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Patterns of care and outcomes of proton and eye plaque brachytherapy for uveal melanoma: Review of the National Cancer Database

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ABSTRACT

PURPOSE: To examine national practice patterns and outcomes of eye plaque brachytherapy compared to proton external beam radiotherapy in the treatment of choroid melanoma.

METHODS AND MATERIALS: Demographic and clinical data for 1224 patients with choroid melanoma treated with either brachytherapy or proton beam therapy from 2004 to 2013 were obtained from the National Cancer Database. Logistic regression and propensity score matching was used to create a 1:1 matched cohort. Kaplan-Meier and Cox regression analyses were performed to evaluate survival in brachytherapy and proton groups.

RESULTS: Median followup was 37 and 29 months for brachytherapy and protons, respectively. Most patients were treated with brachytherapy (n = 996) vs. protons (n = 228). Proton patients came from more urban, affluent, and educated zip codes, and they were more likely to be treated at an academic center (all $p < 0.004$). In the propensity-score matched cohort, 2-year overall survival was 97% vs. 93%, and 5-year overall survival was 77% vs. 51% for brachytherapy and protons, respectively (p = 0.008). Multivariate Cox regression found older age (hazard ratio [HR] = 1.06, 95% confidence interval (CI) = 1.03−1.09), larger tumor diameter (12−18 mm, HR = 2.48, 95% CI = 1.40−4.42, >18 mm, HR = 6.41, 95% CI = 1.45−28.35), and protons (HR = 1.89, 95% CI = 1.06−3.37) were negative prognosticators of survival.

CONCLUSIONS: Patients selected for proton treatment have inferior survival outcomes compared to brachytherapy in this retrospective analysis. There may be unaccounted variables that influence survival, warranting further prospective studies.

Keywords: Uveal melanoma; Choroid melanoma; Plaque brachytherapy; Proton therapy; National Cancer Database

Introduction

Uveal melanoma accounts for 2.9% of all melanoma cases in the United States, with an age-adjusted incidence of 4.3 per million (1). It is the most common primary intraocular tumor and predominantly affects fair-skinned individuals in their 60−70s (2, 3). The Collaborative Ocular Melanoma Study (COMS) established in 2001 that overall survival (OS) was no different between patients receiving enucleation or I-125 plaque brachytherapy, with 5- and 12-year OS of 81% and 57%, respectively (4, 5).

Plaque brachytherapy and eye-preserving therapy are now the preferred treatments of uveal melanoma in the United States (3). The American Brachytherapy Society currently recommends plaque brachytherapy for tumors that are 2.5−10 mm in depth and <16 mm in diameter. Larger tumors, gross extrascleral extension, ring melanoma, or >50% involvement of the ciliary body are contraindications to plaque brachytherapy (6). Therefore, other strategies of eye-preserving therapy have been tested. A recent Surveillance, Epidemiology, and End Results Program analysis showed no difference in 5-year OS (~83%)

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in patients treated with plaque brachytherapy compared to external beam radiotherapy (7). However, the Surveillance, Epidemiology, and End Results Program database does not distinguish between types of external beam radiotherapy or include important clinical factors such as tumor depth and size, as well as socioeconomic factors.

In the only randomized trial comparing brachytherapy to helium ion external beam radiotherapy, local control and salvage enucleation rates were better with helium ions, with no difference in OS (8, 9). However, the prescribed dose was 70 cobalt gray equivalent (CGE) to the tumor apex, which is lower than the current standard of 85 Gy for plaque brachytherapy. Proton therapy is the more popular charged-ion therapy used around the world. A number of retrospective reports of proton therapy in uveal melanoma have shown 5-year local control rates of 85−96% (10−15), but there has not been a direct comparison of proton therapy to brachytherapy. This study analyzes the national patterns of care for plaque brachytherapy and proton therapy for choroid melanoma, reporting on significant factors impacting survival.

Methods and materials

Data source and study population

The National Cancer Database (NCDB) Participant User File (PUF) is a deidentified national registry of cancer patient clinical and demographic data with survival outcomes run by the American College of Surgeons and the American Cancer Society. Approximately 70% of patients treated at Commission on Cancer-accredited cancer centers are included in the registry with standardized coding and data item definitions. NCDB is not population-based and underrepresents rural treatment centers areas and minority populations. A total of 7880 patients aged 18−90 years were identified who presented with choroid melanoma (code 693 from *International Classification of Diseases for Oncology*, third edition) from 2004 to 2013 as their only malignancy. Patients with nodal or metastatic disease, incomplete staging information including basal diameter and tumor thickness, or received surgery or chemotherapy were excluded. Radiation therapy was specified as either brachytherapy or proton therapy for a final total cohort of 1224 patients (Fig. 1).

Demographic and clinical data included age, sex, treatment facility type, treatment year, race, insurance status, Charlson-Deyo comorbidities score, distance to treatment, time to starting radiation, and socioeconomic status of the patient's home address were included. The American Joint Committee on Cancer (AJCC), seventh edition, was introduced in 2010 and included differences in T staging. Due to this shift in staging in the study period, all patients were restaged according to the American Joint Committee on Cancer, seventh edition, from the reported basal diameter and tumor thickness. Ciliary or extraocular extension and proton dose are also reported. The PUF only has deidentified data and was exempt from institutional review board oversight.

Statistical analysis

The χ^2 and Fisher exact tests were used to compare categorized demographic and clinical variables in brachytherapy and proton groups. Student's two-tailed t test was used to compare differences in age and average tumor dimensions. Overall survival was calculated from diagnosis until death with censoring of patients who are still alive at last followup. Significance of Kaplan-Meier estimates of OS was determined by log-rank test. Cox proportional hazards analysis was used for multivariate analysis of predictors of OS. All variables were entered in a forward-conditional manner into the model and significance was set as p-value < 0.05.

Propensity scores and a 1:1 matched cohort of brachytherapy and proton patients were created as previously described (16). Differences in demographic and clinical variables in the brachytherapy and proton groups were identified by logistic regression and distilled into a propensity score for receiving proton therapy. Patients with matching propensity scores were identified in the larger brachytherapy control group for each proton patient. This smaller cohort of 452 patients (226 in each group) was separately analyzed with Kaplan-Meier and Cox proportional hazards analyses as above. Propensity score matching was performed with the MatchIt function (17) in R, version 3.2.3 (2015 The R Foundation for Statistical Computing). All other analyses were done in SPSS Statistics, version 23 (IBM Corporation, Armonk, NY).

Results

Patient demographics

A total of 1224 patients were included in the initial analysis. Median followup was 37 and 29 months for brachytherapy ($n = 996$) and protons ($n = 228$), respectively. Many records of tumor dimensions were incomplete before 2010 and not included. Thus, 93% of patients in this cohort were treated from 2010 to 2013. The mean age was 61 years (range 20−90 years), and 52% were male. Most patients were white (95%), insured (98%), and had no other major comorbidities (83%). The majority of patients traveled more than 60 miles to get treatment (74%) and most were treated within 60 days of diagnosis (87%). Median proton dose was 56 CGE in four fractions (range 50−70.4 in four−seven fractions). Brachytherapy prescription doses were not specified. There were no significant differences in age, sex, insurance status, Charlson-Deyo score, T-stage, ciliary/extraocular extension, or tumor thickness. Patients receiving protons were more likely to be treated at an academic center (99% vs. 76%) with more experience (>50 patients 90% vs. 56%), nonwhite (86% vs. 96%), traveled >60 miles to treatment (81% vs. 72%), started treatment >60 days from diagnosis (19% vs. 11%), and had tumors with basal diameter ≤12 mm (69%