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European Journal of Cardio-thoracic Surgery 22 (2002) 1000–1005

EUROPEAN JOURNAL OF CARDIO-THORACIC SURGERY

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Comparison of clinical and surgical-pathologic staging of the patients with non-small cell lung carcinoma

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Received 13 July 2002; received in revised form 1 September 2002; accepted 4 September 2002

Abstract

Objective: Clinical staging of non-small cell lung cancer helps to determine the extent of disease and separate patients with potentially resectable disease from those that are unresectable. Since, clinical staging is based on radiologic and bronchoscopic findings, overstaging or understaging may occur comparing to the final surgical-pathologic evaluation. We aimed to analyze preoperative and postoperative stagings in order to evaluate stage migrations and our surgical strategy for marginally resectable patients. **Methods**: We did a retrospective analysis of 180 patients with non-small cell lung cancer who underwent resectional surgery between 1994 and 2000. In all patients, a thoracic computerized tomography and bronchoscopy were performed to define clinical staging (cTNM). **Results**: In 86 patients (47.7%) clinical and surgical-pathologic staging concurred. When comparing T subsets alone, correct staging, overstaging and understaging occurred in 133 (73.9%), 28 (15.5%), 47 (26.1%) patients, respectively. Only 13 of 21 patients (61.9%) who were thought to have T4 tumor preoperatively were found to have pT4. Also six patients with cT2 and five patients with cT3 were subsequently found to have T4 disease according to pathology. Clinical staging overestimated the nodal staging in 35 patients (19.4%), while underestimated the lymph node involvement in 45 patients (25%). **Conclusion**: Construction of cTNM stage remains a crude evaluation, preoperative mediastinoscopy in every patient must be performed. Preoperative limited T4 disease is not to deny surgery to patients since a considerable number of patients with cT4 are to be understaged following surgery. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Lung cancer; Clinical staging; Lung resection; T4 tumor; Pathologic staging; Unresectable

1. Introduction

Accurate staging of bronchogenic carcinoma is essential to select the appropriate treatment. Precise tumor (T) and nodal staging (N) are imperative in non-small cell lung cancer (NSCLC) as it determines both correct preoperative assessment and prognostic evaluation.

The TNM staging criteria, as updated by Mountain [1] are now universally accepted by those treating patients with lung cancer. Bronchoscopy and imaging techniques are the most valuable tools for non-invasive staging of patients with potentially resectable NSCLC but their overall accuracy is not satisfactory [2]. However, computed tomography (CT) has somewhat a role in radiologic determination of T and N factors [2,3]; because of its limited sensitivity and specificity, mediastinoscopy is the most accurate method of assessing mediastinal lymph node involvement [4,5]. Above all, surgical-pathologic staging (i.e. pTNM) has been found to be the most powerful statistical factor in prognostic assessment of patients with NSCLC who underwent resectional surgery [1,6].

The aim of the study was to compare the results of radiologic, mediastinoscopic and surgical-pathologic staging in patients with NSCLC.

2. Materials and methods

The records of 180 patients undergoing resection through thoracotomy for carcinoma of the lung between 1994 and 2000 were reviewed. All patients underwent a uniform staging protocol (UICC's, TNM classification revised in 1997) [1] in construction of a clinical evaluative stage (cTNM). Patients, who were treated before 1998, were restaged according to recent TNM classification. Routine

