Joint use of cervical mediastinoscopy and video-assisted thoracoscopy for the evaluation of mediastinal lymph nodes in patients with non-small cell lung cancer*

Utilização conjunta de mediastinoscopia cervical e videotoracoscopia para a avaliação linfática mediastinal em pacientes com carcinoma de pulmão não-pequenas células

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Abstract

Objective: To evaluate the efficacy of the joint use of cervical mediastinoscopy and video-assisted thoracoscopy for the sampling of mediastinal lymph nodes in patients with non-small cell lung cancer (NSCLC) and candidates for pulmonary resection. **Methods:** Sixty-two patients diagnosed with NSCLC were submitted to cervical mediastinoscopy and video-assisted thoracoscopy. The samples obtained (from paratracheal chains, anterior and posterior subcarinal chains, paraesophageal chains and pulmonary ligament) were submitted to frozen section analysis. The following variables were also evaluated: age; gender; weight loss; diagnostic method; tomographic findings; histological type; staging; and location and size of the primary tumor. **Results:** In 11 patients, mediastinoscopy showed no involvement of the subcarinal chain, whereas such involvement was identified when video-assisted thoracoscopy was used: positive predictive value = 88.89% (95% CI: 51.75-99.72); negative predictive value = 94.34% (95% CI: 84.34-98.82); prevalence = 17.74% (95% CI: 9.2-29.53); sensitivity = 72.73% (95% CI: 39.03-93.98); and specificity = 98.77% (95% CI: 93.31-99.97). In 60% of the patients with involvement of the posterior subcarinal chain, the primary tumor was in the right inferior lobe. (p = 0.029) **Conclusions:** The joint use of cervical mediastinoscopy and video-assisted thoracoscopy for the evaluation of posterior mediastinal lymph nodes proved to be an efficacious method. When there is no access to posterior chains by means of ultrasound with transbronchial or transesophageal biopsy, which dispenses with general anesthesia, this should be the method of choice for the correct evaluation of mediastinal lymph nodes in patients with NSCLC.

Keywords: Neoplasm staging; Mediastinoscopy; Biopsy; Lymphatic metastasis.

Resumo

Objetivo: Avaliar a eficácia da utilização conjunta de mediastinoscopia cervical e videotoracoscopia para a amostragem linfonodal mediastinal em pacientes com câncer de pulmão não-pequenas células (CPNPC) candidatos à ressecção pulmonar. **Métodos:** Uma amostra de 62 pacientes com diagnóstico de CPNPC foi submetida à mediastinoscopia cervical e à videotoracoscopia. As amostras obtidas (das cadeias paratraqueais, cadeia subcarinal anterior e posterior, cadeias paraesofágicas e ligamento pulmonar) foram submetidas a exame de congelação. Foram também avaliadas as seguintes variáveis: idade, sexo, perda ponderal, método diagnóstico, achados tomográficos, tipo histológico, estadiamento, localização e tamanho do tumor primário. **Resultados:** Em 11 pacientes, a mediastinoscopia não apresentou comprometimento da cadeia subcarinal, enquanto esse envolvimento foi detectado na videotoracoscopia: valor preditivo positivo = 88,89% (IC95%: 51,75-99,72); valor preditivo negativo = 94,34% (IC95%: 84,34-98,82); prevalência = 17,74% (IC95%: 9,2-29,53); sensibilidade = 72,73% (IC95%: 39,03-93,98); e especificidade = 98,77% (IC95%: 93,31-99,97). Em 60% dos pacientes com comprometimento da porção posterior da cadeia subcarinal, o tumor primário estava no lobo inferior direito (p = 0,029). **Conclusões:** A utilização conjunta da mediastinoscopia cervical e videotoracoscopia para avaliação linfática mediastinal posterior se mostrou um método eficaz. Quando o acesso às cadeias posteriores não for possível através de ultrassom com biópsia transbrônquica ou transesofágica, que prescinde de anestesia geral, esse deve ser o método de escolha para a correta avaliação linfática mediastinal em pacientes com CPNPC.

