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Association between intensity modulated radiotherapy and survival in patients with stage III non-small cell lung cancer treated with chemoradiotherapy

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ABSTRACT

Purpose: To determine the effect of radiotherapy (RT) technique on treatment compliance and overall survival (OS) in patients with stage III non-small lung cancer (NSCLC) treated with definitive chemoradiotherapy (CRT).
Methods and Materials: This study included patients with stage III NSCLC in the National Cancer Database treated between 2003 and 2011 with definitive CRT to 60–63 Gray (Gy). Radiation treatment interruption (RTI) was defined as a break of ≥4 days. Treatment technique was dichotomized as intensity modulated (IMRT) or non-IMRT techniques.
Results: Out of the cohort of 7492, 35% had a RTI and 10% received IMRT. With a median follow-up of surviving patients of 32 months, the median survival for those with non-IMRT vs. IMRT was 18.2 months vs. 20 months ($p < 0.0001$). Median survival for those with and without an RTI ≥ 4 days was 16.1 months vs. 19.8 months ($p < 0.0001$). Use of IMRT predicted for a decreased likelihood of RTI (odds ratio, 0.84, $p = 0.04$). On multivariable analysis for OS, IMRT had a HR of 0.89 (95% CI: 0.80–0.98, $p = 0.01$) and RTI had a HR of 1.2 (95% confidence interval (CI): 1.14–1.27, $p = 0.001$).
Conclusions: IMRT was associated with small but significant survival advantage for patients with stage III NSCLC treated with CRT. A RTI led to inferior survival, and both IMRT and RTI were independently associated with OS. Additional research should investigate whether improved tolerability, reduced normal tissue exposure, or superior coverage drives the association between IMRT and improved survival.

1. Introduction

Concurrent chemoradiotherapy (CRT) is the standard-of-care for patients with unresectable stage III non-small cell lung cancer (NSCLC) [1]. However, due to the intensity of treatment and significant patient comorbidities, acute treatment related toxicities often cause radiation therapy interruptions (RTI) [2]. These delays can lead to accelerated tumor cell repopulation and previous research, albeit limited to single institution studies and pooled cohort analyses, has demonstrated that RTI's are associated with worse local control and overall survival in non-small cell lung cancer [3–8]. Furthermore, randomized studies have revealed the importance of shorter overall treatment courses in the treatment of lung cancer [9–11]. A lower dose to certain normal structures, including the esophagus, could potentially decrease acute toxicities and RTI's in the treatment of lung cancer. In fact, recent data have suggested that IMRT use leads to improved long-term quality-of-life and potentially even overall survival [12,13]. Concerns regarding the use of IMRT for the treatment of lung cancer include the complex interplay between beam delivery and target motion and the potential for worse toxicity associated with low dose irradiation to a larger amount of lung tissue [14].

Previous SEER-Medicare studies have suggested no survival advantage with the use of IMRT, although the elderly patient cohort and limited data on radiotherapy dose and completion may have limited the potential to see a survival gain with improved local therapy [15,16]. In this study, we used the National Cancer Database (NCDB) to examine

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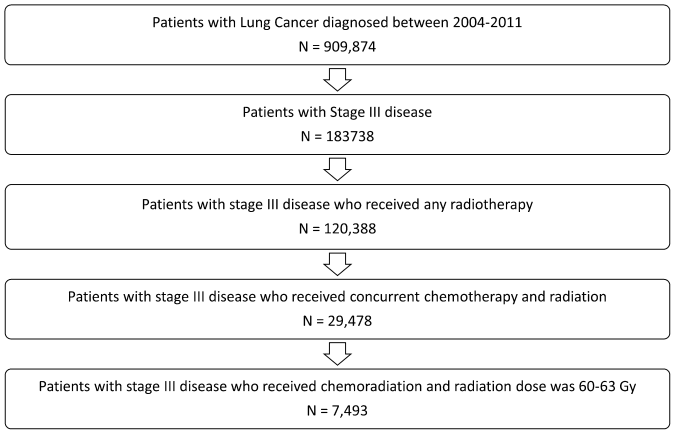

Fig. 1. Flowchart outlining cohort composition.

the impact of IMRT use on overall survival and radiation treatment interruptions in patients treated with CRT for stage III NSCLC. The aims were not only to assess the associations between overall survival and IMRT and RTI, but also to discern a potential mechanism linking IMRT with improved survival.

2. Methods and materials

2.1. Data sources

This study utilized the NCDB, which is a hospital based registry and a combined program of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. The database includes approximately 70% of the cancers diagnosed in the United States and is derived from a de-identified file [17,18]. The Commission on Cancer and the American College of Surgeons have not verified and are not responsible for the analytic or statistical methodology employed, or our conclusions drawn from these data. The NCDB has set criteria to ensure the data submission by each cancer center meets pre-specified quality benchmarks.

