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Original Article / Özgün Makale

Is video-assisted mediastinoscopy superior than standard mediastinoscopy for mediastinal staging of the patients with lung cancer?

Akciğer kanserli hastalarda mediastinal evrelemede video yardımlı mediastinoskopi standart mediastinoskopiden üstün müdür?

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ABSTRACT

Background: In this study, we aimed to compare standard mediastinoscopy (SM) with video-assisted mediastinoscopy (VAM) for mediastinal staging of the patients with lung cancer in terms of safety profile, complication rates, mediastinal station, and lymph node counts.

Methods: Data of 551 patients who were admitted to our clinic between January 2006 and January 2011 with the diagnosis of non-small cell lung cancer (NSCLC) and were scheduled for surgery were retrospectively analyzed. Age and sex of the patients and cell type of the tumor were recorded. A total of 361 patients (65.5%) had SM, while 190 patients (34.5%) had VAM.

Results: Of the patients, 63.2% (n=96) who underwent VAM and 70.1% (n=218) who underwent SM were diagnosed with squamous cell carcinoma. N_2 nodal involvement was detected in 66 of 361 patients (18.3%) who underwent SM and 60 of 190 patients (31.6%) who underwent VAM ($p<0.001$). Sensitivity was 87% and 79% at VAM and SM, respectively. Major hemorrhage was observed in four patients (1.1%) during SM, while none of the patients in the VAM group experienced such complication (p=0.3).

Conclusion: Our study results suggest that VAM is a safe and invaluable method to be used in preoperative mediastinal staging of the patients with lung cancer. We believe that the main superiority of VAM over SM is the prevention of hemorrhage.

Keywords: Lung cancer; standard mediastinoscopy; video assisted mediastinoscopy.

ÖZ

Amaç: Bu çalışmada akciğer kanserli hastalarda mediastinal evrelemede standart mediastinoskopi (SM) ile video yardımlı mediastinoskopi (VAM) güvenlilik profili, komplikasyon oranları, mediastinal istasyon ve lenf nodu sayısı açısından karşılaştırıldı.

Çalışma planı: Ocak 2006 - Ocak 2011 tarihleri arasında küçük hücreli dışı akciğer kanseri (KHDAK) tanısı ile kliniğimize başvuran ve cerrahi yapılması planlanan 551 hastanın verisi retrospektif olarak incelendi. Hastaların yaşı ve cinsiyeti ve tümör hücresi tipi kaydedildi. Hastaların 36'sına (%65.5) SM yapılmış iken 190 (%34.5) hastaya VAM yapılmış idi.

Bulgular: Video yardımlı mediastinoskopi yapılan hastaların %63.2'sine (n=96) ve SM yapılan hastaların %70.1'ine (n=218) skuamöz hücreli karsinom tanısı kondu. standart mediastinoskopi yapılan 361 hastanın 66'sında (%18.3) ve VAM yapılan 190 hastanın 60'ında (%31.6) N_2 nodal tutulum tespit edildi ($p<0.001$). Video yardımlı mediastinoskopi ve SM'nin duyarlılığı sırası ile %87 ve %79 idi. Dört hastada (%1.1) SM sırasında majör kanama gözlenir iken, VAM grubundaki hastaların hiçbirinde bu komplikasyon gelişmedi (p=0.3).

Sonuç: Çalışma bulgularımız VAM'nin akciğer kanserli hastaların ameliyat öncesi mediastinal evrelemesinde kullanılabilecek güvenli ve değerli bir yöntem olduğunu göstermektedir. VAM'nin SM üzerindeki başlıca üstünlüğünün kanamanın önlenmesi olduğu kanısındayız.

Anahtar sözcükler: Akciğer kanseri; standart mediastinoskopi; video yardımlı mediastinoskopi.

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Lung cancer is the most common cause of cancer-related mortality.[1,2] Accurate staging of patients with non-small cell lung cancer (NSCLC) is critical not only for providing information on the extent of the disease, but also serves as a guide for choosing the accurate treatment modality. Accurate staging is also fundamental in determining the prognosis. If the absence of distant metastasis, mediastinal lymph node involvement is the most important prognostic factor which affects the treatment strategies in patients with NSCLC.[3,4]