Descritores: Estadiamento de neoplasias; Mediastinoscopia; Biópsia; Metástase linfática.

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Introduction

In patients who are candidates for surgical treatment of lung cancer, once metastatic spread of the disease has been ruled out, the determination of mediastinal lymph node involvement is crucial for the selection of the best therapeutic strategy.[1] The imaging methods defined as noninvasive and currently available for that purpose—CT, positron emission tomography (PET) and nuclear magnetic resonance—might not suffice for this evaluation, since they do not rule out the need for histological confirmation of lymphatic metastasis.[2-5] The methods known as invasive—such as mediastinoscopy, video-assisted thoracoscopy, transbronchial biopsy and, more recently, endobronchial ultrasound and transesophageal endoscopic ultrasound—can be used in combination with imaging methods for the histological or cytopathologic study of lymph nodes. Cervical mediastinoscopy, which is considered the gold standard among the invasive methods, is used to investigate pretracheal, paratracheal (right and left) and subcarinal (anterior and superior) lymph nodes.[6,7] This method, however, does not allow access to posterior and inferior segments of the subcarinal chain, of the paraesophageal chain and of the pulmonary ligament chain, which is a limitation of cervical mediastinoscopy.[8] Recently, the introduction of endobronchial ultrasound and transesophageal endoscopic ultrasound has allowed, through a nonsurgical method and without general anesthesia, the histological sampling of practically all mediastinal lymph nodes, as well as of hilar and interlobar lymph nodes. This reinforces the idea that mediastinoscopy as an isolated method does not evaluate the entire extension of the lymph node disease.[9,10] The joint use of mediastinoscopy and video-assisted thoracoscopy was first described in the beginning of the 1990s[11] and subsequently validated in other studies[12,13]; since then, it has been considered a strategy to investigate the lymph nodes that are inaccessible by cervical mediastinoscopy. However, no study with a significant number of patients has investigated the joint use of mediastinoscopy and video-assisted thoracoscopy, regardless of the tomographic findings.

The objective of the present study was to evaluate the efficacy of the joint use of cervical mediastinoscopy and video-assisted thoracoscopy for preoperative sampling of mediastinal lymph nodes in patients who were candidates for surgical treatment of non-small cell lung cancer (NSCLC).

Methods

In the period between June of 2006 and June of 2008, 62 patients with NSCLC, were prospectively selected for the present study, after preoperative evaluation compatible with the procedure proposed and absence of systemic disease. Patients were selected at the Department of Thoracic Surgery of the *Hospital Geral da Fundação Universidade de Caxias do Sul* (HG-FUCS, University of Caxias do Sul Foundation General Hospital), in the city of Caxias do Sul, Brazil. The study protocol and the study design were approved by the Research Ethics Committee of the HG-FUCS. The following patients were excluded from the present study: patients with lesions located in the upper lobe of the left lung, since lymphatic drainage of these lesions is not preferentially into subcarinal nodes; patients with pleural adhesions that precluded sampling by video-assisted thoracoscopy; and patients submitted to neoadjuvant radiotherapy with chemotherapy. The noninvasive method used for mediastinal lymph node evaluation was contrast-enhanced chest CT. The results were considered altered when the minimum transverse diameter of mediastinal lymph nodes was larger than 10 mm. The 62 patients underwent surgical evaluation of mediastinal lymph nodes by cervical mediastinoscopy and video-assisted thoracoscopy, regardless of the tomographic findings related to the mediastinal lymph nodes. The designation of the lymph nodes accessed was based on the Mountain-Dresler (MD) map, which was approved by the American Thoracic Society, and the definition of staging was in accordance with the tumor-node-metastasis system.[14] The following variables were also evaluated: gender; age; weight loss (>10%); histological type; staging of the disease; size of the primary tumor; location of the primary tumor (central or peripheral, by visualization through bronchoscopy); and lobe of origin of the primary tumor.

