

The risk of tumor cell dissemination in mediastinoscopy: a cytological study

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Background/aim: Mediastinoscopy is an invasive procedure that is used in the diagnosis of mediastinal diseases and in staging lung cancer. Tumor cell seeding during mediastinoscopy along the mediastinum and the incision line is a very rare complication. This study aimed to test the safety of mediastinoscopy in terms of tumor seeding by cytological evaluation of mediastinal lavage samples taken before and after biopsy.

Materials and methods: The patients who underwent mediastinoscopy in our hospital between 2011 and 2014 were studied prospectively. Seventy-three patients with a diagnosis of lung or mediastinal malignancy were included in the study. All patients underwent classical cervical mediastinoscopy and mediastinal lavages were taken before and after the biopsy. Both lavage samples were sent to the pathology department in syringes for malignant cell cytology screening.

Results: The results of the histopathological examinations of lymph node biopsies were reactive in 25 patients and positive for malignancy in 48 patients. In 2 of 48 patients whose lymph nodes were reported to be positive for malignancy, the mediastinal lavage sample was reported to be positive for malignancy after biopsy, although it was negative preoperatively. In two patients, both the pre- and postbiopsy lavage samples were reported to be positive for malignancy.

Conclusion: While performing dissection and biopsy during mediastinoscopy, tumor seeding into the mediastinum may occur. Long follow-up periods and large patient series are needed to determine how cytopathological examination of both fluids would affect the prognosis.

Key words: Mediastinoscopy, lavage, cytology

1. Introduction

Mediastinoscopy is an invasive procedure used in the diagnosis of mediastinal diseases and in staging lung cancer. A mediastinoscopy performed safely and effectively not only increases the percentage of correct diagnosis but also minimizes the complication rate (1). Tumor cell seeding during mediastinoscopy along the mediastinum and the incision line is a very rare complication.

This study aimed to test the safety of mediastinoscopy in terms of tumor seeding by the cytological evaluation of mediastinal lavage samples taken before and after biopsy.

2. Materials and methods

The patients who underwent mediastinoscopy in our hospital between 2011 and 2014 were studied prospectively. Of these mediastinoscopies, some were performed for staging lung cancer and some were performed for the diagnosis of mediastinal lymphadenopathy. Seventy-three

patients with a diagnosis of lung or mediastinal malignancy were included in the study. Patients with tuberculosis and sarcoidosis were excluded. All patients were evaluated with thorax tomography and positron emission tomography (PET). In all patients, mediastinal lavage was taken before and after the biopsy.

All patients underwent classical cervical mediastinoscopy. After placing a mediastinoscope into the mediastinum, the subcarinal region was reached with a blunt and sharp dissection along the midline without exploring the lymph nodes. A 14-gauge feeding tube was placed into the mediastinum through the mediastinoscope. The mediastinum was washed with 20 mL of physiological saline solution given through this tube, and lavage was taken. The mediastinoscope was then pulled upward and the right, left, upper, and lower paratracheal, subcarinal, and antecarinal regions were evaluated. Biopsies were taken from all explored lymph glands. After the biopsy

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procedures, the mediastinoscope was advanced into the subcarinal region again. While it was being pulled upward, the lavage procedure was repeated by washing the mediastinum with 20 mL of physiological saline solution.

Both lavage samples were sent to the pathology department in syringes for malignant cell cytology screening. The aspirated washing fluid was immediately sent to the cytopathology laboratory without performing fixation. The quantity and properties of the received fluids were recorded by the laboratory. Cyto-centrifuge and direct use of the sediment were the preferred methods for these fluids with low cell and protein content. The fluid was cyto-centrifuged in a Liquid Shandon Cytospin III cyto-centrifuge device (Thermo Scientific, USA) at 1500 rpm for 10 min. The supernatant was removed with a Pasteur pipette, and the remaining sediment was used. Four slides were prepared with the drops taken from this sediment. Three of these slides were immediately fixed with 95% ethyl alcohol for 15 min and stained with Papanicolaou (PAP) stain. One was air dried for 15 min and stained with Diff-Quik, and then all were closed with lamella. In bloody fluids, an equal amount of physiological saline solution was added to the fluid, and initial centrifugation was performed. All samples were studied by a pathologist experienced in cytology and were classified as 'positive', 'doubtful', and 'negative'.

