Lung Cancer 90 (2015) 243–248

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Comparison of survival outcomes among standard radiotherapy regimens in limited-stage small cell lung cancer patients receiving concurrent chemoradiation

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ARTICLE INFO

Article history:
Received 6 March 2015
Received in revised form 1 July 2015
Accepted 3 August 2015

Keywords:
Radiotherapy
Dose
Fractionation
Limited
Small Cell
NCDB

ABSTRACT

Objectives: The optimal radiotherapy dose in concurrent chemoradiation (CRT) for limited-stage small cell lung cancer (SCLC) is controversial. We compared the effectiveness of several high-dose chemoradiation regimens using a large national dataset.
Materials and methods: Patients with non-metastatic SCLC treated with concurrent CRT were identified in the National Cancer Database base. Overall survival (OS) of patients receiving dose-fractionation regimens, matching those in the ongoing CALGB 30610 trial [45 Gy in 30 fractions (Fx) (45 Gy/30Fx), 70 Gy in 35 fractions (70 Gy/35Fx), and 61.2 Gy in 34 fractions (61.2 Gy/34Fx)], were compared using Kaplan-Meier analysis and multivariable Cox proportional hazards modeling.
Results: We included 1228 patients treated between 1998 and 2006 with CRT. Mean age was 62 years and 50% of patients were women. Radiotherapy dose-fractionation was 45 Gy/30Fx in 707 (57.6%), 70 Gy/35Fx in 53 (4.3%), and 61.2 Gy/34Fx in 468 (38.1%). Overall survival was similar among patients treated with 45 Gy/30Fx, 70 Gy/35Fx, and 61.2 Gy/34Fx, with median survival times of 21.5, 21.5, and 20.2 months, respectively ($p = 0.438$). Older age, male sex, larger tumor size, and more advanced stage were associated with inferior OS on Kaplan–Meier (all $p < 0.001$). Cox proportional hazards modeling adjusting for these factors demonstrated similar OS among patients receiving these three dose-fractionation regimens ($p = 0.815$).
Conclusions: We observed equivalent OS among patients with limited-stage SCLC being treated with three dose-fractionation regimens of concurrent CRT. This supports the use of any one of these regimens while awaiting the results of ongoing randomized trials.

1. Introduction

Small cell lung cancer (SCLC) is an aggressive malignancy marked by poor survival, even in patients with localized disease. Given the propensity for distant metastatic disease, chemotherapy represents the cornerstone of therapy. However, in patients without metastatic disease, several randomized trials and meta-analyses have demonstrated the importance of thoracic radiotherapy (RT) in improving local control and overall survival (OS) [1]. The benefit of delivering RT is maximized when delivered concurrently with chemotherapy, particularly when RT is started within a short interval of commencing chemotherapy [2,3].

While many aspects of chemoradiation (CRT) have been optimized, the ideal dose and schedule of RT has not been identified. Accepted doses range from 45 to 70 Gy with daily or twice-daily fractionation [4–6]. CALGB 30610, a phase III randomized controlled trial, was designed to compare three accepted regimens including 45 Gy in 30 twice-daily fractions over 3 weeks, 70 Gy in 35 daily fractions over seven weeks, and 61.2 Gy in 34 fractions delivered with accelerated fractionation over 5 weeks [7]. However, patient accrual to the 45 Gy and 70 Gy arms is ongoing, and results will not be available for several years. In the interim, comparative effectiveness data examining potential survival differences between these regimens is needed. To help fill this knowledge gap while awaiting trial results, we compared OS outcomes among

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http://dx.doi.org/10.1016/j.lungcan.2015.08.002
0169-5002/

patients with limited-stage SCLC treated with CRT using a large national database.

2. Materials and methods

2.1. Study design and data source

We performed a retrospective study using the National Cancer Database (NCDB). The NCDB is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. NCDB contains data pertaining to patient demographics, disease characteristics, treatment details, and overall survival outcomes for approximately 70% of newly diagnosed cancers in the United States. Importantly for this study, NCDB contains information regarding RT dose and timing, which is unavailable in the Surveillance, Epidemiology, and End Results (SEER) database. The data used in this study are derived from a de-identified NCDB file. The American College of Surgeons and the Commission on Cancer have not verified and are neither responsible for the analytic or statistical methodology employed, nor the conclusions drawn from these data by the investigators. This study was approved by the Yale Human Investigation Committee.

2.2. Overall study sample

We identified patients within NCDB diagnosed with non-metastatic SCLC between 1998 and 2006 with available survival information. The sample was further restricted to patients treated with concurrent CRT. This was defined as thoracic RT which began within a range of 30 days before to 90 days after the start of chemotherapy. The validity of this definition was tested using sensitivity analysis.

