

**Extensive intrapulmonary metastases and pleural involvement in primary bronchogenic adenocarcinoma mimicking metastases from primary extrapulmonary cancer and massive pleural effusion\***

Samruay Shuangshoti\*\*

**Shuangshoti S. Extensive intrapulmonary metastases and pleural involvement in primary bronchogenic adenocarcinoma mimicking metastases from primary extrapulmonary cancer and massive pleural effusion. Chula Med J 1986 Oct; 30 (10) : 1013-1021**

*Roentgenographically a 58-year-old woman had multiple cotton-ball lesions in her right lung and a hazy left hemithorax. Clinically, it was thought that she had widespread pulmonary metastases from an obscure primary extrapulmonary carcinoma with massive left pleural effusion. One and a half years before death, she was diagnosed clinically to have pulmonary tuberculosis and was treated medically. Postmortem examination disclosed a primary adenocarcinoma of the left upper lobe bronchus with permeation into the substance of the left lung, contiguous pleura and adjacent pericardium, and widespread metastases to the right lung, regional lymph nodes, liver, left adrenal gland, and left kidney. The left pleural space was obliterated by neoplastic and fibrous adhesions. Hydrothorax and tuberculosis were not confirmed. One should learn from this patient that primary carcinoma of the lung can produce extensive intrapulmonary metastases and that roentgenographically hazy thorax can result from a diffuse carcinomatous infiltration of the pulmonary substance and the thickened pleura.*

---

\* Supported by Anadhamahidol Foundation, Medical Section (1985-1988).

\*\* Department of Pathology, Faculty of Medicine, Chulalongkorn University.

สำรวย ช่างโชติ. อดโนคาร์ชีโนมาปฐมภูมิของปอดแพร่กระจายอย่างกว้างขวางภายในปอดและเยื่อหุ้มปอด ดูประหนึ่งมีมะเร็งทุติยภูมิจากภายนอกมาสู่ปอดและน้ำในถุงเยื่อหุ้มปอด จุฬาลงกรณ์เวชสาร 2529 ตุลาคม; 30 (10): 1013-1021

ผู้ป่วยหญิงอายุ 58 ปี ได้รับการวินิจฉัยว่าเป็นวัณโรคของปอด และได้รับการรักษาทางโอสถมาเป็นเวลา  $1\frac{1}{2}$  ปี ก่อนถึงแก่กรรม ต่อมาเกิดมีอาการหอบเหนื่อย นอนราบไม่ได้ และมีรอยโรคเป็นก้อนกลม ๆ คล้ายปุยฝ้ายทั่วไปในปอดขวา ส่วนปอดซ้ายที่บดตลอด ได้รับการวินิจฉัยเพิ่มทางคลินิกว่ามีการแพร่กระจายของมะเร็ง ซึ่งไม่ทราบว่ายู่ ณ ที่ใดของร่างกายไปสู่ปอด และมีน้ำในช่องปอดซ้าย ตรวจศพพบเยื่อหุ้มปอดที่ไปสู่กลีบบนของปอดซ้าย กลายเป็นอดโนคาร์ชีโนมาปฐมภูมิ แล้วมีการแทรกซึมเข้าไปสู่เนื้อปอดซ้ายอย่างกว้างขวาง เยื่อหุ้มปอดทำให้หนาขึ้นมาก และแพร่กระจายอย่างกว้างขวางสู่ปอดขวา ต่อมน้ำเหลืองที่หัวปอดและแถวตับ ในตับ ต่อมหมวกไตซ้าย และไตซ้าย ไม่มีน้ำในช่องปอดทั้งสองข้าง ไม่พบวัณโรคปอด จึงสรุปว่าคาร์ชีโนมาปฐมภูมิของปอดนั้นเป็นตัวให้คาร์ชีโนมาทุติยภูมิภายในเนื้อปอดเอง และคาร์ชีโนมาที่แทรกแซงภายในเนื้อปอดและในเยื่อหุ้มปอดจนทำให้เยื่อหุ้มปอดหนาขึ้นมาก ๆ นั้น อาจให้เงาที่บดทางรังสีที่คล้ายมีน้ำในช่องเยื่อหุ้มปอดได้

One often considers the probability of metastatic tumors from a remote primary site when roentgenographically one sees multiple nodular lesions resembling cotton balls in the lung<sup>(1)</sup> Moreover when the thorax is hazy in a chest X-ray, hydrothorax is frequently interpreted.<sup>(2)</sup> However, a patient being presented demonstrates that such intrathoracic lesions may be the result of widespread intrapulmonary metastases and pleural involvement of a primary bronchogenic carcinoma.

