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Dose escalation and associated predictors of survival with consolidative thoracic radiotherapy in extensive stage small cell lung cancer (SCLC): A National Cancer Database (NCDB) propensity-matched analysis

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ABSTRACT

Purpose: Randomized studies have demonstrated a survival benefit for consolidative thoracic radiotherapy (TRT) in extensive stage (ES) small cell lung cancer (SCLC), however the radiation dose and optimal selection criteria are often debated.

Methods: We analyzed 3280 stage IV SCLC treated with double-agent chemotherapy and TRT within the National Cancer Data Base (NCDB) and evaluated the differences in selection patterns and survival outcomes for patients who received at least 45 Gy of TRT and those who received < 45 Gy. Univariable and multivariable analyses identified characteristics predictive of overall survival. Propensity-adjusted Cox proportional hazard ratios for survival were used to account for indication bias between the two dose arms.

Results: There were 1621 patients in the < 45 Gy group (most common 30 Gy) and 1659 patients in the 45 Gy or higher group (most common 45 Gy). White patients, T1-T3 lesions, an absence of brain/liver/bone metastases, and starting TRT after 12 weeks of chemotherapy were associated with the higher dose group.

With multivariable analysis, TRT to at least 45 Gy was an independent predictor of improved survival (HR = 0.78, P < 0.001) along with female gender, age < 65, lower comorbidity score, starting TRT 12 weeks after chemotherapy, and the absence of brain/liver/bone metastases (P < 0.01). Propensity adjusted regression model showed a persistent correlation between a higher dose and survival (HR = 0.74, P < 0.001). Survival at 1 and 2 years for the 45 Gy or higher arm was 58.1% and 25.2% compared to 43.8% and 15.1% for the < 45 Gy arm (P < 0.001).

Conclusion: In the largest analysis of consolidative thoracic radiotherapy in ES-SCLC to date, dose escalation to at least 45 Gy was an independent predictor for increased survival. These findings may be validated in ongoing prospective studies.

1. Introduction

With a median survival of 6–12 months, small cell lung cancer (SCLC) most commonly presents with metastatic or extensive stage (ES) disease [1]. Cisplatin-based doublet chemotherapy is the mainstay of therapy with high rates of initial response. However, a proportion of patients harbor residual intrathoracic disease, precipitating the hypothesis that consolidative thoracic radiotherapy (TRT) can improve outcomes [2]. Several prospective and retrospective studies have demonstrated a survival benefit with the addition of thoracic radiation in ES-SCLC, including the recent phase III CREST trial which reported a 10% 2-year overall survival benefit for consolidative TRT to a dose of 30 Gy in 10 fractions [3–9].

Notably, the rate of intrathoracic progression in the CREST trial was 43.7%, leading the authors to propose that dose escalation may further improve outcomes [6]. Yet, given the aggressive nature of SCLC and potentially increased toxicity profile with TRT, the optimal selection characteristics for dose escalated consolidative radiotherapy is unknown [10]. Indeed, while consolidative TRT in ES-SCLC is included in the current National Comprehensive Cancer Network (NCCN)

