Indications for Adjuvant Mediastinal Radiotherapy in Surgically Resected Small Cell Lung Cancer

Elliot Wakeam, MD, MPH, Meredith Giuliani, MBBS, MEd, Natasha B. Leighl, MD, MS, Samuel R. G. Finlayson, MD, MPH, Thomas K. Varghese, MD, MS, and Gail E. Darling, MD

Division of General Surgery, Department of Surgery, Division of Thoracic Surgery, Department of Surgery, Department of Radiation Oncology, and Division of Medical Oncology, Department of Medicine, University of Toronto, Toronto; Radiation Medicine Program Princess Margaret Cancer Centre, Toronto, Ontario, Canada; and Department of Surgery, University of Utah, Salt Lake City, Utah

Background. Adjuvant mediastinal radiotherapy (AMR) is used after surgical resection for patients with small cell lung cancer (SCLC), but data guiding its use are scant. We sought to examine whether AMR was associated with an improvement in survival for resected SCLC patients and to define subpopulations who should be selected for AMR.

Methods. Patients undergoing lobectomy, pneumonectomy, and sublobar resection for SCLC were identified in the National Cancer Database (2004 to 2013). Kaplan-Meier survival curves and Cox proportional hazards were used to evaluate associations between AMR and survival. Hazard ratios were adjusted for patient comorbidity, demographics, tumor characteristics, such as stage, grade, histology, and margin status, and receipt of adjuvant chemotherapy.

Results. We identified 3,101 patients. Those receiving AMR were younger, more likely to have greater pathologic T and N stage, to undergo sublobar resection, and to have a positive margin. Kaplan-Meier curves showed better median survival for patients with pN1 or pN2 disease who received AMR. After adjustment, Cox models showed AMR was associated with a lower risk of death for pN1 (hazard ratio, 0.79; 95% confidence interval, 0.63 to 1.00; $p = 0.05$) and pN2 (hazard ratio, 0.60; 95% confidence interval, 0.48 to 0.75; $p < 0.0001$). In the overall cohort, AMR was not associated with better survival in node-negative patients. AMR was, however, associated with improved survival for patients receiving sublobar resection (hazard ratio, 0.72; 95% confidence interval, 0.57 to 0.90; $p = 0.004$).

Conclusions. AMR is associated with longer survival for node-positive patients after resection for SCLC, especially those with pN2. AMR may also be associated with longer survival in patients undergoing sublobar resections.

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Small cell lung cancer (SCLC) is a deadly malignancy comprising approximately 15% of all new lung cancer diagnoses in the United States each year. It continues to carry a poor prognosis even with modern chemotherapy and radiation-based strategies [1]. The standard of care in most patients with limited, or stage I-IIIA disease, is concurrent chemoradiation therapy with adjuvant platinum-based chemotherapy, followed by prophylactic cranial irradiation [2, 3]. Inclusion of surgical intervention in multimodality treatment has been reported with mixed results [4, 5], although early trials showed little benefit for surgical resection [6, 7].

However, more recent data have demonstrated that surgical resection may in fact benefit patients more than was once thought [8–11]. Current National Comprehensive Cancer Network guidelines, as well as those from the American Society of Clinical Oncology and the European Society of Medical Oncology, recommend invasive mediastinal staging for all T1/T2 patients with no evidence of metastasis [12–14]. Further, these guidelines recommend subsequent lobectomy for medically fit patients who are found to be pathologically node-negative. Prior work has shown that the subset of resectable patients has reasonable 5-year survival of approximately 40% to 50% [8], especially with the addition of adjuvant chemotherapy [11]. Some investigations have additionally found associated survival improvements with the addition of resection, even for patients with more advanced clinical stages, up to IIIB [10].

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However, further strategies for adjuvant treatments such as irradiation have been less well studied. Two recent analyses of the National Cancer Database (NCDB) of radiotherapy in the adjuvant setting have been completed. Yang and colleagues [11] examined adjuvant brain irradiation but did not examine chest radiotherapy. Postoperative radiotherapy has been investigated with regard to radiation delivered to the peripheral lung fields [15], but no investigations to date have focused on mediastinal radiation fields. We use the term adjuvant mediastinal radiotherapy (AMR) to denote radiation delivered specifically to the mediastinum, in distinction to the term postoperative radiotherapy. AMR thus does not include radiation delivered to peripheral lung fields.

