Should Large Cell Neuroendocrine Lung Carcinoma be Classified and Treated as a Small Cell Lung Cancer or with Other Large Cell Carcinomas?

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Background: To compare the presenting and prognostic characteristics of patients with large cell neuroendocrine lung cancer (LCNELC) with those of patients with small cell lung cancer (SCLC) or other large cell carcinomas (OLCs) and to compare overall survival (OS) and lung cancer-specific survival (LCSS) rates for patients undergoing definitive resection without radiotherapy (S-NoRT).

Methods: The Surveillance Epidemiology and End Results Database-17 from 2001 to 2007 was used. Differences between population characteristics were compared using χ^2 and Wilcoxon tests. The log-rank test and Cox models were used to compare differences in OS and LCSS.

Results: There were 1211 patients with LCNELC (324 in the S-NoRT group), 8295 patients with OLC (1120 S-NoRT), and 35,304 patients with SCLC (355 S-NoRT). The proportion of all large cell carcinomas constituted by LCNELC increased from 8 to 21% during the study period; and the proportion of patients with large cell carcinoma undergoing S-NoRT increased from 16 to 26%. Presenting and histopathologic characteristics and treatment factors of patients undergoing S-NoRT for patients with LCNELC were more similar to those of patients with OLC than to those with SCLC. OS and LCSS rates for patients with LCNELC undergoing resection without radiation were similar to those of patients with OLC and better than those for patients with SCLC, but the differences were not statistically significant on multivariate analysis.

Conclusions: The clinical, histopathologic, and biologic features of LCNELC are more similar to OLC than to SCLC. Therefore, LCNELC should continue to be classified and treated as a large cell carcinoma.

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In 1991, Travis et al.[1,2] described a rare but distinct histologic lung cancer, described as having large cell sizes with abundant cytoplasm, a high mitotic rate, extensive necrosis, and a neuroendocrine growth pattern. These large cell neuroendocrine lung cancers (LCNELCs) shared some histologic features with small cell lung carcinoma (SCLC), but SCLC consists of smaller cells with scant cytoplasm, which invades tissues in sheets. The higher mitotic rates and more extensive necrosis of LCNELC and SCLC distinguish them from the lower grade neuroendocrine tumors, typical and atypical carcinoids. The World Health Organization (WHO) currently classifies LCNELC as a distinct subtype of pulmonary large cell carcinoma.[3] Diagnosis of LCNELC hinges on recognition of a neuroendocrine architectural pattern, appropriate cytologic features and mitotic rate, and confirmation of neuroendocrine differentiation by immunohistochemistry or electron microscopy.[4]

A previous retrospective report demonstrated that survival rates of patients with surgically-resected LCNELC and SCLC were similar to each other and inferior to that of patients with atypical carcinoid and typical carcinoid tumors.[5] The authors concluded that histology-specific sensitivity to treatment should be clarified. Nevertheless, questions remain whether LCNELC is best classified and treated as a SCLC or as a large cell carcinoma. The purposes of our study were, therefore, to help determine these issues by comparing the presenting patient and histopathologic characteristics of all patients with LCNELC with those of patients with SCLC and other large cell carcinomas (OLCs); and comparing patient, histopathologic, and treatment factors and lung cancer-specific survival (LCSS) and overall survival (OS) rates of patients with LCNELC undergoing surgical resection without radiation (S-NoRT) with those of patients SCLC and OLC.

PATIENTS AND METHODS

Data were obtained from the Surveillance, Epidemiology, and End Results (SEER) program of the US National Cancer Institute. The SEER-17 database includes patients diagnosed from 1973 to 2007 and is derived from a set of

geographically defined, population-based, cancer registries operated under direct contract by local nonprofit organizations in Connecticut, Iowa, Hawaii, New Mexico, Utah, Atlanta, Detroit, Los Angeles, San Francisco-Oakland, San Jose-Monterey, Seattle-Puget Sound, Rural Georgia, Kentucky, Louisiana, New Jersey, and among Arizona Indians and Alaskan Native populations.[6] The case ascertainment rate from the SEER registries has been reported to be 97.5% and is felt to be generally representative of the entire American population.[7] Data on patients diagnosed from 2001 to 2007 were accessed on May 9, 2010. Because we used existing data which did not identify individual subjects, informed consent by the study participants was not necessary.

Patients diagnosed with LCNELC, OLC, and SCLC were selected for analysis by using histology codes in the database. LCNELC, code 8013; SCLC, code 8041 plus combined small cell (8045) and fusiform cell carcinomas (8043); and OLC, large cell carcinoma-nos (8012), large cell carcinoma with rhabdoid phenotype (8014), lymphoepithelioma-like carcinoma (8082), basaloid carcinoma (8123), and clear cell carcinoma (8310).