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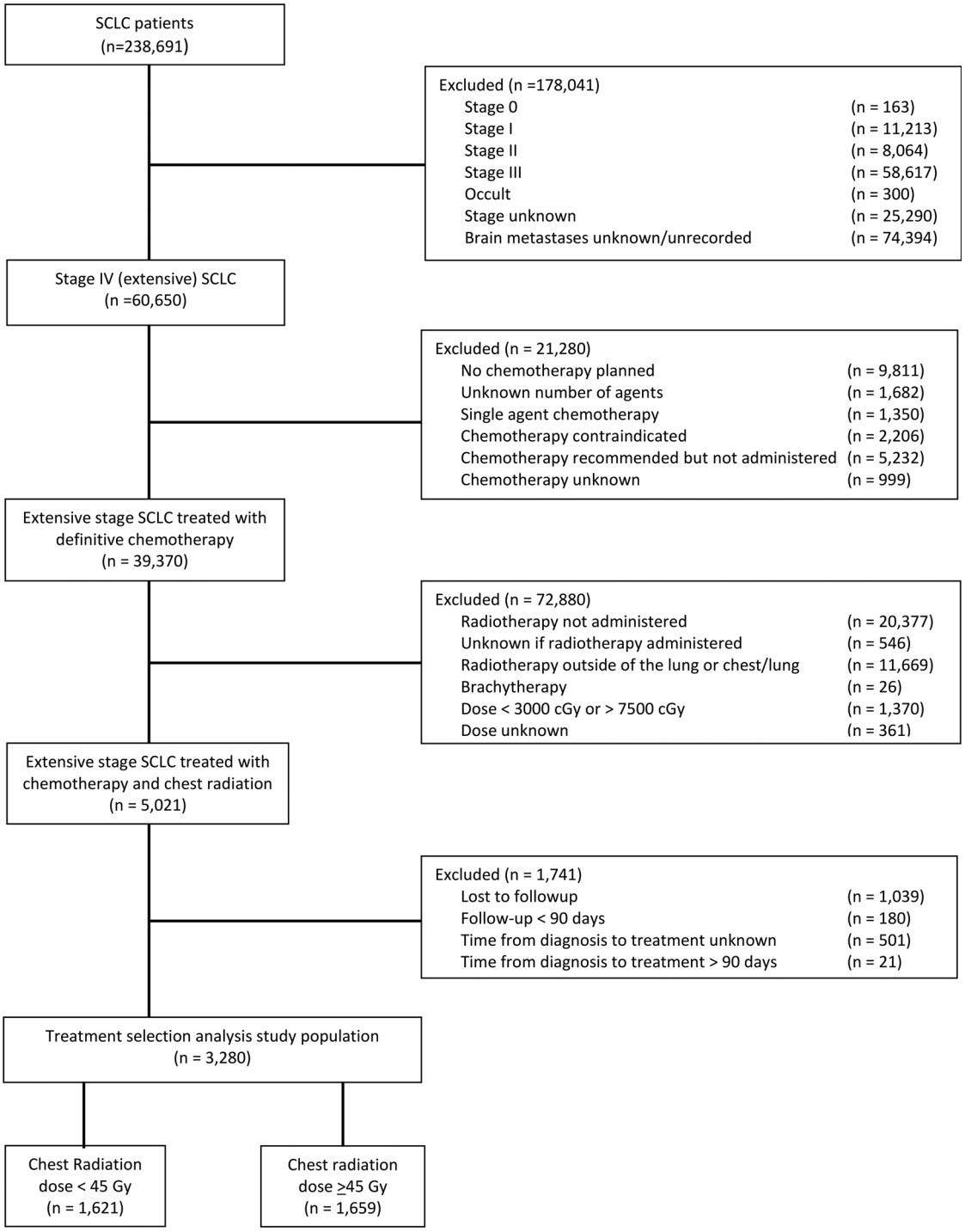

Fig. 1. CONSORT diagram. SCLC, small cell lung cancer. n, number of patients. Gy, Gray.

guidelines, the recommended dose ranges between 30 Gy in 10 fractions and 60 Gy in 30 fractions [11].

The recently closed NRG/RTOG 0937 phase II clinical trial compared prophylactic cranial irradiation with prophylactic cranial irradiation and consolidative TRT to 45 Gy, with reduced time to progression in the latter arm but without a difference in survival [12,13]. To date there have been no randomized trials to evaluate the impact of dose escalation in thoracic RT for ES-SCLC. We herein utilized the National Cancer Database (NCDB) to define factors affecting selection for dose escalation, and survival outcomes for stage IV SCLC patients who received chemotherapy and TRT in the modern era.

2. Methods

2.1. Patient selection

This study was exempt from institutional review board supervision due to the utilization of de-identified data provided by the NCDB, a tumor registry jointly managed by the American Cancer Society and American College of Surgeons. The database captures approximately 70% of cancer cases in the United States from over 1500 hospitals accredited by the Commission on Cancer. We queried the database to identify ES-SCLC patients treated with chemotherapy and TRT between the years 2004–2015, although ultimately only data between the years