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Original article

Cardiac dose is associated with immunosuppression and poor survival in locally advanced non-small cell lung cancer

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ABSTRACT

Purpose: Studies have associated increased radiation therapy (RT) heart dose with cardiac toxicity. Others have correlated RT-related immunosuppression with worsened survival. Given the large vascular volumes irradiated during locally advanced non-small cell lung cancer (LA-NSCLC) treatment, we hypothesized an association between increased heart dose and immunosuppression.

Methods: We identified 400 LA-NSCLC patients treated with definitive RT ± chemotherapy between 2001 and 2016. Absolute lymphocyte counts (ALC), absolute neutrophil counts (ANC), and neutrophil-to-lymphocyte ratio (NLR = ANC/ALC) were analyzed pre-RT, during RT, and post-RT. Multivariable analysis (MVA) was performed to correlate Clinical factors with both hematologic toxicity and overall survival. An upper tertile threshold to increase specificity of NLR was chosen to dichotomize continuous hematologic variables.

Results: Median follow up was 17 months (range 0.2–174 months) in all patients and 46 months (range 0.2–161 months) in survivors. A total of 94% of patients had stage III disease and 77% received concurrent chemo radiation. Two-year overall survival (OS), freedom from local recurrence (FFLR), and freedom from distant metastases (FFDM) was 42%, 60% and 45%, respectively. Median survival was 18 months. On MVA for OS ($n = 207$), male gender (Hazard Ratio [HR] 1.7; 95% CI 1.2–2.3), RT alone (HR 2.1; 95% CI 1.9–4.0), the percentage of heart receiving ≥50 Gy (V50) (HR 1.02; 95% CI 1.01–1.03), and higher NLR at 4 months (HR 1.02, 95% CI 1.01–1.03) were associated with reduced OS. ALC nadir was not associated with treatment outcomes. NLR >10.5 was associated with decreased OS ($p < 0.001$) and decreased FFDM ($p = 0.04$). On MVA evaluating factors associated with hematological toxicity ($n = 247$), adjuvant chemotherapy (HR 2.6; 95% CI 1.3–5.0; $p = 0.006$), RT alone (HR 3.6; 95% CI 1.1–12; $p = 0.04$), and heart V50 >25% (HR 2.0; 95% CI 1.1–3.5; $p = 0.02$) were associated with a NLR >10.5 4 months post-RT.

Conclusion: RT related immunosuppression is associated with worse patient outcomes, and may represent a source of increased mortality beyond cardiac toxicity alone.

Radiotherapy (RT) is a cornerstone in the definitive treatment of patients with unresectable locally advanced non-small cell lung cancer (LA-NSCLC). Concurrent RT and chemotherapy is the standard of care for this patient population [1]. However, outcomes continue to be suboptimal with a median overall survival (OS) of at best 28.7 months in large prospective trials [1,2]. RTOG 0617 was a RT dose escalation trial from 60 Gy to 74 Gy which showed worse survival in the patients receiving 74 Gy, although the cause is unclear [2]. One potential cause was that patients who received escalated therapy had an increased heart dose, which predicted worsened survival. In long-term breast cancer and lymphoma survivors, thoracic RT is known to increase risk of cardiovascular disease (CVD) including myocardial infarction, congestive heart failure, and valvular disorders [3,4]. The relationship between heart dose and cardiac events has also been demonstrated in patients with LA-NSCLC shortly after the completion of treatment [5–7]. Nevertheless, the increased risk of CVD alone cannot completely account for the worsened OS observed in prospective studies and prior retrospective analyses [2,5].

The innate and adaptive immune system has been widely recognized as an important mediator in tumor progression and outcomes in patients with solid malignancies [8,9]. The systemic

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response to cancer is comprised of a complex interplay between various inflammatory cells including lymphocytes and neutrophils. In NSCLC, a lower lymphocyte nadir during RT has been associated with worse OS [10], and elevated circulating neutrophils conferred an unfavorable prognosis [11]. As such, a combined neutrophil to lymphocyte ratio (NLR) has been widely studied as a prognostic biomarker of immunosuppression and is associated with worse cancer specific survival (CSS) in patients with solid malignancies [12].

Radiation-associated lymphopenia has been explored in a variety of malignancies [10,13,14], but most have not singled out actionable RT dose constraints. Dosimetric analyses in glioma have demonstrated that increasing vascularized volumes exposed to long courses of fractionated radiation increase lymphopenia [14,15]. Given the large vascularized volumes exposed to RT during lung cancer treatment, we hypothesized that there is an association between increased heart dose and elevated NLR. Here we present our institutional experience of patients with LA-NSCLC who received definitive radiation and present a dosimetric analysis exploring the impact on hematologic toxicities and their associations with clinical outcomes.

