Radiotherapy and Oncology 120 (2016) 48–55

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Head and neck radiotherapy

Intensity-modulated proton beam therapy (IMPT) versus intensity-modulated photon therapy (IMRT) for patients with oropharynx cancer – A case matched analysis

Pierre Blanchard [a,f], Adam S. Garden [a], G. Brandon Gunn [a], David I. Rosenthal [a], William H. Morrison [a], Mike Hernandez [b], Joseph Crutison [a], Jack J. Lee [b], Rong Ye [b], C. David Fuller [a,g], Abdallah S.R. Mohamed [a,h], Kate A. Hutcheson [c], Emma B. Holliday [a], Nikhil G. Thaker [a], Erich M. Sturgis [c], Merrill S. Kies [d], X. Ronald Zhu [e], Radhe Mohan [e], Steven J. Frank [a,*]

[a] Department of Radiation Oncology; [b] Department of Quantitative Sciences; [c] Department of Head and Neck Surgery; [d] Department of Thoracic/Head & Neck Medical Oncology; [e] Department of Radiation Physics, The University of Texas MD Anderson Cancer Center, Houston, USA; [f] Department of Radiation Oncology, Institut Gustave Roussy, Villejuif, France; [g] Medical Physics Program, The University of Texas Graduate School of Biomedical Sciences, Houston, USA; [h] Department of Clinical Oncology and Nuclear Medicine, University of Alexandria, Egypt

ARTICLE INFO

Article history:
Received 10 February 2016
Received in revised form 17 May 2016
Accepted 18 May 2016
Available online 21 June 2016

Keywords:
Intensity-modulated proton therapy
Intensity-modulated radiotherapy
Oropharyngeal cancer
Radiation therapy
Chemoradiation
Human papilloma virus

ABSTRACT

Background: Owing to its physical properties, intensity-modulated proton therapy (IMPT) used for patients with oropharyngeal carcinoma has the ability to reduce the dose to organs at risk compared to intensity-modulated radiotherapy (IMRT) while maintaining adequate tumor coverage. Our aim was to compare the clinical outcomes of these two treatment modalities.

Methods: We performed a 1:2 matching of IMPT to IMRT patients. Our study cohort consisted of IMPT patients from a prospective quality of life study and consecutive IMRT patients treated at a single institution during the period 2010–2014. Patients were matched on unilateral/bilateral treatment, disease site, human papillomavirus status, T and N status, smoking status, and receipt of concomitant chemotherapy. Survival analyzes were performed using a Cox model and binary toxicity endpoints using a logistic regression analysis.

Results: Fifty IMPT and 100 IMRT patients were included. The median follow-up time was 32 months. There were no imbalances in patient/tumor characteristics except for age (mean age 56.8 years for IMRT patients and 61.1 years for IMPT patients, p-value = 0.010). Statistically significant differences were not observed in overall survival (hazard ratio (HR) = 0.55; 95% confidence interval (CI): 0.12–2.50, p-value = 0.44) or in progression-free survival (HR = 1.02; 95% CI: 0.41–2.54; p-value = 0.96). The age-adjusted odds ratio (OR) for the presence of a gastrostomy (G)-tube during treatment for IMPT vs IMRT were OR = 0.53; 95% CI: 0.24–1.15; p-value = 0.11 and OR = 0.43; 95% CI: 0.16–1.17; p-value = 0.10 at 3 months after treatment. When considering the pre-planned composite endpoint of grade 3 weight loss or G-tube presence, the ORs were OR = 0.44; 95% CI: 0.19–1.0; p-value = 0.05 at 3 months after treatment and OR = 0.23; 95% CI: 0.07–0.73; p-value = 0.01 at 1 year after treatment.

Conclusion: Our results suggest that IMPT is associated with reduced rates of feeding tube dependency and severe weight loss without jeopardizing outcome. Prospective multicenter randomized trials are needed to validate such findings.

The prognosis of oropharyngeal cancer (OPC) has improved in the past decades, especially in terms of locoregional control and overall survival, likely due to the increased proportion of human papillomavirus (HPV)-related tumors. It is now widely accepted that HPV infection is a major causal factor for OPC, especially among non-smoking, non-drinking patients [1–3], and is responsible for the increase in OPC incidence that is observed worldwide, and notably in North America and Europe. Patients with HPV-positive OPC are usually younger, have fewer comorbid conditions, and more often present with lower T status but advanced N status

* Corresponding author at: Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 853, Houston, TX 77030, USA.
E-mail address: sjfrank@mdanderson.org (S.J. Frank).

http://dx.doi.org/10.1016/j.radonc.2016.05.022
0167-8140/

[4], and have an improved prognosis compared with patients with HPV-negative disease [5].

Radiotherapy, with or without chemotherapy, is the treatment of choice for most patients with early [6,7] and advanced [8–10] OPC because it allows organ preservation and avoids the morbidity associated with surgical procedures. Avoiding long-term sequelae of radiation or chemoradiation is particularly important for patients with OPC as the combination of younger HPV-positive patients with improved disease control outcomes means survivors have the potential to live with the side effects and complications of treatment for many years. Because it maintains dose levels to the tumor, this strategy could be of interest in all OPC tumors regardless of HPV status.