3. Results

Of the patients, 30 were female and 43 were male. The mean age was 63.4 years (range: 37-76 years). The primary diagnosis was small cell lung cancer in 6 patients, epidermoid carcinoma in 30 patients, adenocarcinoma in 22 patients, lymphoma in 10 patients, carcinoma in situ in 1 patient, vaginal malignant melanoma in 1 patient, renal cell carcinoma in 1 patient, skin squamous cell carcinoma in 1 patient, and papillary thyroid carcinoma in 1 patient (Figure 1).

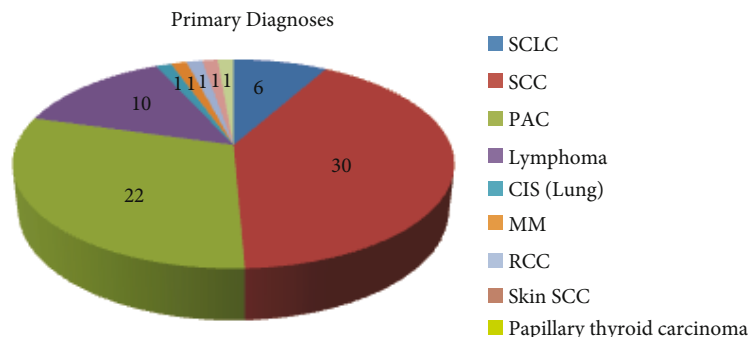


Figure 1. Primary diagnoses.

SCLC: Small cell lung cancer, SCC: squamous cell carcinoma, PAC: pulmonary adenocarcinoma, CIS: carcinoma in situ (lung), MM: malignant melanoma, RCC: renal cell carcinoma.

Since there are no established criteria for mediastinal fluid, all samples containing cellular elements were included in the study. Although small, there was an increase in the number of mesothelial and inflammatory cells in lavages after biopsy. In 2 patients, tumor cells were detected in both pre- and postbiopsy lavage fluids. In 2 patients, although there were only a few inflammatory cells in prebiopsy lavage fluid, malignant cells were detected in postbiopsy lavage fluid. In the rest of the patients, no malignant cells were observed in pre- or postbiopsy lavage fluids. (Figures 2 and 3) There were no washing fluid samples with mediastinitis.

While the most sampled lymph node in patients was the right lower paratracheal lymph node, the least sampled one was the left upper paratracheal lymph node. The numbers of the sampled lymph node stations are given in Figure 4. The results of the histopathological examinations of lymph node biopsies were reactive in 25 patients and positive for malignancy in 48 patients. In 2 of the 48 patients whose lymph nodes were reported to be positive for malignancy, the mediastinal lavage sample was reported to be positive for malignancy after biopsy, although it was negative preoperatively. In two patients, both the pre- and postbiopsy lavage samples were reported to be positive for malignancy (Figures 5 and 6). Biopsy samples were taken from right lymph nodes 2, 4, and 7 in two patients, and in the other two, they were taken from the lung-originated masses invasive to the mediastinum. Primary diagnosis was small cell lung carcinoma in 1 patient, lung adenocarcinoma in 2, and epidermoid lung cancer in 1. No procedure-related morbidity or mortality was observed.

4. Discussion

In patients with lung cancer, correct staging achieved by evaluating the size of the tumor, the regional lymph nodes, and the presence of metastases is crucial. In the absence of remote metastasis, the evaluation of the

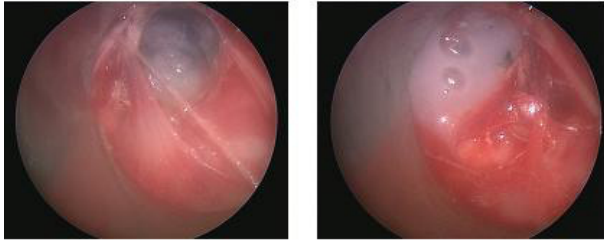


Figure 2. Images of a patient with positive postbiopsy lavage a) before biopsy and b) after biopsy.

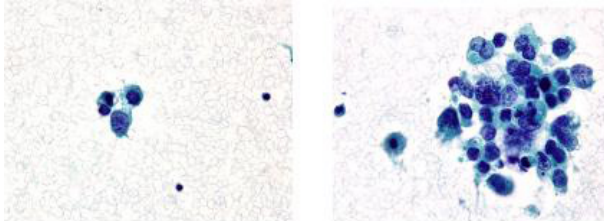


Figure 3. Malignant cells in the washing liquid a) before biopsy and b) after biopsy (PAP staining, magnification: 1000×).

