

The role of standard and extended cervical mediastinoscopy in the staging of non-small cell lung cancer patients

Küçük hücreli dışı akciğer kanseri hastalarının evrelemesinde standart ve genişletilmiş servikal mediastinoskopinin rolü

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Background: In this study, our experience with standard cervical mediastinoscopy (SCM) and extended cervical mediastinoscopy (ECM)-performed for preoperative staging of non-small cell lung cancer (NSCLC) is presented.

Methods: Two hundred and eight consecutive patients with the diagnosis or prediagnosis of NSCLC admitted to our clinic between September 2005 and December 2007 were evaluated. Twelve patients were excluded from the study due to neoadjuvant treatment (n=7) and abnormal morphology preventing proper mediastinoscopy (n=5). Standard cervical mediastinoscopy was performed in all patients and concurrent ECM and SCM in 47 patients who had a tumor in the left lung. We performed thoracotomies in patients with a negative mediastinoscopy result.

Results: The pathological results were compared with 676 lymph nodes which were evaluated with SCM and 86 lymph nodes which were evaluated with ECM. Forty-nine true-positive, 136 true-negative, and 11 false-negative results were found in SCM and ECM. With these results, the sensitivity, specificity, negative predictive value, and accuracy for combined technique were calculated as 81.7%, 100%, 92.5% and 94.4%, respectively.

Conclusion: We recommend that SCM and ECM should be classified together under "mediastinoscopy" in the staging of NSCLC when other non-invasive procedures are unavailable.

Key words: Mediastinoscopy; non-small cell lung cancer; staging.

Mediastinal lymph node evaluation was first introduced by Daniels in 1949.^[1] Carlens^[2] described standard cervical mediastinoscopy (SCM) in 1959.

Amaç: Bu çalışmada küçük hücreli dışı akciğer kanserinin (KHDAK) ameliyat öncesi evrelemesinde uyguladığımız standart servikal mediastinoskopi (SSM) ve genişletilmiş servikal mediastinoskopi (GSM) deneyimimiz aktarıldı.

Çalışma planı: Eylül 2005 ila Aralık 2007 tarihleri arasında KHDAK tanısı veya öntanısı ile kliniğimize başvuran ardışık 208 hasta değerlendirildi. Neoadjuvan tedavi uygulanan (n=7) ve anormal morfoloji nedeni ile mediastinoskopi yapılamayan (n=5) toplam 12 hasta çalışmadan çıkarıldı. Tüm hastalara standart servikal mediastinoskopi ve sol akciğer tümörü bulunan 47 hastaya eşzamanlı GSM ve SSM uygulandı. Mediastinoskopi sonucu negatif olan hastalara torakotomi uygulandı.

Bulgular: Patoloji sonuçları, SSM ile değerlendirilen 676 lenf nodu ve GSM ile değerlendirilen 86 lenf nodu ile karşılaştırıldı. Standart servikal mediastinoskopi ve GSM'de 49 gerçek pozitif, 136 gerçek negatif ve 11 yanlış negatif sonuç saptandı. Bu sonuçlarla kombine mediastinoskopinin duyarlılığı, özgüllüğü, negatif öngörü değeri ve etkinliği sırasıyla %81.7, %100, %92.5 ve %94.4 olarak hesaplandı.

Sonuç: Biz KHDAK'nin evrelemesinde, diğer noninvazif işlemlere ulaşılamayan durumlarda, SSM ve GSM'nin "mediastinoskopi" başlığı altında birlikte sınıflandırılmasını öneriyoruz.

Anahtar sözcükler: Mediastinoskopi; küçük hücreli dışı akciğer kanseri; evreleme.

Extended cervical mediastinoscopy (ECM), which allows an assessment of subaortic and paraaortic lymph nodes for left lung tumors through the same

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SCM incision, was described by Ginsberg in 1987.^[3] The most common indication for SCM is the initial staging and diagnosis of lung cancer. Other indications of SCM are restaging after neoadjuvant treatment of non-small cell lung cancer (NSCLC), evaluation of mediastinal masses, treatment of cystic mediastinal masses, and diagnosis of granulomatous diseases, such as tuberculosis and sarcoidosis. Together with SCM, ECM is a valuable tool, especially in left lung tumors that invade the aortic-pulmonary window. Mediastinoscopy provides a good exploration area, allows for the collection of sufficient lymph nodes in number and size, and is associated with very low mortality and morbidity. In this study we aimed to investigate the morbidity, mortality, and false negative results of mediastinoscopy performed in our clinic as well as the superiority of mediastinal lymph node staging via the combined method of SCM and ECM, for NSCLC.