We had two goals in this investigation: the first was to examine whether AMR was associated with longer survival in patient strata defined by pathologic T and N stage; and second, we sought to define high-risk groups in whom administration of AMR might be considered. Patients undergoing sublobar resection and those not receiving chemotherapy are known to be at high risk for poor outcomes, and hence, these patients were examined as possible populations that may benefit from AMR.

Patients and Methods

Population and Data Sources

The NCDB is a national cancer registry administered jointly through the American College of Surgeons' Commission on Cancer and the American Cancer Society [16]. The database contains approximately 26 million patients from more than 1,500 participating institutions and captures approximately 70% of newly diagnosed cancer cases in the United States. Standardized collection and data definitions have been previously described. The NCDB collects data on patient and hospital characteristics, cancer diagnosis, staging, treatments, and outcomes. The data used in this study are derived from a deidentified NCDB participant user file. The American College of Surgeons and the Commission on Cancer have not verified and are neither responsible for the analytic or statistical methodology used nor the conclusions drawn from these data by the investigators. The University of Utah IRB exempted this investigation from review.

The study population included patients aged 18 years or older, with no other history of malignancy, diagnosed from 2004 to 2013. Patients were restricted to histologic diagnosis of invasive small-cell bronchogenic carcinoma confirmed by microscopic examination of tissue specimen or cytologic specimen, and International Classification of Diseases for Oncology, Third Edition codes 8041 to 8045. Clinical and pathologic stages are reported according to the Seventh Edition of American Joint Committee on Cancer's tumor, node, and metastases (TNM) staging criteria [17].

We examined patients who underwent lobectomy, pneumonectomy, or sublobar resection during the study period. Patients with other procedures, such as radiofrequency ablation, were excluded. Only those patients with complete pathologic TNM staging information as well as nonmissing survival and follow-up information were included. Palliative status, which is recorded as a separate variable in NCDB data, was used to identify patients treated with palliative intent for exclusion. Patients with pathologic stage N3 and M1 were excluded. Lastly, we excluded any patient with a radiation dose of less than 40 Gy to the mediastinum/central chest because these patients may be receiving noncurative doses of radiation. Our main outcome of interest was overall survival. The NCDB defines two survival variables: the vital status (alive/dead) and months to the last contact or death (survival time).

AMR and Chemotherapy Data

We used the variable "radiation treatment volume" in the NCDB to identify the anatomic radiation target. This variable reflected what was thought by the reporting radiation oncologist to be "the most clinically significant regional radiation therapy delivered to the patient during the first course of treatment" [16]. This variable was used to identify patients if radiation was administered to the mediastinal nodes/central chest. This field can include lung but is coded separately from patients receiving targeted radiation to peripheral lung structures.

Total radiation doses in centigray (cGy) were abstracted from the databases and reported as median doses. Boost doses were added to the initial radiation doses and included in the total. The number of fractions is not recorded in the NCDB data. The NCDB does not record separate data on prophylactic cranial irradiation for those patients receiving radiation to the primary site, and hence this information was not included.

Adjuvant chemotherapy is recorded as multiagent or single agent, but the specific agents and cycle numbers are not recorded. Further, although we can ascertain that a patient received both chemotherapy and radiotherapy in the adjuvant setting, whether these adjuvant therapies were given sequentially or concurrently is not known.

Primary Analyses: Survival Stratified by TNM Stage

The primary aim of our investigation was to evaluate the effect of AMR in patients stratified by stage. To do this, patients were stratified by pathologic T and N categories to evaluate the effect of AMR on overall survival. Adjusted Cox proportional hazards models and Kaplan-Meier survival analyses were used, as described below.

Secondary Analyses: Identification of High-Risk Subgroups

One of our aims was to identify high-risk subgroups in which AMR might be considered. We sought to evaluate the differential effect of AMR in several subpopulations known to be at risk for relatively poor overall survival. We hypothesized that AMR might be associated with longer survival in those patients who undergo sublobar resection and those not receiving adjuvant chemotherapy because both of these groups are known to be at higher risk for recurrence and worse overall survival [8, 11]. Patients receiving sublobar resection and those not receiving