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Original article

Cardiac mortality in limited-stage small cell lung cancer

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ABSTRACT

Introduction: Life expectancy of patients with limited-stage small cell lung cancer (LS-SCLC) continues to rise; thus, characterization of long-term toxicities is essential. Although there are emerging data linking cardiac irradiation doses with survival for non-small cell lung cancer, there are currently minimal data on cardiac-specific mortality (CSM) in LS-SCLC. The goal of this investigation was to evaluate CSM between left- and right-sided cases.

Methods: The Surveillance, Epidemiology, and End Results database was queried for stage I–III primary SCLC patients receiving radiotherapy; CSM was compared between left- and right-sided diseases. Accounting for mortality from other causes, Gray's test compared cumulative incidences of CSM between both groups. Multiple multivariate models examined the independent effect of laterality on CSM, including the Fine and Gray competing risk model and the Cox proportional hazards model.

Results: Of 19,692 patients, 7991 (41%) were left-sided and 11,701 (59%) were right-sided. Left-sided patients experienced significantly higher CSM overall (3.3% vs. 2.6%, $p = 0.004$). Laterality was an independent predictor of CSM in the overall population in the Fine and Gray competing risk model ($p = 0.006$) as well as the Cox proportional hazards model ($p = 0.007$). The overall hazard ratio for CSM by disease laterality was 1.27 (95% confidence interval, 1.08–1.50). Laterality had no statistical association with non-cardiac mortality in the Fine and Gray competing risk model ($p = 0.130$).

Conclusions: Although causation between radiotherapy and CSM in LS-SCLC cannot be stated based on these data, we encourage clinical attentiveness to cardiac-sparing radiotherapy for LS-SCLC, along with further investigation evaluating dosimetric correlates for cardiotoxicity.

Introduction

Limited-stage small cell lung cancer (LS-SCLC) has traditionally been associated with a poor prognosis, with historical trials reporting a median overall survival (OS) around one year [1]. However, survival has since increased based on improvements in medical imaging, staging, therapy paradigms, and salvage therapies. The landmark Intergroup 0096 trial demonstrated a median OS of 19 months in the once-daily arm and 23 months in the twice-daily group [2]. The most contemporary trial, the Concurrent Once-Daily versus Twice-Daily Chemoradiotherapy (CONVERT) study, the observed median OS was 25 months in the once-daily cohort and 30 months in the twice-daily arm [4]. That trial was notable for utilizing positron emission tomography – computed tomography (PET-CT) staging in many patients. This imaging modality can refine patient selection (related to stage migration) in LS-SCLC patients treated with chemoradiation [3], along with three-dimensional radiotherapy (RT) techniques.

As the life expectancy of LS-SCLC continues to rise, long-term therapy-related toxicities are increasingly critical to evaluate. Indeed, figures from the CONVERT trial are numerically comparable to, or higher than, those of modern trials for locally-advanced non-small cell lung cancer (NSCLC) in both the definitive [5] and neoadjuvant [6] settings.

To this extent, a token and striking finding of the landmark Radiation Therapy Oncology Group (RTOG) 0617 trial was the impact of heart RT doses on OS. Namely, the volume of heart receiving at least 5 Gy (V5) and that receiving at least 30 Gy (V30) correlated with OS on multivariate analysis therein. Those findings have been corroborated by several other analyses [7–12].

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Owing to the historically poor prognosis of LS-SCLC, notable trials have not detailed cardiotoxicity in these patients, and it is currently unknown whether this stems from a lack of cardiac events or from lack of documentation/reporting [2,13–14]. One of the few reported instances in randomized trials showed a 0.6–0.7% incidence of severe or lethal cardiac toxicity, but the attribution was made to chemotherapy and not RT [15]. In the modern CONVERT trial, 3 of 274 patients in the twice-daily arm died of cardiovascular causes, as compared with 8 of 273 patients in the once-daily group [4].

The Surveillance, Epidemiology, and End Results (SEER) database has been of substantial utility for impactful studies evaluating cardiac-specific mortality (CSM) for NSCLC in the postoperative and definitive settings [16–18], but there is a current lack of data evaluating this for patients with LS-SCLC. The goal of this work was to characterize potential associations between CSM and RT in left- versus right-sided cases. Although this study cannot imply causation between RT and CSM, it may serve as an impetus to alert radiation oncologists to consider heart doses when performing treatment planning for LS-SCLC.

Materials and methods

In order to preserve a degree of uniformity from study to study, the methodology of this study paralleled existing publications that compared CSM between left- versus right-sided patients [16–18]. The SEER database (SEER 18 Regs Research Data Nov 2014 Sub) was queried using SEER * Stat software (version 8.3.4) to identify patients $\geq$18 years of age diagnosed with stage I-III SCLC between 1988 and 2014. These years corresponded to the start of TNM staging by SEER and most recent available patient information, respectively. Patients without RT, unknown laterality or bilateral disease, or who received surgery were excluded. Chemotherapy is not available through the SEER database, thereby precluding exclusion based on this parameter. SCLC was defined by the International Classification of Diseases for Oncology-3 codes 8041-8045. For each patient, information regarding demographics and clinical/-pathologic variables were extracted. Data regarding CSM were also collected, which referred to the proportion of patients dying from cardiac causes (per SEER coding) after the date of diagnosis.