PATIENTS AND METHODS

Between September 2005 and December 2007, 208 consecutive patients diagnosed with NSCLC were enrolled in this study. Twelve patients were excluded because of neoadjuvant treatment (n=7) or abnormal morphology which precluded mediastinoscopy (kyphosis, previous laryngectomy, etc. n=5). The final study sample consisted of 196 patients (186 males, 10 females; mean age 58.4 years; range 34 to 81 years). Patients hospitalized for lung resection had been examined with a routine physical examination; laboratory tests including respiratory function tests, arterial blood gas tests, and electrocardiograms. Patients underwent further respiratory and cardiac examinations as required by their situation. Radiological evaluations, including thoracic computed tomography (CT), integrated positron emission tomography and computed tomography (PET/CT), and cranial magnetic resonance imaging (MRI), were performed in all patients. We performed a routine mediastinoscopy in every patient in the study regardless of the presence or absence of mediastinal lymph node involvement through the radiological evaluation. Regardless of the results of PET/CT, all patients with an operable tumor had SCM, and patients with a tumor located in the left upper lobe or left hilar tumor underwent simultaneous ECM. A thoracotomy was performed in patients without evidence of metastatic lymph node involvement after mediastinoscopy. A systematic mediastinal lymph node dissection was performed in all patients who underwent thoracotomies.

Data was analyzed according to the results of a pathological examination of the lymph node

specimens obtained from SCM, ECM and the thoracotomy. The mortality, morbidity, sensitivity, specificity, negative predictive value, and accuracy of mediastinoscopy for the staging of NSCLC were analyzed.

RESULTS

Histopathological examinations revealed squamous cell carcinoma in 107 patients, adenocarcinoma in 65, unclassified NSCLC in 16, and other cell types in eight patients. The modality of surgery was a lobectomy in 95 patients, a pneumonectomy in 47, and an exploratory thoracotomy in five patients. In 49 patients with mediastinal lymph node involvement, no further surgical intervention was carried out. Patient characteristics are given in table 1.

As previously stated, SCM was performed in all patients, and ECM was performed in 47 patients (24%). Seven hundred and sixty-two (mean 3.89/patient) lymph nodes were examined by mediastinoscopy (SCM: 676, mean 3.45 per patient; ECM: 86, mean 1.83 per patient). Standard cervical mediastinoscopy and ECM yielded true positive (TP) results in 49, true negative (TN) in 136, and false negative (FN) in 11 patients. The sensitivity, specificity, negative predictive value, and accuracy for mediastinoscopy were 81.7%, 100%, 92.5%, and 94.4%, respectively. In those patients who underwent only ECM (n=47), it yielded a TP result in nine, a TN result in 36, and a FN result in two patients. The sensitivity, specificity, negative predictive value, and accuracy for ECM were 81.8%, 100%, 94.7%, and 95.8%, respectively. The frequencies of station 2R, 2L, 4R, 4L, 7, 5, and 6 lymph nodes sampling were 66.8%, 18.9%, 92.9%, 69.9%, 94.7%, 95.7% and 87.2%, respectively.

There were 13 lymph node station involvements in 12 out of 147 patients who had a thoracotomy despite having a negative mediastinoscopy. The PET/CT and operative findings of these patients are presented in table 2. In fact, 11 of 13 lymph node stations were reached by mediastinoscopy, but the tumor invasion could not be detected. One patient having a left main bronchial tumor and paraesophageal lymph node involvement was excluded from the analysis since the location of the lymph node was out of the range of both SCM and ECM.

One patient (0.5%) died after mediastinoscopy because of myocardial infarction, and other complications related with mediastinoscopy occurred in seven patients (3.6%). In two patients, hoarseness developed following mediastinoscopy, and one of them

Table 1. Patient characteristics

	n	%
Sex		
Male	186	95
Female	10	5
Cell types		
Squamous cell carcinoma	107	54.6
Adenocarcinoma	65	33.1
Non-small cell lung cancer	16	8.2
Large cell carcinoma	4	2.1
Adenosquamous carcinoma	3	1.5
Spindle cell carcinoma	1	0.5
Types of operations		
Lobectomy	85	43.3
Sleeve lobectomy	10	5.1
Pneumonectomy	42	21.4
Right sleeve pneumonectomy	5	2.6
Exploratory thoracotomy	5	2.6
Mediastinoscopy (N2+)	49	25.0
Pathological staging*		
IA	19	9.6
IB	51	26.1
IIA	3	1.5
IIB	43	21.9
IIIA	55	28.1
IIIB	25	12.8

*: 6th tumor-node-metastases staging system.

resolved spontaneously. The procedural bleeding rate was 2.6% (5 patients). In four patients, the bleeding was controlled by a conservative approach; however, in one patient with a left upper lobe tumor, the bleeding could not be controlled, and an urgent sternotomy had to be performed. Seven patients who had complications underwent SCM alone, and no complication occurred related to ECM.

