Large cell neuroendocrine carcinoma: An aggressive form of non–small cell lung cancer

Richard J. Battafarano, MD, PhD,[a] Felix G. Fernandez, MD,[a] John Ritter, MD,[b] Bryan F. Meyers, MD,[a] Tracey J. Guthrie, RN,[a] Joel D. Cooper, MD,[a] and G. Alexander Patterson, MD[a]

Objective: Large cell neuroendocrine carcinomas of the lung display morphologic and immunohistochemical characteristics common to neuroendocrine tumors and the morphologic features of large cell carcinomas. Surgical resection of large cell neuroendocrine carcinomas in many series has been described, with 5-year actuarial survivals ranging from 13% to 57%. Considerable debate has emerged as to whether these tumors should be classified and treated as non–small cell lung cancers or small cell lung cancers. The objective of this study was to report the outcome of surgical resection in patients with large cell neuroendocrine carcinomas.

Methods: An analysis of our tumor registry was performed to identify all patients undergoing surgical resection of lung cancer between July 1, 1988, and December 31, 2002, for large cell tumors. Cases were then segregated into large cell neuroendocrine carcinomas, mixed large cell neuroendocrine carcinomas (in which at least one portion of the tumor was a large cell neuroendocrine carcinoma), or large cell carcinomas on the basis of morphology and differentiation. Follow-up was complete on all patients, with a mean follow-up of 48 months. Type of resection, mortality, and survival by stage were analyzed. Kaplan-Meier survival was determined for all patients from the date of surgical intervention. Cox proportional hazards model analysis incorporating the variables of age, sex, histology, and stage estimated the effect of large cell neuroendocrine carcinomas and mixed large cell neuroendocrine carcinomas on recurrence and death. The stage of disease in all patients was assessed according to the 1997 American Joint Committee on Cancer guidelines.

Results: Of the 2099 patients who underwent resection, 82 (3.9%) had large cell lung cancers. Perioperative mortality was 2.4%. Overall survival and freedom from recurrence at 5 years for the entire group was 47.1% and 58.4%, respectively. Overall survival by histologic subtype at 5 years was 30.2% for patients with large cell neuroendocrine carcinomas (n = 45), 30.3% for patients with mixed large cell neuroendocrine carcinomas (n = 11), and 71.3% for patients with large cell carcinomas (n = 21). Survival was significantly worse for patients with large cell neuroendocrine carcinomas than for patients with large cell carcinomas ($P = .013$). The presence of large cell neuroendocrine carcinomas in the specimen (the large cell neuroendocrine carcinoma and mixed large cell neuroendocrine carcinoma groups combined) was significantly associated with decreased survival (relative risk, 2.44; 95% confidence interval 1.29-4.58; $P = .003$) and decreased freedom from recurrence (relative risk, 4.52; 95% confidence interval, 1.76-11.57; $P < .001$).

Conclusion: Patients with large cell neuroendocrine carcinomas have a significantly worse survival after resection than patients with large cell carcinomas, even in stage I disease. Accurate differentiation of large cell neuroendocrine carcinoma from large cell carcinoma is important because it identifies those patients at highest risk for the development of recurrent lung cancer.

From the Department of Surgery, Division of Cardiothoracic Surgery,[a] and the Department of Pathology,[b] Washington University School of Medicine, St Louis, Mo.

Read at the Eighty-fourth Annual Meeting of The American Association for Thoracic Surgery, Toronto, Ontario, Canada, April 25-28, 2004.

Received for publication April 22, 2004; revisions received Feb 1, 2005; accepted for publication Feb 24, 2005.

Address for reprints: Richard J. Battafarano, MD, PhD, 1 Barnes-Jewish Plaza, 3108 Queeny Tower, St Louis, MO 63110-1013 (E-mail: battafarano@msnotes.wustl.edu).

J Thorac Cardiovasc Surg 2005;130:166-72

0022-5223/$30.00

Copyright © 2005 by The American Association for Thoracic Surgery

doi:10.1016/j.jtcvs.2005.02.064

GTS

Large cell neuroendocrine carcinomas (LCNECs) of the lung display the morphologic and immunohistochemical characteristics common to neuroendocrine tumors and the morphologic features of large cell carcinomas (LCCs). The 1999 World Health Organization International Association for Staging of Lung Cancer histologic classification of lung and pleural tumors grouped a number of histologic variants under the heading "large cell carcinoma," including LCNEC, combined LCNEC, basaloid carcinoma, lymphoepithelioma-like carcinoma, clear cell carcinoma, and LCC with rhabdoid phenotype.[1] Although this classification scheme placed all lung cancers with large cell characteristics in a separate category, it did not address the biologic behavior of these histologic variants.