Cervical mediastinoscopy allowed the biopsy of the following lymph node stations: right upper paratracheal (MD: 2D); right lower paratracheal (MD: 4D); and anterior and superior subcarinal (MD: 7A). The samples from these

lymph node stations were sent for frozen section analysis, which, when positive, was considered final. If there was no neoplasia, surgical staging was performed by video-assisted thoracoscopy during the same anesthesia. Patients were in lateral decubitus and samples of the posterior lymph node stations (subcarinal, pulmonary ligament and paraesophageal nodes) were obtained through three accesses. The subcarinal station was exposed by anterior traction of the upper segment of the lower lobe and opening of the mediastinal pleura, which allowed biopsy of the posterior subcarinal nodes (MD: 7P). After the pulmonary ligament was freed, samples were obtained from the pulmonary ligament nodes (MD: 9) and paraesophageal nodes (MD: 8). These samples were also sent for frozen section analysis. If there was absence of neoplasia, pulmonary resection was performed. On the other hand, positive anatomopathological results at that time determined that the patient should be excluded from isolated surgical treatment and referred for neoadjuvant therapy. In patients surgically treated, pulmonary resection was followed by systematic mediastinal lymphadenectomy, and all lymph nodes were sent for anatomopathological examination using the paraffin method (H&E). Only for the present study, for the analysis of the results, the samples sent for frozen section analysis were also analyzed using the paraffin method.

Predictive values, sensitivity, specificity and prevalence were calculated using the StatsDirect statistical software (StatsDirect Ltd., Altrincham, UK). A 95% CI was adopted. The chi-square test was used to compare proportions, with a p value < 0.05.[15,16]

Results

The present study investigated 62 patients. Most of the patients were male (n = 40). Mean age was 64 years (variation: 45-81 years). Contrast-enhanced CT scans were considered altered in only 8 patients (13%), and weight loss > 10% was observed in 18 patients (29%). Adenocarcinoma was the most frequent histological type (52%), followed by epidermoid carcinoma (42%), undifferentiated large cell carcinoma (3%) and large cell neuroendocrine carcinoma (3%). Early stages (IA, IB, IIA and IIB) were present in 46 patients (74%) and more advanced stages (IIIA, IIIB and IV) were present in 16 patients. The primary

tumor was predominantly located in the right upper lobe in 27 patients, in the right lower lobe in 20 patients, in the middle lobe in 5 patients and in the left lower lobe in 10 patients. In the present study, mean tumor size was 4.1 cm. With regard to location of the tumors, 31 had a central location and 31 had a peripheral location. The joint use of mediastinoscopy and video-assisted thoracoscopy ruled out the presence of lymphatic metastasis in 51 patients (82.3%). In 11 cases (17.7%), the evaluation of anterior

Table 1 – Variables studied, according to the results of cervical mediastinoscopy and video-assisted thoracoscopy.

Variable	Group M–/V– (n = 51)	Group M–/V+ (n = 11)	p
Mean age, years	64.6	64.9	NS
Males, n	31	9	NS
Weight loss > 10%, n (%)	15 (29)	3 (27)	NS
CT scan, n (%)			
Normal	45 (88)	9 (82)	NS
Abnormal	6 (12)	2 (18)	
Histological type, n (%)			
Epidermoid carcinoma	20 (40)	6 (54)	NS
Adenocarcinoma	27 (52)	5 (46)	NS
Undifferentiated large cell carcinoma	2 (4)		
Neuroendocrine carcinoma	2 (4)		
Staging, n (%)			
IA	15 (30)	8 (73)	NS
IB	20 (40)	1 (9)	NS
IIA	2 (4)	2 (18)	NS
IIB	9 (16)		
IIIA	2 (4)		
IIIB	2 (4)		
IV	1 (2)		
Lobe of origin, n (%)			
Right upper	26 (50)	1 (9)	NS
Middle	4 (8)	1 (9)	NS
Right lower	13 (24)	7 (64)	0.029
Left lower	8 (18)	2 (18)	NS
Location, n (%)			
Central	24 (47)	7 (64)	NS
Peripheral	27 (53)	4 (36)	NS
Mean size, cm	3.9	4.3	NS

M–/V–: Negative mediastinoscopy and negative video-assisted thoracoscopy; M–/V+: Negative mediastinoscopy and positive video-assisted thoracoscopy; and NS: non-significant.

