Radiotherapy and Oncology xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

Early ultrasonographic tumor regression after linear accelerator stereotactic fractionated photon radiotherapy of choroidal melanoma as a predictor for metastatic spread

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ARTICLE INFO

Article history:
Received 22 December 2017
Received in revised form 14 April 2018
Accepted 17 April 2018
Available online xxxx

Keywords:
Choroidal melanoma
LINAC radiotherapy
Tumor regression
Prognosis

ABSTRACT

Background and purpose: During extended follow-up (of up to 15 years), approximately fifty percent of patients with choroidal melanoma will develop metastatic disease and eventually die. Thus, continuing research on prognostic factors, early detection and treatment is necessary. Height regression rates both after plaque brachytherapy and proton beam irradiation have been shown to have prognostic value. The purpose of this study was to analyze the influence of early tumor regression rate after treatment of choroidal melanoma with LINAC stereotactic fractionated radiotherapy (SFRT) as an independent risk factor for metastasis.

Material and methods: 256 patients with choroidal melanoma treated with LINAC SFRT were included. Follow-up included standardized echography yielding apical height, smallest and largest basal linear diameter, tumor volume and mean reflectivity. The influence of baseline measurements and of a longitudinal, normalized area under the curve coefficient (NAC) of the latter marker on metastasis risk was assessed.

Results: NAC for tumor thickness at months 3, 6, and 12 had a statistically significant ($p < 0.001$) non-linear effect on risk of metastasis. Additionally, ultrasonographic baseline tumor dimensions, but not internal reflectivity were found to be statistically significant risk factors for metastasis.

Conclusions: Our results demonstrate a non-linear influence of regression rate of choroidal melanoma as independent risk factor of metastatic disease after LINAC SFRT. These prove the clinical experience that, in comparison to rather slow regressions, very quick and very slow early tumor responses to LINAC SFRT are associated with a significantly higher metastasis risk.

Uveal melanoma is the most common primary intraocular malignancy in adults and can present in the choroid (90%), the ciliary body (6%) and in the iris (4%) [1]. Treatment options include plaque brachytherapy (mostly using iodine-125, ruthenium-106, and strontium-90), charged-particle proton beam radiation, linear accelerator (LINAC) based stereotactic fractionated radiotherapy (SFRT), gamma knife radiosurgery and enucleation [2–16]. It was shown that, concerning mortality rates, iodine-125 brachytherapy and primary enucleation did not differ for up to 12 years after treatment [17]. In contrast to single-fraction radiosurgery, stereotactic radiotherapy using LINAC offers the advantage of fractionated therapy resulting in reduced toxicity while providing tumor control rates reported over 90%, 5 and 10 years after treatment [18–23]. At the Medical University of Vienna, SFRT is applied according to a standardized protocol if the initial height of the choroidal melanoma is 7 mm or higher, in case of juxtapapillary and/or juxtamacular location, and if the central tumor distance to the optic disc and/or the macular is less than 3 mm [22,24–26]. The articles published by our group provide an extensive overview about tumor control and radiation side effects of this treatment [18,22,27]. Although metastasis is rare at the time of initial ocular presentation, approximately 50% of patients develop metastatic disease and eventually die of melanoma [28]. Therefore, global research focuses on prognostic factors, early detection and treatment of metastatic disease. It is a well-known fact that the most significant prediction of melanoma-specific mortality is dependent on tumor specific genetic alterations [29–34]. Additionally, age, initial tumor dimensions and location, retinal detachment, as well

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https://doi.org/10.1016/j.radonc.2018.04.019
0167-8140/

as histological subtypes indicate a higher risk for metastatic disease too [3,26–28,34,35] However, in most centers fine needle aspiration is not performed in every clinically diagnosed choroidal melanoma, thus, genetic information is not available in most cases. Easily accessible, non-invasive, morphometrical prognostic factors, acquired with imaging modalities such as ocular ultrasonography, offer a valuable source of clinical biomarkers. For eyes treated with Cobalt-60, Ruthenium-106 brachytherapy, or proton beam irradiation, height regression rates were shown to have a prognostic value for the prediction of metastasis-free survival, and specifically that higher regression rate indicates a worse cumulative survival [36–38]. No similar analysis for eyes treated with LINAC SFRT has been published so far. The aim of the present study was to investigate the prognostic value of dynamic morphometric parameters, specifically regression rate, for the prediction of the metastasis risk after treatment of choroidal melanoma with LINAC SFRT.

Methods

Stereotactic treatment

At the Medical University of Vienna, patients presenting with choroidal melanoma unsuitable for plaque brachytherapy or surgical resection have been treated with LINAC SFRT at the Department of Radiotherapy with a total dose of 60 Gy since 1998, and a smaller total dose of 50 Gy since 2005, to limit the effects of irradiation to organs at risk as far as possible. The treatment itself was planned ensuring that the planning target volume was encompassed within at least the 80% isodose while minimizing the dose to organs at risk [39]. Counter-indications for brachytherapy were an initial height of 7 mm or higher, juxtapapillary and/or juxtamacular location with a height of >2.0 mm and distance to the optic disc and/or the macula of <3.0 mm. Details about the protocol, including treatment indication, the exact LINAC SFRT radiotherapy scheme and internal/ophthalmological follow-up protocol applied at our department are described in detail elsewhere [18,22,25–26]. Patients with metastatic disease at presentation were excluded.