Definitive mediastinal staging is able to prevent unnecessary thoracotomies and to guide the treatment after resection.[5] Accurate staging of the patients with lung cancer is of paramount importance in planning the treatment.[6] Determination of the mediastinal stage of the disease prior to the treatment of patients without distant metastasis is important for the treatment modality to be chosen and, consequently, for prognosis.[7] Computed tomography (CT) and positron emission tomography-computed tomography (PET-CT) are commonly used imaging modalities to assess the superior mediastinum in patients with lung cancer.[5,8,9] Despite the fact that endobronchial ultrasound-guided transbronchial fine needle aspiration (EBUS-FNA) biopsy is a frequently used noninvasive assessment tool, it is usually performed to radiologically assess patients with lymph node metastasis.[10]

Cervical mediastinoscopy is the standard method in mediastinal staging of lung cancers and in the diagnosis of malignant and benign mediastinal diseases.[6,10] Mediastinoscopy has become popular after Pearson published in 1968 his experience in staging of lung cancers. De Leyn and Lerut[11] and Sortini et al.[12] introduced the use of a camera for mediastinoscopy, modified Sortini technique and defined video-assisted mediastinoscopy (VAM). To date, VAM has been frequently employed thanks to its improved imaging ability and sampling of more lymph node stations than standard mediastinoscopy (SM), which offer improved staging.[7,13,14] Video-assisted mediastinoscopy is also superior to SM in such ways that the image can be magnified on the screen, it is easier to master the technique, and document, offering a comfortable working environment for the surgeon.[14]

In this study, we aimed to compare SM with VAM for mediastinal staging of the patients with lung cancer in terms of safety profile, complication rates, mediastinal station, and lymph node counts.

PATIENTS AND METHODS

Data of 606 patients who were admitted to our clinic between January 2006 and January 2011 and for whom surgery was planned for NSCLC were reviewed retrospectively. All patients underwent CT, pulmonary function tests, and routine blood examination. The patients who were older than 60 years or had any sign of cardiac diseases underwent electrocardiography. Positron emission tomography-CT was not routinely used and was performed only on 314 of the patients. For staging of lung cancer, mediastinal lymph nodes were assessed based on the seventh edition of The International Association for the Study of Lung Cancer (IASLC) Staging System.[15] N_2 disease was defined as presence of a mediastinal lymph node ≥10 mm in short-axis diameter on CT and/or any mediastinal lymph node involvement on PET-CT imaging. Stage 1 NSCLC patients, as confirmed by PET/CT, underwent thoracotomy without prior mediastinoscopy. In our practise, EBUS-FNA was not performed routinely. In the patient with radiologically staged N_0 disease undergoing EBUS-FNA with confirmed results, we did not perform mediastinoscopy. However, mediastinoscopy was performed to be able to decide whether indication chemotherapy or definitive chemotherapy was to be administered to patients with radiologically multiple N_2, irrespective of EBUS findings resulting in an N_2 or N_0). Patients who underwent EBUS were excluded from the study to avoid the selection bias. Patients who received neoadjuvant treatment and/or had re-mediastinoscopy were also excluded from the study. A total of 551 patients were included in the study.

Surgical technique

For both SM and VAM, a transverse surgical incision was made through which the mediastinoscope was inserted and advanced along the trachea towards the bifurcation by blunt and sharp dissections. For the purpose of staging lung cancer, mediastinal lymph nodes were sampled according to the lymph node classification by the American Thoracic Society (ATS).[16] The mediastinal lymph node station groups included for routine mediastinal assessment were 2R, 2L, 4R, 4L, 7, and the anterior aspect of 3. All lymph nodes accessible during SM and VAM were dissected and excised completely, where applicable. However, in all cases, the lymph nodes were unable to be excised *en-bloc* and the number of dissected lymph nodes was not recorded for each station. As an alternative, the numbers of punch biopsy samples for each station were recorded separately.

Among the patients who underwent mediastinoscopy, 165 were not referred to thoracotomy, while 126 of whom were either included in our neoadjuvant treatment protocol as a result of N_2-N_3 status or were considered to be inoperable. Fourteen of the remaining 39 patients rejected to have a surgical resection after mediastinoscopy, whereas the other 25 patients, despite their being N_0, received an indication therapy due to their T status.

Since our institution has four thoracic surgery rooms and only one of these rooms is equipped with VAM, selection of mediastinoscopy type was depended on the availability of the mediastinoscopy equipment in the operation room at the time of surgery, but not on the status of the patient or the preference of the surgeon. Mediastinoscopy was randomly performed by one of four experienced surgeons. During mediastinal assessment, lymph node stations 2R, 2L, 4R, 4L, and 7 were routinely examined. Systematic lymph node dissection was carried out in patients who were N_0, as confirmed by mediastinoscopy and underwent thoracotomy. On the right side, stations 2R, 4R, 7, 8, and 9 were dissected. On the left side, stations 5, 6, 7, 8, and 9 were routinely dissected. If station 4L was accessible through mediastinal shift, these lymph nodes were also dissected. All excised lymph nodes were assessed by three pathologists who were experienced in lung cancers. Even if the samples were initially assessed by frozen-section examination, they were re-examined. Immune histochemical staining was not routinely performed.