### Case Report

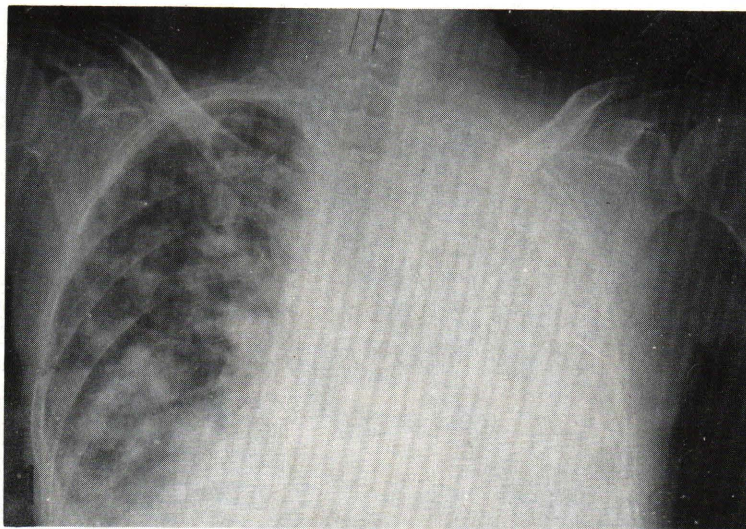
One and a half year before death, a 58-year-old woman had been clinically diagnosed to have pulmonary tuberculosis and treated orally with isoniazid hydrazide and para-aminosalicylic acid. Unfortunately, details of the investigations employed in reaching that clinical diagnosis and about the precise location of the lesion were not available. Seven months before death, the patient experienced a gradual loss of body weight. Three weeks before death, she developed progressive dyspnea. She was hospitalized 3 days later because of the

dyspnea and a cough with blood-stained sputum.

Her body temperature was 37° C, pulse rate 98 beats/min, respiratory rate 32/min, and blood pressure 120/80 mm Hg. The patient was emaciated. The right lung had crepitations while the left lung exhibited increased dullness on percussion and decreased breath sounds on auscultation.

Laboratory studies revealed 11.7 gm/100 ml of hemoglobin and 9,600 leucocytes/mm<sup>3</sup> with 87% neutrophils, 5% eosinophils, 2% basophils, and 6% lymphocytes. There were 20 leucocytes per high power microscopic field in the urine. Serum albumin was 2.4 gm/100 ml, and globulin 3.7 gm/100 ml.

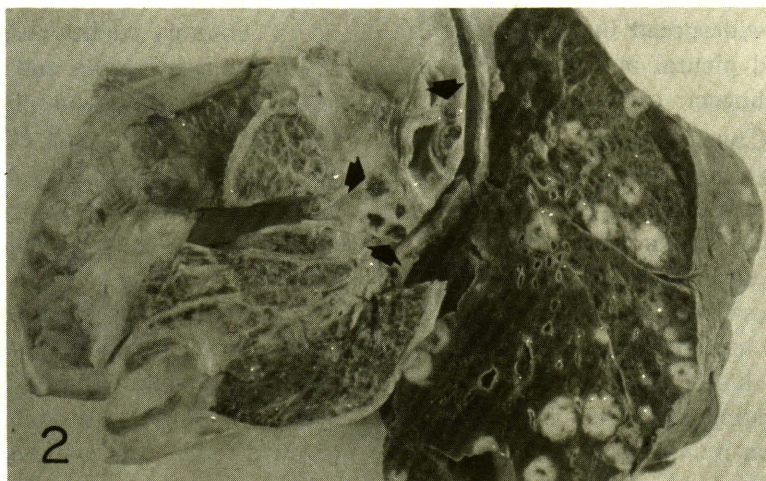
A chest X-ray demonstrated multiple discrete nodular lesions resembling cotton balls in the right lung and hazy left hemithorax (Fig. 1). Bronchoscopy gave a negative result. The working diagnosis was metastatic tumors of the lungs with a massive left pleural effusion. The primary site of the cancer was considered obscure. The patient died 18 days after hospitalization.



**Figure 1** Chest X-ray showing multiple nodular lesions resembling cotton balls in the right lung and haziness of the left hemithorax.