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PII: S1010-7940(02)00581-X

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blood tests included hemoglobin, alkaline phosphatase and serum calcium estimations. All patients underwent postero-anterior and lateral chest radiographs and bronchoscopy. A thoracic CT scan was performed in every patient and 10-mm thick contiguous sections were used to evaluate N and T status. The clinical diagnosis of nodal involvement was determined by an experienced diagnostic radiologist and was based on the CT findings: that is, mediastinal or hilar lymph nodes 1.0 cm or larger in the shortest axis were diagnosed as metastatic (cN) [7]. In 89 out of 180 patients, mediastinal lymph node samplings from the enlarged lymph nodes using cervical mediastinoscopy were carried out. The mediastinal exploration was supplemented by a left anterior mediastinotomy in patients whose tumor lay in the left upper lobe or left main bronchus and in patients with enlarged (>1 cm) anterior mediastinal and/or aorticopulmonary lymph nodes. The preoperative determination of mediastinal nodal metastases contraindicated thoracotomy in all cases except for the patients with limited N2 disease confined to subcarinal or anterior mediastinal lymph nodes. CT scanning or ultrasonographic examination of the upper abdomen was performed in all patients. In the rare circumstances in which an abdominal CT scan or ultrasonograhy showed an isolated extrathoracic abnormality (e.g. suspected adrenal or hepatic mass), fine needle aspiration and/or chemical-shift examination of abdominal magnetic resonance imaging directed to the mass were undertaken. Cranial CT was performed in patients with symptoms suggestive of brain metastasis or routinely (after 1999) (a total of 140 patients). Whole-body-bone scan was accomplished in patients with extremity pain without a trauma history or in patients with elevated calcium or serum alkaline phosphatase levels. According to these rules, 89 patients had bone scintigraphy. Thoracotomy was recommended in all patients with clinical stage IA, IB, IIA, IIB and selected patients assessed to have IIIA (with limited N2) and IIIB (T4N0) diseases. At thoracotomy T and N stage were carefully re-evaluated before undertaking resection. Particular attention was paid to the presence or absence of invasion of visceral and parietal pleura, pericardium or diaphragm. Mediastinal node stations were removed separately, and sent separately for microscopic evaluation labeled according to the chart of AJCC [8]. Using information obtained at thoracotomy and supplemented by pathological examination, a surgical-pathological stage was constructed (pTNM).

All patients except for ten underwent resectional surgery. Patients undergoing less than lobectomy and the patients were found to have contralateral nodal tumor involvement (i.e. N3, $n = 5$) via mediastinsocopy and deemed inoperable were excluded from the study. These patients were not included in the study population of 180 patients. During thoracotomy, a systematic search for lymph nodes in mediastinum was undertaken. All resected lymph nodes were formalin fixed and examined microscopically by standard hematoxylin-eosin stain. Intraoperative 'frozen section' examination was done in every critical resection material (suspected involvement, chest wall resection, etc.). Histological typing was determined according to World Health Organization classification [9]. Performed operations were shown in Table 1.

CT and mediastinoscopy findings were compared with surgical results on the basis of TNM classification.

Patient survival was expressed by actuarial analysis according to the method of Kaplan–Meier, using time zero as the date of thoracotomy and death as the end point.

3. Results

One-hundred-eighty patients (167 men, 13 women) with a mean age of 54 years (range 28–82 years) were reviewed. These patients were treated from 1994 to 2000. All 180 patients underwent thoracotomy and 170 patients (94.4%) proceeded to have resection of their tumors. The evaluation for N and T staging was done in also these ten unresectable patients. Of these 170 patients, 158 patients (92.9%) were reported to have complete resection (i.e. R0), while eight patients (4.7%) had microscopic disease at resection margin (i.e. R1) and remaining four patients (2.4%) had macroscopic remnants (i.e. R2) found at surgical margin of the specimens. All patients except two with residual tumors were referred to an oncology department. One patient underwent completion bilobectomy and one had undergone completion pneumonectomy For the ten patients that did not proceed to resection, clinical staging underestimated the extent of disease in all cases. Five patients changed from cT2N0 to pT4N2, 1 from cT1N0 to pT3N2, 3 from cT3N0 to pT3N2 and the last from cT2N0 to T3N2 (with extracapsular involvement of paraesophageal lymph node).

The histology of tumors was shown in Table 2. Squamous cell carcinoma was the most frequent type, followed by adenocarcinoma and large cell carcinoma. In ten patients histological type was NSCLC which was not otherwise specified (NOS).