Travis and colleagues[2] proposed a separate category of pulmonary neuroendocrine tumors in which LCNEC was distinct from typical carcinoid tumors, atypical carcinoid tumors, and small cell lung cancer (SCLC). LCNEC was described as having a cell size at least 3 times that of SCLC, an organoid growth pattern, cellular palisading or rosette-like areas, a high mitotic rate, and a variably granular chromatin pattern.[3] The spectrum of neuroendocrine tumors was further classified by Dressler and associates[4] on the basis of histologic characteristics and clinical behavior. Grade I neuroendocrine lung cancers corresponded to classic typical carcinoid tumors. Grade II neuroendocrine lung cancers corresponded most closely with atypical carcinoid cancers. Grade III tumors were divided into small cell neuroendocrine lung cancer (SCLC) and LCNEC. Regardless of which classification scheme is preferred, accurate differentiation of LCNEC from other variants of non–small cell lung cancer (NSCLC) and SCLC might be difficult and often requires specific immunohistochemical stains for neuroendocrine markers.

The true incidence of LCNEC is in all probability very low, although it has not been well defined. In a series reported by Jiang and coworkers[5] of 766 resected primary lung cancers, 22 (2.9%) were classified as LCNECs. Takei and colleagues[6] reported a similar rate of 3.1% (87/2790) in their series. In published series the overall 5-year actuarial survivals for surgically resected LCNEC range from 13% to 57% (Table 1).[3-11] These results appear to be substantially worse than those observed in other histologic types of NSCLC. Therefore, considerable debate has emerged as to whether these tumors should be classified and treated as NSCLC or considered together with small cell carcinoma because of their apparent aggressive behavior. The objective of this study was to examine the effect of LCNEC on survival after surgical resection in patients with this histologic subtype of NSCLC.

TABLE 1. Previous series examining overall survival for LCNEC

Author	Year	No. of patients	5-year OS	5-year OS stage I (n)
Dressler et al[4]	1997	40	13%	18% (25)
Travis et al[3]	1998	37	27%	NA
Jiang et al[5]	1998	22	44.8%	NA
Garcia-Yuste et al[8]	2000	22	21%	33% (13)
Iyoda et al[7]	2001	50	~35%*	NA
Zacharias et al[9]	2003	20	47%	88% (9)
Takei et al[6]	2003	87	57%	67% (41)
Paci et al[10]	2004	48	21%	27% (29)
Doddoli et al[11]	2004	20	36%	NA

LCNEC, Large cell neuroendocrine carcinoma; *OS*, overall survival; *NA*, not applicable. *Number estimated from survival curve.

Methods

Population Under Study

The Barnes-Jewish Hospital Cancer Registry and the Thoracic Surgery database were queried for patients undergoing surgical resection of lung cancer between July 1, 1988, and December 31, 2002, for large cell tumors. All slides of LCCs encountered during that time were individually reviewed by one pathologist (J.H.R.) and segregated into the categories of LCNEC, mixed LCNEC (in which at least one portion of the tumor was LCNEC), or LCC on the basis of morphology and differentiation. The pathologist was blinded to the clinical data associated with the pathologic specimens. Surgical pathology reports of all patients selected from this database query were individually reviewed, and the final pathologic staging was assigned according to the 1997 revisions in the International System for Staging Lung Cancer.[12]

Tumor recurrence, patient survival, and cause of death were determined for each patient. Follow-up information, including cause of death, was acquired within the last 6 months for all patients through clinic follow-up notes, direct patient or family contact, contact with the patient's primary care physician, and review of all death certificates. This study represents a secondary data analysis of a prospective cohort study. Approval for this study was granted from the Washington University School of Medicine Human Studies Committee.

Statistical Analysis

Descriptive statistics were used to describe the patients' characteristics and outcomes. Kaplan-Meier (product limit) graphs were used to demonstrate survival over time and freedom from recurrence of disease. Survival and event-free survival comparisons between groups of patients were completed by the Mantel-Haenszel log-rank test. The Cox multivariate proportional hazards regression model was used to identify independent risk factors for death and recurrence in the studied patient population, including the variables of age, sex, histology, and stage. All data analysis was performed with SPSS (SPSS 11.0 for Windows; SPSS, Inc, Chicago, Ill).

Results

Patient Demographics

Of 2089 patients undergoing resection for NSCLC between July 1, 1988, and December 31, 2002, 82 (3.9%) had large cell lung cancers. Of these 82 cancers, 45 (54.9%) were

Download English Version:

https://daneshyari.com/en/article/9979460

Download Persian Version:

https://daneshyari.com/article/9979460

Daneshyari.com