Clinical Investigation: Central Nervous System Tumor

Local Recurrence After Uveal Melanoma Proton Beam Therapy: Recurrence Types and Prognostic Consequences

Jean-Pierre Caujolle, MD,* Vincent Paoli, MD,* Emmanuel Chamorey, PharmD,[†,‡]
Celia Maschi, MD,* Stéphanie Baillif, MD,* Joël Herault, PhD,[†] Pierre Gastaud, MD,*
and Jean Michel Hannoun-Levi, MD[†]

*Department of Ophthalmology, Saint Roch Hospital, Nice Teaching Hospital, Nice, France; †Department of Radiation Oncology, Protontherapy Center, Centre Antoine Lacassagne, Nice, France; ‡Department of Biostatistics and Epidemiology, Centre Antoine Lacassagne, Nice, France

Summary

We have studied 61 cases of uveal melanoma local recurrences after proton beam therapy. Our local recurrence rate was 6.1%. These local control failures were divided into 4 recurrence types. The large tumoral diameter has been the sole statistical significant recurrence risk factor found. The overall survival at 10 years was 68.7% for recurrence-free patients and 43.1% for local recurrence patients. The multivariate analysis has shown a better prognosis for marginal recurrences.

Purpose: To study the prognosis of the different types of uveal melanoma recurrences treated by proton beam therapy (PBT).

Methods and Materials: This retrospective study analyzed 61 cases of uveal melanoma local recurrences on a total of 1102 patients treated by PBT between June 1991 and December 2010. Survival rates have been determined by using Kaplan-Meier curves. Prognostic factors have been evaluated by using log-rank test or Cox model.

Results: Our local recurrence rate was 6.1% at 5 years. These recurrences were divided into 25 patients with marginal recurrences, 18 global recurrences, 12 distant recurrences, and 6 extrascleral extensions. Five factors have been identified as statistically significant risk factors of local recurrence in the univariate analysis: large tumoral diameter, small tumoral volume, low ratio of tumoral volume over eyeball volume, iris root involvement, and safety margin inferior to 1 mm. In the local recurrence-free population, the overall survival rate was 68.7% at 10 years and the specific survival rate was 83.6% at 10 years. In the local recurrence population, the overall survival rate was 43.1% at 10 years and the specific survival rate was 55% at 10 years. The multivariate analysis of death risk factors has shown a better prognosis for marginal recurrences.

Conclusion: Survival rate of marginal recurrences is superior to that of the other recurrences. The type of recurrence is a clinical prognostic value to take into account. The influence of local recurrence retreatment by proton beam therapy should be evaluated by novel studies. © 2013 Elsevier Inc.

Introduction

Uveal melanomas (UMs) are the main adult intraocular tumor. The local control by proton beam therapy (PBT) of these tumors is good in the different series results (1-9). Many studies showed higher death and metastatic rates in case of local control failure (6-8, 10, 13). However, different types of recurrence are possible, with various definitions and descriptions in the literature (2, 3, 7, 8, 13, 14). Moreover, the recurrence type is seldom specified in most studies.

Methods and Materials

Patients

All our patients have been treated by PBT according to the technique previously described after positioning 4 tantalum rings on the sclera after UM localization by transillumination (3, 15). The safety margin was usually 2.5 mm. A lower safety margin was used for some posterior pole tumors to increase functional results (3). This is made possible by our beam ballistic properties with a short distal penumbra. The total dose delivered was 60 cobalt Gray equivalents in 4 fractions. After undergoing treatment, patients were regularly followed by their local ophthalmologist. A thorough examination was performed by our physicians at each half-yearly check-up as for the initial work-up with fundus examination after dilatation, retinography, B-mode ultrasound, or ultrasound biomicroscopy, fluorescein angiofluorography, computed tomography scan, and/or magnetic resonance imaging. Patients were examined in our clinic every 6 months for 2 years and then every year for 5 years and at 7, 10, and 15 years. They were checked earlier in case of problem or doubt on treatment efficiency. In case of recurrence, we firstly look at initial the images to eliminate errors in the initial treatment planning. Liver ultrasonography or tomodensitometry was performed to detect metastases every 6 months for 5 years and then every year for 10 years.

We studied the local recurrence cases in a total of 1102 UMs treated by PBT between June 1991 and December 2010. For statistical analysis, the patients have been divided into 2 subgroups (ie, patients controlled by their PBT and patients with a local control failure).

Description of the different types of local control failure

For this study, we have divided the local control failures according to 4 possible types (3, 11). The "marginal recurrences" are a tumor growth on the lesion margin with initially a lateral flat extension of the UM. The "global recurrences" are a persistent growth or a regrowth of the tumor in all their dimensions. The "extrascleral extensions" are the development of the tumor in the orbit through the sclera. The "distant recurrences" are a new tumoral localization inside the eyeball with a free choroidal interval of at least 5 mm outside the irradiated area. The irradiated area that receives more than 90% of the dose is defined as the "clinical target volume" extended by a standard 2.5-mm margin also referred to as "planning target volume."

A tumoral growth was only considered as a recurrence if it kept progressing after the first 6 months and/or after 2 consecutive examinations. Most recurrences are tumoral regrowths after an initial stabilization or tumor shrinkage except for the distant and the extrascleral recurrences. In case of a doubt, the patients were seen earlier (ie, 3 months later) in order to eliminate false recurrences (7), namely subretinal and/or tumoral hemorrhage, lipidic exudation, or edema following proton beam irradiation (16).

Statistical methods

All categorical data were described using figures and percentages.

Quantitative data were presented using medians and ranges or means and standard deviations. Censored data were described using Kaplan-Meier estimation, including the number of patients, number of events, median survival, and a 95% confidence interval (CI). Whenever the information was not available, the status was coded as missing data. Statistical analyses were 2-sided and performed using R-2.5.0 software for Windows. All censored data intervals were calculated from the date of the first intraocular tumor treatment to the event (patient death, lost to follow-up, or metastatic or local recurrence).

Univariate analyses

Statistical comparisons were performed using the chi-square test or Fisher's exact test for categorical data, Student t test or Wilcoxon test for quantitative data, and log-rank test for censored data.

Multivariate analyses

Multivariate analyses were performed by creating a Cox proportional hazard model or a logistic regression. Choice of the final model was made by performing a backward stepwise model selection by exact Akaike information criterion. Usually, all variables associated with a P value $<.10$ on univariate analysis were included in the model. Colinearity between variables was evaluated using the Pearson r correlation coefficient value between all variables entered in the model. Whenever r was >0.30, 1 of the 2 variables was considered redundant and was removed from the model.

Results

We have found 61 cases of local recurrences on a total of 1102 UMs treated by PBT. Seven patients were lost to follow-up; they belonged to the recurrence-free patients (RFPs) group. Our RFP rate was 93.9% ($\pm$0.9%) at 5 years, 91.3% ($\pm$1.2%) at 10 years, and 90.6% ($\pm$1.4%) at 15 years. A total of 77% of our local recurrences occurred within the first 3 years of the treatment. The last recurrence was observed 16 years after the PBT.

Qualitative and quantitative tumoral features concerning our series are displayed Tables 1 and 2. There was no statistical difference between local recurrence patients (LRPs) and recurrence free patients for the gender, the affected eye, the localization, and the 7th TNM classification. There was no statistical difference between LRPs and RFPs regarding the age and the initial tumoral thickness. Conversely, there was a statistical difference between LRPs and RFPs concerning the initial tumoral