Statistical analysis

The chi square test, Fisher's exact test, student t test, and Mann-Whitney U test were used to analyze nominal or numerical distribution of the data. A p value of ≥0.05 was considered statistically significant.

RESULTS

Thirty-five patients (6.4%) who had mediastinoscopy were females (mean age 52.2±8.7 years; range 33-80 years). A total of 361 patients (65.5%) had SM, while 190 patients (34.5%) had VAM. Non-small cell lung cancer was diagnosed by preoperative diagnostic modalities. Histological type of the tumor was squamous cell

Table 1. Demographic characteristics of patients

	Standard mediastinoscopy (n=361)			Video-assisted mediastinoscopy (n=190)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (years)			57.6±8.8			56.7±8.4	0.16
Gender							0.57
Male	338			178			
Female	23			12			
cN_2	133	36.8		82	43.2		0.17
Squamous cell carcinoma	218	60.4		102	53.7		0.13
Right side tumor	197	56.4		111	58.4		
Upper lobe	124	34.3		72	37.9		
Middle lobe	6	1.7		2	1.1		
Lower lobe	64	17.7		35	18.4		
Central mass	3	0.8		2	1.1		0.71
Left side tumor	164	43.6		76	41.6		
Upper lobe	110	30.5		60	31.6		
Lower lobe	53	14.7		18	9.5		
Central mass	1	0.3		1	0.5		
cT status							
cT_{1a}	12	3.3		5	2.6		
cT_{1b}	34	9.4		13	6.8		
cT_{2a}	141	39.1		78	41.1		0.90
cT_{2b}	67	18.6		38	20.0		
cT_3	81	22.4		44	23.2		
cT_4	26	7.2		12	6.3		
Tumor size (mm)			52.5±20.4			53.2±21.2	0.81

SD: Standard deviation; cN_2: Radiologically mediastinal lymph node involvement; cT: Radiologically T stage.

carcinoma, adenocarcinoma, large cell carcinoma in 314 (57.0%), 149 (27.0%), and 11 patients (2.0%), respectively. Eighteen patients (3.3%) had other types of cancer (adenosquamous, brachioloalveolar, etc.). Subtype was not recorded or identified in 59 patients (10.7%).

Squamous cell carcinoma was identified in 63.2% (n=96) of the patients who had VAM and 70.1% (n=218) who had SM. The difference between the two groups was not statistically significant (p=0.13). Males comprised 93.7% of the patients (n=178) who had VAM and 93.6% (n=338) of the patients who had SM. Sex was equally distributed between the groups (p=0.57). The number of patients with right-sided tumors in the SM group and VAM group were 197 (56.4%) and 111 (58.4%), respectively, indicating no statistically significant difference (p=0.42). There was no statistically significant difference in lobe-specific distribution (p=0.71) (Table 1). There were 158 patients (83.2%) who were under the age of 65 in the VAM group and 282 patients (78.1%) in the SM group. No statistically significant difference in age was observed between the groups (p=0.16). The percentage of radiologically assessed N_2 was 38.8% (n=133) in VAM group and 43.2% (n=82) in SM group, indicating no statistically significant difference (p=0.17). Radiological tumor size was also similar in both groups (p=0.81). Finally, there was no statistically significant difference in radiologically T stage distribution. Demographic characteristics of the patients are shown in Table 1 in detail.

In the VAM group, lymph node stations 2R, 2L, 4R, 4L, and 7 were dissected in 149 (78.4%), 175 (92.1%), 169 (89.9%), 181 (95.3%), and 185 (97.4%) of the patients, respectively. In the SM group, lymph node stations 2R, 2L, 4R, 4L, and 7 were dissected in 235 (65.1%), 299 (82.8%), 274 (75.9%), 329 (91.1%), and 346 (93.1%) of the patients, respectively. The sampling number of all of five stations during SM and VAM were 144 (39.9%) and 119 (62.6%), respectively (p<0.001).

