Surgery for oligometastatic non–small cell lung cancer: Long-term results from a single center experience

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Objective: The role of surgery in the multimodal therapy for selected stage IV oligometastatic non–small cell lung cancer (NSCLC) is still a forum of open discussion.

Methods: We have retrospectively analyzed the records of 53 patients with oligometastatic NSCLC who had been treated with curative intent in the period January 1997 to May 2010.

Results: The mean age and the male/female ratio were 61 years and 32:21, respectively. A single metastatic lesion was present in 45 (84.9%) subjects, in 2 patients there were 2 different anatomic sites involved, and in 8 patients there were 2 metastases in the same site. The most common involved sites were brain (39), followed by adrenal gland (7), bone (3), vertebrae (3), liver (1), and contralateral supraclavicular lymph node (1). Distant disease was completely resected in 42 patients; 10 patients were treated with exclusive chemotherapy and/or radiotherapy and 1 with local laser therapy. Twenty-nine patients had been administered concurrent chemoradiation in a neoadjuvant setting before the surgical treatment at the lung or both sites (primary/distant). The pulmonary resection was complete (R0) in 42 patients (79.2%). Overall, 1- and 5-year survivals were 73.1% and 24%, respectively (median follow-up, 28 months). Median overall survival, local disease-free survival, and distant disease-free survival, estimated using the Kaplan-Meier method, were respectively 19, 72, and 12 months. After stepwise multivariate analysis, the weight loss ($P < .001$), the completeness of pulmonary resection ($P = .0019$), and, interestingly, the performance of a positron emission tomography–computed tomography scan in preoperative staging ($P = .05$) maintained their independent prognostic value as overall survival determinants.

Conclusions: Surgical treatment for selected stage IV NSCLC is feasible and safe. Furthermore, good survival can be expected in those patients in whom a complete resection of the primary tumor and radical control of the distant diseases are accomplished. (J Thorac Cardiovasc Surg 2012;144:444-52)

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In the majority of patients with lung cancer, the disease is metastatic at the time of diagnosis. According to the most recent data from the American Cancer Society, Surveillance Health and Policy Research,[1] an estimated 221,130 new cases of lung cancer were expected in 2011, accounting for about 14% of cancer diagnoses. Historically, metastatic non–small cell lung cancer (NSCLC) has been labeled as stage IV with a single class of M1 disease[2]; in the New Lung Cancer Stage System[3] a certain degree of variability is described in the M1 status, therefore recognizing a significant heterogeneity within stage IV: M1a indicates positivity for neoplastic cells in the pleural effusion or contralateral lesions (in the lung) and M1b indicates positivity for distant metastases. Within the dismal prognostic setting of stage IV, the M1b class has a very poor prognosis (1% at 5 years; overall survival time, 7-11 months). The standard therapeutic approach for stage M1 NSCLC is normally administered with palliative intent on the basis of the invariably very poor outcome, consistently independent from the performance status. Coherently, the common attitude of clinical research efforts in this subgroup of patients with NSCLC has been toward the reduction/control of side/detrimental effects of therapy with specific focus on the quality of life.[4] However, the subgroup of patients with 1 or 2 distant metastases at the moment of diagnosis and clinical staging (so-called ''oligometastatic'') probably is encompassed in a prognostic pattern that is different from that of the diffuse distant disease.[5] Reports from clinical series in which a single brain or adrenal metastasis has been surgically removed would indicate that, indeed, there is justification for a more aggressive, tentatively curative, therapeutic approach in this setting.[6-8] To the best of our knowledge, very few reports exist about the surgical treatment of oligometastatic NSCLCs, regardless of the metastatic site.[6,9]

The aim of this study is to add knowledge on these subjects by evaluating the feasibility and efficacy of a treatment

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Abbreviations and Acronyms

CT = computed tomography
D-DFS = distant disease-free survival
ECOG = Eastern Cooperative Oncology Group
FDG = fluorodeoxyglucose
L-DFS = local disease-free survival
LTS = long-term survival
NSCLC = non–small cell lung cancer
PET = positron emission tomography

strategy planned with curative intent performed on all sites of metastatic disease in oligometastatic NSCLCs, in addition to the radical surgical treatment of the primary tumor. In this group of patients we aimed at evaluating survival and identifying prognostic factors influencing overall survival and local and distant recurrence.