Table 2. Patients with positive lymph nodes discovered during thoracotomy (n=12)

No	Localization	PET/CT (+) LN		Sampled lymph nodes on mediastinoscopy	Thoracotomy (+) LN	
		N2	N1		N2	N1
1	Right upper lobe	2R		2R, 4R, 4L, 7	2R	10R
2	Right upper lobe		10R	2R, 2L, 4R, 4L, 7	4R	
3	Right upper lobe	4R, 7	10R	2R, 4R, 7	4R	10R
4	Right main bronchus	4R		4R, 7	2R, 4R	10R
5	Left main bronchus	7		2L, 7, 5, 6	7	10L
6	Left lower lobe	7	10L	4R, 4L, 7	7	10L
7	Right upper lobe	4R	10R	2R, 4R, 7	4R	10R
8	Right upper lobe	4R, 7	10R	2R, 4R, 4L, 7	4R	10R
9	Right main bronchus	4R	10R	2R, 2L, 4R, 7	4R	10R
10	Left upper lobe	5		4R, 7, 5, 6	5	10L
11	Left upper lobe	5		4R, 7, 5, 6	5	
12*	Left main bronchus	7, 8	10L	2R, 4R, 4L, 7, 5	8	

PET: Positron emission tomography; CT: Computed tomography; LN: Lymph node; *: Patient having station 8 positivity was excluded from the statistical analysis.

DISCUSSION

Surgery is the most effective therapeutic strategy in selected patients with NSCLC. Following distant organ metastases, mediastinal lymph node involvement is one of the most important factors in the selection of the treatment modality. Thoracic CT has been used for a long time for noninvasive tumor staging, but this have been replaced recently by the PET/CT imaging which has been shown to be superior over CT in many studies.^[4,5] However, invasive mediastinal staging is still necessary because of the high rate of false positive results with PET/CT.^[6,7] Currently, the most accepted approach in preoperative mediastinal staging is to favor the relatively noninvasive endoscopic technique and to reserve mediastinoscopy for patients with no adequate results from the endoscopic technique.

Lymph node involvement is considered an absolute contraindication for surgery. However, in single station N2 patients, down-stage following neoadjuvant therapy justifies the surgical resection whenever possible.^[8]

The first method of lymph node assessment is thoracic CT which provides information about location and morphological characteristics. The diameter of the short axis of a lymph node is considered a predictor of malignancy if it is larger than 10 mm. Recently, the most valuable method for NSCLC staging has become PET/CT.^[4,5] However, in patients with positive PET/CT results, mediastinal lymph node involvement needs to be confirmed by histological examination.^[6,7]

Improvement in endobronchial technologies, such as transbronchial needle aspirations and fine needle aspiration biopsies with the guidance of endobronchial and endoesophageal ultrasonography, yielded better

results compared with other less invasive methods. Although these techniques have high specificity, negative predictive values are low, and mediastinoscopy is again needed to confirm the negative results. Positive results with fine needle aspiration biopsies are sufficient to diagnose mediastinal lymph node invasion.^[9] Detection of the N2 disease with first staging by endoscopic techniques would facilitate the second staging following neoadjuvant therapy. Difficulties in re-mediastinoscopy can be overcome, and the procedure have more success. By using SCM, biopsies in the right and left upper paratracheal (2R-2L), lower paratracheal (4R-4L), and subcarinal (7) lymph nodes can be obtained. According to the latest International Association for the Study of Lung Cancer (IASLC) mediastinal lymph node map, even right hilar (10R) lymph nodes can be biopsied.^[10] Mediastinoscopy may also facilitate the differential diagnosis of pulmonary disease associated with lymph node involvement. Although the SCM technique has been clearly described in the literature, the results mainly depend on the surgeon's experience. The European Society of Thoracic Surgeons (ESTS) working group also recommends to systematically always explore and perform a biopsy on the right and left lower paratracheal and subcarinal nodes, and, if present, upper paratracheal lymph nodes should be sampled in staging mediastinoscopy.^[9] In a study assessing the results of six different surgeons working in the same institution, mean lymph node sampling detected 4.1 nodes per patient, but the sampling rate showed a wide range between the surgeons. For example, the sampling rate was 15 to 90% for subcarinal lymph nodes and 39 to 84% for left upper paratracheal nodes. However the right lower paratracheal lymph node sampling rate didn't differ dramatically.^[11] In our study, 3.5 lymph node stations per patient were sampled, similar to previous studies. The frequencies of station 2R, 2L, 4R, 4L, and 7 lymph node samplings were 66.8%, 18.9%, 92.9%, 69.9%, and 94.7%, respectively. The most frequently sampled stations were 7 and 4R.