N_2 nodal involvement was noted in 66 of 361 patients (18.3%) who had SM and 60 of the 190 patients (31.6%) who had VAM (p<0.001). Sensitivity was 87% with VAM and 79% with SM. Among the patients who were considered negative for N_2 during mediastinoscopy and referred to thoracotomy, 17 of the 271 patients in the SM group (6.3%) and nine of the 115 patients in the VAM group (7.8%) were found to have N_2 disease during thoracotomy, although the difference was not statistically significant (p=0.67). Negative predictive values (NPVs) were 93.7% and 92.2% for the SM and VAM groups, respectively. The lymph nodes found to be positive during thoracotomy were in stations 2R in two patients, 4R and 7 in one patient, 4R in two patients, and 7 in 20 patients. Negative predictive values for stations 2R, 4R, and 7 were 99.5%, 99.2% and 94.6%, respectively. Five of 115 patients (4.3%) in the VAM group and 16 of the 271 patients (5.9%) in the SM group were positive in station 7; however, the difference was not statistically significant (p=0.37). As a result, the total number of station 7 positivity during surgery was 21.

The number of biopsy samples taken from the lymph node stations during SM and VAM were 2R=2.2±1.6, 4R=3.0±2.5, 7=5.8±4.7, 2L=3.7±2.8, 4L=5.0±3.6 and 2R=2.2±2.0, 4R=3.5±3.2, 7=6.7±5.2, 2L=4.7±3.3, 4L=5.7±4.1, respectively. More samples were taken from the stations 2L, 4L and 7 in the VAM group. *P* values associated with the comparison of mediastinoscopy groups in terms of the number of biopsy sample were 0.38 for 2R, 0.36 for 4R, 0.04 for 7, 0.003 for 2L and 0.11 for 4L (Table 2). The mean number of biopsy samples in the SM and VAM groups were 14.2±8.8 and 17.3±9.9, respectively (p=0.001). Mortality was found to be 0 in both groups of patients. Major hemorrhage was observed in four patients (1.1%) during SM, while none of the patients in the VAM group experienced such complication (p=0.3). Permanent hoarseness was noted in four patients (1.1%) in the SM and five patients (2.6%) in the VAM group (p=0.16). Temporary hoarseness, on the other hand, was noted in 11 patients (3.0%) in the SM and four patients (2.1%) in the VAM group (p=0.37) (Table 3).

Table 2. Number of biopsy samples and sampling rate

Lymph node stations	Standard mediastinoscopy	Video-assisted mediastinoscopy	*p*
2R	2.2±1.6	2.2±2.0	0.38
	65.1%	78.4%	0.01
4R	3.0±2.5	3.5±3.2	0.36
	75.9%	89.9%	0.002
7	5.8±4.7	6.7±5.2	0.04
	93.1%	97.4%	0.02
2L	3.7±2.8	4.7±3.3	0.003
	82.8%	92.1%	0.001
4L	5.0±3.6	5.7±4.1	0.11
	91.1%	95.3	0.08
Total	14.2±8.8	17.3±9.9	0.001
All*	39.9%	62.6	<0.001

* Sampling rate of all stations.

Table 3. Distribution of complications

	Types of complications								
	Temporary hoarseness			Permanent hoarseness			Major hemorrhage		
	n	%	*p*	n	%	*p*	n	%	*p*
Standard mediastinoscopy	11	3.0	0.37	4	1.1	0.16	4	1.1	0.30
Video-assisted mediastinoscopy	4	2.1		5	2.6		0	0	
Total	15			9			4		

DISCUSSION

Mediastinoscopy is still the gold standard for lymph node staging of lung cancer.[10] The VAM has been described recently.[12] Its higher field of view and improved surgical maneuverability make VAM a useful technique.[13]

Is VAM really superior to SM? There are few studies in the literature which compared these modalities.[7,17,18] As in the present study, more lymph nodes were being sampled in patients undergoing VAM (Table 4).[7,17,18] It can be attributed to the advantage of better exposure offered by VAM. However, neither we nor other comparative studies found a significant difference between the SM and VAM groups in NPVs (Table 4). Consistent with the other study findings, our study showed that VAM did not offer a significant advantage in terms of NPV (Table 4).[7,17,18] On the contrary, Ergene et al.[19] had found higher NPVs in the VAM group. False negativity in mediastinoscopy patients varies between 2 and 19%.[7,18] The difference can be attributed to the clinical stages of patients undergoing mediastinoscopy. Mediastinoscopy also appears to be useful in excluding mediastinal node involvement in patients with normal-sized nodes.[6] In the present study, mediastinoscopy was carried out on all operable patients with the exception of $cT_1N_0M_0$ patients. Venissac et al.[13] performed mediastinoscopy in patients with lung cancer which was radiological N_2 cases, whereas mediastinoscopy was performed on patients with stage 1 lung cancer by Cho et al.[17] In our practice, the patients with potentially resectable lung cancer underwent cervical mediastinoscopy except those with $cT_1N_0M_0$.

