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Tumor Control Probability and Time-Dose Response Modeling for Stereotactic Radiosurgery of Uveal Melanoma

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Abstract
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Abstract

Objectives:

Uveal melanoma (UM) is a rare malignant neoplasia but represents the most common intraocular malignancy in adults. Treatment options comprise brachytherapy, stereotactic radiosurgery (SRS), stereotactic radiotherapy, proton beam therapy, and enucleation. Given its radioresistance, radiotherapy of UM requires a considerable dose to achieve durable local control (LC). Analyses of the tumor control probability time-dose response may help individualize treatment decision-making in the management of patients. Therefore, it is essential to incorporate the time to a specific outcome as a function of dose, as radiation oncologists, neurosurgeons, and radiosurgeons have the most control over prescription dose. This study reports the tumor control probability and dose-response of UM receiving photon-based SRS.

Methods:

This retrospective, single-center analysis included patients with confirmed UM diagnosis treated between 2005 and 2019. A complete ophthalmologic examination was mandatory. All patients underwent single-fraction SRS using a robotic radiosurgery system (CyberKnife, Accuray Inc., Sunnyvale, CA, USA). Patients were staged according to the TNM classification (8th edition) and had at least one available follow-up. To create the dose-response model, data were divided into four dose groups (17-19, 20, 21, 22 Gy), and Kaplan-Meier analysis was performed for each dose group. Dose-response models for LC were then created from Kaplan-Meier values at 2, 4, and 7 years. A multivariable Cox proportional hazards model determined the impact of treatment-associated variables on LC.

Results:

Outcomes from 594 UM patients undergoing SRS were used to create the time-dose response models. The prescribed doses and the number of patients were as follows: 17-19 Gy (25 patients), 20 Gy (121 patients), 21 Gy (435 patients), and 22 Gy (13 patients). Averaged over all patients and dose levels, LC rates at 3, 5, and 7 years were 90.7% (95% CI = 87.5% - 93.1%), 82.4% (95% CI = 77.4% - 86.4%), and 69.0% (95% CI = 60.9% - 75.8%), respectively. Multivariable Cox regression only demonstrated a significant association of the prescription dose with LC (HR = 0.73, 95% CI = 0.56 - 0.95, p = 0.018, with no significant association with tumor size or ciliary body involvement). The calculated dose-response models for LC at 2, 4, and 7 years confirmed a dose-dependent effect, showing 2-year LC rates of more than 90% with 20 Gy and more than 95% with 22 Gy. For 4 years and an LC of 90%, a dose of approximately 21 Gy was required. After 7 years, the 21 Gy prescription dose is predicted to maintain an LC above 70%, with a sharp decline to less than 60% LC with 19 Gy and around 40% with 18 Gy.

Conclusion(s):

Time-dose response modeling of UM receiving SRS highlights the importance of the prescription dose to achieve durable LC. The choice of prescription dose should be carefully considered against the risk of toxicity, taking into account tumor geometry and patient characteristics to individualize treatment. While Kaplan-Meier analysis illustrates the response over time, radiation oncologists, neurosurgeons, and radiosurgeons have control over the dose, making dose-response models, including time kinetics, vital for

well-informed treatment decision-making. Further research is needed to validate the reported time-dose modeling.