**Postmortem findings.** Both lungs weighed together 1,330 gm. The left visceral pleura ranged from 5 to 8 mm in thickness. It was white, hard, and adherent to the parietal pleura, pericardium, and left dome of the diaphragm. The left pleural cavity was obliterated and free from fluid. About 100 ml of serous fluid filled the

pericardial sac. The left lung was severely collapsed and firm (Fig. 2). The left upper lobe bronchus, 2.0 cm from its origin, exhibited thick and rough mucosa (Fig. 3). The entire left lung and contiguous visceral pleura were permeated by white neoplastic tissue.



**Figure 2** Lungs demonstrating severe thickening of the left visceral pleura, collapsed left lung with white neoplastic patches, and many secondary tumors in the right lung as well as in the hilar and paratracheal lymph nodes (arrows).



**Figure 3** Left lung showing cross sections of the upper lobe bronchus (arrows). Note thickening of the bronchial mucosa. White neoplastic patches are seen on the pulmonary cut surfaces.

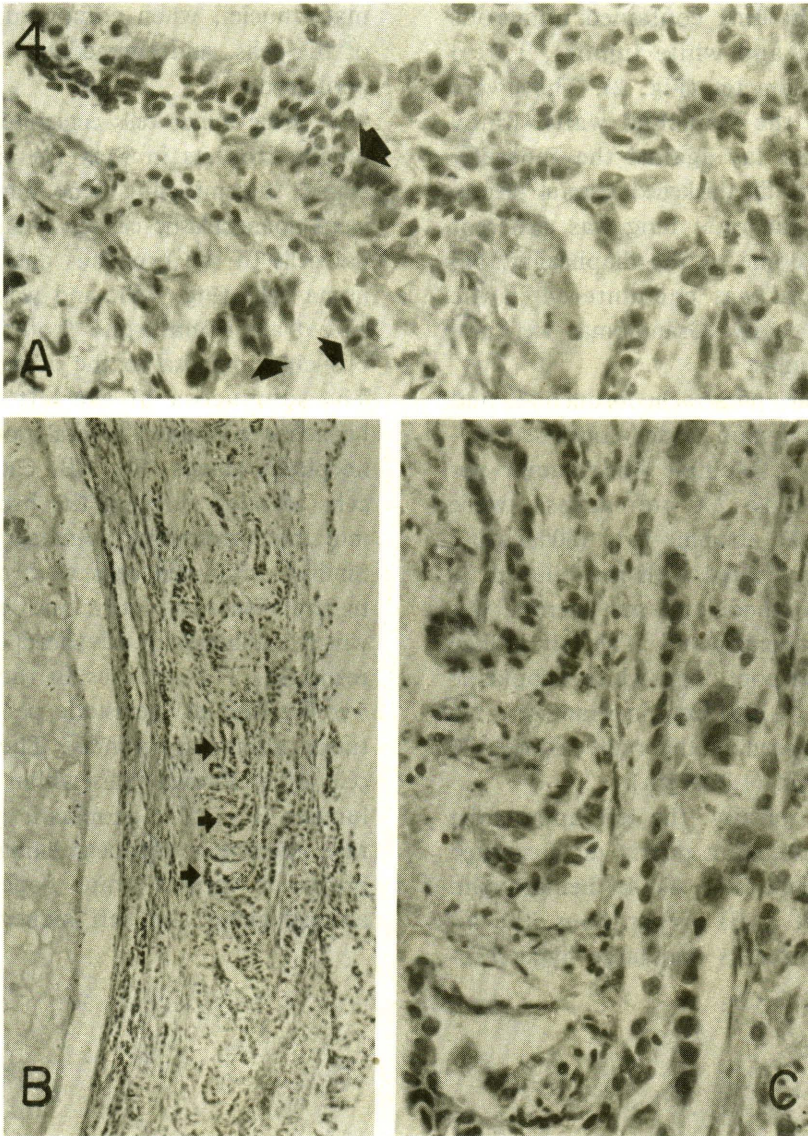
The right lung contained numerous discrete firm and white tumors, 1.0 to 2.5 cm in diameter (Fig. 2). They were unrelated to the bronchial walls. Many tumor nodules lay against the generally opaque and mildly thickened visceral pleura. The base of the right lung was adherent to the right dome of the diaphragm. No excessive fluid was encountered in the right pleural cavity. Granulomas were not seen in the lungs.