PATIENTS AND METHODS

This is an observational study that does not include any experimental treatment. The analysis has been realized on prospectively collected data within the setting of standard clinical practice. Relevant notice has been provided to local ethical committees. Based on the information available from the clinical records, demographic and clinical features were collected and taken into consideration in the statistical analysis. Follow-up information was obtained from our clinical database and from the hospital administrative records. All patients had at least 6 months of follow-up. Patients were censored for either relapse or death. Pretreatment evaluation included patient history, physical examination, lung function tests, baseline hematochemical tests, and computed tomographic (CT) scan of the chest, abdomen, and brain. Histologic confirmation was obtained through standard cytohistology on material from biopsy specimens obtained during fiberoptic bronchoscopy and/or CT-guided fine needle aspiration. Nuclear magnetic resonance imaging of the brain was performed only in nonunivocal cases or to confirm a feature suggestive of metastatic pattern on a CT scan; radiologically suspected N2 disease was always pathologically proven via mediastinoscopy or endoscopic/endobronchial ultrasound endoscopy. A bone radionuclide study was performed in all patients with NSCLC up to the moment when an 18-fluorodeoxyglucose (FDG) positron emission tomographic (PET) scan was routinely performed in addition to other standard staging procedures (as of June 2005). In the preoperative staging, we defined ''oligometastatic'' disease as a surgically resectable NSCLC primary tumor with 1 or 2 metastatic lesions that were considered, as well, to be radically resectable. Inspired by other similar experiences,[9] a dedicated multidisciplinary team composed of medical and radiation therapy oncologists, pneumonologists, radiologists, anesthesiologists, and thoracic surgeons established the eligibility criteria; these criteria were (1) local disease and metastatic lesion confined in 1 or 2 sites, both considered radically curable; (2) optimal general clinical condition (evaluated as Eastern Cooperative Oncology Group [ECOG] 0 or 1); (3) no history of other malignant disease; and (4) age less than 76 years. At the moment of surgery, all patients had given their informed consent for the use of data for research purposes, among the other procedures. Surgical criteria were designated as follows: (1) extent of the resection, no less than lobectomy (otherwise considered oncologically inadequate); (2) pneumonectomy, indicated only if less extensive resections were deemed inadequate for completeness; (3) systematic mediastinal lymph node dissection[10,11] planned and performed in all cases; (4) incompleteness of resection/control at the metastatic site(s): exclusion from the study. Pathologic stage was assigned according to the International Staging System for Lung Cancer 1997[2] and, accordingly, the resection was considered complete if the proximal resection margins and the highest mediastinal node were microscopically free of tumor. In the period between January 1997 and December 2010, a total of 1847 patients underwent major pulmonary resection for NSCLC at the Department of Thoracic Surgery of Catholic University of Rome, Italy. Among these, based on the criteria illustrated above, the relevant data of 53 patients with oligometastatic disease (2.8%) were used for the purposes of this study. As well, with respect to the surgical and pathologic features relevant to the analysis reported herein, we collected data on (1) the extent of resection, (2) the pathologic staging, (3) the completeness of resection, (4) the type of mediastinal involvement, and (5) the 30-day morbidity and mortality rates. Follow-up was carried out along standard procedures. Duration of follow-up, survival, and time to first recurrence were available for all patients. For the purpose of the overall survival assessment, time 0 (T_0) was arbitrarily selected as the date of last intervention on the primary lung cancer or on the metastatic lesion and the terminal event (T_{end}) was death or status for survivors.

Statistical Analysis

Survival curves were obtained using the Kaplan-Meier method. Survivals were calculated by the Kaplan-Meier method and compared by the log–rank and the Breslow tests. The independent variables that were tested in the univariate analysis were as follows: weight loss (>10% in the last 6 months before treatment), ECOG score, PET–CT, clinical T stage (0-1 vs 2-4) and clinical N stage (0 vs 1-2), metastatic site, number of metastatic sites and number of metastatic lesions, type of treatment for metastatic disease, whole brain radiation, neoadjuvant therapy, histology, pathologic T stage (0-1 vs 2-4) and pathologic N stage (0 vs 1-2), surgical completeness, and adjuvant therapy. The univariate analysis was carried out on Kaplan-Meier curves via the application of the Breslow and log–rank tests. Three different end points were analyzed: 5-year overall survival (LTS), defined as the percentage of patients alive at 5 years after the last treatment (on primary or distant site); 5-year local disease-free survival (L-DFS), defined as the percentage of patients alive without local recurrence of disease at 5 years after the last treatment (on primary or distant site); and 5-year distant disease-free survival (D-DFS), defined as the percentage of patients alive without distant recurrence of disease at 5 years after the last treatment (on primary or distant site). All the variables showing a possible association with survival ($P < .1$) at the univariate analysis were entered in a multivariate analysis (Cox proportional hazards model) to identify independent prognostic factors. A backward elimination approach was used to obtain hazard ratios with 95% confidence intervals. SPSS 12.0 software for Windows (SPSS, Inc, Chicago, Ill) was used to perform the analysis.

RESULTS

Preoperative Staging and Metastatic Pattern

Results characteristics of the entire group are reported in Table 1 and summarized herein: 40 cases of adenocarcinoma, 8 of squamous cell carcinoma, and 5 of undifferentiated carcinoma. Thirteen patients had ''chest only'' stage III disease, of whom 3 had T4 disease (2 patients with a satellite nodule on the same lobe and 1 patient with pulmonary artery infiltration). Most of the cases were N0 (39/53, 73.6%); 10 cases were N2 and 4 N1. Sixteen patients (enrolled in the study from June 2005) underwent PET–CT scan at preoperative diagnostic workup evaluation. In all patients a pathologic uptake of the metastatic lesions was detected. In 45 (84.9%) patients a solitary metastasis was

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