Role of Mediastinal Staging of Lung Cancer*

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The Lung Cancer Study Group (LCSG) assured objective surgical/pathologic staging of clinical trial patients by requiring histologic examination of lymph nodes from anatomically identified specific mediastinal locations. Therefore, within the larger population of heterogeneous patients with lung cancer, subsets of more homogeneous patients were identified. The addition of mediastinal exploration and removal of lymph nodes to the intraoperative procedure did not increase patient morbidity or mortality. The clinical trials designed using surgical/pathologic mediastinal lymph node staging provided definitive answers to several important questions relative to adjuvant and neoadjuvant treatment of patients with non-small cell lung cancer. The LCSG recommended that objective histopathologic mediastinal lymph node staging be accepted as the standard of care for patients with lung cancer.

The Lung Cancer Study Group (LCSG) recognized the necessity for accurate staging of patients with lung cancer and designed all clinical trials with mandatory requirements for surgical/pathologic examination of mediastinal lymph nodes. All patients accrued to postresection adjuvant clinical trials were required to have careful, systematic intraoperative mediastinal node sampling, and patients entered in neoadjuvant studies were required to have mediastinoscopic mediastinal node sampling. Anatomic identification of sites of lymph node origin was assured by using the numerical code recommended by the American Joint Committee for Cancer Staging and End-Results Reporting proposed by the Task Force on Lung Cancer. The unique requirement common to all LCSG clinical trial patients was mandatory examination of lymph nodes from paratracheal, subcarinal, hilar, and bronchopulmonary locations, and in addition, that all histopathologic material be reviewed for consistency by the study group Reference Center for Anatomic and Pathologic classification of Lung Cancer (MD Anderson Hospital, Houston).

A primary clinical trial objective is to detect measurable outcome differences between groups of patients subjected to alternative interventions. The population of patients with lung cancer is heterogeneous in many respects including histopathologic findings and stage of malignancy when first diagnosed. However, more homogeneous subpopulations of patients with lung cancer can be described using surgical/pathologic staging criteria. This was clearly demonstrated by LCSG analysis of patients with surgical resection with T1N0 non-small cell lung cancer accrued sequentially to three studies: (1) an adjuvant BCG (bacillus Calmette-Guerin) immunotherapy trial (771); (2) a natural history catalogue (NCH) of T1NO patients; and (3) a limited resection trial (821). Extensive cross-tabulations and statistical validations disclosed no differences between the three source populations of patients. The malignancy-free intervals and survival times were identical for these three groups of patients. Therefore, the total number of aggregated eligible patients, 907, available for analysis was sufficient to make definitive observations relative to histopathologic variance, malignancy recurrence rates, new malignancy incidence rates, and nonmalignancy death rates as determined by postresection malignancy-free survival.

Mandatory intraoperative sampling of mediastinal lymph node sites required by the LCSG assured optimal quality of the clinical trials conducted by this multicenter cooperative group. The addition of this step, dissection of the mediastinum, and sampling of non-cancer-bearing lymph nodes, was evaluated as a potential source of increased mortality rates across the spectrum of procedures from limited resection to pneumonectomy and through a wide range of patient ages. Mediastinal lymph node dissection did not increase mortality. In addition, there were no observable institution- or surgical team-dependent mortality rate outliers. Therefore, the LCSG recommended that mediastinal lymph node staging be adopted as the standard of care for all patients with lung cancer submitting to thoracotomy.

The objective of the first LCSG clinical trial was to confirm or reject the report of McKneally and coworkers that intrapleural administration of BCG after surgical resection of stage I non-small cell lung cancer was beneficial to patients. In this prospective, double-blind, randomized clinical trial postoperative instillation of intrapleural BCG did not extend the malignancy-free interval or improve survival in patients with completely resected stage I non-small cell lung cancer. For the first time, data analysis of lung cancer outcome was based on objective examination of all major lymph node-bearing sites not on subjective surgical recovery of suspicious-appearing lymph nodes. Differences in 5-year survival within TN subsets of stage I patients with non-small cell cancer were observed to be histopathology-dependent. Patients with squamous cell carcinoma experienced 5-year survival probabilities of 83% T1N0, 75% T1N1, and 64% T2N0. Corresponding 5-year survival probabilities for patients with non-squamous, non-small cell carcinoma were 69% T1N0, 52% T1N1, and 57% T2N0. Histopathologic dependency was also observed in patients with T1N2 cancers following complete surgical resection; 46% 5-year survival for squamous cancer, and 24% for nonsquamous, non-small cell cancer.

Subsequent to the design and initiation of the first clinical immunotherapy trial, the LCSG developed a series of studies for patients with surgically resected stage II and stage III non-small cell lung cancer. These clinical trials addressed the efficacy of adjuvant chemotherapy and/or radiation therapy. Patients with N2 metastases were included in these trials. Retrospectively, patient records were reviewed for presence of discrepant N2 site-specific lymph node metastases. The following groups of patients were identified: (1) subcarinal lymph node only (40 patients); (2) high mediastinal lymph node only (32

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patients); (3) midmediastinal lymph node only (48 patients); and (4) subcarinal lymph node plus one other site identified in patient groups 1, 2, and 3 (45 patients). Analysis of recurrence rates and death rates for these groups of patients revealed an increased probability of recurrence or death for patients in group 4 compared with patients in group 3 (Fig 1). Therefore, it is essential that all anatomically identifiable lymph node locations be histologically examined in patients with lung cancer to define the extent of disease and for prognostic assessment as a guide to management.

Pilot studies have demonstrated the feasibility of converting nonresectable lung cancers to resectable in patients with locally advanced cancer by neoadjuvant treatment. Histopathologic staging prior to the initiation of neoadjuvant therapy and again at the time of surgical intervention is critical for objective assessment of the extent of malignancy and the therapeutic response. Therefore, mediastinoscopy and histologic examination of mediastinal lymph nodes must be required for pretreatment clinical staging of patients selected for neoadjuvant therapy. In a retrospective analysis of 58 patients with stage IIIA lung cancer, a total of 170 mediastinal lymph node sites were biopsied at mediastinoscopy. The primary lung cancer was in the right lung in 66% of patients. Seventy-eight biopsies were positive histologically for malignancy. Almost half of the nonmalignant lymph nodes (44 of 92) were recovered from contralateral mediastinal or hilar locations. As a result of this study, the LCSG was confident that sufficient mediastinal lymph node staging is possible via mediastinoscopy to define patients suitable for accrual to neoadjuvant treatment for locally advanced lung cancer.

CONCLUSIONS

The staging of patients with lung cancer based on systematic surgical removal and histologic examination of mediastinal lymph nodes must be mandatory for clinical trials and should be standard for all patients submitting to pulmonary resection. Analysis of the LCSG clinical trials data provides convincing evidence supporting this requirement for surgical/histologic staging. In addition, there is a need for accurate correlation of objective histopathologic findings with diagnostic imaging examinations to define future applications. Therefore, intraoperative mediastinal lymph node staging should be performed as a routine part of every thoracotomy for patients with resectable lung cancer.

REFERENCES