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Post-operative radiation effects on lymphopenia, neutrophil to lymphocyte ratio, and clinical outcomes in palatine tonsil cancers

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ABSTRACT

Objective: To evaluate radiation-induced lymphopenia associated with unilateral vs. bilateral neck radiation and to test post-treatment neutrophil to lymphocyte ratio (NLR) as a prognostic clinical biomarker.
Methods: This was a single academic center retrospective review of palatine tonsil squamous cell cancer patients treated with post-operative intensity modulated radiation therapy (IMRT) from 1997 to 2013. Absolute lymphocyte count (ALC) and NLR were evaluated during and after radiation for up to a year. Correlations of lab values with loco-regional control (LRC), freedom from distant metastases (FFDM), and overall survival (OS) were assessed.
Results: Ninety-nine patients with median follow up 5.8 years had ALC recorded at least at baseline and within one year of starting RT. Acute grade 3–4 lymphopenia (< 10 weeks from RT start) occurred in 79% of bilateral neck RT patients (n = 70) and 58% of unilateral neck RT patients (n = 29), p = 0.03. There was no significant difference in late grade 3–4 (p = 0.12) lymphopenia. In a multivariable Cox regression model, acute NLR > 11.875 correlated with worse OS (HR = 4.4, 95% CI 1.2–16). Late NLR > 6.875 independently correlated with significantly worse FFDM (HR = 16, 95% CI 1.9–137) and OS (HR = 12, 95% CI 3.0–48).
Conclusions: Unilateral neck radiation may prevent acute iatrogenic immunosuppression. In exploratory analyses, elevated post-treatment NLR was associated with risk for distant metastases and death.

Introduction

The incidence of human papilloma virus (HPV, p16+) associated oropharyngeal cancers (OPC) in developed countries has been increasing over the last couple decades [1]. Despite excellent loco-regional control [2,3], 11–15% of p16+ OPC patients develop metastases up to five years after treatment [4,5]. Recently, there has been interest in peripheral blood biomarkers of immunosuppression, which may predict for systemic progression. An elevated baseline neutrophil to lymphocyte ratio (NLR) has been associated with worse progression-free survival (PFS), cancer-specific survival (CSS), and overall survival (OS) in a number of solid tumor sites [6], including OPCs [7–9]. Furthermore, treatment-related lymphopenia from daily fractionated radiation and/or chemotherapy has been associated with cancer relapse and worse survival [10–12].

Since HPV+ OPCs are responsive to chemoradiation, de-intensifying local therapy may reduce iatrogenic immunosuppression. In well-lateralized tonsil squamous cell carcinomas (SCCs), unilateral neck radiation has shown a < 3% rate of contralateral neck failure in multiple institutional reviews [13–23]. In other primary sites, reduced radiation volumes has been associated with a lower risk of lymphopenia [24,25]. Therefore, we sought to characterize the effect of either unilateral or bilateral neck radiation on absolute lymphocyte count (ALC), absolute neutrophil count (ANC), and NLR during and after treatment in post-operative palatine tonsil cancer patients. Lymphopenia and NLR were tested as prognostic biomarkers for clinical endpoints.

Methods

Patient population and tumor characterization

Patients with palatine tonsil squamous cell cancer treated with post-

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operative intensity modulated radiation therapy (IMRT) at [Washington University in St. Louis] from 1997 to 2013 were reviewed. Data was collected retrospectively for patients treated from 1997 to 2004 and prospectively collected from 2005 to 2013. The study was approved by the Institutional Review Board. Patients were staged according to the American Joint Committee on Cancer Staging Manual (AJCC) 7th edition. Positive $p16^{INK4A}$ (p16) immunohistochemistry staining (> 75% of tumor cells) was used as a surrogate marker for HPV [26]. Starting September of 2007, patients with lateralized primary tumors (> 1 cm from midline) and nodal stage N0-N2b were recommended to receive unilateral neck radiation according to our institutional policy [27]. Prior to 2007, these patients received bilateral neck radiation. Patients with non-lateralized primary tumors or N2c-N3 disease received bilateral neck IMRT throughout this study.

Surgery

All patients underwent tonsillectomy, the majority of which were trans-oral (96%). Patients also received either ipsilateral or bilateral neck dissections. Bilateral neck dissection was indicated for an FDG-avid contralateral lymph node on PET or CT evidence of contralateral lymph node metastasis (> 1 cm on short axis or central necrosis) if PET was not performed.

Radiation therapy

Adjuvant IMRT was given to all patients at a median time of seven weeks after surgery. CT simulation scans were fused with pre-operative CT and/or FDG-PET/CT scans. Pre-operative gross tumor volumes (GTVs) were contoured based on physical examination, nasopharyngoscopic examination, FDG-PET/CT, as well as operative and pathology reports. The high-risk clinical target volume (CTV1) was defined as the primary tumor (pGTV + 1.5–2.0 cm) and positive lymph nodes (nGTV + 0.5–1.0 cm). CTV1 received 66 or 60 Gy in 33 or 30 fractions of 2 Gy each over 7 or 6 weeks, respectively. The elective clinical target volume (CTV2) was defined as the uninvolved elective neck, which included at least ipsilateral nodal levels II-IV. CTV2 received 54 or 52 Gy in 1.73 or 1.63 Gy per day over the 6–7 weeks. These volumes were expanded by 0.5 cm to obtain a planning target volume (PTV).