The hilar, paratracheobronchial, and porta hepatic lymph nodes contained metastatic tumors. Multiple white tumor nodules, 5 mm to 2.0 cm across, were scattered in the atrophic liver (800 gm) ; none were associated with the bile ducts. A white tumor nodule, 6 mm across, was in the left adrenal gland. The left kidney (80 gm). also contained white neoplastic nodules, 1.0 to 2.0 cm in diameter. No tumors were seen in the right kidney (70 gm) and brain (1,200 gm).

Microscopically, the left upper lobe bronchus contained a poorly differentiated adenocarcinoma (Fig. 4). In hematoxylin and eosin (H & E) preparations, the individual tumor cells had large hyperchro-

matic nuclei, when compared to the size of the cells, and rimmed by fine granular perikaryon.

Some tumor cells contained cytoplasmic mucin droplets in Mayer's mucicarmine stains. Intermingling zone was noted between nonneoplastic ciliated columnar epithelial cells of the bronchus and adenocarcinoma cells (Fig. 4A), and was interpreted as a transitional zone from the normal bronchial mucosa to the adenocarcinoma. The submucosa of the left upper lobe bronchus contained several poorly formed neoplastic glands (Fig. 4B, C). The tumor cells invaded through the bronchial wall into the surrounding pulmonary substance. Similar carcinoma cells were disseminated in the visceral pleura and pericardium which exhibited an advanced desmoplastic response. The nodules in the right lung were verified as metastatic poorly differentiated adenocarcinomas. The neoplastic cells often formed balls within the alveolar lumens (Fig. 5) ; neoplastic glands were rare. Metastatic adenocarcinomas were also present in various lymph nodes, liver, left adrenal gland, and left kidney.

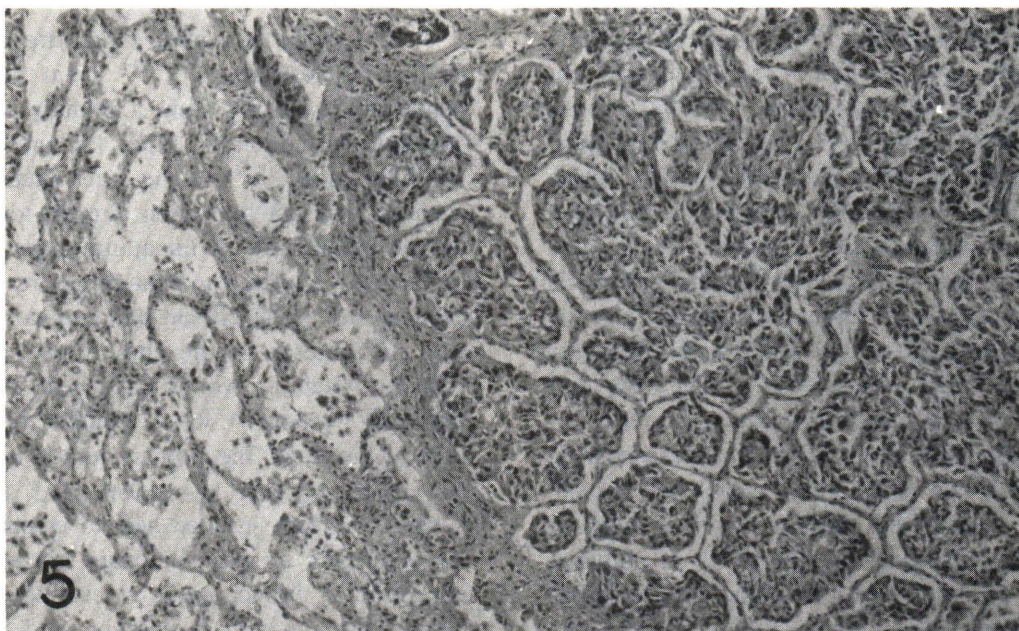


**Figure 4** Microscopic features of the tumor.

A. Section of the left upper lobe bronchus exhibiting a transitional zone (upper arrow) between normal ciliated low columnar epithelial cells on the right of this arrow and poorly differentiated adenocarcinoma cells on the left of this arrow. Adenocarcinoma cells are also clustered in the submucosa (lower arrows). (H & E,  $\times 400$ ).

B. Upper lobe bronchus demonstrating multiple glands of the poorly differentiated adenocarcinoma infiltrating submucosa. Glands indicated by the arrows are further exhibited in C. Bronchial cartilage lies on the left margin of the photomicrograph. (H & E,  $\times 100$ ).

C. Higher magnification of the neoplastic glands showing cells having large hyperchromatic nuclei rimmed by scanty fine granular cytoplasm. (H & E,  $\times 400$ ).



