Survival after resection of synchronous non–small cell lung cancer

Thomas Fabian, MD, FCCP,[a] Ayesha S. Bryant, MSPH, MD,[b] Angela L. Mouhlas, MD,[a] John A. Federico, MD,[c] and Robert J. Cerfolio, MD, FACS, FCCP[b]

Objectives: Our objective was to determine the long-term survival of patients with resected synchronous multiple pulmonary malignant tumors.

Methods: This is a multi-institutional retrospective study of patients who underwent surgical resection of synchronous (nonbronchioloalveolar) non–small cell lung cancer.

Results: Between March 1996 and December 2009, 67 patients (30 men) underwent 121 operations. Forty-four patients had bilateral tumors. Positron emission tomographic scans were performed in 58 (87%) patients, computed tomographic scans and magnetic resonance imaging of the brain in 53 (79%), and mediastinoscopy in 56 (84%). N2 lymph nodes were benign in all patients before undergoing resection of bilateral tumors of the same histologic type. Types of resection were lobectomy in 62, sublobar in 73, and pneumonectomy in 1. Eleven patients (16%) had postoperative morbidities. Cancer-specific 3- and 5-year survivals were 73% and 69%, respectively, and overall 3- and 5-year survivals were 64% and 53%, respectively. Subgroup analysis demonstrated no difference in overall survival at 5 years between bilateral tumors of the same histologic type (M1a) (49%) versus different histologic types 42% ($P = .88$), or between bilateral tumors (50%) and ipsilateral tumors (54%) ($P = .83$).

Conclusions: The 5-year survival of surgically resected, synchronous, N2-negative, nonbronchioloalveolar, non–small cell lung cancer is excellent, even in patients who have bilateral lung lesions that harbor the same histologic features. Although the new TNM classification system labels this disease as clinical stage IV M1a, survival acts more like a separate T1 lesion after surgical resection. Thus, surgical resection should be considered in appropriately selected patients who have multiple pulmonary malignant tumors that are N2 negative. (J Thorac Cardiovasc Surg 2011;142:547-53)

GTS

With improved imaging studies, particularly high-resolution computed tomography (CT) and positron emission tomography (PET), patients with lung cancer frequently have more than 1 suspicious lung nodule. In many instances, these tumors represent metastatic disease from a single original tumor and are classified correctly by current TNM classification as T3, T4, or M1a.[1] Still other possibilities include nonrelated synchronous multiple primary lung cancers (SMPLC). Stedman's Medical Dictionary[2] defines synchronous as ''occurring simultaneously'' and metachronous as ''not synchronous; multiple separate occurrences such as multiple primary cancers developing at intervals.'' Few studies accurately or consistently describe patients with synchronous lung cancer, their evaluation, treatment, or long-term outcomes. This limits the understanding of this clinical scenario. Past[3] and present[1] international systems for the staging of lung cancer have added little to this issue, further leading to confusion among physicians who care for such patients. Although it can be inferred that different histologic features would be classified independently, this is not true of tumors of the same histologic classification. Presently, these disease states are defined as T3 (same lobe), T4 (ipsilateral different lobe), or contralateral lung (M1a). However, some of these multiple tumors are in fact synchronous and unrelated even when histologically similar. When current guidelines are implemented and dictate patient care, this frequently results in undertreatment of potentially curable SMPLC.

The primary objective of this study was to determine long-term survival in patients who underwent complete surgical resection of truly SMPLC in the hopes of clarifying optimal treatment and to serve as a reference for future study in this group of patients.

METHODS

This is a multi-institutional retrospective cohort study of patients who underwent surgical resection of synchronous lung cancer (non-BAC) between March 1996 and September 2009. The study received institutional review board approval at all 3 participating institutions: Albany Medical

From the Section of Thoracic Surgery,[a] Department of Surgery, Albany Medical Center, Albany, NY; the Division of Cardio-thoracic Surgery,[b] Department of Surgery, University of Alabama at Birmingham, Birmingham, Ala; and the Section of Thoracic Surgery,[c] Department of Surgery, Hospital of St Raphael, New Haven, Conn.

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Address for reprints: Thomas Fabian, MD, Associate Professor of Surgery, 47 New Scotland Ave, Albany, NY 12208 (E-mail: FabianT@mailamc.edu).

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Abbreviations and Acronyms

CT = computed tomography
BAC = bronchioloalveolar cancer
MRI = magnetic resonance imaging
PET = positron emission tomography
SMPLC = synchronous multiple primary lung cancer

Center, Albany, New York, Hospital of St Raphael, New Haven, Connecticut, and University of Alabama at Birmingham, Birmingham, Alabama. Waiver of individual patient consent was granted.