Chemotherapy

Concurrent chemotherapy was not routinely given until EORTC 22931 and RTOG 9501 validated the role of adjuvant chemoradiation in 2004 [28,29]. The majority of patients received concurrent cisplatin (100 mg/m^2 every three weeks) for 2–3 cycles if chemotherapy was indicated. No patients received adjuvant chemotherapy after RT.

Hematologic toxicity

All patients were analyzed for Common Terminology Criteria for Adverse Events (CTCAE, version 4.03) grade 3–4 (ALC < 500 cells/mm^3) and grade 4 (ALC < 200 cells/mm^3) lymphopenia. Acute lymphopenia was evaluated between surgery and RT start, at 2–4 weeks, 5–7 weeks, and 8–10 weeks after start of RT. Prolonged lymphopenia was evaluated at 4–8 months (16–32 weeks) and 10–14 months (40–56 weeks) post-RT. Absolute neutrophil counts were analyzed at the same time points to calculate the neutrophil to lymphocyte ratio, NLR = ANC/ALC. For analysis, acute lymphopenia refers to the nadir ALC within 10 weeks after start of RT, and late lymphopenia refers to the nadir ALC from 16 to 56 weeks after start of RT. Similarly, acute NLR refers to the maximum NLR within 10 weeks after start of RT, and late NLR refers to the maximum NLR from 16 to 56 weeks after start of RT.

Follow-up

Patients were evaluated with a physical exam and neck CT at 6–8 weeks after radiation. Starting in 2000, patients also received FDG-PET/CT at 10–16 weeks. Subsequently, patients were evaluated every 3–4 months with additional imaging if indicated. After 4 years, examinations occurred annually. Chest CT or X-ray was done annually.

Statistical analyses

Patient and tumor characteristics were compared using Fisher's exact test or $\chi 2$ test as appropriate for categorical variables. Two-sided student's T test was used for continuous variables. P value < 0.05 was considered statistically significant. Receiver operating characteristic (ROC) analysis was used to determine NLR thresholds that were predictive of clinical outcomes. Logistic regression was used to determine clinical and treatment-related predictors of lymphopenia and elevated NLR. Kaplan-Meier and Cox analyses were done to show the association of lymphopenia and elevated NLR with loco-regional control (LRC), freedom from distant metastases (FFDM), and overall survival (OS). Events for LRC and FFDM were locoregional failure and distant metastases, respectively, and death was not included. All events were measured from date of diagnosis. When more than one variable was significant in univariate analysis, each significant variable was entered into a multivariate model using a forward stepwise method. Adjusted odds ratios (OR), hazard ratios (HR), and 95% confidence intervals (CI) were reported. All statistical analyses were done in IBM SPSS Statistics software, version 23 (Armonk, NY).

Results

Baseline patient and tumor characteristics

Out of 154 patients treated with post-operative IMRT, 99 patients had ALC recorded at least at baseline and within one year of starting RT. Patients receiving bilateral neck RT (n = 70) and unilateral neck RT (n = 29) were predominantly younger (mean age 54), white race (94–96%), stage IVA (79% vs. 93%, respectively), p16 + (90% vs. 96%, respectively), current or ex-smokers (71% vs. 59%, respectively), and received concurrent chemotherapy (69% vs. 86%, respectively). About a quarter of patients in each group received bilateral neck dissections. There were more females receiving unilateral neck RT, and the median CTV1 dose for unilateral RT was lower at 60 Gy compared to 66 Gy [30]. There were no differences in baseline ALC, ANC, or hemoglobin concentration (Table 1).

Hematologic toxicity

There was a decrease in mean ALC, ANC, and hemoglobin concentration from baseline during RT, with a nadir at 6 weeks. Mean hemoglobin concentration returned to baseline by 6 months after RT, but ALC and ANC remained depressed 12 months after RT (Fig. 1). There was a statistical difference in ALC and NLR at 3 and 6 weeks after start of RT (Fig. 1A, D). Acute grade 3–4 lymphopenia (ALC < 500/mm^3) occurred in 79% of bilateral neck RT patients and 58% of unilateral neck RT patients, p = 0.03. Acute grade 4 lymphopenia (ALC < 200/mm^3) occurred in 15% of bilateral neck RT patients and none of the unilateral neck RT patients, p = 0.04. There were no significant differences in late grade 3–4 (21% vs. 5%) or grade 4 (3% vs. 0%) lymphopenia (Supplemental eTable 1). There was no difference in the average ALC velocity change from baseline to 3 weeks after RT start between bilateral and unilateral neck RT (-342 lymphocytes/day vs. -304 lymphocytes/day, respectively, p = 0.530). Unilateral neck RT associated with reduced acute grade 3–4 lymphopenia (OR = 0.322, 95% confidence interval [CI] 0.113–0.920) and acute NLR > 11.875 (OR = 0.156, 95% CI 0.043–0.568), but not late lymphopenia or late