ORIGINAL ARTICLE

Importance of Routine Mediastinal Staging in Women With Nonsmall Cell Lung Cancer

J.L. Martín de Nicolás, A. Gómez-Caro Andrés, F.J. Moradiellos Díez, V. Díaz-Hellín, O. Gigirey Castro, E. Larrú Cabrero, J.A. Pérez Antón, and C. Marrón Fernández

Servicio de Cirugía Torácica, Hospital Universitario 12 de Octubre, Madrid, Spain.

OBJECTIVE: To study the specific importance of mediastinal staging in women with nonsmall cell lung cancer.

PATIENTS AND METHODS: Between July 1981 and September 2003 we surgically staged 2172 patients with nonsmall cell lung cancer who met the inclusion criteria for resectability and operability. A subgroup of 108 women was studied. Cervical mediastinoscopy was performed in all cases, with the addition of anterior mediastinotomy in cases with left upper lobe involvement. All patients underwent a preoperative computed tomography chest scan.

RESULTS: Cervical mediastinoscopy was performed on all 108 patients, 26 of whom also underwent anterior mediastinotomy. Positive findings were recorded in 44 (40.7%) of the 108 cases: 39 of the 108 mediastinoscopies (36.1%), 9 of the 26 mediastinotomies (34.6%), and in 5 cases (19.2%) both mediastinoscopy and mediastinotomy. Nodal involvement was found in 13% of cases in clinical stage IA and 30.8% of cases in clinical stage IB. The percentage of positive findings was significantly higher for cases with adenocarcinoma or large cell carcinoma (*P*<.05). We performed 67 thoracotomies: 46 patients underwent lobectomy (42.6% of the 108), 7 bilobectomy (6.5%), 9 pneumonectomy (8.3%), and 5 exploratory thoracotomy (4.6%). The agreement between clinical staging after mediastinoscopy and pathological staging after thoracotomy was 47% (stage IA) and 57% (stage IB).

CONCLUSIONS: Routine mediastinoscopy is indicated for all women with nonsmall cell lung cancer, regardless of clinical stage.

Key words: *Mediastinoscopy. Women. Sex. Bronchogenic carcinoma.*

Importancia de la estadificación mediastínica, sistemática en mujeres con carcinoma broncogénico, no microcítico

OBJETIVO: Investigar la importancia específica de la estadificación mediastínica de mujeres con carcinoma broncogénico, no microcítico.

PACIENTES Y MÉTODOS: Entre julio de 1981 y septiembre de 2003 estadificamos quirúrgicamente a 2.172 pacientes con carcinoma broncogénico no microcítico que cumplían criterios de resecabilidad y operabilidad. Se realizó mediastinoscopia cervical de forma habitual, y mediastinotomía anterior en caso de afectación del lóbulo superior izquierdo. Todos los pacientes tenían una tomografía axial computarizada de tórax preoperatoria. Se estudió al subgrupo de 108 mujeres.

RESULTADOS: Realizamos mediastinoscopia cervical en 108 casos y mediastinotomía anterior en 26. Fueron positivas 44 (40,7%) —39 (36,1%) mediastinoscopias, 9 (34,6%) mediastinotomías y en 5 (19,2%) casos ambas—. Se objetivó afectación ganglionar en un 13% de los casos en estadio IA y en un 30,8% en estadio IB. El porcentaje de positividad fue significativamente mayor en caso de adenocarcinoma o carcinoma de células grandes (p < 0,05). Realizamos 67 toracotomías: 46 (42,6%) lobectomías, 7 (6,5%) bilobectomías, 9 (8,3%) neumonectomías y 5 (4,6%) toracotomías exploradoras. La concordancia entre estadificación clínica posmediastinoscopia y patológica postoracotomía fue del 47% (IA) y del 57% (IB).

CONCLUSIONES: La mediastinoscopia sistemática está indicada en todas las mujeres con carcinoma broncogénico no microcítico independientemente del estadio clínico.