Statistical analysis was performed using either STATA (version 14, College Station, TX) or R (versions 3.3.1, R Foundation for Statistical Computing, Vienna, Austria). Statistical tests were two-sided, with $p < 0.05$ denoting statistical significance. First, demographic differences were assessed between right- and left-sided patients using the chi-squared test. Second, the time course of cardiac deaths as a proportion of all deaths were graphed for yearly intervals following initial diagnosis, recognizing that the SEER database does not record information on RT completion time. For this tabulation, deaths were tabulated for each interval and not in a cumulative fashion (i.e., deaths were not counted twice). Third, cumulative incidence curves of CSM (from the date of diagnosis) were constructed for right- versus left-sided cases, accounting for mortality from other causes. The underlying hazards were statistically compared using Gray's test. The multivariate Fine and Gray competing risk model evaluated the effect of laterality while factoring in mortality from other causes. This encompassed many factors in the SEER dataset, including laterality, age, gender, race, site, and stage. Lastly, exploratory analysis of cardiac-specific survival (CSS, defined as survival pertaining to cardiac causes only) was conducted; stage I/II patients were only used, given that virtually all stage III patients received RT. CSS was compared (using the log-rank test) between subjects that received RT versus no RT; this was first done for the right-sided population alone and then repeated separately for left-sided cases.

Results

A complete patient selection diagram is shown in Fig. 1. From 884,610 total lung cancer patients, 125,368 had small cell lung cancer, and 19,692 patients met study criteria. Of these, 7991 (41%) were left-sided and 11,701 (59%) were right-sided. Table 1 gives patient characteristics according to laterality. There were similar proportions of right- and left-sided patients in each group. For all patients, the median follow-up was 14 months.

The time course of cardiac deaths as a proportion of all deaths (Fig. 2) was highest after 5 years (12.5%). Within 3 years of initial diagnosis, 7.8% of deaths were cardiac (2.9% within 1 year, 1.9% between years 1–2, and 3.0% between years 2–3). At 3–4 and 4–5 years, cardiac deaths were 5.0% and 7.2% of all deaths, respectively.

In the overall population, left-sided patients experienced similar overall mortality as their right-sided counterparts (84.1% vs. 84.1%, log-rank $p = 0.929$), but significantly higher CSM (3.3% vs. 2.6%, $p = 0.004$, Fig. 3). The overall hazard ratio was 1.27 (95% confidence interval, 1.08–1.50).

Table 2 shows results of univariate and multiple multivariate models, accounting for several confounding variables and mortality from other causes. Left-sided laterality was independently predictive of CSM in both the Fine and Gray competing risk model ($p = 0.006$) as well as the Cox proportional hazards model ($p = 0.007$). Of note, laterality had no statistical association with non-cardiac mortality ($p = 0.130$). Age, gender, and stage were also associated with cardiac mortality ($p < 0.05$ for all; Supplemental Fig. 1).

Lastly, exploratory analysis of CSS was performed by laterality and RT status. Of 4532 patients with right-sided disease, the 2393 patients undergoing RT actually experienced superior cardiac-specific survival in comparison to the 2139 without RT ($p < 0.001$). Of the 3297 left-sided cases, patients receiving RT ($n = 1666$) had worse cardiac-specific survival than patients without RT ($n = 1631$) ($p < 0.001$) (Supplemental Fig. 2).

Discussion

This is the first known study reporting incidence and trends of cardiac mortality in patients with LS-SCLC, and we show that CSM is independently linked to left-sided disease in LS-SCLC patients. This is especially important to report given the clear influence of the cardiac irradiation findings of RTOG 0617 for locally-advanced NSCLC.

There are several reasons to believe that the effect size (hazard ratios) of laterality on CSM for LS-SCLC patients may be more pronounced than numerical figures herein. First, many patients herein were not worked up with PET-CT and/or brain magnetic resonance imaging (thus presumably including a proportion of truly extensive-stage patients), and some were not treated with CT-based planning (thus presumably exposing more heart tissue to irradiation). Additionally, because SCLC is more likely to be centrally located and involve the mediastinum, it is often diagnosed as a bulky mediastinal mass that results in bilateral lung and heart irradiation, which can be different from the presentation of NSCLC. Although we statistically compared patients with a coded laterality, the centrally-located nature of SCLC may have served to blur the distinction between left- and right-sided diseases, especially relative to NSCLC. However, those with so-called "ambiguous" or "bilateral" disease that more closely involves the heart could possibly stand to benefit even more from cardiac-sparing RT (discussed subsequently). These results are also noteworthy given that stage I/II patients were included in this analysis given the time intervals included patients before the concept of delivering stereotactic body radiation therapy for early stage SCLC [19–21], and

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