Sociodemographic and clinical factors recorded included age; sex; race; marital status; tumor stage; T-stage; N-stage; M-stage; extension coding (see later); number of nodes examined (for patients undergoing surgery); number of nodes positive; pathologic tumor size; tumor location (right upper, right middle, right lower, left upper, left lower lobe, mainstem bronchi, lung not otherwise specified, and overlapping lesions); type of resection for patients undergoing definitive surgery (wedge/segmental resection, [bi]lobectomy, or pneumonectomy); the use of radiation and its sequencing with surgery; and tumor grade (well differentiated, moderately differentiated, unknown, poorly differentiated, and undifferentiated). Fewer than 1% of LCNELC, OLC, and SCLC were classified as grade 1 or 2, and these were excluded from further analysis due to possible confusion with atypical or typical carcinoids.

Extension codes used to describe different presentations of lung cancer were different between the years 2001–2003 and 2004–2007, resulting in slightly different definitions of central-based lesions during the two time periods. Codes used from 2001 to 2003 were separate tumor nodules in the same lobe (65); malignant pleural effusion (72); separate tumor nodules in a different lobe (77); and metastatic disease involving the contralateral lung (78). Central-based lesions included those with extension to the mainstem bronchus greater than 2 cm from the carina (20); tumor confined to the carina (25); tumor involving the mainstem bronchus less than 2 cm from carina (50); involvement of major blood vessels, esophagus, mediastinum, carina or trachea (70); involvement of the heart or visceral pericardium (71); and malignant pericardial effusion (79). Codes used from 2004 to 2007 included multiple lesions in same lobe (65) and malignant pleural effusion (72). Central lesions were identified as superficial tumors involving bronchial wall (11); tumors extending to (20) or involving (21) the mainstem bronchus; tumor confined to the hilus (23) or carina (25); atelectasis or obstructive pneumonitis extending to the hilar region (40) plus tumor involving the mainstem bronchus less than 2 cm from the carina (52); tumor involving the mainstem bronchus less than 2 cm from the carina (50) plus extension to visceral pleura plus tumor (53); atelectasis or obstructive pneumonitis involving the entire lung (55); involvement of the parietal pericardium or pericardium, not otherwise specified (56); involvement of major blood vessels, esophagus, mediastinum or trachea (70); involvement of the heart or visceral pericardium (71); extension to the aorta (74); invasion of vertebral body (75); involvement of the inferior vena cava (77); and malignant pericardial effusion (79). The presence of tumor nodules in a different ipsilateral lobe (35) was differentiated from having metastatic disease in the contralateral lung (39).

The proportion of patients with SCLC, OLC, LCNELC, and NSCLC in the SEER database was compared. Differences between these proportions and characteristics of these histologic groups were compared using χ^2 and Wilcoxon tests.

OS was defined as the time from date of diagnosis until the date of death. Patients alive at last follow-up were censored at that time. LCSS was defined as the time from the date of diagnosis until the date of death due to lung cancer. Patients alive at last follow-up were censored at that time, and patients who died due to other causes were censored at the time of death. Kaplan-Meier curves were constructed for OSS and LCSS; the log-rank test and Cox models were used to compare differences between these in different subgroups.

RESULTS

There were 1211 patients with LCNELC (324 in the S-NoRT group), 8295 patients with OLC (1120 S-NoRT), and 35,304 patients with SCLC (355 S-NoRT) identified in the database. LCNELC constituted only 0.4 to 0.6% of all lung cancers and 0.8 to 1% of lung cancers in patients undergoing definitive resection during the study period. The proportion of all large cell carcinomas constituted by LCNELC increased by 160% during the study period (from 8 to 21%, $p < 0.01$); and the proportion of patients with large cell carcinoma undergoing S-NoRT increased by 60% (from 16 to 26%, respectively, $p < 0.01$). The proportion of OLC and LCNELC together as a proportion of all lung cancers slightly decreased over the years of our study for all patients (from 5 to 3%) and for those undergoing surgery (from 6 to 4%).

Presenting characteristics for all patients presenting with SCLC, OLC, and LCNELC are described in Table 1. There were significant differences between patients with LCNELC and OLC in 7 of 10 categories and between LCNELC and SCLC in 9 of 10 categories. Patients with LCNELC and OLC were more likely to be male and undergo surgical resection, but less likely to be non-Hispanic white or present with metastatic disease than patients with SCLC. Furthermore, patients with either OLC or LCNELC were less likely to experience death due to lung cancer than patients with SCLC. Comparison of these characteristics for only patients undergoing surgery without radiotherapy is listed in Table 2. Again, LCNELC was closer to OLC than SCLC, differing significantly from the former in 3 of 15 categories and from the latter in 7 of 15 categories. In particular, patients with SCLC were more likely to be in advanced stages, have a lower a number of nodes examined, and have a higher lymph node

