

Combination of tissue biopsy and fine needle aspiration cytology reduces false negativity of mediastinoscopy for non-small cell lung cancer

Küçük hücre dışı akciğer kanserinde doku biyopsisi ile ince iğne aspirasyon sitolojisinin kombinasyonu mediastinoskopinin yanlış negatiflik oranını azaltır

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Background: This study aims to compare tissue biopsy with fine needle aspiration (FNA) and investigate whether the combination reduces false negativity of mediastinoscopy.

Methods: Between January 2004 and October 2005, 92 patients with non-small cell lung cancer (NSCLC) who underwent cervical video mediastinoscopy were included in this prospective study. Tissue biopsy samples and FNAs were obtained from the same lymph node and were sent for a pathologic examination. Tissue samples and FNAs were stained with Hematoxiline-Eosine. All specimens were evaluated by two histopathologists.

Results: Using tissue biopsy samples, no metastasis was found in 54 patients, while 38 patients were metastatic. Forty-eight patients had no metastasis, while 44 patients were metastatic using FNA samples. The difference was statistically non-significant ($p>0.05$). The false negativity of the FNA and tissue biopsy were 5.4% and 12%, respectively. Subsequently, 43 patients with negative FNA and tissue biopsy underwent lung resection with thoracotomy and systematic lymph node dissection. Following lymph node dissection, lymph node metastases were found in two cases (4.6%). As a result, false negativity of mediastinoscopy was reduced to 4.6% when two techniques were combined. There was no complication related to the technique.

Conclusion: The FNA of mediastinal lymph nodes is a safe and effective method, compared to tissue biopsy and reduces the false negativity of mediastinoscopy when combined with tissue biopsy.

Key words: Biopsy; fine needle aspiration; lung cancer; lymph node; mediastinoscopy.

Amaç: Bu çalışmada, doku biyopsileri ile ince iğne aspirasyonu (İİA) karşılaştırıldı ve bu kombinasyonun mediastinoskopideki yanlış negatiflik oranını azaltıp azaltmama-ya-çağı araştırıldı.

Çalışma planı: Ocak 2004 ve Ekim 2005 tarihleri arasında servikal video mediastinoskopi uygulanan küçük hücreli dışı akciğer kanserli (KHDAK) 92 hasta bu prospektif çalışmaya dahil edildi. Aynı lenf nodundan hem doku biyopsisi hem de İİA yapıldı ve patolojik incelemeye gönderildi. Doku örnekleri ve İİA'lar Hematoksilin-Eosin ile boyandı. Tüm örnekler iki histopatolog tarafından incelendi.

Bulgular: Doku biyopsisi örnekleri ile 54 hastada metastaza rastlanmaz iken, 38 hastada metastaz saptandı. İİA'da ise 48 hastada metastaza rastlanmaz iken, 44 hastada metastaz saptandı. Farklılık istatistiksel olarak anlamlı değil idi ($p>0.05$). Yanlış negatiflik oranları, İİA ve doku biyopsisi sonrası sırasıyla %5.4 ve %12 idi. Negatif İİA ve doku biyopsisi 43 hastaya takiben torakotomi ile akciğer rezeksiyonu ve total sistemik lenf nodu diseksiyonu yapıldı. Mediastinal lenf nodu diseksiyonu sonrası iki olguda (%4.6) lenf nodu metastazı saptandı. Buna bağlı olarak iki yöntem kombine edildiğinde mediastinoskopinin yanlış negatifliği %4.6'ya indi. Tekniğe bağlı herhangi bir komplikasyon ile karşılaşılmadı.

Sonuç: Mediastinal lenf nodlarının İİA'sı doku biyopsisi ile karşılaştırıldığında güvenli ve etkili bir yöntem olup, doku biyopsisi ile kombine edildiğinde mediastinoskopinin yanlış negatiflik oranını azaltabilir.

Anahtar sözcükler: Biyopsi; ince iğne aspirasyonu; akciğer kanseri; lenf nodu; mediastinoskopi.

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The correct staging of patients with non-small cell lung cancer (NSCLC) is the most important evaluation in order to improve selection criteria for curable patients. Noninvasive staging modalities, such as computed tomography (CT) and positron emission tomography (PET), are not sensitive or specific enough to assess mediastinal lymph node metastases. Mediastinoscopy is considered to be the “gold standard” of invasive intervention for lung cancer staging and, in recent guidelines, it has been recommended to be performed prior to all lung cancer resections as a curative intent.^[1] Standard cervical mediastinoscopy permits access to the right and left paratracheal, tracheobronchial, and anterior subcarinal lymph node stations, but access to the posterior subcarinal region is limited.^[2] Although it is the most widely used invasive procedure, N2-N3 disease following negative mediastinoscopy is diagnosed in only 5.5-8.8% of patients after surgery.^[3] Because of the access limitation to all lymph node regions and the difficulties in removing whole lymph nodes for pathological examination, endoscopic ultrasound (US)-guided fine needle aspiration (FNA) has been developed as an alternative method to mediastinoscopy in order to improve staging.^[1,2] Cytopathological methods are quicker, simpler, and more efficient; therefore, they should be preferred when multiple samples are submitted for analysis within a short period of time.^[4]

We have designed a prospective study in order to compare the results of FNA and tissue biopsy of lymph nodes during mediastinoscopy performed for lung cancer staging and combined them with the results for decreasing the number of false negative results of mediastinoscopy.