Methods

Patient population and study design

This is a single institution retrospective review of 400 patients with LA-NSCLC treated with definitive RT with or without chemotherapy from 2001 to 2016. Patients were included if they received a total radiation dose of at least 50 Gy with standard daily fractionation (1.8–2.5 Gy per fraction) and had complete blood counts (CBC) either before, during, and/or after RT. The data source for this review was the Washington University School of Medicine Radiation Oncology Department's IRB-approved, retrospective registry of locally advanced lung cancer (IRB Approval # 20131149). The data were de-identified by an "honest broker" before research use [16]. A Charlson co-morbidity index (CCI) score was calculated (current lung cancer diagnosis not included) to estimate the 10-year pre-treatment risk of mortality [17]. After treatment, physician follow-up included chest computed tomography (CT) every 3 to 6 months to evaluate for local, regional, and distant failure. Patient follow-up was updated and censored on August 15, 2017.

Radiation treatment and dosimetric analysis

Dosimetric analysis was performed on a subset of 328 patients where viable Digital Imaging and Communications in Medicine-Radiation Therapy (DICOM-RT) plans could be imported into the Computational Environment for Radiological Research (CERR) platform [18]. The planning target volume (PTV), right and left lungs, and heart contours were reviewed and recontoured (if appropriate) according to the RTOG 0617 secondary analysis atlas [19]. Dosimetric data were extracted with CERR software and reviewed by a physician. Heart and total lung minus-PTV relative percent volumes receiving at least 5 Gy, 10 Gy, 25 Gy, and 50 Gy were identified by V5, V10, V25, and V50, respectively. Mean dose and integral dose (mean dose x organ at risk volume) were also evaluated.

Hematologic toxicities

Absolute lymphocyte counts (ALC) and absolute neutrophil counts (ANC) were analyzed at pre-RT (closest lab date within 2 months before RT start), ALC nadir (lowest ALC within 3 months after RT start), 2 months post-RT start (allowed 1–3 month range), and 4 months post-RT start (allowed 3–6 month range). Lymphopenia was graded by the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. Neutrophil-to-lymphocyte ratio (NLR) was calculated by dividing the ANC by the ALC. Patients with an ALC of 0 ($n = 10$ at the ALC nadir) were censored for NLR calculations.

Statistical methods

Wilcoxon's rank sum test was used to compare ALC, ANC, and NLR values at each time point, sub-grouped by RT and chemotherapy sequencing. Clinical endpoints included overall survival (OS), progression free survival (PFS), freedom from distant metastasis (FFDM), and freedom from local recurrence (FFLR). Follow up time and time to clinical endpoints were calculated from the end of RT. Cox regression was performed to find associations of clinical, hematologic, and dosimetric factors with OS. A multivariable model was then created from variables significant on univariate analysis, which were entered and tested in a forward-conditional manner. An upper tertile threshold to increase specificity of NLR was chosen to dichotomize continuous hematologic variables that were significant in Cox regression. OS, PFS, FFDM, and FFLR rates were estimated with Kaplan–Meier's analyses. Log-rank test was used to calculate significance of survival estimate differences. Associations of continuous clinical and dosimetric variables with hematologic toxicity were performed with Pearson's correlations. In exploratory analysis, a multivariable logistic regression model including chemotherapy sequencing and radiation dosimetric variables was created to predict an elevated NLR. A p value of 0.05 or less was considered statistically significant. Hazard ratios (HR) and odds ratios (OR) are reported with a 95% confidence interval (CI). All analysis was completed with SPSS statistical software, version 23 (SPSS IBM, Armonk, NY).

Results

Patient outcomes

Patient and tumor characteristics are summarized in Table 1. The majority of patients were current or former smokers (97%) with non-squamous tumor histology (52%). Most patients received a PET/CT (91%) with brain imaging (98%) as part of their staging work up. The majority of patients received photon radiation (99%) with either a 3-dimensional conformal radiation therapy (3D-RT) plan or intensity-modulated radiation therapy (IMRT) plan. One patient was treated with passive-scatter proton radiation [20] delivered with a 3D-RT plan. The median prescribed dose was 66 Gy (range 50–75.25 Gy). Chemotherapy was given either sequentially and/or concurrently with RT in 362 (90%) of patients. Thirty-eight (10%) patients were treated with RT alone due to co-morbidities precluding chemotherapy or patient refusal. A total of 310 (77%) patients received concurrent chemotherapy with RT (CRT). Patients given weekly carboplatin/paclitaxel with RT received a median number of 5 cycles (range 1–7). Patients given cisplatin/etoposide every four weeks with RT received a median number of 2 cycles (range 1–3). Median follow up was 17 months (range 0.2–174 months) in all patients and 46 months (range 0.2–161 months) in survivors. The estimated median overall survival was 18 months in all patients (95% CI: 15.3–20.7). The estimated median progression free survival was 12.8 months (95% CI: 10.0–15.7). The estimated 2 year FFLR and FFDM was 60% and 45%, respectively.

Hematologic toxicity

Pre-RT CBCs were available in 369 patients. Median pre-RT ALC, ANC, and NLR were 1300 cells/mm^3 (range: 100–4200), 6100 cells/mm^3 (range: 1600–53,800), and 4.4 (range: 0.69–107), respec-

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