Table 3 shows the comparison of clinical and surgical staging according to TNM staging categories. Clinical staging overestimated the extent of disease in 47 patients

Table 1
Types of pulmonary resection

Operative procedures	*n*
Standard resections	
Lobectomy	68
Pneumonectomy	60
Bilobectomy	12
Complex resections	
Sleeve lobectomy/bilobectomy	9
Pneumonectomy and chest wall Resection	2
Lobectomy and chest wall resection	5
Lobectomy and vertebral resection	2
Other	2

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Table 2
Clinical and surgical characteristics of patients

Age (mean ± SD) (years)	54 ± 10
Male	167
Female	13
Histology	
Adenocarcinoma	47 (26.1%)
Squamous cell carcinoma	94 (52.2%)
Adenosquomous cell carcinoma	12 (66.6%)
Large cell carcinoma	14 (7.8%)
Adenoid cystic carcinoma	1 (5.5%)
Small cell carcinoma	2 (1.1%)
NSCLC[a], NOS[b]	10 (5.6%)

[a] NSCLC, non-small cell lung carcinoma.
[b] NOS, not-otherwise specified.

(26.1%) and underestimated the true extent of disease in 47 patients (26.1%).Preoperative staging was true in ten patients with IA disease. The concurrence between clinical and surgical-pathologic staging was found to be highest in IA patients (i.e. 76.9%). The agreement between two staging systems were 51.6, 48.2, 33.3 and 52.0% in patients with clinical IB, IIB, IIIA and IIIB patients respectively. No tumor was staged as IIA (i.e. T1N1) preoperatively. Nearly half of the patients ($n = 12$; 48%) with pIIIB disease were underestimated according to preoperative evaluation. Of these, four (16.6%) patients were deemed to have cIB disease, whereas two (8.3%) and five patients (20.3%) were evaluated to be cIIB and cIIIA patients, respectively. Twenty out of 24 patients had pT4N0, whereas four patients were found to have pT4N2 tumor. Importantly, preoperative evaluation suggested that 25 patients had IIIB disease. Post-operatively this classification was confirmed in 13 patients (52%), but in 12, the disease was subsequently down-staged following surgery with three proving to have IB disease, four having IIB disease and five IIIA disease.

A total of 47 patients (26.1%) were downstaged following thoracotomy while 47 (26.1%) were up-staged according to pTNM. Eighty-six patients (47.7%) remained unchanged following resection.

Individual T subsets are compared in Table 4. Preoperative T factor remained unchanged following final pathologic evaluation in 133 patients (73.9%). Twelve of 16 patients (75.0%) deemed to have T1 disease preoperatively, remained the same postoperatively, whereas three patients were upstaged to T2 and one patient to T3. No patient was found to have T4 disease in this subset. There were 102 patients who were evaluated to have T2 disease preoperatively. However, of these, 82 (80.4%) were proved to have the same (pT2) tumor, while one patient was downstaged to T1, 13 and six patients were upstaged to T3 and T4, respectively. Of the 41 patients thought to have cT3 tumors, 26 patients (63.4%) were unaltered according to surgical-pathologic evaluation. Although, ten patients were downstaged to T2 and five were upstaged to T4. A total of 21 patients were clinically thought have T4 disease. Despite this evaluation, they were operated on and only 13 patients (61.9%) were found to have T4 tumors, whereas three and five patients were downstaged to T2 and T3, respectively. From pathological point of view, a total of 24 patients who were staged as T4 tumor, only 13 patients were evaluated as T4 before operation. Other six and five patients were thought to have cT2 and cT3 tumors, respectively. In these 24 patients with pT4 disease, six tumors involved the carina ($n = 5$), or lateral tracheal wall ($n = 1$), nine invaded the proximal (i.e. intrapericardial) pulmonary artery ($n = 4$), or atrium ($n = 5$), five tumors diffusely involved the mediastinum, two invaded vertebral body. There was an innominate artery involvement in one patient and intrapulmonary metastasis in the lobe in which the primary lesion was located was found in one patient.

Follow-up assessment was complete in 19 of 24 patients with pT4 disease (N0–2). Mean follow-up time was 19.8 months. The 5-year survival was 32.9% and the median survival time was 18 ± 8 months (95% CI 8–38 month) (Fig. 1).