The main advantage of VAM is the improved field of view and the opportunity to combine with other instruments.[7,13] Therefore, the ratio of hemorrhage during VAM was found to be lower in our study. However, since complications were rare, the difference did not reach statistical significance. In addition, Anraku et al.[7] reported that the ratio of hemorrhage was lower in VAM patients, in consistent with other studies (Table 4).[7,17,18]

On the other hand, vocal cord paralysis is a known complication of mediastinoscopy. Video-assisted mediastinoscopy enables better identification of the recurrent nerve.[17] Venissac et al.[13] reported a lower mortality rate of 0.83% with VAM. However, neither Anraku et al.[7] nor we were unable to find

Table 4. Published results of standard mediastinoscopy and video-assisted mediastinoscopy in lung cancer patients

	Negative predictive value			Major hemorrhage			Hoarseness			Mean number of samples		
	VAM	SM		VAM	SM		VAM	SM		VAM	SM	
	%	%	*p*	%	%	*p*	%	%	*p*	Mean±SD	Mean±SD	*p*
Our study* (n=551)	92.2	93.7	0.67	0	1.1	–	2.6	1.1	–	17.3±9.9	14.2±8.8	0.001
Cho et al.[17] (n=521)	95.5	94.7	0.88	0	0.4	–	0.9	3.1	–	8.5±5.9	7.1±4.8	0.006
Leschber et al.[18] (n=366)	83	81	–	0.9	2.3	–	2.1	3.0	–	–	–	–
Anraku et al.[7] (n=500)	98.6	95.7	–	1.9	0.2		0	0.96	–	7.0±3.2	5.0±2.8	0.001
Turna et al.[21]‡	94.3	90.6	0.03	–	–		9.0	4.1	0.03	–	–	<0.001

VAM: Video-assisted mediastinoscopy; SM: Standard mediastinoscopy; * In the section "Mean number of samples" show the numbers of punch biopsy samples; ‡ Video-assisted mediastinoscopic lymphadenectomy versus standard mediastinoscopy.

an additive advantage of VAM for the preservation of the recurrent laryngeal nerve. Given an improved visualization and safer perception of the surgeon, it is possible that a more thorough and liberal dissection of the mediastinum during VAM may lead to a higher complication rate. The increased vocal cord paralysis in the VAM group in our study may be explained by more aggressive dissection of mediastinum due to the visualization advantage of the VAM method.

Furthermore, VAM lymphadenectomy developed by Hürtgen et al.[20] is considered to be the best method for the determination of the mediastinal stage of the disease prior to the treatment. Moreover, recently Turna et al.[21] reported that patients with operable NSCLC who underwent VAM lymphadenectomy had not only improved NPVs but also improved survival. They argued that by using VAM lymphadenectomy method, the sampling rate of all the nodal stations, particularly the 2L and 4L stations, was improved. The complete mediastinocopic dissection of 2L and 4L lymph nodes is particularly more important than the other station nodes.[21] Both 2L and 4L lymph nodes cannot be completely dissected during the resection, since it is technically challenging and needs the elevation of the aorta.[21] We found that the sampling rate from all of the five stations in the VAM group is more than the SM group. In addition, both the sampling rate and the number of samples were higher 2L and 4L stations in the VAM group.

There are some limitations to our study. Firstly, as this is a retrospective study, patients' characteristics and surgeons may not have been distributed in a completely randomized way, although the mediastinoscopy method of patients fully depended on the appropriateness of the mediastinoscopy equipment (despite the presence of four operation rooms, only one had videomediastinoscopy equipment). Secondly, although the difference was not statistically significant, the number of patients diagnosed with squamous cell carcinoma in the SM group was higher than that in the VAM group. Thirdly, patients did not randomly undergo VAM or SM and the clinical condition of the patients or the preference of the surgeon were not taken into consideration. Finally, lymph nodes were unable to be excised *en-bloc* in all cases. Although the nodes were fragmented in such cases, each piece was examined by the pathologist.

In conclusion, by offering a large field of view and surgical maneuverability, it is a matter of broad consensus that VAM is a useful technique. Our study results also support that VAM is a safe and invaluable method to be used in preoperative mediastinal staging of the patients with lung cancer. We believe that the main superiority of VAM over SM is the prevention of hemorrhage.

Declaration of conflicting interests

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