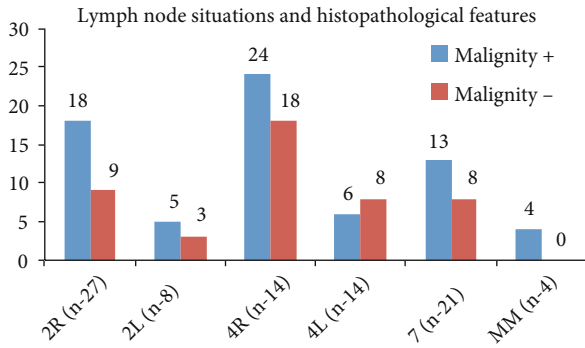


Figure 4. Lymph node stations and histopathological features. 2R: Upper right paratracheal lymph nodes, 2L: upper left paratracheal lymph nodes, 4R: lower right paratracheal lymph nodes, 4L: lower left paratracheal lymph nodes, 7: subcarinal lymph nodes, MM: lung-originated mediastinal mass.

status of regional lymph nodes is the main factor in determining the treatment method. Furthermore, in patients with malignant mediastinal lymph nodes detected in the preoperative examination, choosing multimodal treatments contributes greatly to an improved prognosis. Therefore, the evaluation of the status of the mediastinal lymph nodes preoperatively and after induction therapies is very important (2).

The main noninvasive radiological diagnostic method used to evaluate the mediastinum is computed tomography (CT). However, in many studies in the literature, it has been reported that CT is limited in staging the lymph nodes (3,4). Furthermore, while lymph nodes smaller



Figure 5. Right no. 4 lymph node (postbiopsy mediastinal lavage “malignancy +”).

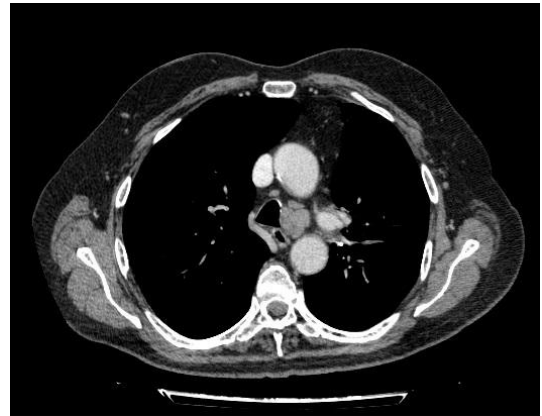


Figure 6. Left no. 4 lymph node (pre- and postbiopsy mediastinal lavage “malignancy +”).

than 1 cm in CT can be positive for malignancy, the larger lymph nodes can be negative. Thus, taking the lymph node size as a benchmark is not a proper approach in staging lung tumors (5). In a series of 100 patients with nonsmall cell lung cancer who underwent mediastinoscopy, Gdedo et al. reported that the sensitivity and specificity of mediastinoscopy were 89% and 100%, respectively, while they were 63% and 57% in CT (6). In our series, although the lymph nodes were smaller than 1 cm in 10 of the 48 patients with positive mediastinal lymph nodes, they were positive for malignancy in histopathological evaluation. On the other hand, in 5 patients with lymph nodes larger than 1 cm, the lymph nodes were negative for malignancy.

Today, the PET imaging method with F-18 fluoro-2-deoxy-D-glucose (FDG) is commonly used in staging mediastinal lymph nodes. The biological activity of the tumor can be determined by this method. In many metaanalyses in the literature, it has been demonstrated that

PET is significantly superior to CT in staging mediastinal lymph nodes. However, in PET, the accurate evaluation of FDG uptake is possible only when the size of the lymph node is greater than 1 cm (7-9). Additionally, the evaluation of histopathological and immunological features is more important than the evaluation of radiological features in determining the appropriate treatment method. Because of all these mentioned reasons and despite the new methods developed in recent years (PET-CT, endobronchial ultrasound-guided transbronchial needle aspiration, or endoscopic ultrasound-guided fine-needle aspiration), mediastinoscopy is still considered the “gold standard” in mediastinal staging of lung cancer (10,11).

The factors limiting the safety of mediastinoscopy and increasing the rate of complications are: 1) it is an invasive method, 2) it requires general anesthesia, 3) not all lymph node stations can be reached, 4) cervical goiters, 5) presence of permanent tracheostomy after laryngectomy and/or radiotherapy, and 6) a previously performed mediastinoscopy (12). In our series, large thyroid glands were detected in 12 patients. Therefore, the thyroid gland was dissected at the midline and pulled up to perform the procedure. Except for this problem, no other problems that would cause technical difficulties were encountered.