PATIENTS AND METHODS

Following the approval of the university’s ethics committee (2003-22/16), 92 patients (7 males, 85 females; mean age 56.4 years; range 37 to 78 years) with lung cancer who underwent staging mediastinoscopy between January 2004 and October 2005 were prospectively enrolled into the study in order to compare the diagnostic value of tissue and fine needle aspiration biopsies (FNAs) of mediastinal lymph nodes. Only patients who had undergone both biopsy methods were included in the study. Classic cervical mediastinoscopy using a Karl-Storz (STORZ GmbH, Tuttlingen, Germany) videomediastinoscope was performed in all cases by the same surgical team. Although the combinations changed from patient to patient, biopsies were taken from lymph node stations 2R, 4R, 4L, and 7. Aspiration using a 22F syringe needle through the mediastinoscope was applied only to the lymph node that was suitable for a tissue biopsy, and

at least two aspirations followed by tissue biopsy from the same lymph node were performed. Two section samples were prepared from each aspiration. The whole tissue samples underwent routine tissue fixation. For the FNAs, a smear was prepared by placing the needle aspirate on the slide and fixing it immediately in alcohol. At least two adequate samples were obtained using the smear method for cytology and were stained with Hematoxylin-Eosin (HE). Two histopathologists examined all samples in a blind fashion. The patients with positive tissue or aspiration biopsies were excluded from the curative intent surgery and evaluated for neoadjuvant chemoradiotherapy.

The statistical analysis was done by using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, Illinois, USA) version 11.5 software. Differences between groups were calculated using McNemar’s test. The concordance of biopsy and cytology methods for the whole study group and cell type was assessed with “kappa” statistics. A *p* value ($p < 0.05$) was considered significant in all statistical analysis.

RESULTS

Only one sentinel lymph node station according to tumor location was sampled in 68 patients. Two stations were sampled in 19 patients, and three stations in five patients. A total of 121 lymph nodes were examined (Table 1). Histopathological examination of lymph nodes revealed no metastasis in 54 (59%) patients and metastases in 38 (41%) versus no metastasis in 48 (52%) and metastasis in 44 patients (48%) in the FNA group. The difference was not statistically significant ($p = 0.332$). The tissue biopsy failed to diagnose metastases in 11 patients whereas the FNA was falsely negative in only five patients. Therefore, the false negative rate was 12% (11/92) in the tissue biopsy group but only 5.4% (5/92) in the FNA group. Histopathological results of lymph nodes are shown in Table 2. In total, 49 patients (53%) were excluded from curative intent surgery. The sensitivity and diagnostic values of tissue biopsy were 78% and 88% while they were 90% and 95% for biopsy + FNA. Forty-three patients with negative FNA and tissue biopsy underwent thoracotomies and subsequent lung resections. Total mediastinal lymph node dissections were performed in all cases that revealed lymph node metastases in station four and only in two cases (4.6%) that had negative FNA and tissue biopsy. Therefore, the false negative rate of mediastinoscopy was reduced to 4.6% when the two techniques were combined.

The difference was not statistically significant (McNemar’s test $p = 0.332$). The combined results of FNA and tissue biopsy are shown in Table 2. It was also

Table 1. The numbers of lymph node cytology and biopsy

Station of lymph node	Biopsy (+)/ Cytology (+)	Biopsy (+)/ Cytology (-)	Biopsy (-)/ Cytology (+)	Biopsy (-)/ Cytology (-)	Total
2R	1	-	-	3	4
4R	31	5	8	43	87
4L	1	-	1	5	7
7	1	-	2	20	23
Total	34	5	11	71	121

found that the results were highly comparable ($\kappa=0.705$ and $p<0.05$). There was no morbidity or mortality related to either procedure.