Preoperative and post-operative nodal stagings are shown in Table 5. Preoperative N status was not changed following surgery in 100 patients (55.5%). One-hundred eight patients

Table 3
Comparison of clinical and surgical-pathologic staging

	Clinical staging						
	cIA	cIB	cIIB	cIIIA	cIIIB	Total	% of total
Surgical-pathologic stages							
pIA	10	–	–	1	–	10	5.6
pIB	2	33	6	15	3	59	32.8
pIIA	–	–	–	1	–	1	0.6
pIIB	–	17	13	12	4	46	25.6
pIIIA	1	10	6	17	5	39	21.7
pIIIB	–	4	2	5	13	24	13.3
Total	13	64	27	51	25	180	100
% of total	7.2	35.6	15.0	28.3	13.9	100	100
Probability that clinical stage = surgical-pathologic stage	76.9	51.6	48.2	33.3	52.0	47.7 (86/180) × 100	

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Table 4
Comparison of cT and pT factors

	cT1	cT2	cT3	cT4	Total	% of total
PTNM						
pT1	12	1	0	0	13	7.2
pT2	3	82	10	3	98	54.4
pT3	1	13	26	5	45	25.0
pT4	0	6	5	13	24	13.3
Total	16	102	41	21	180	
% of total	89	56.7	22.8	11.7	100	100
Probability that cT = pT	75.0	80.4	63.4	61.9	73.9 (133/180) × 100	

were evaluated to have no nodal metastasis (N0) preoperatively. Seventy nine of these (73.1%) were confirmed to have N0 disease following operation but one (0.9%) upstaged to have N1 disease and 28 (25.9%) upstaged to have N2 disease. Of these 28 patients, four patients had N2 involvement in multiple stations or with extracapsular invasion. Of 31 patients thought to have hilar node involvement (N1) preoperatively, two patients (6.5%) remained N1, whereas 13 patients (41.9%) were found to have no nodal disease (N0) and 16 patients (51.6%) were shown to have N2 disease according to postsurgical pathologic evaluation. None of these patients who were staged to have N1 disease preoperatively had undergone mediastinoscopy. Of these 16 pN2 patients, five (31.3%) were evaluated to have mediastinal node invasions in multiple stations or extracapsular invasion. There were 41 patients who were staged to have N2 disease preoperatively. Twenty of these 41 patients (48.8%) underwent negative mediastinoscopy who had undergone mediastinoscopy and found to have no mediastinal nodal involvement. Of these, 19 patients (46.3%; three patients with extracapsular or multiple involvements) were found to have N2 disease after resection. Of these 19 patients with pN2 disease, only three patients had undergone mediastinoscopy and two of these three patients were found to have limited N2 disease after mediastinoscopy and referred to surgery, while the remaining patient was found to have no nodal disease after mediastinoscopy. The 19 of 41 patients (46.3%) with cN2 disease were downstaged to N0 while four (9.8%) were downstaged to N1. Sixteen of these 19 patients with pN0 disease and one of four patients with pN1 had undergone mediastinoscopy and had been evaluated to have N0 disease.

4. Discussion

A primary goal of clinical staging is to separate patients with potentially resectable disease from those that are unresectable. For clinical staging, patients almost always undergo a postero-anterior and lateral chest radiograph, CT of the chest and upper abdomen and bronchoscopy. Although these evaluations provide exquisite information,