Morbidity and mortality after mediastinoscopy is rare. In the literature, morbidity and mortality rates are reported as 0.08% and 0%, respectively. Abundant bleeding, tracheobronchial laceration, esophageal perforation, recurrent nerve paralysis, phrenic nerve paralysis, thoracic duct injury, mediastinitis, venous air embolism, and tumor cell seeding along the mediastinum and incision line implantation have been reported as major complications (12). In our patients, none of the major complications were observed. However, in 2 patients, malignant cells were observed in both the predissection and postbiopsy mediastinal lavage fluids, and in 2 patients only in the postbiopsy lavage fluid. In 2 of these patients, biopsy samples were taken from lung-originated mediastinal masses, whereas they were taken from lower paratracheal and subcarinal lymph nodes in the other two.

Dissection is essential in all phases of mediastinoscopy for exploration and biopsy. Cellular seeding into the mediastinum may occur during dissection or biopsy procedures (13). In the literature, the incidence of tumor seeding after mediastinoscopy is reported to be 0.12% along the entire incision line down to the mediastinum. In the metaanalysis of a study including 6490 patients who underwent cervical mediastinoscopy, tumor cells along the incision line were detected only in 8 patients (14).

The mechanism of tumor seeding during mediastinoscopy is not known in full. The most likely explanation is considered to be the direct seeding of the tumor cells into the mediastinum during biopsy.

However, this theory could not explain the mechanism of the metastasis in patients whose mediastinoscopies are negative but who have tumors in the incision line. In the early recovery period, excessive blood build up is observed along the incision and dissection lines. It is considered that in these patients, the increased hematogenous or lymphogenic flow transports the tumor cells into the mediastinum and incision line (15).

The number of stage 3 lung cancer patients with incisional tumor metastasis is very limited in the literature. Two of these were reported to have adenocarcinoma, 2 epidermoid carcinoma, 1 small cell adenocarcinoma, and 1 large cell adenocarcinoma. It is understood that the development of metastasis along the incision and dissection lines are independent of the pathological type of the tumor and the degree of the cellular differentiation. Additionally, it is not clear if it is related to the stage of the tumor or not. In 4 of these patients, tumors were reported to be stage 3a, whereas in one it was stage 2a and in one the stage was indefinable. In our series, all patients were defined as having stage 3b lung cancer. As the number of positive lymph node stations and biopsies increase, and as the dissections go deeper, there may be an increase in the incidence of tumor seeding (15-18). In our series, in 2 of the patients with positive mediastinal lavage, biopsy samples were taken from lymph node stations 2, 4, and 7; in the other 2, the samples were taken from the lung-originated masses invasive into the mediastinum.

In the literature, there are numerous studies investigating the relation between pleural lavage fluid cytology and survival in lung tumors (19). However, no data about the cytological examination of the mediastinal lavage fluid could be found in the literature. Thus, we believe that “presence of any kind of cellular elements in prebiopsy washings” and “presence of several mesothelial cells in the postbiopsy samples” can be the criteria for defining the suitability of the lavage fluid. Although no operation was performed in 2 patients, their first lavage fluids contained malignant cells. This could be a remarkable finding indicating a poor prognosis. Of these patients, one died in the first postoperative month; the other patient was still alive at month 16. Scattering of the free tumor cells is an expected situation. In our series, mediastinal lavage fluid was found to be positive after the operation in 2 patients. Both of the patients died within 2 postoperative years. Whether or not these positive results could be accepted as clues for tumor seeding can only be clarified by this phenomenon itself. The pleural washing studies in the literature reported that survival decreases in patients with preoperative negative but postoperative positive pleural fluid. However, we still do not have enough data to determine the effects of cytologically positive mediastinal lavage fluid on the prognosis and risk of recurrence.

In conclusion, mediastinoscopy is an invasive diagnostic method with high effectiveness and low morbidity and mortality. During cervical mediastinoscopic biopsy, cellular tumor seeding into the mediastinum is a rare complication. However, it should be kept in mind that while performing dissection and biopsy, particularly in the presence of multistation lymph nodes or lung

tumors invasive into the mediastinum, tumor seeding into the mediastinum may occur. Long follow-up periods and large patient series are needed to determine how mediastinal washing before and after the mediastinoscopy and cytopathological examination of both fluids would affect the prognosis.

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