Palabras clave: *Mediastinoscopia. Mujeres. Sexo. Carcinoma broncogénico.*

Introduction

Mediastinoscopy is an essential tool for mediastinal staging of lung cancer and, consequently, for later therapeutic interventions. Recent decades have seen an increase in the number of noninvasive techniques to assess the mediastinum. Examples are contrast-enhanced computed tomography (CT) of the chest and,

more recently, positron emission tomography (PET). However, the sensitivity and specificity of these techniques are unsatisfactory; mediastinal lymph node metastases are found in approximately 10% of negative chest CT scans.[1-3] Mediastinoscopy is an invasive yet safe technique with minimal morbidity and mortality.[4] It has a higher diagnostic yield than bronchoscopic transbronchial needle aspiration, transesophageal needle aspiration, and ultrasound-guided fine-needle aspiration of the chest.[5] The identification of nodal disease prior to thoracotomy makes neoadjuvant treatment possible and improves survival rates—nearly 30% at 5 years—especially for cases involving only a single nodal station.[6] Several working groups recommend systematic mediastinal exploration—even in early stages—for all cell types, even when enlarged lymph nodes are not detected on the CT scan.[7-9] However, when enlarged nodes are noted on the chest CT scan and in hilar tumors, the indication is clear.[3]

The objective of this study was to assess the specific importance of mediastinal staging in a subgroup of women with nonsmall cell lung cancer and the relation between these results and the post-thoracotomy pathologic classification.

Patients and Methods

Between July 1981 and September 2003, 2172 surgical explorations of the mediastinum were performed at our unit in patients with nonsmall cell lung cancer who met the oncological and functional criteria for resectability. No patient received chemotherapy or radiotherapy prior to the mediastinal evaluation. For the subgroup of 108 (5%) women included in this study, we performed preoperative CT chest scans and staging based on histology, symptoms, and standard laboratory workup. Clinical staging was performed according

to the revised (1997) TNM system. Nodal stations were identified according to the mediastinal mapping system of the American Thoracic Society.[10,11] All cases were subject to clinical, mediastinoscopy, and pathological staging.

Cervical mediastinoscopy was performed in all patients, with the addition of anterior mediastinotomy in patients with left upper lobe or left main bronchus involvement. Anterior mediastinotomy was also performed in certain patients with left lower lobe involvement and significantly enlarged nodes in the aortopulmonary window or anterior mediastinum. All explorations were carried out or supervised by a thoracic surgeon. The presence or absence of complications was studied retrospectively by reviewing the computer files and medical history of the patients. The mediastinal nodes biopsied were 2R, 2L, 4R, 4L, 7, 5, and 6. Bimanual palpation was used to examine the pulmonary hilum during anterior mediastinotomy. Findings were considered positive when pathological indications of a diseased mediastinal node station were present, with mediastinal invasion confirmed pathologically or with indirect indication that the tumor was highly likely to be nonresectable—such as in cases of aortic invasion or spread to the hilum.

A thoracotomy was performed a few days later if findings from the mediastinal exploration were negative. Patients with only 1 station with intracapsular involvement were given neo-adjuvant treatment and surgery was ruled out for patients who had more than 1 affected node station or extranodal involvement. Anatomical lung resection was performed if no oncological or functional contraindication was present and staging was completed by systematic mediastinal sampling according to pulmonary lymphatic drainage.

Statistical Analysis

Statistical analysis was performed with the SPSS 11.0 Statistical Software Package (SPSS; Chicago, IL, USA). The χ^2 test and, when indicated, Fisher exact test were used to compare qualitative variables; all P values less than .05 were considered significant. The percent agreement of clinical staging and staging by mediastinoscopy in relation to pathologic classification was calculated by dividing the clinical or mediastinoscopy stage by the pathologist's classification.[12]

Results

Cervical mediastinoscopy was performed on all 108 women, 26 of whom also underwent anterior mediastinotomy. The mean (SD) age was 59 (12.7) years (range: 31-83). Preoperative clinical staging is given in Table 1. The histologic cell types were as follows: 67 (62%) adenocarcinomas; 18 (16.7%) squamous cell carcinomas; 13 (12%) large-cell undifferentiated carcinomas, and 10 (9.3%) alveolar cell carcinomas (Table 2).