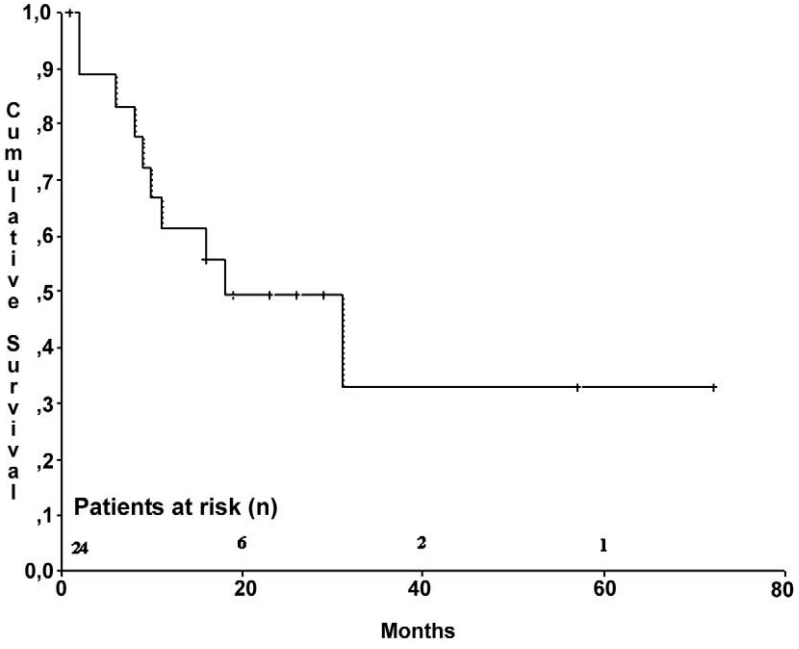

Fig. 1. Survival for patients with pT4N0–2 non-small cell lung cancer.

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these are suboptimal for determining lymph node status and T status in especially marginally resectable patients. For this reason, it is almost unavoidable to find a subset of patients non-resectable during thoracotomy. However, every effort should be made to predict the postoperative TNM stage preoperatively which leads to fewer unnecessary thoracotomies. In our study, 86 of 180 patients (47.7%) were correctly staged preoperatively. Only 13 of 21 patients thought to have T4 preoperatively were staged to have T4 postoperatively.

Although, T4 lung tumor is often considered unresectable by most of the thoracic surgeons, selected certain T4 tumors without mediastinal nodal involvement may be curable by complete surgical resection, which could improve the survival rate of patients in comparison with chemotherapy and radiotherapy [10,11]. Stage IIIB constitutes of a heterogeneous patient group with tumors of different biological aggressiveness and prognosis (e.g. T4N0/1 versus T1N3) [12]. It is also widely accepted that some subgroups of T4 disease can be potential candidates for surgical approaches (T4 carina, proximal pulmonary artery, proximal pulmonary vein, mediastinum), while others are generally not considered for any inclusion of surgery (T4 malignant effusion) [10–13]. Since, a preoperative T4 tumor was not deemed as unresectable, we operate on the selected cT4 patients. Selection criteria for the patients with cT4 disease were: (1) cN0 disease or negative mediastinoscopy in cN2 patients; and (2) T4 factor for only one anatomic site seen on thoracic CT. If we had not operated any of 21 cT4 patients we would not have had operated three patients with pT2 and five patients with pT3. According to final pathologic evaluation, there were 24 patients with pT4 tumor. Thirteen out of 24 patients with pT4 tumor underwent complete resection and they were found to have no nodal metastasis. It remains our policy to advise surgery for the selected patients with T4 disease thought preoperatively and underwent negative mediastinoscopy (i.e. N0). There were also 11 patients who were found to have T4 tumors postoperatively but were thought to have T2 ($n = 6$) or T3 ($n = 5$) tumors preoperatively. These patients had undergone complete resection and were not denied after realizing that they had T4 tumor by exploration. Only three of those 24 patients with T4 tumor had incomplete resection (two R1 and one R2) and two patients underwent exploratory thoracotomy. In the patients with cT4 disease, downstaging occurred at a rate of 38.2%. For this reason, one must not deny all the patients with preoperative T4 tumor. Additionally the 5-year survival rate of 32.9% was promising, justifiable and was comparable to those of others [10–13].

We seem better able to evaluate the T status of the patient preoperatively. In 73.9% of our patients T status was unchanged following surgical-pathological staging, while in only 55.5% of the patients; N status was unaltered postoperatively despite mediastinoscopic evaluation in 89 out of 180 patients. Despite more frequent usage of mediastinoscopy in our study, Fernando and Goldstraw reported very similar results [14]. Unlike theirs, in our study, we were able to assess stage-migration pattern in patients thought to have T4 tumor and in patients found to have T4 tumor postoperatively.

