Radiotherapy and Oncology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

Severe lymphopenia during neoadjuvant chemoradiation for esophageal cancer: A propensity matched analysis of the relative risk of proton versus photon-based radiation therapy

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ARTICLE INFO

Article history:
Received 13 August 2017
Received in revised form 24 November 2017
Accepted 27 November 2017
Available online xxxx

Keywords:
Lymphopenia
Proton beam therapy
Intensity modulated radiation therapy
Chemoradiation
Esophageal cancer

ABSTRACT

Background and purpose: Circulating lymphocytes are exquisitely sensitive to radiation exposure, even to low scattered doses which can vary drastically between radiation modalities. We compared the relative risk of radiation-induced lymphopenia between intensity modulated radiation therapy (IMRT) or proton beam therapy (PBT) in esophageal cancer (EC) patients undergoing neoadjuvant chemoradiation therapy (nCRT).

Material and methods: EC patients treated with IMRT and PBT were propensity matched based on key clinical variables. Treatment-associated lymphopenia was graded using CTCAE v.4.0. Using matched cohorts, univariate and multivariable multiple logistic regression was used to identify factors associated with increased risk of grade 4 lymphopenia as well as characterize their relative contributions.

Results: Among the 480 patients treated with nCRT, 136 IMRT patients were propensity score matched with 136 PBT patients. In the matched groups, a greater proportion of the IMRT patients (55/136, 40.4%) developed grade 4 lymphopenia during nCRT compared with the PBT patients (24/136, 17.6%, $P < 0.0001$). On multivariable analysis, PBT was significantly associated with a reduction in grade 4 lymphopenia risk (odds ratio, 0.29; 95% confidence interval, 0.16–0.52; $P < 0.0001$).

Conclusion: PBT is associated with significant risk reduction in grade 4 lymphopenia during nCRT in esophageal cancer.

A number of studies have associated treatment-induced lymphopenia with worse clinical outcomes in cancer patients [1–4]. Radiation therapy (RT) is an important contributor to treatment-induced lymphopenia as lymphocytes and their precursors are very sensitive to ionizing radiation [5]. Although lymphocytes are known to play a critical role in promoting systemic anti-tumor responses, examination of possible mitigating treatment factors on treatment-associated lymphopenia and correlation with clinical outcomes in esophageal cancer patients is lacking.

RT-induced lymphopenia can likely be mitigated by modifying RT technique, fractionation, and possibly, modality. For instance, altered RT fractionation using shorter courses with stereotactic body radiation therapy (SBRT) for pancreatic cancer over 2 weeks has been associated with significantly less radiation-induced lymphopenia than standard chemoradiation therapy (CRT) over 5 weeks [6]. Radiation target volume has also been identified as an important factor with greater treated volumes associated with lower posttreatment lymphocyte counts in non-small cell lung cancer [7]. Radiation-induced lymphopenia could be further reduced by the volume of radiation exposure, which is known to be substantially different comparing photon therapy to charged particles like proton beam therapy (PBT) [8]. However, there is a paucity of evidence that this difference has clinical impact on lymphopenia. We therefore conducted this propensity matched

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https://doi.org/10.1016/j.radonc.2017.11.028
0167-8140/

analysis with the hypothesis that PBT compared to photon RT could result in a lower risk of clinically significant lymphopenia with treatment.

Materials and methods

Patients

This was an Institutional Review Board approved retrospective analysis of 480 patients with esophageal cancer treated with surgical resection after CRT at our institution between March 2005 and March 2016. Patients were included in the analyses if they had no distant metastases at presentation and were treated with preoperative concurrent CRT using PBT or IMRT with or without induction chemotherapy followed by surgery.

Treatment

Patients were typically treated with neoadjuvant CRT with or without induction chemotherapy to a median dose of 50.4 Gy at 1.8 Gy per fraction. Patients were simulated supine in an upper body cradle with their arms abducted overhead. Four-dimensional (4D) computed tomography (CT) simulation was used to track tumor motion throughout the respiratory cycle, as patients were treated with free-breathing. IMRT plans were generated using the Pinnacle treatment planning system (version 9.0, Philips, Andover, MA). Proton plans were generated using the Eclipse treatment planning system (Varian medical systems, Liverpool, NY).

Chemotherapy agents consisted of fluoropyrimidine, were typically given alone or in combination with either a platinum compound (classified as FP) or a taxane (classified as FT). Types of surgical procedures included Ivor Lewis esophagectomy (with proximal gastrectomy and mediastinal + abdominal lymph node dissection), transthoracic esophagectomy, transhiatal esophagectomy, three-field esophagectomy, and minimally invasive esophagectomy.

Peripheral blood absolute counts, including lymphocyte count, were recorded prior to any therapy including induction chemotherapy and RT, at least monthly during induction chemotherapy, weekly during RT, and at first follow-up after completing RT. White blood cell, neutrophil, lymphocyte and platelet count nadir during induction chemotherapy and CRT were obtained, and scored using the Common Terminology Criteria for Adverse Events, version 4.0.