Extended cervical mediastinoscopy, anterior mediastinotomy, or video-assisted thoracoscopic surgery can be used in order to assess aortic lymph node stations (5 and 6) as these are frequently involved in left upper lobe tumors. In this study, ECM has been performed in all patients with left upper lobe and left centrally located tumors. Several advantages led to a preference of this technique, including short operation time, safety, and usage of the same incision site with SCM. The ECM technique used in this study was defined by Lopez et al. in 1994.^[12] A total of 86 lymph nodes were examined (mean 1.83 per patient), and the sampling ratios were 95.7% and 87.2% for stations 5 and 6, respectively. Call

et al.^[13] compared routine ECM and selective ECM in the staging of left lung carcinoma, and they suggested that ECM should be performed selectively based on CT and PET findings. In our study, there were 26 patients with CT and/or PET/CT positivity in the left lung tumor. In this selective group of patients, ECM yielded a TP result in nine, a TN result in 15, and a FN result in two patients. The sensitivity, specificity, negative predictive value, and accuracy for the selective group of ECM were 81.8%, 100%, 88.2%, and 92.3%, respectively.

We examined 762 (mean 3.89 per patient) lymph nodes by SCM and ECM. The numbers of TP, TN and FN cases were 49, 136, and 11, respectively. The sensitivity, specificity, negative predictive value, and accuracy for mediastinoscopy were 81.7%, 100%, 92.5%, and 94.4%, respectively. Whereas the sensitivity and specificity values of SCM and ECM have frequently been reported separately in the English literature,^[12-14] we combined the results of both techniques since both procedures were performed through the same incision, and the main purpose of each technique was to assess lymph node status.

In 12 out of 147 mediastinoscopy negative patients, thoracotomy revealed lymph node involvement in 13 stations. Although 11 of these lymph node stations had been sampled by mediastinoscopy, tumor invasion could not be detected. The most significant causes of false negative results of mediastinoscopy were insufficient amounts of specimen, incorrect lymph node selection, and inadequate frozen section evaluation.

In two patients with lymph node station 5 positivity, inaccurate sampling could be due to technical reasons because in both patients, examinations were done in the early learning period of the ECM procedure. In another two patients, lymph node station 7 positivity probably originated from the access problem of mediastinoscopy into the posterior subcarinal area. In six of the remaining seven patients with N2 positivity, N2 invasion had been detected in the right lower paratracheal region. In a majority of these patients, postoperative invasion in hilar lymph nodes was detected. In addition, the rate of N1 positivity on PET/CT examination was high in this group. Dissemination to the right hilus is easier since the locations of 4R and 10R stations are close to each other. In patients with positive 4R and 10R involvement on PET/CT, more specimen collection from the right lower paratracheal lymph node station and a total lymphadenectomy using a video mediastinoscope may decrease the false negative results.

The mediastinoscopy false negative rate has been reported as 5-6%.^[7,14] Similar to the previous reports,

the false negative rate in our study was 5.6%. In cases of limited N2 invasion detected by thoracotomy, survival in patients with false negative mediastinoscopy is considered higher than that in patients with positive mediastinoscopy.^[15]

In a single-center experience with 2145 mediastinoscopy cases, the mortality rate was reported as 0.05%. The mortality rate in our study was 0.5% (n=1). In this patient, the mediastinoscopy was completed successfully, but myocardial infarction developed in the perioperative period. Our overall complication rate of 3.6% is relatively high compared to previous studies.^[14] The common complications of mediastinoscopy are vocal cord paralysis, bleeding, pneumothorax, tracheal or esophageal injury, and mediastinitis. In this study, five patients (2.6%) had bleeding, and an urgent sternotomy was required in one patient. In the remaining patients, the bleeding could be controlled by conservative techniques, including tampons, cautery, and clips. We believe that the higher bleeding rate in our study could be due to aggressive lymph node sampling.

In conclusion, mediastinoscopy is still the gold standard for the evaluation of lymph nodes. Experienced surgeons can perform it safely. Standard cervical mediastinoscopy and ECM should be assessed under the same title of “mediastinoscopy” in patients with pathological aorta-pulmonary window lymph nodes and left hilar tumors. The literature on the thoracic surgical practice of mediastinoscopy describes only cervical mediastinoscopies. Therefore, the yield of mediastinoscopies seems to be low in left central tumors. Whenever the benefit of mediastinoscopy is discussed for specific situations, it would be better to combine the outcomes of both SCM and ECM.

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