The mean hospital stay was 2.69 (1.64) days, operating time 32.6 (12.6) minutes, and lymph node stations biopsied per procedure 3.6 (1.4). No deaths occurred. The only complications were 1 (0.9%) case of intraoperative hemorrhage of the internal mammary artery and 1 (0.9%) case of recurrent laryngeal nerve paralysis. No conversions to thoracotomy or sternotomy

TABLE 1
TNM Clinical Classification and Positive Findings on Exploration

Stage	Negative Findings	Positive Findings	No. of Patients
IA	25 (86.2%)	4 (13.8%)	29 (26.9%)
IB	27 (69.2%)	12 (30.8%)	39 (36.1%)
IIA			
IIB	2 (40%)	3 (60%)	5 (4.6%)
IIIA	7 (26.9%)	19 (73.1%)	26 (24.1%)
IIIB	2 (28.6%)	5 (71.4%)	7 (6.5%)
IV	1 (50%)	1 (50%)	2 (1.9%)

TABLE 2
Positive Findings on Exploration by Cell Type*

Type of NSCLC	Negative Findings	Positive Findings	No. of Patients
Adenocarcinoma	45 (67.2%)	22 (36.8%)	67 (62%)
Squamous cell carcinoma	9 (50%)	9 (50%)	18 (16.7%)
Large-cell undifferentiated carcinoma	3 (23.1%)	10 (76.9%)	13 (12%)
Alveolar cell carcinoma	7 (70%)	2 (30%)	10 (9.3%)

*NSCLC indicates nonsmall cell lung cancer.

TABLE 3
**Univariate Analysis of Characteristics and Cases
With Positive Findings on Mediastinoscopy**

Characteristics	Exploration	P
Size, cm		
<3	8/36 (22.2%)	<.005
>3	36/72 (50.0%)	
Stages		
I-II	19/73 (26.0%)	<.0005
III-IV	25/35 (71.4%)	
Cell type		
Adenocarcinoma	22/67 (36.8%)	<.03
Squamous cell carcinoma	9/18 (50%)	>.05
Alveolar cell carcinoma	3/10 (30%)	–
Large-cell undifferentiated carcinoma	10/13 (76.9%)	<.005
Age, years		
>50	29/79 (36.7%)	>.05
<50	15/29 (51.7%)	
Computed tomography		
Nodes ≥1 cm	24/36 (66.7%)	<.0005
Nodes ≤1 cm	20/72 (27.7%)	

TABLE 4
**Comparison of Clinical Staging (cE), Postmediastinoscopy
Staging (mE), and Surgical Staging (pE) and Percent
Agreement***

Stage	cE	mE	pE	Agreement cE/pE	Agreement mE/pE
IA	29 (26.9%)	21 (19.4%)	10 (9.3%)	34%	47%
IB	39 (36.1%)	37 (34.3%)	29 (26.9%)	43%	56.7%
IIA			3 (2.8%)		
IIB	5 (4.6%)	4 (3.7%)	8 (7.4%)	40%	25%
IIIA	26 (24.1%)	23 (21.3%)	24 (22.2%)	42%	82.6%
IIIB	7 (6.5%)	21 (19.4%)	29 (26.9%)	85%	100%
IV	2 (1.9%)	2 (1.9%)	5 (4.6%)	100%	100%

*Agreement was calculated by dividing the clinical or mediastinoscopy stage by the pathological stage.

due to hemorrhage or other causes were required in this subgroup.

Findings were positive in 44 (40.7%) cases: 39 (36.1%) of the 108 cervical mediastinoscopies, 9 (34.6%) of the 26 anterior mediastinotomies, and in 5 (4.6%) cases both cervical mediastinoscopy and

anterior mediastinoscopy were positive. Local T4 invasion occurred in 5 (4.6%) cases, only 1 of which could not be confirmed histologically, although hilar spread—indicative of a nonresectable tumor—was noted on bimanual palpation. Positive findings by clinical stage (Table 3) were significantly higher (P<.005) in advanced stages and in tumors larger than 3 cm (P<.05). The percentage of positive findings was significantly higher for cases with adenocarcinoma or large-cell undifferentiated carcinoma (P<.05). Nodal involvement detected by mediastinoscopy was significantly greater in cases with lymph nodes larger than 1 cm on the chest CT scan when compared to smaller nodes (P<.0005). Sixteen (14.8%) cases involved multiple lymph node stations and 10 (9.3%) had contralateral nodal involvement (N3).