2.2. Analysis population

Eligible patients were diagnosed with histologically-confirmed, stage III NSCLC between 2004 and 2011 and received all or part of their first course of treatment at a CoC-accredited facility. Patients were included if they received CRT between a dose of 60 and 63 Gy in 1.8 Gy or 2 Gy fraction sizes. The dose range of 60–63 Gy was used to approximate the standard RT dose used in stage III NSCLC following the results of RTOG 0617, which examined 60 vs. 74 Gy and found improved outcomes in the standard 60 Gy arm [19]. There were 10,007 patients who received between 64 and 66 Gy who were excluded from the analysis. The year 2004 was used as the initial start time because this was the first year the National Cancer Database began collecting detailed information on radiation dose while 2011 was the last year in the database with survival information. The cohort composition as derived from the whole database is shown in Fig. 1.

2.3. Statistical analysis

Candidate variables were placed into three categories: clinical (e.g. histology, age, T-stage, N-stage, Charleson-Deyo comorbidity index), socioeconomic (e.g. race, insurance status), and institutional (treatment volume, facility type). Facility types are designated by the CoC criteria and include: “community cancer” programs, “comprehensive cancer” programs, and “academic research” programs. The treatment volume category was calculated by arranging the facilities’ average number of patients treated per year into tertiles: Low (≤1.8 case per year), Medium (1.9–3.1) per year, High (≥3.2 per year). The low rate of cases per year was due to the strict selection criteria that were employed to ensure data completeness in the study, shown in Fig. 1. When all patients with stage III disease who received radiation (n = 120,388) were separated into facility volume tertiles the following values were obtained: Low (≤13.1 case per year), Medium (13.2–23.8 per year), High (≥23.9 per year). Radiation technique was coded according to treatment technique (IMRT vs. non-IMRT) received during the first initial phase of treatment.

An RTI was defined as at least a 4-day prolongation in treatment compared to a standard course of therapy. The three dose cohorts included in the study with the typical approximate days elapsed during treatment were 60 Gy in 2 Gy fractions (40–42 days), 61.2 Gy in 1.8 Gy fractions (46–48 days), and 63 Gy in 1.8 Gy fractions (47–49 days). The range of days takes into account the possibility of patients starting treatment on a day other than Monday which could add up to two additional days to a typical course [20]. An RTI was then defined as a minimum of a 4-day prolongation compared to the typical approximate days elapsed during treatment. The RTI associated with the total elapsed days by dose level were as follows: greater than 46 days, 52 or 53 days for total doses of 60 Gy, 61.2 Gy, and 63 Gy, respectively. An RTI ≥ 4 days was used to allow for comparison to previously published studies which have examined this issue [7,8].

Differences in IMRT use and prevalence of RTI by clinical, socioeconomic, and institutional factors were estimated using the chi-square test. Multivariable logistical regressions were performed to calculate independent predictors of the use of IMRT and development of a RTI.

Survival curves were calculated using the Kaplan–Meier method and compared with the log-rank statistic. Cox proportional hazards regression was used to determine the effect of IMRT and RTI on survival while adjusting for known confounding variables. All variables mentioned were included as categorical covariates. Hazard ratios (HR) and the 95% confidence intervals (CI) were estimated in models adjusting for the covariates of interest. To further control for confounding, a propensity score model was developed for the likelihood of receiving IMRT, including all the covariates in the binomial logistic regression. Then a 1:1 match was performed using a caliper width of 0.0001 and the two cohorts were compared using the log-rank test, with the HR for survival calculated using univariable Cox regression. All statistical tests were two-sided, and a 0.05 level of significance was utilized. Data were analyzed using SPSS v23 (Armonk, New York).

3. Results

A total of 7493 patients met criteria for inclusion into the analysis (Table 1). The median age was 67 years (interquartile range, IQR 59–74). Among the cohort, 35% had a RTI ≥ 4 days and 9.9% received IMRT. For those classified as having an RTI, the corresponding dose level and median elapsed days on treatment (interquartile range) were as follows: 60 Gy–median 50 days (IQR: 47–54 days), 61.2 Gy–median 56 days (IQR: 53–60 days), and 63 Gy – median 57 days (IQR: 54–61 days).

The use of IMRT was strongly associated with treatment at low-volume facilities (Odds ratio (OR): 1.91 vs. high-volume facilities, 95% CI = 1.55–2.17, $p < 0.0001$), academic centers (OR: 3.1 vs. community cancer centers, 95% CI = 2.25–4.23, $p < 0.0001$) and during 2008–2011 (OR: 6.23 vs. 2004–2007, 95% CI = 4.98–7.78, $p < 0.0001$) (Table 2). In 2004, 0.5% of the cohort received IMRT vs. 22.8% in 2011 ($p < 0.0001$).

The adjusted likelihoods of having a RTI are shown in Table 3. Female patients, high comorbidity scores, squamous histology, not having insurance, treatment at a community cancer program and low volume facilities were all associated with an increased risk of experiencing a RTI. Treatment with IMRT was associated with a decreased risk of having a RTI (OR: 0.84, 95% CI: 0.77–0.99, $p = 0.035$). Among patients with N3 disease, IMRT was associated with a further decreased