Endpoints

The primary endpoint of this retrospective analysis was the time to the onset of metastatic disease, starting from the follow-up examination at month 12. We analyzed biomarker dynamics gathered until up to month 3, 6, and 12. The hypothesis is predictability of metastasis-free survival based on ultrasonographic tumor height regression (measured with standardized A-scan and B-scan ultrasonography) of choroidal melanoma after LINAC SFRT. In further analyses, the prognostic value of the dynamics of the largest and smallest linear basal tumor diameters (LTD, STD; measured with B-scan ultrasonography), tumor volume (VOL; calculated using the rotation ellipsoid volume model based on A- and B-scan ultrasonography) and mean internal tumor reflectivity (REF; measured with standardized A-scan ultrasonography), as well as the prognostic value of the morphometric baseline characteristics were evaluated [40–41].

Evaluation method and statistical analysis

An integrative area under the curve (AUC) coefficient was introduced in order to summarize the change of any measured parameter over time numerically. The AUC refers to a patient's biomarker measurement dynamics (e.g. tumor height) from baseline to a pre-specified landmark (LM, a measurement at a specific follow-up examination). After dividing all measurements by the baseline value, normalized AUC coefficient (NAC) is then calculated as AUC/LM – 1 (detailed explanation available as Electronic Appendix). Thus, a patient with constant tumor height measurements over the whole period until the landmark corresponds to a month-12 NAC value equal to zero (see Fig. 1, example 1). If a patient's parameter remains constant for the first half of the period until the landmark and then stays at the double of the baseline value for the second half he/she has a month-12 NAC of +0.5 (see Fig. 1, example 2). The same value is obtained for a patient with a linear increase from baseline to the double of the baseline at the landmark (see Fig. 1, example 3). A patient decreasing linearly to half the baseline value has a month-12 NAC of −0.25 (see Fig. 1, example 4), whereas a patient decreasing to the same value earlier has a month-12 NAC of −0.44 (Fig. 1, example 5). An even faster decrease to a lower value results in a month-12 NAC of -0.65 (see Fig. 1, example 6). For each LM for which the NAC was calculated a Fine & Gray model is used to investigate the influence of NAC on the time from the LM until metastasis. Each model is restricted to patients who have survived without metastasis until the respective LM. The reported subdistribution hazard ratios (HR) quantify the effect of each 0.25 difference in NAC for tumor height, GTD, STD, REF, and VOL with LMs at 3, 6 and 12 after treatment. Hazard ratios for NAC were adjusted for the respective baseline measurement including the tumor's distance to the optic disc (DO). The latter was the strongest, albeit non-significant, predictor among age, gender, distance to the macula and DO. An indicator for distinguishing between a total dose of 50 Gy and 60 Gy was not significant in a single-variable Cox model (HR = 1.12, $p = 0.770$). Since it was not significant in any of the models including NAC variables and its inclusion did not alter the hazard ratio estimates or p-values of the NAC variables this indicator was omitted. For tumor height, cumulative incidence functions are shown graphically (see Fig. 2).

Categorical variables are described as counts and percentages, continuous variables by medians and quartiles due to skewed distributions. Median follow-up time was calculated using the reverse Kaplan–Meier method. The potential influence of baseline ultrasonographic tumor characteristics on the time to metastasis was assessed by Fine & Gray models to take the variable 'death from any cause' as competing risk into account. Therefore, all reported hazard ratios (HR) refer to the hazard of the subdistribution [42]. Missing ultrasonographic tumor characteristics were multiply imputed by first producing a monotone missingness pattern using

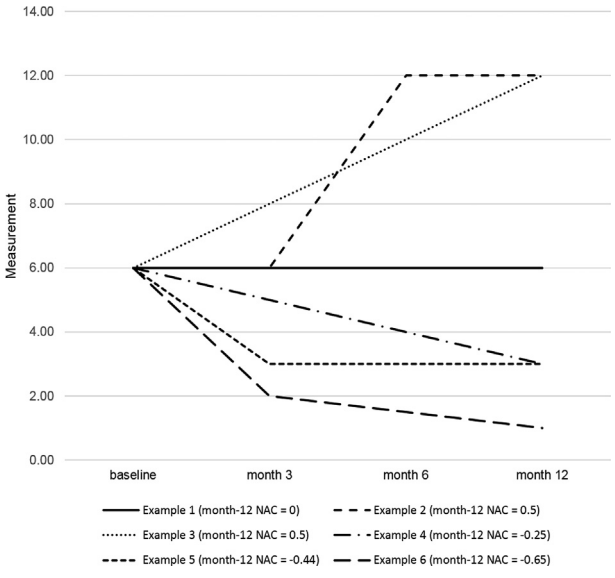

Fig. 1. Area under the curve scale coefficient descriptive examples. See text for explanations.

Please cite this article in press as: Mitsch C et al. Early ultrasonographic tumor regression after linear accelerator stereotactic fractionated photon radiotherapy of choroidal melanoma as a predictor for metastatic spread. Radiother Oncol (2018), https://doi.org/10.1016/j.radonc.2018.04.019