Proton therapy, because of its intrinsic physical properties, has the ability to reduce the integral dose delivered to the patient while maintaining highly conformal target coverage. Dosimetric studies have shown that intensity-modulated proton therapy (IMPT) allowed dose reductions for various normal tissue structures, including the contralateral submandibular and parotid glands, oral cavity, spinal cord and brainstem, as well as the volume of normal tissue receiving doses of 10, 30, and 50 Gy [11] and in a pediatric population [12,13]. We previously reported a dosimetric comparison of the first 25 oropharyngeal cancer patients treated with IMPT at our institution and found that mean doses to the anterior and posterior oral cavity, hard palate, larynx, mandible and esophagus were significantly lower with IMPT than with IMRT comparison plans generated for the same patients, as were doses to several central nervous system structures involved in the nausea and vomiting response [14].

Although dosimetric analyses can be hypothesis-generating, analyzing comparative clinical outcomes including safety and efficacy of IMPT relative to photon-based IMRT is critical. Therefore, the aim of this study was to report the first case-matched analysis of patients with OPC treated with IMPT or IMRT at a single center from 2010 through 2014.

Material and methods

Patient population and matching strategy

From 2011 to 2014, 50 adult OPC patients receiving spot-scanning IMPT with curative intent were included in an institutional review board-approved observational study in which clinical outcomes were prospectively recorded. Participants provided study-specific informed consent. Although tumor outcomes and toxicity for this population have been reported, a comparative analysis could not be performed at that time [15]. For comparative purposes, IMRT patients were selected from our institutional database which included 512 consecutive patients with OPC treated with IMRT from 2010 to 2012.

IMRT patients were matched with IMPT patients based on factors that influence treatment volumes and expected toxicity during or after radiotherapy. A 2:1 ratio was used to increase statistical power. These factors were, in order: laterality of treatment (unilateral vs bilateral), disease site (tonsil vs base of tongue), p16/HPV status (positive vs negative, missing data being considered as any category), T status (T1–T2 vs T3–T4), N status (N0–N1 vs N2–N3), receipt of concomitant chemotherapy, and smoking status. For smoking status, the cut-off chosen was 5 pack-years (PY, ($\leqslant$5 vs >5 PY) because of difficulty in matching when using the more widely used cut-off of 10 PY. Further matching was attempted on age, but even when a large age matching range was used (case age ±10 years), the addition of this criterion resulted in the loss of a significant number of patients. We therefore decided not to match on age but to investigate the age distribution between the two groups and to adjust the toxicity analyses using this factor.

Treatment

The vast majority of OPC cases managed at our institution are treated with a radiation therapy-based approach, and these results have previously been reported [16]. Before therapy was begun, all patients underwent multidisciplinary evaluation within our institution and all cases were presented at our head and neck cancer multidisciplinary tumor board for individualized treatment recommendations regarding the sequence and combination of treatment modalities. All patient underwent nutritional counseling and follow-up during and after treatment. Gastrostomy (G-) tube placement was based on a reactive approach, with the decision made after discussion among the patient, the treating radiation oncologist, and the dietician. Reasons for G-tube insertion varied but often included weight loss, inability to maintain oral nutrition, and dehydration.

Detailed treatment processes were previously described [15,17,18] and are briefly summarized below. All patients underwent non-contrast computed tomography (CT) simulation while immobilized in the supine position with full-length thermoplastic mask, bite block with or without an oral stent, and a posterior customized head, neck and shoulder mold for IMPT patients. During our Head and Neck Radiation Oncology Planning and Development Clinic, all IMRT and IMPT patients were examined by at least two radiation oncologists and target volumes were peer-reviewed for quality assurance purposes [19]. 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. Carefully selected patients with well-lateralized tonsil cancers underwent ipsilateral neck irradiation [20,21].

IMPT planning was performed with an Eclipse proton therapy treatment planning system (version 8.9, Varian Medical Systems, Palo Alto, California). Typically 3 beams were used for whole-field bilateral neck IMPT plans: a left and right anterior oblique and single posterior beam. Multi-field optimization was used for bilateral treatments, and single-field optimization was used for unilateral cases. The robustness of each treatment plan was also considered to evaluate the sensitivity to uncertainties associated with variations in patient setup and proton beam range in each patient [22,23]. Plan-specific quality assurance measurements were made before treatment delivery [24]. Daily kilovoltage image guidance was used for all patients. Verification CT scans were obtained at week 1 and 4 of therapy and adaptive re-planning was considered if inadequate doses were delivered to the targets or the organs at risk.

IMRT planning was performed with a Pinnacle planning system (Philips Medical Systems, Andover, MA). Treatment was delivered with a static gantry approach. The template for patients treated to both sides of the neck used 9 beams set equidistant through 360 degrees. Plans for patients treated to only one side of the neck involved a template using 7 beams equidistant through a 190 degree arc. Beam angles and number were modified during the optimization process. In general, IMRT was used to treat the primary tumor and upper neck nodes, whereas the lower neck below the isocenter was treated with an anterior beam, with a larynx and/or full midline block. A "whole-field" IMRT approach was used for situations in which the patient's anatomy or primary tumor location created concerns that tumor might be under-dosed using the "split-field" approach. IMRT was delivered with Varian (Varian Medical Systems, Palo Alto CA) linear accelerators as 6-MV photons with daily image guidance [18]. No systematic re-planning was performed for IMRT patients. Appropriate recommendations from the International Commission on Radiation Units and Measurements were followed [25,26].