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subcarinal nodes by mediastinoscopy did not detect neoplasia; however, sampling of posterior subcarinal nodes by mediastinoscopy and video-assisted thoracoscopy revealed neoplasia. Only 1 patient had involvement of both the pulmonary ligament nodes (MD: 9) and the posterior subcarinal nodes. Intraoperative frozen section analysis yielded 3 false-negative results (4.8%)—1 in the right paratracheal nodes and 2 in the subcarinal nodes—and 1 false-positive result (1.6%)—in the posterior subcarinal nodes. Video-assisted thoracoscopy successfully identified 1 patient (1.6%) with a pleural implant, which was not visualized in the preoperative CT scan. Mean time to perform the cervical mediastinoscopy and video-assisted thoracoscopy with frozen section analysis was 45 min. Mortality and morbidity rates were zero.

The statistical analysis of the results of the present study included 95% CIs and revealed a positive predictive value of 88.89% (95% CI: 51.75-99.72), a negative predictive value of 94.34% (95% CI: 84.34-98.82), prevalence of 17.74% (95% CI: 9.20-29.53), sensitivity of 72.73% (95% CI: 39.03-93.98) and specificity of 98.77% (95% CI: 93.31-99.97).

The results that show the comparison between the two populations (negative mediastinoscopy + negative video-assisted thoracoscopy and negative mediastinoscopy + positive video-assisted thoracoscopy) according to the variables analyzed are shown in Table 1. In the comparative analysis between these two populations, location in the right lower lobe was the only statistically significant variable (p = 0.029; 95% CI: 0.35-0.84).

Discussion

The definition of N2 disease in patients with NSCLC based on the simple presence of metastasis to ipsilateral mediastinal lymph nodes certainly underestimates an extremely complex and challenging disease. At least four presentation forms of N2 disease have been described and each one has different impacts on the survival of patients.[17] The challenge of selecting the best candidates for the best therapy, which will provide 20% of the patients with an average survival of five years, lies in the joint use of noninvasive and invasive methods for mediastinal evaluation and characterization of the subgroups that comprise N2 disease.[18]

The use of CT for the evaluation of mediastinal lymph nodes in patients with NSCLC is controversial due to the high rates of false-positive and false-negative results (> 20%). Central tumors, tumors with a diameter greater than 4 cm and obstructive pneumonia are associated with a greater risk of incorrect interpretation.[19] In the present study, the 2 patients who presented an altered CT scan, negative mediastinoscopy results and positive video-assisted thoracoscopy results had tumors that were larger than 4 cm and centrally located in the lower lobe of the right lung. Even in the early stages of the disease, defined as T1N0M0, in which the rates of false-negative CT results can be as high as 15%, tomographic evaluation does not suffice and tissue sampling is required.[20] In a series of 291 patients with clinical stage I NSCLC submitted to routine mediastinoscopy, N2 disease and N3 disease were not detected in CT scans from 20 patients (7%). The rate of false-negative mediastinoscopy results was 9.2% (25/291). More importantly, this rate was 52% (13/25) for subcarinal nodes and 8% (2/25) for pulmonary ligament nodes.[21] There is clear evidence that posterior lymph node stations, principally the posterior subcarinal nodes, are not entirely accessed by cervical mediastinoscopy.[8,22] In a series of 383 patients with NSCLC prospectively submitted to chest CT and PET, 199 patients were classified as N0 stage. Of those 199 patients, 28 (14%) were identified as having unsuspected N2 disease after cervical mediastinoscopy and endoscopic ultrasound-guided fine-needle aspiration.[22] A very significant finding of that study was that the posterior nodes, which are inaccessible by mediastinoscopy, were the principal location of N2 disease that had not been detected by noninvasive methods (38% in posterior subcarinal nodes). The authors concluded that it was necessary to combine mediastinoscopy with another invasive method in order to thoroughly evaluate the mediastinum. The only methods available for histological or cytopathologic evaluation of posterior mediastinal lymph nodes are endobronchial ultrasound-guided fine-needle aspiration, transesophageal endoscopic ultrasound-guided fine-needle aspiration and video-assisted thoracoscopy.[10] The choice of the method depends on the training of the examiner and on the availability of the method. Adenocarcinoma is