2.3. Construction of variables

Demographic and disease covariates including tumor, node, and group stage, Charlson/Deyo comorbidity score, insurance type, median household income and estimated education level within patients' zip code of residence, and reporting facility type and geographic location were analyzed in the form in which they were received from NCDB. Age was stratified into categories of $\leq$49, 50–59, 60–69, 70–79, and 80–90. Race was classified as white, black, Asian, or other. Distance from patients' residences to the reporting facility was classified as up to 50 miles or greater than 50 miles. Finally, the setting of patients' residences was classified as counties with populations of one million or more, 250,000 to one million, or less than 250,000. Regional and boost doses (i.e., larger field and cone-down dose, respectively) are recorded separately in NCDB. For the purposes of this study, these values were summated and expressed as total dose. For patients without a recorded boost dose, total dose equaled the regional dose. Information pertaining to RT modality (i.e., 3D-conformal RT vs. intensity-modulated RT) was missing for the majority of patients in this sample. As a result, RT modality was not considered in this analysis.

2.4. Statistical analyses

2.4.1. Primary analysis—comparison of standard CRT regimens

The primary aim of this study was to compare OS between published CRT regimens from three published trials, Intergroup 0096, CALGB 39808, and RTOG 9712 [4–6]. To achieve this, patients were classified to one of three groups if their recorded total dose and fraction (Fx) numbers matched exactly that of the trial regimens [45 Gy in 30 fractions (45 Gy/30Fx), 70 Gy in 35 fractions (70 Gy/35Fx), or 61.2 Gy in 34 fractions (61.2 Gy/34Fx)]. These regimens were chosen in part because they represent the original arms of the ongoing CALGB 30610 trial [7]. Patients with total doses or fraction numbers not matching these regimens were not categorized and thus not included in comparisons of these dose-fractionation regimens. Patients in the 45 Gy/30Fx and 61.2 Gy/34Fx were assumed to have received accelerated fractionation (twice daily and concomitant boost, respectively), as frequency of fractionation information (i.e., daily versus twice daily) is unavailable in NCDB. The validity of this assumption was tested in sensitivity analysis.

The influence of demographic, pathologic, and treatment details on survival outcomes was assessed within this sample using Kaplan Meier analysis. Factors with at least borderline significance ($p < 0.10$) were included in multivariable analysis. Next, Kaplan–Meier analysis was used to compare OS outcomes based upon dose fractionation regimen. Multivariate analysis was then performed with Cox multivariable models integrating demographic, pathologic, and treatment details which were significant in univariate analysis, in order to adjust for potential confounders. While RT treatment duration is recorded in NCDB, extreme values (e.g., 20% with RT duration over 9 weeks) for this variable were found in approximately 20% of patients. Because of this uncertainty, calculation of biologically effective dose to account for the effect of accelerated fractionation regimens was not performed.

Sensitivity analyses were then performed using this three-regimen categorization. As described above, patients with thoracic RT starting within 30 days prior to 90 days after the initiation of chemotherapy (day – 30 to +90) were included in the study sample and assumed to have received concurrent CRT. To test the validity of this assumption, two sensitivity analyses were performed restricting the study sample to patients with RT starting between the first day of chemotherapy and 30 days after the start of chemotherapy (day 0 to +30) and also between the first day of chemotherapy and ninety days after the start of therapy (day 0 to +90). Because fractionation frequency (daily vs. twice-daily fractionation) is not recorded in NCDB, for the primary analysis it was assumed that patients receiving 45 Gy/30Fx received twice daily fractionation, and that patients receiving 61.2 Gy/34Fx received concomitant boost fractionation. To check the validity of this assumption, a second sensitivity analysis was performed. The 45 Gy/30Fx and 61.2 Gy/34Fx groups were restricted to patients with treatment durations which were only compatible with accelerated fractionation (i.e. 45 Gy over 19 to 32 days and 61.2 Gy over 33 to 45 days). With these restricted groups, the survival analyses described above were repeated.

2.4.2. Secondary analysis—comparison of CRT dose strata

A secondary aim of this study was to address the value of dose-escalation in SCLC. For this analysis, a larger sample of patients with non-metastatic SCLC treated with concurrent CRT to a dose of 30.01 Gy to 80 Gy was used. For this analysis, patients treated with total doses of less than or equal to 30 Gy were excluded given the high likelihood of either incomplete therapy or palliative rather than curative treatment intent. Similarly, patients recorded as having received greater than 80 Gy were excluded given the potential that these doses represented data entry errors. Total dose was subsequently stratified in units of 10 Gy (i.e., 30.01–40 Gy, 40.01–50 Gy, 50.01–60 Gy, 60.01–70 Gy, 70.01–80 Gy). Kaplan–Meier analysis was used to compare OS between the dose strata. Cox multivariable analysis was then used to adjust for potentially confounding demographic and pathologic factors.