Curative resection (R0) was achieved in 62 (92.5%) of the 67 thoracotomies performed, of which 46 (68.5%) were lobectomies, 7 (10.4%) bilobectomies, 9 (13.4%) pneumonectomies, and 5 (7.5%) exploratory thoracotomies. The exploratory thoracotomies were carried out after observing pleural metastases within the surgical field (1 case), pericardial metastasis (1 case), invasion of the superior vena cava (1 case), and local mediastinal invasion (2 cases). There were no postoperative deaths. Unforeseen N2 disease, which would have been reached by cervical mediastinoscopy or anterior mediastinotomy, was found in 5 (4.6%) cases during thoracotomy; 2 (1.9%) of these cases were stage IA and 1 (0.9%) was stage IB. Table 4 shows the findings from clinical staging, staging by mediastinoscopy, and pathology, as well as the percent agreement between these staging techniques. Tables 5 and 6 show stage migration and the percentage of stage agreement between the clinical stage and mediastinoscopy stage after applying certainty criteria for classification to both.

Discussion

Cervical mediastinoscopy has the highest positive predictive value of all lung cancer staging techniques. Systematic mediastinoscopy—even for small tumors (<3 cm) and mediastinal lymph nodes whose smallest

TABLE 5
**Percent Agreement and Will Rogers Effect on Stage
Migration After Application of Pathological Certainty
Criteria. Migration of Clinical and Pathologic Stage
and Agreement**

Clinical Stage	IA	IB	IIA	IIB	IIIA	IIIB	IV	Total	Agreement
IA	10	7	2	2	4	3	1	29	34%
IB	0	17	1	3	7	9	2	39	43%
IIA	0	0	0	0	0	0	0	0	
IIB	0	0	0	2	2	1	0	5	40%
IIIA	0	4	0	1	11	10	0	26	42%
IIIB	0	1	0	0	0	6	0	7	85%
IV	0	0	0	0	0	0	2	2	100%
Total	10	29	3	8	24	29	5	108	

TABLE 6
**Percent Agreement and Will Rogers Effect on Stage
Migration After Application of Pathological Certainty
Criteria. Migration of Mediastinoscopy and Pathologic Stage
and Agreement**

Mediastinoscopy Stage	IA	IB	IIA	IIB	IIIA	IIIB	IV	Total	Agreement
IA	10	7	0	2	2	0	0	21	47%
IB	0	21	3	5	2	3	3	37	56.7%
IIA	0	0	0	0	0	0	0	0	
IIB	0	0	0	1	1	2	0	4	25%
IIIA	0	1	0	0	19	3	0	23	82.6%
IIIB	0	0	0	0	0	21	0	21	100%
IV	0	0	0	0	0	0	0	2	100%
Total	10	29	3	8	24	29	5	108	

diameter is less than 1 cm—detects mediastinal lymph node metastasis in 9% to 11% of cases.[7,8] In our series of women, mediastinal nodal involvement was found after a negative CT scan in an even higher percentage, approximately 13%. It is difficult to diagnose diseased mediastinal lymph nodes based on their size on the chest CT scan; the error rate is more than 10% in early stages, regardless of the node size used as a cutoff point and despite the use of complementary radiological techniques such as transesophageal echocardiography.[13]

Women represent 5% of the total number of operable lung cancers diagnosed in Spain, a figure that is lower than that found in Asian countries, Canada, or the United States, where the percentage is 36%. However, the incidence of lung cancer in women in Spain is increasing and is likely to become epidemic over the next few years, as it already is in the United States and Canada.[14] For women with lung cancer, curative resection seems to offer a better survival rate compared to men.[15,16] However, in our practice, the percentage of women with mediastinal lymph node involvement at diagnosis, even in early stages, was higher than percentages that have been reported for men; likewise mediastinal dissemination was also more common in our patients than in other published series that did not differentiate between sexes and in which the incidence of clinical T1N0 was close to 10%.[7,8] One possible explanation for this difference may be that—like heart disease—lung cancer is less prevalent among women than among men and, therefore, women are screened less frequently. Another explanation might be that women have a higher incidence of adenocarcinoma— which is less strongly associated with tobacco use for women and more likely to spread to the mediastinum. Women also have a lower incidence of squamous cell carcinoma, because they smoke less, and that cancer has a better prognosis.[17,18] Nevertheless, the oncological characteristics and comorbidity of lung tumors affecting women are usually favorable.[16] In general, the tumors are small, peripheral, more likely to be T1N0, require fewer major lung resections, and are often asymptomatic.[18] Only 20% to 25% of lung carcinomas in women are tobacco related.[14] As a result, comorbidity associated with smoking addiction, such as chronic obstructive pulmonary disease and vascular disease, is lower.[16,19] The combination of less weight loss—and therefore a lower incidence of wasting syndrome—and women's longer life expectancy is associated with a lower rate of postoperative morbidity and mortality and a higher survival rate compared to men.[15-17] The tumor expression of estrogen receptors suggests an increased risk for lung cancer with estrogen replacement therapy because most women with lung cancer are postmenopausal; however, more comprehensive studies are needed.[19]