**Figure 5** Metastatic poorly differentiated adenocarcinoma in the right lung demonstrating balls of the tumor cells in the alveolar lumens. (H & E,  $\times 100$ ).

The pathologic diagnosis was a poorly differentiated adenocarcinoma of the left upper lobe bronchus with direct extension into the substance of the left lung, contiguous pleura, and adjacent pericardium, and widespread metastases to the right lung, lymph nodes (hilar, peritracheobronchial, and porta hepatic), liver, left adrenal gland, and left kidney.

### Discussion

The identification of a transitional zone of the left upper lobe bronchial mucosa into carcinoma supported the diagnosis of a primary pulmonary adenocarcinoma.<sup>(3,4)</sup> Additionally, secondary tumors in the hilar lymph nodes, liver, adrenal gland, and kidney were in accord with the metastatic pattern of bronchogenic carcinoma.<sup>(5)</sup> Anderson,<sup>(6)</sup> moreover, had emphasized the ipsilateral pattern in the spreading of bronchogenic carcinomas which was also seen in our patient, eg primary adenocarcinoma of the left lung metastatic to the left adrenal gland and left kidney.

The present author did not regard the current adenocarcinoma to have been primary from the intrahepatic bile duct, or left adrenal gland, or left kidney with widespread metastases to the lungs, pleura, pericardium, and lymph nodes (porta hepatic, paratracheobronchial, and hilar). The tumors in the liver were not connected to any bile duct. Grossly, the primary adrenal and renal adenocarcinomas are brightly yellow which were not so in this patient. Furthermore, the cytoplasm of a primary adenocarcinoma cell of the kidney is distinctly clear.<sup>(3)</sup> Hence, the term renal clear cell adenocarcinoma is often used. However, the current adenocarcinoma cells had fine granular cytoplasm, so that their origin in the bile duct, adrenal gland, and kidney could be excluded.

Bryson and Spencer<sup>(7)</sup> have encountered in a clinical and pathologic survey of 866 bronchogenic carcinomas that 626 of them (72.3%) displayed secondary growths. The metastatic sites of these were : liver (49.0%),

adrenal gland (32.9%), lymph nodes (cervical, supraclavicular, axillary, and abdominal, 31.4%), brain (23.6%), bones (18.0%), kidney (17.1%), heart and pericardium (12.9%), pancreas (11.6%), spleen (5.6%), skin (5.0%), thyroid (3.0%), and other combined sites (12.5%). They stated briefly that primary bronchogenic carcinoma may spread by direct infiltration into the adjacent lung but did not give the frequency of such occurrence.<sup>(7)</sup> It is surprising that they did not mention the prevalence of metastases to the hilar and peritracheobronchial lymph nodes which should be common.

Leibow has cited the work of Ochsner and DeBakey<sup>(9)</sup> and Fried<sup>(10)</sup> in showing the prevalence of metastatic sites in bronchogenic carcinomas. In a series of 3,047 bronchogenic carcinomas, Ochsner and DeBakey<sup>(9)</sup> have noted the following percentages of metastatic sites : regional lymph nodes (72.2%), liver (33.3%), bones (21.3%), adrenal glands (20.3%), kidneys (17.5%), brain (16.5%), heart and pericardium (12.7), and pancreas (7.3%). Fried<sup>(10)</sup> studied 319 bronchogenic carcinomas and found similar order of metastatic sites but in different percentages as follows: regional lymph nodes (81.00%), liver (40.06%), bones (40.04%), adrenal glands (38.00%), kidneys (20.03%), brain (11.01%), heart and pericardium (9.03%), and pancreas (6.35%). Johnson and Lindskog<sup>(11)</sup> investigated 100 tumors metastatic to the lung and mediastinum. They noted 96 primary carcinomas from the following sites metastatic to the lung : kidney (14.6%), breast (14.6%), colon and rectum (13.5%), uterus including cervix (11.4%), ovary (6.2%), melanoma (5.2%), thyroid (4.2%), larynx (4.2%), stomach (3.1%), miscellaneous (13.5%), and unknow primary site (9.4%). These workers<sup>(8,11)</sup> did not mention intrapulmonary metastases from a primary bronchogenic carcinoma.