All patients who underwent surgical resection of more than 1 non–small cell lung cancer (NSCLC) were reviewed for possible inclusion. Patient demographics, preoperative evaluation, surgical treatment, pathologic stage, mortality, cancer-free survival, site of recurrence, overall survival, and cause of death were primary end points and were identified by multiple sources including medical records, follow-up radiographic studies, hospital computer information systems, tumor registry, Social Security Death Index, and, when necessary, telephone contact with patients or surviving family members. Patients who did not meet the inclusion criteria were excluded from further evaluation. Patients with SMPLC, by our inclusion criteria, received 2 separate staging designations.

Inclusion/Exclusion Criteria

Patients who were admitted with or were identified intraoperatively or pathologically as having more than 1 tumor and who underwent surgical resections with the intent of cure were eligible for inclusion in this study. Patients with typical carcinoid tumors, BAC, or nonmalignant nodules were excluded. Patients in whom metachronous pulmonary nodules developed were also excluded. Multiple ipsilateral tumors were included only if the tumor had different histologic features. Ipsilateral tumors of the same histologic type but different subtypes were excluded. Bilateral tumors of the same histologic type were included in this study, provided mediastinal evaluation proved N2 lymph node stations were benign. Bilateral tumors of different histologic types with positive N2 lymph nodes were included in this study.

Stages of disease were recorded according to the seventh edition of the TNM classification. We reported a stage for each of the 136 tumors as if it were a separate cancer and the other nodules were not present. If a patient had a T2 and a T1 lesion in the same side of the chest, of different histologic type, and 1 of the N1 lymph nodes was positive, both lesions were listed as N1 if the specific histologic type of the N1 lymph node could not be determined, that is, T2 N1 M0 and the other T1 N1 M0.

Statistical analysis was completed using SAS 9.1 (SAS Institute, Inc, Cary, NC). Continuous data are presented as means and categorical data are presented as percentages. Fisher's exact test or the Pearson χ^2 test was used to assess categorical data and the Wilcoxon rank sum was used for continuous data. Actuarial survival of patients was estimated by Kaplan-Meier analysis, with P values calculated by log-rank statistics. For the multivariable survival analysis, variables with a univariate P value $< .08$ were entered into a Cox stepwise proportional hazards model. Patients alive at the end of the study period were censored for purposes of survival analysis, and time-related events were calculated from the time of the initial procedure. Death from any cause was used to determine the overall survival, and only cancer-related deaths were included in the cancer-specific mortality. Recurrence of cancer was used to determine the disease-free survival. Local recurrence was defined as recurrence of tumor within the same lobe, regional recurrence was defined as the involvement of mediastinal lymph nodes ipsilateral to the side of surgery, and distant recurrence was defined as recurrence in the contralateral lung or in the remaining lung on the same side but in a different lobe from the one on which the operation was performed or tumor recurrence elsewhere in the body. Operative deaths were included in the survival analyses. Follow-up consisted of chest and abdominal CT every 6 months for the first 2 years and yearly afterward. The final data acquisition was December 2009.

RESULTS

Between March 1996 and September 2009, a total of 67 patients (30 men) underwent 121 surgical procedures to resect 136 lung cancers. Patient characteristics are shown in Table 1. Forty-four patients had bilateral tumors and 23 had ipsilateral tumor locations as shown in Figure 1. PET scans were performed in 58 (87%) patients and CT/magnetic resonance imaging (MRI) of the brain in 53 (79%) patients. N2 lymph nodes were determined to be to be negative for metastatic disease in all patients before resection of same-histology tumors. Tumor details and pathologic stage are shown in Table 2. Mediastinal (N2) lymph nodes were positive in 2 patients before resection of bilateral tumors of different histologic cell type. Surgical resections included lobectomy in 62, sublobar resection in 73, and pneumonectomy in 1 patient. Median interval between operations for those with bilateral tumors was 2.0 months. Of the 67 patients, 11 (16.4%) had major postoperative morbidities and 2 (2.9%) died after their second operative procedure. Operative mortality occurred in 2 (1.7%) of 121 surgical resections.

Overall survival and cancer-specific survival are shown in Figure 2. Cancer-specific 3- and 5-year Kaplan-Meier survival was 73% and 69%, respectively, and overall 3- and 5-year survival was 64% and 53%, respectively. Univariate analysis demonstrated no difference in overall survival at 5 years between bilateral tumors of the same histologic type (M1a) (49%) versus different histologic types (42%) ($P = .88$) or between bilateral tumors (50%) and ipsilateral tumors (54%) ($P = .83$). Mean follow-up was 45.5 months.

Table 3 shows the results of the univariate analysis that was performed to identify variables associated with survival. Analysis was performed both for overall survival and for cancer-specific survival. There was a significant difference based on highest pathologic stage for both overall survival ($P = .001$) analysis and cancer-specific survival analysis ($P = .009$). Additionally, there was a trend toward significantly greater cancer-free survival in patients who had all 3 preoperative staging tests (5-year cancer-free survival 75% in patients who had all 3 preoperative tests and 57% in those that did not), but these differences did not achieve statistical significance ($P = .160$). There were no significant differences in survival between men and women by age, histologic type, or tumor location.