The high rate of positive findings from cervical mediastinoscopy and anterior mediastinotomy in this subgroup of women indicates a higher rate of positive findings overall—particularly in stages IA (13.8%) and IB (30.8%) and with significantly higher rates of adenocarcinoma and large-cell undifferentiated carcinoma ($P<.05$)—compared to series comprised predominately of men without differentiation of results by sex. If we take into account the 2 (1.8%) stage IA cases considered false negatives, mediastinal node involvement represents an even larger percentage. The incidence of alveolar cell carcinoma is also higher in women and in our study mediastinoscopy gave a positive finding in 3 out of 10 cases. For this reason, despite opinions to the contrary, we also perform systematic mediastinoscopy for this cell type—even though it is impossible to draw conclusions based on case series. Cervical mediastinoscopy can be performed on an outpatient basis, although at our unit we currently require a 1-day hospital stay.[20]

The most common complication of cervical mediastinoscopy is dysphonia; in most cases this is transitory and caused by a lesion to the recurrent laryngeal nerve. To minimize the possibility of injuring the nerve, we do not use electrocautery in this anatomical region. In our series, we observed no cases of supraventricular tachycardia, which is often described in other studies.[20] Anterior mediastinotomy is associated with mammary vessel hemorrhage and accidental incision of the pleura, although these complications are easy to resolve. Exploration of regions not accessible by cervical mediastinoscopy should be comprehensive—especially for hilar tumors and when mediastinal invasion is suspected—to avoid exploratory thoracotomies. We have no experience with extended cervical mediastinoscopy, although the results may be similar to those of anterior mediastinotomy in certain cases, such as nonhilar tumors and when the supraaortic trunks present no atheromatous vascular disease.[21]

Staging agreement between mediastinoscopy and histology (Table 4) reveals a migration from stage IA to IB that may be related to the time delay between the diagnostic chest CT scan and thoracotomy; in certain cases, the delay was more than 3 months. Nonetheless, agreement for stage IIIA was 82.6%, with 17.4% of cases presenting metastatic nodes in early stages—2 (1.9%) in stage IA, 2 (3.8%) in IB, and 1 (0.9%) in IIB. Agreement between clinical staging and pathologic classification was much lower, especially in identifying patients at pathologic stage IIIA; agreement was 34% in stage IA and 43% in IB. As a result, we are unable to identify those patients who might benefit from complementary treatment. Stage migration has important prognostic and therapeutic implications and it is therefore important that staging agreement be as high as possible (Table 6).[12] Mediastinoscopy for staging is very useful for detecting N2 disease prior to thoracotomy and, therefore, for identifying these patients for neoadjuvant treatment.[22,23]

Systematic mediastinoscopy was indicated in more than 13% of the patients in this study with nodal involvement up to stage T1N0, even for cell types

unlikely to spread to the lymph nodes, such as squamous cell or alveolar cell carcinoma. Recent studies have evaluated the relation between tumor size, serum levels of tumor markers, and cell type to determine if mediastinal explorations could be avoided; very high positive predictive values (greater than 90%) were found, but the number of patients was limited.[24] In our study, the quality of the chest CT scan was not the same for all patients because this retrospective study took place over an extended time period and more sensitive radiological techniques were not available to earlier patients. Consequently, these factors may have skewed the results of the study.

We believe that the systematic use of prognostic mediastinoscopy in women is justified given the results achieved in this series, even for early stages of the disease.

Acknowledgments

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