DISCUSSION

In the management of lung cancer, the individual therapeutic approach depends on the histological type of malignancy and tumor staging. Nearly half of the patients presenting with carcinoma of the lung harbor metastases in the mediastinal lymph nodes.^[5-7] The presence of mediastinal lymph node metastases or mediastinal tumor invasion is considered to be advanced stage disease (IIIA or IIIB) according to the American Joint Commission on Cancer. Patients with stage IIIB disease have a poor prognosis and are generally treated with chemoradiotherapy without surgery. However, the treatment of stage IIIA disease is more controversial, and many centers treat it with chemoradiotherapy unless surgery is added under an investigational protocol. These patients have a poorer prognosis compared with patients with stage I-II disease.^[6,7] If pathological specimens examined with immunohistochemical (IHC) staining are added to HE, IHC detects more than twice as many positive regional lymph nodes as does HE staining, and the foci of the tumors it detects are significantly smaller than those detected by HE staining.^[8]

Non-invasive methods, such as CT and PET, do not provide sufficient information on N2-N3 disease.^[11] Suzuki et al.^[9] showed that in patients with NSCLC and N0-N1 disease on the CT scan, mediastinoscopy revealed 17.9% N2 disease despite a negative CT scan. The mediastinal lymph nodes can be surgically staged

by using mediastinoscopy, mediastinotomy, or thoracoscopy, or even by performing a thoracotomy. Mediastinoscopy, which allows direct visualization and localization of most superior, anterior subcarinal, and hilar nodes, has been regarded as the “gold standard” for staging of the mediastinum and has excellent access to stations 2R, 4R, 4L, 2L, and 7 along with the anterior subcarinal stations. The diagnostic value of the technique has been reported as between 83-89% in lung cancer patients whereas access to the main or lower aspect of the subcarinal lymph nodes is limited.^[2,10-12] As an alternative to mediastinoscopy, endoscopic US-guided FNAs^[7,10,13] or CT-fluoroscopy-guided^[14] FNAs have been developed which have had an impact on lung cancer staging by facilitating access to virtually all mediastinal lymph node stations. Diagnostic yields of up to 90% have been seen. Wieserma et al.^[15] demonstrated that endoscopic US-guided FNAs are safe and accurate for evaluating mediastinal lymph nodes arising in the lower paratracheal, subcarinal, aortopulmonary, and posterior regions. Endoscopic US-guided FNAs had a sensitivity of 96% and a specificity of 100%. However, these procedures require expensive and specific tools and devices.

In 1927, Dudgeon and Patric^[16] described the use of cytology procedures for the rapid diagnosis of tumors in the operating room. It has also been shown in several studies that FNAs performed through the tracheobronchial wall, esophagus, or chest wall are safe and reliable and also provide high accuracy and similar false negative rates compared to mediastinoscopies.^[10-12,15,17] Cytological or histological confirmation of malignancy and accurate tumor, node, and metastasis staging is critical for

Table 2. Histopathological results of lymph nodes ($\kappa=0.705$; $p<0.05$)

Cytology/biopsy	Benign reactive hyperplasia	Squamous cell carcinoma	Adenocarcinoma	Total
Benign reactive hyperplasia	43	2	3	48
Squamous cell carcinoma	7	11		18
Adenocarcinoma	4		22	26
Total	54	13	25	92

κ : Kappa.

the delivery of effective lung cancer management.^[18] Cytodiagnosis is useful for small specimens but not suitable for tissue block and has the advantage of easy preparation. Cytopathological methods are quicker, simpler, and more efficient and should be the option of choice when multiple samples are submitted for analysis within a short period of time. Thus, intraoperative cytology using FNAs has been preferred for many years in the histopathologic diagnosis of lesions from different organs.^[4] In cytological examinations, the quality of results depends on the skill of the surgeon and the level of cytopathologic expertise.^[17] Therefore, we have added FNAs of mediastinal lymph nodes during mediastinoscopy in order to obtain aspiration material from the whole lymph node and to reach the posterior subcarinal lymph nodes. Although tissue biopsies yielded metastases in 38 (41%) patients, FNAs diagnosed metastases in 44 (48%) patients. The false negative rate was 12% for the tissue biopsy group and 6% for the FNA group. The reduced false negative rate may be explained by having at least two samples aspirated from each lymph node and by the evaluation of posterior subcarinal lymph nodes. In FNAs, the needle also travels from the top to the bottom of the lymph node (a needle can be pushed up to the distal end of the lymph nodes). In open biopsies, it is very difficult and sometimes impossible to sample the distal side of the lymph node. When the process was repeated in different directions, we could take biopsies from different parts of the lymph node. Therefore, needle aspiration scans the lymph nodes in a broad spectrum. Fine needle aspiration failed to diagnose only two 4R lymph nodes that were found to be positive during thoracotomy. The combination of two techniques resulted in reduced N2 disease found during the surgery and increased surgical rates following induction chemotherapy at our center.

In conclusion, FNAs of mediastinal lymph nodes during mediastinoscopy is simple, reliable, and accurate while also being less time-consuming and less labor-intensive. It has also proven to be useful for the intraoperative evaluation of mediastinal lymph nodes in lung cancer and should be added to the standard tissue biopsy during mediastinoscopy in order to select patients who will benefit from curative intent surgery.

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