for the pathologists in processing the specimens. However, this might be worthwhile if the patients are at a curable stage. Unfortunately, all of the presented patients were in the late stage of the disease.

In cases where BW_s were not added to EBB_s/BR_s, 6 patients we're misdiagnosed. The total cost of rebronchoscopies and repeated histocytology for those 6 patients was $ 270, which was 6 times cheaper than the cost of doing BW_s in all patients. Although this approach can cause diagnostic delay and increase the risk of complications from repeated bronchoscopy, the prognosis of the patient may not be changed due to the end-stage of the lung cancer.

Govert et al found that the addition of BW_s to EBB_s increased sensitivity for the diagnosis of lung cancer from 80.8% to 84.8%[10]. They concluded that the addition of BW_s to EBB_s was cost-effective by assuming $ 500 as a threshold of cost-effectiveness in terms of reduced-quality day (days of reduced quality of life due to morbidity and diagnostic delay). This threshold might not be applicable to developing countries such as Thailand. Therefore, the authors tried to find the most appropriate approach for the diagnosis of endoscopically visible lung cancer at our center. Mak and Jones suggested the idea of holding washing specimens for processing until a time when the EBB_s/BR_s results were negative in highly suspicious cases of lung cancer[4,11]. This would be the best approach if the pathologists were constantly available. Unfortunately, that is impossible at the authors' center due to service-overloading.

Therefore, the authors tried to find bronchoscopic findings that might predict how positive the histocytologic results are. It was found that exophytic tumors and irregular mucosa had no predictive value. In contrast, tumors on-top with necrotic debris and tumors with active bleeding might be positive and negative predictors of BW_s results, respectively. A study by Buccheri et al showed that tumors with necrosis were associated with a low yield in any diagnostic technique and they suggested performing all the procedures and number of attempts in patients with this bronchoscopic finding [12]. The present study supports Buccheri in that the addition of BW_s to EBB_s/BR_s may be useful in this subgroup of bronchoscopic findings. However, the lack of statistical significance in the present study resulted from the low number of subjects. Further study that recruits more patients is needed to see the statistical significance.

Conclusion

Bronchial washings, as an additional diagnostic tool to endobronchial biopsies/bronchial brushings for pathologic diagnosis of endoscopically visible lung cancer are beneficial, but they may not be cost-effective. This procedure should be performed in selected cases according to the readiness of pathologists at each center. Processing bronchial washing specimens only when the histocytologic results of endobronchial biopsies/bronchial brushings are negative is the best diagnostic approach if the pathologists are available all the time. At the authors' center, that service is overloaded. Therefore, an alternative approach is performing bronchial washings in combination with endobronchial biopsies/bronchial brushings under rebronchoscopy later if the result of initial bronchoscopy is negative. In cases that have necrotic material on top of the tumor, bronchial washings should be done following endobronchial biopsies or bronchial brushings during the first bronchoscopy. In contrast, bronchial washings may be less useful when the bronchoscopy shows a tumor with active bleeding. BW_s can then be withheld during the initial bronchoscopy and performed later if the initial results of endobronchial biopsies or bronchial brushings are negative.

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บทบาทของการล้างหลอดลมในการวินิจฉัยมะเร็งปอดที่สามารถเห็นได้จากกล้องส่องหลอดลม

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วัตถุประสงค์ *: เพื่อทราบประโยชน์ของการล้างหลอดลมเพิ่มเติมจากการตัดชิ้นเนื้อของหลอดลม และ/หรือ การแปรงหลอดลมในการวินิจฉัยมะเร็งปอดที่สามารถเห็นได้จากกล้องส่องหลอดลม*

