Clinical and Translational Radiation Oncology 7 (2017) 28–35

Contents lists available at ScienceDirect

Clinical and Translational Radiation Oncology

journal homepage: www.elsevier.com/locate/ctro

Original Research Article

Prognostic impact of leukocyte counts before and during radiotherapy for oropharyngeal cancer

Garrett L. Jensen [a], Pierre Blanchard [a,b], G. Brandon Gunn [a], Adam S. Garden [a], C. David Fuller [a], Erich M. Sturgis [c], Maura L. Gillison [d], Jack Phan [a], William H. Morrison [a], David I. Rosenthal [a], Steven J. Frank [a,*]

[a] Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
[b] Department of Radiation Oncology, Gustave Roussy Cancer Campus, Villejuif, France
[c] Department of Head and Neck Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
[d] Department of Thoracic/Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

ARTICLE INFO

Article history:
Received 30 July 2017
Revised 25 September 2017
Accepted 26 September 2017

Keywords:
Head and neck cancer
Radiotherapy
Proton therapy
Leukocytosis
Lymphopenia

ABSTRACT

Introduction: Peripheral blood count components are accessible and evidently predictive in other cancers but have not been explored in oropharyngeal carcinoma. We examine if there is an association between the use of intensity-modulated radiotherapy (IMRT) or intensity-modulated proton therapy (IMPT) and lymphopenia, as well as if there is an association between baseline neutrophilia, baseline leukocytosis and lymphocyte nadir in oropharyngeal cancer.

Materials and Methods: Analysis started with 150 patients from a previous case to case study design, which retrospectively identified adults with oropharyngeal carcinoma, 100 treated with IMRT in 2010-2012 and 50 treated with IMPT in 2011–2014. Pretreatment leukocyte, neutrophil, lymphocyte, and hemoglobin levels were extracted, as were neutrophil and lymphocyte nadir levels during radiotherapy. We retained 137 patients with recorded pre-treatment leukocyte and neutrophil levels for associated analysis and 114 patients with recorded lymphocyte levels during radiation and associated analysis. Multivariate survival analyses were done with Cox regression.

Results: The radiotherapy type (IMRT vs. IMPT) was not associated with lymphopenia (grade 3 $P > .99$; grade 4 $P = .55$). In univariate analyses, poor overall survival was associated with pretreatment neutrophilia (hazard ratio [HR] 5.58, 95% confidence interval [CI] 1.99–15.7, $P = .001$), pretreatment leukocytosis (HR 4.85, 95% CI 1.73–13.6, $P = .003$), grade 4 lymphopenia during radiotherapy (HR 3.28, 95% CI 1.14–9.44, $P = .03$), and possibly smoking status >10 pack-years (HR 2.88, 95% CI 1.01–8.18, $P = .05$), but only T status was possibly significant in multivariate analysis (HR 2.64, 95% CI 0.99–7.00, $P = .05$). Poor progression-free survival was associated with pretreatment leukocytosis and T status in univariate analysis, and pretreatment neutrophilia and advanced age on multivariate analysis.

Conclusions: Treatment modality did not affect blood counts during radiotherapy. Pretreatment neutrophilia, pretreatment leukocytosis, and grade 4 lymphopenia during radiotherapy were associated with worse outcomes after, but establishing causality will require additional work with increased statistical power.

Introduction

Radiotherapy, with or without chemotherapy, is the treatment of choice for most patients with early [1,2] or advanced [3–5] oropharyngeal carcinoma (OPC). Five-year survival rates remain less than optimal for patients with localized disease (83%), regional disease (59%), and distant disease (36%) [6], although the discovery of human papillomavirus (HPV) as a causal factor in OPC has led to the identification of subgroups of patients with improved prognosis [7]. Although other biomarkers of survival have been examined, none other than HPV status have affected clinical care or are used routinely [8–14].

Both leukocytosis and neutrophilia at diagnosis and leukopenia during treatment have been previously associated with survival.

* Corresponding author at: Department of Radiation Oncology, Unit 1422, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, USA.
E-mail address: sjfrank@mdanderson.org (S.J. Frank).

https://doi.org/10.1016/j.ctro.2017.09.008
2405-6308/

Pretreatment leukocytosis is a marker of heightened inflammation and is associated with poor survival in many types of cancer [15–29]. Tumor-related leukocytosis has been associated with resistance to radiotherapy, immune suppression, and promotion of metastasis [28,29]. Like leukocytosis, neutrophilia may be a marker of late or aggressive disease [25,30]. Increased neutrophil to lymphocyte ratio and neutrophilia itself have been associated with survival in multiple cancers [17,25,27].

An unintended consequence of chemotherapy and radiation is suppression of the immune system, sometimes reflected by lymphopenia. Treatment-related lymphocytopenia, both during treatment and for up to 1 month afterwards, has been associated with shorter survival in a variety of cancer types [31,32–38]. Lymphocytes are known to be extremely radiosensitive [39], and there is a concern that radiotherapy-related lymphopenia may affect responses to immunotherapy [40,41].