It may be assumed from the data of these investigators<sup>(7,8,11)</sup> that intrapulmonary metastasis from a primary bronchogenic carcinoma is either known<sup>(7)</sup> or not fully known.<sup>(8,11)</sup> In the latter situation, attention may not have been directed toward the probability of an intrapulmonary metastasis of a primary bronchogenic carcinoma when the cotton-ball appearance was encountered in the chest X-ray of a patient. Attempts would have been made fruitlessly to search for a primary tumor outside the lung. The primary tumor within the lung would have been overlooked. Thus, it would be fully justified here to emphasize the occurrence of intrapulmonary metastases in a primary bronchogenic carcinoma. The lung is big and rich in vascular and lymphatic supplies. Primary bronchogenic carcinoma cells would have a great chance to invade blood and lymphatic vessels and to spread along them to regional lymph nodes as well as to adjacent and distant organs. While on their way, these cells would have the opportunity to implant themselves into the vast pulmonary tissue in addition to a direct infiltration.<sup>(7)</sup> It is suggested that intrapulmonary metastasis of a primary carcinoma of the lung should equally be considered as those from extrapulmonary sites when cotton-ball appearance of the lung is seen roentgenographically. A negative bronchoscopic examination should not exclude a primary bronchogenic carcinoma, since it may arise in a bronchus that branches from the main stem and escape detection of a bronchoscope inserted into the main bronchus.

The clinical impression of a massive left pleural effusion in the present patient was not confirmed at autopsy. However, there were extensive neoplastic infiltrations and fibrous adhesions of the pleura which resulted in the obliteration of the left



pleural space. The total haziness of the left hemithorax seen is regarded here as related to the pleural thickening and adhesions as well as to neoplastic permeation into the left lung. It is less likely to be associated with a hydropericardium; a small amount of fluid (100 ml) in the pericardial sac should not have produced such a widespread opacity.

Tuberculosis of the lung was also not confirmed at postmortem. This suggests that the patient did not have pulmonary tuberculosis at all or that the tuberculous lesion had healed in the course of the medical treatment. However, a healed tuberculous lesion should have left some

evidence such as a scarred focus. Tuberculosis, a chronic caseous granulomatous disease, is well known to produce extensive tissue response. An absolutely healed tuberculous lesion without a trace of its previous existence should not be expected even in primary tuberculosis. It is probable that the clinically diagnosed pulmonary tuberculous lesion, 1½ years prior to death, was the focus of the pulmonary adenocarcinoma.

### Acknowledgment

Permission to use figure 1 was granted by Boontiang Sitisara, M.D., Head of Department of Radiology, Faculty of Medicine, Chulalongkorn University.

### References

1. Fraser RG, Pare' JAP. Diagnosis of Diseases of the Chest. Vol 1. 2 ed. Philadelphia : WB Saunders, 1978. 568-601
2. Fraser RG, Pare' JAP. Diagnosis of Diseases of the Chest. Vol 2. 2 ed. Philadelphia : WB Saunders, 1978. 1117-1134
3. Shuangshoti S. Primary carcinomas of esophagus and bronchus with presentation simulating primary carcinoma of thyroid gland. J Med Assoc Thai 1982 Jan ; 65 (1) : 38-44
4. Shuangshoti S. Metastasis of bronchogenic adenocarcinoma to renal adenocarcinoma. South Med J 1983 Jun; 76 (6) : 791-794
5. Anderson W. Boyd's Pathology for the Surgeon. 8 ed. Philadelphia : WB Saunders, 1967. 775
6. Anderson JR. Muir's Textbook of Pathology. 10 ed. Chicago: Year Book Medical Publishers, 1976. 445
7. Bryson CC, Spencer H. Carcinoma of the bronchus: a clinical and pathological survey of 866 cases. Quart J Med 1951 Apr; 20 (2) : 173-186
8. Leibow AA. Tumors of the lower respiratory tract. In: Atlas of Tumor Pathology. Section V--Fascicle 17. Washington, DC : Armed Forces Institute of Pathology, 1952. 92
9. Ochsner A, De Bakey M. Significance of metastases in primary carcinoma of the lung: report of 2 cases with unusual site of metastasis. J Thoracic Surg 1942 Apr; 11A : 357-387 (cited by Leibow<sup>8</sup>)
10. Fried BM. Bronchogenic Carcinoma and Adenoma. Baltimore : Williams & Wilkins, 1948 (cited by Leibow<sup>8</sup>).
11. Johnson RM, Lindskog GE. 100 cases of tumor metastatic to lung and mediastinum : treatment and results. JAMA 1967 Oct 9 : 202 (1) : 94-98