Propensity matched analysis

To control for potential imbalances in prognostic risk factors for lymphopenia arising from differences in patient selection, we conducted a propensity matched analysis that used key clinical factors to match each PBT patient with an IMRT patient exhibiting similar demographic and clinical characteristics. An appropriate prognostic model was identified through multivariable logistic regression with backward elimination based on the Akaike information criterion [9]. The initial model included gender, clinical stage, KPS, tumor location, induction chemotherapy, histology, age and PTV. Age, PTV, and histology remained as contributors to a final model attaining the highest degree of goodness-of-fit. Propensity scores were estimated based on these factors as well as, tumor location which exhibited a marginally significant association with grade 4 lymphopenia.

Statistical analysis

The analysis plan endeavored to identify risk factors associated with an extent of lymphopenia that was considered clinically significant as well as ascertain the relative partial contribution of RT modality after adjusting for baseline clinical risk factors. Lymphopenia during radiation therapy was dichotomized to grade 4 lymphopenia versus those with grade 0–3 lymphopenia. Clinical and treatment factors were tested for significant association with presence/absence of grade 4 lymphopenia in univariate analysis. Adhering to conventional assumptions, the univariate hypothesis tests utilized two-sample t-test or Wilcoxon's tests for continuous variables as well as Chi-square test or Fisher's exact test for categorical variables. Thereafter, univariate and multivariable logistic regression models were used to identify factors associated with an increased risk of grade 4 lymphopenia as well as estimate the impact of RT modality. The estimated odds ratios (ORs) and their 95% confidence intervals (CIs) are reported. Overall survival (OS) and distant metastasis-free survival (DMFS) were estimated using the Kaplan–Meier method. Event times were calculated from surgery date to the first occurrence of death or distant progression. Multivariable Cox proportional hazards regression was used to characterize the independent partial effects of patient, disease, and treatment factors associated with OS and DMFS. The estimated hazard ratios (HRs) and their 95% CIs are reported. All statistical tests were two-sided with $P < 0.05$ used to confer statistical significance. All analyses were conducted using SAS 9.4 (SAS Institute INC, Cary, NC).

Results

Patient characteristics and propensity score matching

Table 1 summarizes baseline characteristics for the entire patient cohort ($N = 480$) by RT modality. From the initial dataset of 480 patients, a subset of 272 patients were chosen consisting of 136 matched pairs, with equal numbers treated with PBT and IMRT by propensity score matching, which formed a commensurate subset of patients exhibiting similar baseline clinical and demographic characteristics based on our propensity score model (Supplementary Fig. S1). Table 2 summarizes baseline characteristics for the two matched groups.

Radiation-induced lymphopenia for the entire cohort

For the entire study cohort ($N = 480$), the incidence of grade 1, 2, 3, and 4 lymphopenia nadir during CRT was seen in 9 (1.9%), 43 (9.0%), 266 (55.4%), and 159 (33.1%) patients, respectively. Since nearly 90% of patients developed grade 3–4 lymphopenia during CRT, we focused subsequent analysis on grade 4 lymphopenia. During the same period, comparable rate of other severe grade 4 hematologic toxicities for leukopenia, neutropenia, and thrombocytopenia was rather low, occurring in only 2 (0.4%), 1 (0.2%), and 2 (0.4%) patients, respectively. For the patients who received induction chemotherapy ($N = 179$), grade 4 hematologic toxicities were not common during the induction chemotherapy phase, as only 0 (0%), 2 (1.1%), 1 (0.6%) and 0 (0%) patients experienced grade 4 leukopenia, neutropenia, lymphopenia and thrombocytopenia prior to CRT.

We compared patients with or without grade 4 lymphopenia during CRT in the entire study cohort ($N = 480$). Age ($P = 0.02$), PTV ($P < 0.0001$) and RT modality ($P < 0.0001$) were significantly different between patients with grade 4 lymphopenia versus grade 0–3 lymphopenia. Distal tumor location was borderline significantly associated with grade 4 lymphopenia ($P = 0.06$) (Supplementary Table S1). Univariate logistic regression identified older age ($P = 0.07$), larger PTV ($P = 0.0002$), lower tumor location ($P = 0.07$) and IMRT relative to PBT ($P < 0.0001$) as factors potentially associated with increased risk of grade 4 lymphopenia (Supplementary Table S2). A multivariable logistic regression

Please cite this article in press as: Shiraishi Y et al. Severe lymphopenia during neoadjuvant chemoradiation for esophageal cancer: A propensity matched analysis of the relative risk of proton versus photon-based radiation therapy. Radiother Oncol (2017), https://doi.org/10.1016/j.radonc.2017.11.028