ORIGINAL ARTICLE

Dosimetric Predictors of Symptomatic Cardiac Events After Conventional-Dose Chemoradiation Therapy for Inoperable NSCLC

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ABSTRACT

Introduction: We hypothesized that higher cardiac doses correlates with clinically significant cardiotoxicity after standard-dose chemoradiation therapy (CRT) (~60 Gy) for inoperable NSCLC.

Methods: We retrospectively reviewed the records of 140 patients with inoperable NSCLC treated with concurrent CRT from 2007 to 2015. Extracted data included baseline cardiac status, dosimetric parameters to the whole heart (WH) and cardiac substructures, and the development of post-CRT symptomatic cardiac events (acute coronary syndrome [ACS], arrhythmia, pericardial effusion, pericarditis, and congestive heart failure [CHF]). Competing risks analysis was used to estimate time to cardiac events.

Results: Median follow-up was 47.4 months. Median radiation therapy dose was 61.2 Gy (interquartile range, 60 to 66 Gy). Forty patients (28.6%) developed 47 symptomatic cardiac events at a median of 15.3 months to first event. On multivariate analysis, higher WH doses and baseline cardiac status were associated with an increased risk of symptomatic cardiac events. The 4-year cumulative incidence of symptomatic cardiac events was 48.6% versus 18.5% for mean WH dose $\geq$ 20 Gy versus $<$ 20 Gy, respectively (p = 0.0002). Doses to the WH, ventricles, and left anterior descending artery were associated with ACS/CHF, whereas doses to the WH and atria were not associated with supraventricular arrhythmias. Symptomatic cardiac events (p = 0.0001) were independently associated with death.

Conclusions: Incidental cardiac irradiation was associated with subsequent symptomatic cardiac events, particularly ACS/CHF, and symptomatic cardiac events were associated with inferior survival. These results support the minimization of cardiac doses among patients with inoperable NSCLC receiving standard-dose CRT.

Keywords: NSCLC; Radiation therapy; Cardiac toxicity; Cardiac dosimetry

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Introduction

Accumulating evidence suggests that radiation therapy (RT) potentially contributes to cardiotoxicity in patients with NSCLC.[1-5] In the Radiation Therapy Oncology Group (RTOG) 0617 study, patients treated on the high-dose, 74 Gy, chemoradiation therapy (CRT) arm experienced inferior overall survival (OS) compared to patients treated on the standard-dose, 60 Gy, CRT arm.[6] Increasing heart volume receiving $\geq$ 5 Gy (V5) and heart volume receiving $\geq$ 30 Gy (V30) were independently associated with inferior OS after 2 years of follow-up, suggesting a possible association between inferior OS in the dose escalation arm and adverse cardiac sequelae of RT. Subsequent studies proposed a direct relationship between cardiac doses and symptomatic cardiac events in the setting of dose-escalated RT (median prescribed doses, 70 to 74 Gy) for locally advanced NSCLC.[3,4] One might expect the impact of RT-associated cardiotoxicity in NSCLC to increase as therapeutic advances improve longevity.[7-9]

Although current evidence indicates the significance of cardiotoxicity after dose-escalated RT, the link between cardiac doses, clinically significant cardiotoxicity, and OS remains incompletely defined among patients treated with conventional, standard-dose RT ($\sim$60 Gy). Prior studies in this setting focused primarily on the association between cardiac dosimetry and OS, reaching conflicting conclusions.[10-13] Furthermore, the data appear limited about the significance of specific types of cardiotoxicities and the relationship with doses to cardiac subvolumes.[14] We thus assessed these relationships within a modern cohort of inoperable NSCLC patients treated with curative standard-dose RT (median prescribed dose, 61.2 Gy) and concurrent chemotherapy.

Materials and Methods

Patient Population

We performed an IRB-approved review of the Rutgers Cancer Institute of New Jersey's database to identify patients treated with curative intent CRT for unresectable stage II-III NSCLC or stage IV oligometastatic NSCLC between January 2007 and August 2015. We included patients with stage IV oligometastatic disease, defined as those with a solitary extrathoracic metastasis who received definitive CRT to the primary tumor and metastatic focus, based on comparable long-term survival rates to patients with locally advanced NSCLC in our and others' experiences.[15,16] We identified 165 patients for this retrospective review. We included patients who subsequently received thoracic re-irradiation (e.g., for NSCLC recurrence) but censored them at the time of their re-irradiation. We excluded patients who did not receive concurrent chemotherapy (typically because of poor performance status) (n = 14) or complete the planned course of RT (because of either an inability to tolerate treatment or death) (n = 6). We also excluded patients who previously received thoracic RT (e.g., for a prior malignancy) (n = 5). This left 140 patients for the study. All patients underwent full staging work-up including positron-emission tomography/computed tomography (CT) scans. We used the American Joint Committee on Cancer seventh-edition criteria for staging classification.[17]

Treatment

RT was delivered with three-dimensional conformal radiotherapy (3DCRT), intensity-modulated radiation therapy (IMRT), or a mix of 3DCRT and IMRT to a typical dose of 60 to 66 Gy in 1.8 or 2 Gy per fraction. RT dose constraints were as follows: maximum spinal cord dose $\leq$ 50 Gy, mean lung dose $<$ 20 Gy, lung V5 $<$ 60% to 70%, lung volume receiving $\geq$ 20 Gy (V20) $<$ 37%, and heart volume receiving $\geq$ 40 Gy (V40) $<$ 100%. Following the publication of Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) in 2010, our institution attempted to limit the mean whole heart (WH) dose to $\leq$ 26 Gy (based on suggested limits to the pericardium).[18] For reference, the National Comprehensive Cancer Network (NCCN) at the time recommended a mean WH dose $\leq$ 35 Gy.

The typical chemotherapy regimen consisted of intravenous infusional drug delivery with either weekly paclitaxel (45 mg/m^2) and carboplatin (area under the curve = 2) or cisplatin (50 mg/m^2 on days 1, 8, 29, and 36) and etoposide (50 mg/m^2 on days 1–5 and 29–33).

Follow-up and Evaluation of Cardiotoxicity

Patients were typically seen by the radiation and medical oncologists every 1 to 3 months for the first year post-CRT, every 3 to 6 months for the following 2 years, and every 6 to 12 months thereafter. Follow-up chest CT scans were generally obtained 6 to 8 weeks after the completion of CRT, and then every 3 to 4 months for the first year, every 6 months for the following 2 years, and yearly thereafter.

We noted post-CRT symptomatic cardiac events via patient chart review. All available records were reviewed, including medical and radiation oncology follow-up notes, inpatient notes and discharge summaries, follow-up imaging (including CT, positron-emission tomography/CT, and echocardiogram reports), and outpatient cardiology notes. We defined five classes of symptomatic cardiac events, adapted from Wang et al.,[3] as follows:

1. Acute coronary syndrome (ACS): myocardial infarction or unstable angina.
2. Significant arrhythmia: new onset arrhythmia requiring either medical or procedural intervention.