วิธีการศึกษา *: เป็นการศึกษาย้อนหลังโดยดูข้อมูลผู้ป่วยมะเร็งปอดที่ได้รับการวินิจฉัยในช่วงระยะเวลาตั้งแต่ มกราคม 2538 ถึง ธันวาคม 2541 ที่โรงพยาบาลมหาราชนครเชียงใหม่ ผู้ป่วยที่ศึกษา คือ ผู้ป่วยที่ลักษณะพยาธิสภาพของมะเร็งจากกล้องส่องหลอดลมเป็นชนิดก้อน หรือเยื่อบุหลอดลมที่ขรุขระ และผู้ป่วยทุกรายจะต้องได้รับการล้างหลอดลมร่วมกับการตัดชิ้นเนื้อของหลอดลมหรือการแปรงหลอดลม ผู้ป่วยที่เข้าเกณฑ์ดังกล่าวจะถูกแบ่งเป็น 3 กลุ่มตามผลทางพยาธิสภาพ คือ กลุ่ม A เป็นกลุ่มที่การล้างหลอดลมและการตัดชิ้นเนื้อ/การแปรงหลอดลมได้ผลบวก, กลุ่ม B คือ การตัดชิ้นเนื้อ/การแปรงหลอดลม ได้ผลบวกเท่านั้น และกลุ่ม C คือ การล้างหลอดลมได้ผลบวกเท่านั้น จำนวนผู้ป่วยในแต่ละกลุ่มจะถูกนำมาประเมินเพื่อดูประโยชน์ของการล้างหลอดลม ผู้วิจัยยังศึกษาลึกลงไปถึงลักษณะย่อยของมะเร็ง คือ มะเร็งที่มีเนื้อตายปกคลุม และมะเร็งที่กำลังมีเลือดไหลอยู่ ว่ามีผลต่อการล้างหลอดลมหรือไม่อีกด้วย การวิเคราะห์ทางสถิติใช้วิธีทดสอบชนิด likelihood-ratio chi-square*

ผลการศึกษา *: มีผู้ป่วย 222 คน ที่เข้าเกณฑ์การศึกษา จำนวนผู้ป่วยในกลุ่ม A, B และ C เป็น 108, 108 และ 6 คน ตามลำดับ นั่นหมายความว่าการล้างหลอดลมให้ผลบวกเพียงอย่างเดียวในผู้ป่วย 6 ราย (คิดเป็นร้อยละ 2.7) เมื่อดูลักษณะของผู้ป่วยทั้ง 6 ราย พบว่าทั้งหมดไม่ใช่มะเร็งชนิดเซลล์เล็ก และอยู่ในระยะที่ไม่สามารถจะรักษาให้หายขาดได้แล้วทั้งสิ้น โอกาสที่การล้างหลอดลมจะให้ผลบวกไม่แตกต่างกันในมะเร็งชนิดก้อนหรือเยื่อบุหลอดลมขรุขระ แต่โอกาสในมะเร็งที่ปกคลุมด้วยเนื้อตาย จะได้ผลบวกมากกว่ามะเร็งที่ไม่ถูกปกคลุมด้วยเนื้อตาย ในขณะที่มะเร็งที่กำลังมีเลือดออกจะมีโอกาสให้ผลบวกจากการล้างหลอดลมน้อยกว่ามะเร็งที่ไม่มีเลือดออก อย่างไรก็ตามเมื่อวิเคราะห์ทางสถิติก็ไม่พบความแตกต่างอย่างมีนัยสำคัญ*

สรุป *: การล้างหลอดลมเพิ่มเติมจากการตัดชิ้นเนื้อหลอดลม/แปรงหลอดลมในผู้ป่วยมะเร็งปอดที่เห็นพยาธิสภาพจากการส่องกล้องเป็นชนิดก้อน หรือเยื่อบุหลอดลมขรุขระมีประโยชน์แต่อาจไม่คุ้มค่า ประโยชน์อาจเห็นได้ชัดขึ้นในผู้ป่วยกลุ่มที่มีเนื้อตายปกคลุมมะเร็งแต่จะไม่ค่อยมีประโยชน์ในมะเร็งที่กำลังมีเลือดออก ดังนั้นหัตถการนี้จึงควรเลือกทำในผู้ป่วยบางรายเช่น มะเร็งที่มีเนื้อตายปกคลุม หรือผลการตรวจโดยวิธีตัดชิ้นเนื้อหลอดลม/แปรงหลอดลม ให้ผลลบแล้วเท่านั้น*