ORIGINAL ARTICLE

Concomitant Chemotherapy and Radiotherapy with SBRT Boost for Unresectable Stage III Non–Small Cell Lung Cancer: A Phase I Study

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ABSTRACT

Objectives: Stereotactic body radiation therapy (SBRT) is now the standard of care in medically inoperable stage I NSCLC, yielding high rates of local control. It is unknown whether SBRT can be safely utilized in the locally advanced NSCLC setting. This multi-institution phase I study evaluated the safety of 44 Gy of conventionally fractionated thoracic radiation with concurrent chemotherapy plus dose-escalated SBRT boost to both the primary tumor and involved mediastinal lymph nodes. The primary end point of this study was to establish the maximum tolerated dose (MTD) of the SBRT boost.

Methods: Inclusion criteria included unresectable stage IIIA or IIIB disease, primary tumor 8 cm or smaller, and N1 or N2 lymph nodes 5 cm or smaller. Tumors were staged with positron emission tomography/computed tomography (CT), and four-dimensional CT simulation was used for radiation planning. The treatment schema was 44 Gy of thoracic radiation (2 Gy/d) with weekly carboplatin and paclitaxel chemotherapy. A second CT simulation was obtained after 40 Gy had been delivered, and a SBRT boost was planned to the remaining gross disease at the primary site and involved mediastinal lymph nodes. Consolidation chemotherapy was given at the discretion of the treating medical oncologist. Four SBRT boost dose cohorts were tested: cohort 1 (9 Gy $\times$ 2), cohort 2 (10 Gy $\times$ 5), cohort 3 (6 Gy $\times$ 5), and cohort 4 (7 Gy $\times$ 5). Patients were treated in cohorts of three patients, and the Bayesian escalation with overdose control method was used to determine the MTD of the SBRT boost. Dose-limiting toxicities (DLTs) were defined as any grade 3 or higher toxicities within 30 days of treatment attributed to treatment, not including hematologic toxicity, or any grade 5 toxicity attributed to treatment.

Results: The study enrolled 19 patients from November 2012 to December 2016. There were four screen failures, and 15 patients were treated on study. There were no DLTs in dose cohort 1 (n = 3) and 2 (n = 6). DLT developed in one patient in dose cohort 3 (n = 3) and in 2 patients in dose cohort 4 (n = 3). The calculated MTD was 6 Gy $\times$ 5. The DLT observed at this dose level was a tracheoesophageal fistula; given this substantial toxicity, there was investigator reluctance to enroll further patients at this dose level. Thus, the calculated MTD was 6 Gy $\times$ 5; however, 10 Gy $\times$ 2 is thought to be a reasonable dose as well, given that no grade 5 toxicities occurred with that dose.

Conclusions: The MTD of a SBRT boost combined with 44 Gy of thoracic chemoradiation was 6 Gy $\times$ 5. A SBRT boost dose of 10 Gy $\times$ 2 could be considered safer, with no grade

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3 or higher toxicities observed at this dose level during the follow-up period in this study.

Keywords: Lung cancer; Stage III; Radiation; SBRT; SABR

Introduction

The standard of care for unresectable stage III NSCLC lung cancer is radiation with concurrent chemotherapy, which has been set forth by multiple studies showing an overall survival advantage with the addition of concurrent platinum-based chemotherapy to daily radiation with sequential chemotherapy.[1–3] The accepted radiation dose for NSCLC remains 60 Gy, which was established from Radiation Therapy Oncology Group (RTOG) 73-01, a randomized trial comparing varying dose fractionation regimens.[4] In an effort to improve clinical outcomes for this population, the RTOG completed RTOG 0617, a large randomized trial examining standard dose (60 Gy at 2 Gy per fraction) versus high-dose (74 Gy at 2 Gy per fraction) thoracic radiation with concurrent chemotherapy. This contemporary randomized study demonstrated a median survival of 29 months in the control arm.[1] Survival in the high-dose arm was found to be inferior, with a median survival of 20 months. It was therefore concluded that dose escalation at 2 Gy/d is not a valid method of treatment intensification for this group of patients.

Over the past decade, stereotactic body radiation therapy (SBRT) techniques have been developed and applied to patients with early-stage lung cancer. SBRT specifically refers to delivery of radiation using three-dimensional (3D) localization of the target lesion, allowing for hypofractionated radiation (10–20 Gy) to be delivered with a high degree of precision and accuracy. The phase II RTOG 0236 demonstrated a 3-year local control rate of 91% for patients with T1 or T2, N0 medically inoperable lung cancer receiving 18 Gy to the primary tumor $\times$ 3.[5] These results are superior to those of historical studies treating medically inoperable early-stage lung cancer with conventionally fractionated radiation (2 Gy per fraction), in which local control rates were more modest at approximately 50%.[6] Overall survival rates are also higher with SBRT techniques than with conventionally fractionated radiation in medically inoperable patients.[7] A recent pooled analysis of two randomized trials comparing SBRT with surgical resection in medically operable patients yielded better overall survival at 3 years compared with lobectomy, indicating that SBRT is a highly effective treatment in peripheral early-stage NSCLC.[8]

There were initial concerns for toxicity with SBRT treatment, especially for central tumors located within 2 cm of the bronchial tree. Early studies demonstrated higher rates of grade 5 toxicities with SBRT to central tumors when treated with 18 Gy $\times$ 3.[9] However, a phase I/II safety trial to determine the optimal SBRT dose when treating central tumors showed an acceptable 7.2% probability of a dose-limiting toxicity (DLT).[10] In North America, early-stage central tumors are typically treated with fractionation schemes ranging from five to eight fractions, with cumulative doses ranging from 50 to 60 Gy.

A method of dose modeling referred to as the biologically effective dose (BED) takes into account the radiation dose per fraction and the inherent radiation response of a particular tissue.[11] Thus, BED is essentially a measure of radiation dose intensity. SBRT treatments, because of the high dose per fraction, are able to achieve a much higher BED than conventional radiation delivered at 2 Gy per fraction. Multiple studies have demonstrated that a higher BED leads to improved local control and survival.[12,13] One study examining outcomes associated with varying BEDs in patients receiving SBRT for early-stage lung cancer demonstrated superior local control with a BED of 100 Gy or higher when assuming an α/β ratio of 10 for tumors.[11]

The feasibility of incorporating SBRT techniques into treatment of the population with locally advanced, unresectable NSCLC remains an unanswered question. Although the high local control rates seen in early-stage NSCLC are encouraging, it is unknown whether SBRT to larger, locally advanced tumors with mediastinal adenopathy will be safe and well tolerated. Several pertinent and unanswered questions include Is it safe and/or feasible to give SBRT to the primary and mediastinal nodes at the same time? Is it safe to give SBRT directly after the administration of systemic therapy? and Is it safe to give SBRT to large primary tumors larger than 5 cm and bulky mediastinal lymph nodes? To that end, we undertook a multi-institutional phase I study to determine the optimal dose of SBRT when used as a boost in combination with daily fractionated radiation with concurrent chemotherapy.

Methods

Study Design

This study was a phase I safety clinical trial, with a primary end point of determination of the maximum tolerated dose (MTD) of a SBRT boost after delivery 44 Gy of external beam radiation (2 Gy/d) with concurrent chemotherapy. Secondary end points included local regional failure, distant metastasis–free survival, and overall survival, as well as determination of toxicities with this treatment regimen. This study was approved by the Emory University institutional review board. The schema