more often associated with mediastinal involvement[21,22] in patients with NSCLC; however, this was not observed in the present study, since we found the same incidence for epidermoid carcinoma and adenocarcinoma.

The probability of lymphatic metastasis, as well as its correlation with the lobe in which the lesion originated, is of utmost importance. Various studies [23-25] suggest the same route of spread: right upper lobe to ipsilateral paratracheal nodes; middle lobe to paratracheal and subcarinal nodes; right lower lobe to paratracheal and subcarinal nodes; left upper lobe to subaortic and anterior mediastinal lymph nodes; and left lower lobe to subcarinal nodes. A recent retrospective analysis[26] involving 954 patients investigated the incidence and the location of N2 disease, as well as its correlation with the primary tumor location, and reported the same results as those previously reported in the literature. Based on this analysis, the authors recommended the use of video-assisted thoracoscopy for the evaluation of lymph node tumors in the left upper lobe (MD: 5 and 6), mediastinoscopy for the evaluation of tumors in the right upper lobe (MD: 2 and 4D) and endoscopic ultrasound for the evaluation of tumors in the middle lobe and in the lower lobe (MD: 7). The present study identified 11 cases (17.7%) in which the evaluation of the subcarinal nodes yielded negative results in the cervical mediastinoscopy and positive results in the video-assisted thoracoscopy. Of these, 81% (9/11) had primary tumors in the lower lobes, predominantly in the right lower lobe (p = 0.029).

Mediastinal evaluation in patients with NSCLC by cervical mediastinoscopy alone requires a more thorough critical analysis. When we choose against the histological evaluation of the posterior lymph nodes, especially the posterior and lower subcarinal nodes, there is a reasonable chance (safely greater than 15%) that we are not offering the patient the best therapeutic strategy. Even presenting data that have not yet been confirmed by phase III randomized studies, recent guidelines[27] have shown that there is no scientific evidence for the use of combined treatment (chemotherapy and radiotherapy + surgery) in patients with preoperative confirmation of N2 disease, which further increases the need for thorough sampling of mediastinal lymph nodes.

The rates of false-negative results in the frozen section analysis were 4.8%, which is in accordance with the means reported in the literature.[6,21,28] However, due to the therapeutic impact of selecting the best candidates for curative surgical treatment, we should consider performing the procedure known as surgical staging (mediastinoscopy + video-assisted thoracoscopy) separately from the pulmonary resection, considering the risks and costs of this choice.

Video-assisted thoracoscopy has become a routine procedure in thoracic surgery and is therefore available at all general thoracic surgery centers. The probability of performing endoscopic ultrasound for the analysis of the posterior lymph nodes or even preferring this method over video-assisted thoracoscopy is a reality in many countries[8,9,29,30] and a near-future perspective in Brazil.

We conclude that the joint use of cervical mediastinoscopy and video-assisted thoracoscopy for the evaluation of posterior mediastinal lymph nodes was an effective method. In NSCLC patients who are candidates for pulmonary resection, in which there is no access to the posterior lymph nodes by transbronchial or transesophageal ultrasound-guided biopsy (which dispenses with general anesthesia), the combined use of cervical mediastinoscopy and video-assisted thoracoscopy should be the method of choice to adequately evaluate mediastinal lymph nodes.

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