Exact prethoracotomy assessment of the T status is of pivotal importance and it would be suitable to avoid exploratory thoracotomy for unresectable T4 tumors. Videothoracoscopy has been widely used for diagnostic purposes and some authors referred it as a staging tool [15,16]. However, in our series, videothoracoscopy has not been utilized for neither diagnostic nor staging purposes. Discovery of T4 tumor has also been thought to indicate a neoadjuvant therapy as Giacomo and associates suggested [17]. Similarly Rusch et al. reported promising prognoses after neoadjuvant therapy in patients with T4 tumors [18]. Favorable prognoses can be expected by means of judicious selection of patients with T4 disease for surgery without neoadjuvant therapy [12,13]. However, adjuvant chemo/radiotherapy has to be given to these patients. In our study, all patients with pT4 disease were referred to an oncology department.

Nodal staging is in many respects a more important assessment of tumor extent. We also documented postoperative results of the patients with cN2 disease. Of 41 patients with cN2 disease, only 19 patients (46.3%) were found to have mediastinal nodal involvement of tumor.

According to our results, it was almost impossible to predict hilar lymph node involvement preoperatively. Only 6.5% of our patients with cN1 were confirmed to have hilar node involvement while half were upstaged to N2. Despite these data, we believe that, any radiographic suggestion of such involvement is confirmed by mediastinal exploration before excluding the patient from surgery. Of the 107 patients in our study who were thought to have no

Table 5
Comparison of cN and pN factors

	cN0	cN1	cN2	Total	% of total
pN					
pN0	79	13	18	110	61.7
pN1	1	2	4	7	3.9
pN2	8	16	19	63	35.0
Total	108	31	41	180	100
% of total	60.0	17.2	23.3	100	100
Probability that cN = pN	73.1	6.5	46.3	55.5 (100/180) × 100	

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nodal mediastinal or hilar lymph node involvement preoperatively, nodal dissection and subsequent pathological analysis showed metastasis to be present in mediastinal glands of 24 (22.4%) patients.

Mediastinal staging of NSCLC by mediastinoscopy suffers from low sensitivity, and leads to a number of patients with unforeseen N2 disease at thoracotomy. Oosterhuis and his associates showed that, unforeseen N2 rate could be reduced 10% by using immunohistochemical staining with MNF 116 [19]. On the other hand, Positron emission tomography seems to be a promising technique in order to disclose mediastinal lymph node involvement without any invasive procedure, but its usefulness remains to be determined [20]. We were unable to achieve any further investigation such as positron emission tomography or immunohistochemical staining to overcome aforementioned low sensitivity of clinical nodal evaluation.

The preoperative CT scan relies upon size criterion to suggest metastatic spread to lymph nodes. At operation the use of routine nodal dissection allows us to detect small, intracapsular deposits and evaluate nodes beyond mediastinoscope. These subtle degrees of mediastinal node involvement have been shown to be associated with good surgical results [21]. Essentially, our preoperative evaluation of the mediastinum seeks to exclude patients who have mediastinal nodal metastasis at any degree, and our preoperative evaluation of the tumor extent seeks to exclude patients who have T4 tumor because of more than one anatomic localization and not to deny surgery to patients with one extrathoracic involvement (i.e. T4) in one localization since preoperative evaluation may overestimate the extent of disease.

In conclusion, clinical evaluation of the patients with NSCLC and construction of a cTNM category remains a crude evaluation. Preoperative mediastinal exploration using mediastinoscopy plays a crucial role and may prevent a subset of patients from unnecessary thoracotomies. However, since a downstaging has been shown to be a possibility in nearly half of the patients, patients with limited T4 disease without nodal involvement should be given a chance of operation. This may lead more patients with limited resectable disease to have a chance of resectional surgery and fewer patients with resectable pT1–T4 tumor to deny surgery.

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