Radiotherapy for OPC delivers high radiation doses to the cervical lymph nodes, which are located near the carotid arteries and jugular vein, and to the large amounts of blood circulating through these vessels. Use of intensity-modulated proton therapy (IMPT) for OPC has been shown to reduce the radiation dose to normal structures relative to intensity-modulated radiation therapy (IMRT) by an average of 25 Gy [42–46]. We hypothesized here that IMPT would be associated with lower rates of treatment-related lymphocytopenia in a cohort of 2:1 case-matched patients given IMRT or IMPT with curative intent. We analyzed the predictive significance of pretreatment leukocytosis, neutrophilia, and lymphopenia along with nadir levels of lymphocytes and neutrophils during radiotherapy.

Materials and methods

Patients

This is an update of a previous case-matched study not conducted for this purpose. That study included 50 adult OPC patients treated with IMPT from 2011 through 2014 as part of a prospective observational study of clinical outcomes, as well as 100 adult OPC patients treated with IMRT, selected from an institutional database of 512 consecutive adult patients treated with IMRT from 2010 through 2012 [43]. Out of the 150 patients, we retained 137 patients with recorded pre-treatment leukocyte and neutrophil levels for associated analysis and 114 patients with recorded lymphocyte levels during radiation for associated analysis. Because we found no difference between treatment modalities regarding blood counts or prognosis, both modalities were combined for analysis. The two groups were matched based on treatment laterality (unilateral vs. bilateral), disease site (tonsil vs. base of tongue), p16/HPV status (positive vs. negative, with missing data considered as "any category"), T status (T1–T2 vs. T3–T4), N status (N0–N1 vs. N2–N3), receipt of concurrent chemotherapy, and smoking status. Patients were not matched by age to ensure inclusion of sufficient numbers of patients. This case-matched study was approved by the appropriate institutional review board.

Treatment

The standard processes and sequence of treatment for patients with OPC at MD Anderson Cancer Center have been reported elsewhere [47–49]. At least two radiation oncologists examined all patients and target volumes were peer-reviewed for quality assurance purposes. Gross tumor plus margins were prescribed a dose of 66 Gy for small-volume disease and 70 Gy for more advanced disease, and elective regions received 54–63 Gy. For IMPT patients, a relative biological effectiveness (RBE) value of 1.1 was used. Planning for IMPT was done with an Eclipse proton therapy treatment planning system (version 8.9, Varian Medical Systems, Palo Alto, CA, USA). Planning for IMRT was done with a Pinnacle planning system (Philips Medical Systems, Andover, MA, USA). Treatment was delivered with a static gantry approach. IMRT was delivered with a Varian Medical Systems (Palo Alto CA) linear accelerator as 6-MV photons with daily image guidance [50].

Data collection and endpoint definition

Baseline patient and tumor characteristics, including smoking status (as number of pack-years [PY]) and comorbid conditions according to the Charlson Comorbidity Index [51] (CCI) were collected from the medical record. All data were prospectively recorded for the IMPT cohort and retrospectively collected for the IMRT cohort. For the current study, pretreatment leukocyte, lymphocyte, and hemoglobin levels were extracted from the electronic medical record along with nadir levels of lymphocytes and neutrophils during radiotherapy, which were measured weekly when concurrent chemotherapy was administered and sporadically if it was not. For patients who received induction chemotherapy, pretreatment levels had been measured in the blood sample drawn soonest before induction was begun. For patients who did not receive induction chemotherapy, pretreatment levels had been measured in the blood draw soonest before radiotherapy was begun. Lymphopenia was graded using the Common Terminology Criteria for Adverse Events (CTCAE), and neutrophilia and leukocytosis were defined when patient values exceeded upper normal limits.

Vital status and the dates of local and/or distant failure were updated using the electronic medical record. Survival times were updated and calculated from the end of radiotherapy to the date of the first event of interest. Events were defined as follows: death from any cause for overall survival (OS); death from any cause or disease recurrence for progression-free survival (PFS); and locoregional recurrence or distant recurrence for locoregional control and distant control. Patients were censored at their last follow-up date.

Statistical analysis

Follow-up was calculated by the reverse Kaplan–Meier method [52]. The distribution of categorical variables between patients, regardless of radiotherapy modality, with and without neutrophilia, leukocytosis, or lymphopenia were compared with chi-square or Fisher's exact tests. Survival distributions were compared with log-rank tests. Survival curves and estimates of survival at specific time points were computed with the Kaplan–Meier method. Multivariate survival analyses were done with Cox regression and included variables with $P < .25$ in univariate analysis, as well as neutrophilia or lymphopenia status, selected through an ascending stepwise selection procedure. The statistical analysis plan was predefined before the statistical analysis. All P values were 2-sided and $P < .05$ was considered to indicate a statistically significant difference. Statistical analyses were done with SAS software (Release 9.3; SAS Institute, Cary, NC, USA).

Results

Patient characteristics

Patient, tumor, and treatment characteristics according to the presence or absence of baseline pretreatment neutrophilia and grade 4 lymphopenia during treatment are presented in Tables 1 and 2. Patients with and without baseline neutrophilia differed