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Overview

Clinical Outcomes of Proton Radiotherapy for Uveal Melanoma

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Abstract

Aims: Although clinical experience with proton beam radiotherapy (PBT) for most tumours is limited, there is relatively longstanding experience for uveal melanomas. Because of potential to reduce ocular toxicities, PBT is an attractive option for these tumours. However, summative data remain scarce. We systematically reviewed clinical outcomes of uveal melanoma patients treated with PBT, to comprehensively assess outcomes such as tumour control, survival, enucleation rates, toxicity and visual acuity preservation.

Materials and methods: A systematic search of PubMed, EMBASE, abstracts from meetings of the American Societies for Radiation Oncology and Clinical Oncology, and the Particle Therapy Co-Operative Group was conducted from 2000 to 2015. Fourteen original investigations from 10 different institutions were analysed.

Results: Most tumours were choroidal and medium-/large-sized, and received 50–70 Cobalt Gray equivalent dose; more recent data reported lower doses. Five year local control rates exceed 90%, which persisted at 10 and 15 years. Five-year overall survival rates ranged from 70 to 85%, 5 year metastasis-free survival and disease-specific survival rates from 75 to 90%, with more recent series reporting higher values. With the removal of smaller studies, 5 year enucleation rates were consistently between 7 and 10%. Many patients (60–70%) showed a post-PBT visual acuity decrease, but still retained purposeful vision (>20/200); more recent, higher-volume series reported superior numbers. Complication rates were quite variable but showed improvements on historical plaque brachytherapy data. Only one randomised trial directly compared particle therapy (helium) with plaque brachytherapy, showing the former to be superior; this is addressed separately.

Conclusions: PBT is an excellent modality to treat uveal melanomas, with high survival outcomes and visual acuity preservation. Although there are low toxicity and enucleation rates, the recent development of supportive therapies for radiation toxicities can further decrease clinical adverse effects.

Key words: Enucleation; ocular tumours; proton radiotherapy; radiation therapy; uveal melanoma

Introduction

Primary uveal melanoma is a relatively uncommon tumour that arises from the uvea, anatomically consisting of the choroid posteriorly and ciliary body/iris anteriorly. It can cause loss of vision, metastasis and death; thus, considerable efforts have been made to best address treatment. The Collaborative Ocular Melanoma Studies (COMS), first published in 2001 [1], established the role of plaque radiotherapy in lieu of enucleation [2].

The excellent dosimetric profiles, conformality and ability to spare critical organs and structures characteristic of proton beam radiotherapy (PBT) make it especially attractive as a treatment for ocular tumours [3]. The use of PBT for uveal melanomas is in fact not a new concept, having been used since the mid-1970s [4], but broad, summative views are lacking [3]. We systematically reviewed the literature for published data from all available institutions evaluating oncological and ophthalmological outcomes after PBT for primary therapy for uveal melanoma.

Materials and Methods

This systematic review was conducted using the Preferred Reporting Items for Systematic Reviews and

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Meta-Analyses (PRISMA) guidelines [5]. A meta-analysis was not carried out due to substantial, multifaceted methodological/technical treatment heterogeneity between various studies that would bias results and interpretation to some degree. Previous attempts (albeit with different focus as this review) have found high degrees of bias, probably due to the observational nature of these studies, as well as significant data heterogeneity that resulted in many flaws in quantitative data analysis and interpretation [6]. Eligibility criteria included published work in English evaluating clinical outcomes of proton radiation therapy for melanoma of the eye. Sources of information for this review included PubMed, EMBASE, abstracts from annual meetings of the American Society for Radiation Oncology (ASTRO), Particle Therapy Co-Operative Group (PTCOG) and the American Society of Clinical Oncology (ASCO), those found in references from the major articles identified and articles known to the authors. The searches were conducted to identify any and all articles addressing clinical outcomes of proton radiotherapy for ocular melanoma with the following headings: proton, proton radiation therapy, proton beam therapy, ocular melanoma, uveal melanoma, choroidal melanoma, eye melanoma. Due to substantial lack of knowledge regarding technical aspects of PBT delivery in the past, which can cause vastly different side-effects and outcomes, we restricted search terms from 2000 to 2015. All searches were completed by 1 June 2015. Based on the initial searches, 173 articles/abstracts were identified (Figure 1). Care was taken to ensure that the inclusion criteria were sufficiently broad in order to ensure that possibly pertinent publications were not excluded by individual screening rather than the initial database search. In case of journal publications and meeting abstracts being from the same group, the abstract was excluded in favour of the journal article. If updates with larger sample sizes were available from the same group, these were chosen preferentially. Commonly, if the same institution published multiple articles with overlapping patients (e.g. examining all tumours versus examining a location-based subset), the article with the largest sample size was chosen (although both were cited, if appropriate) so as not to over-represent institutions that publish multiple articles on similar patients. However, if outcome measures were incompletely reported in one publication but were present in another publication, both were included (provided they were in the 2000–2015 time frame; if not, they were only cited) in order to effectively analyse outcomes (e.g. the same institution reporting local control in one publication and survival outcomes in another). After duplicates were removed, each of the 156 remaining eligible items was independently screened for the criteria described below by a single author (VV) and a further 121 were excluded. Specifically, articles without specific assessments or reflections on clinically relevant outcomes of proton radiotherapy for previously untreated melanoma of the eye (e.g. medical physics-oriented publications), thus being outside the scope of this review, were excluded. Additionally, letters to the editor, direct commentary to other articles and small reports (<25 patients) were also excluded. Of the 35 publications remaining, an additional 21 were review articles and although some were cited, they were not included in the primary analysis. Thus, 14 original investigations were found to have sufficient focus and relevance to be incorporated into the review.

Results

Full details of the included studies can be found in Table 1. The earliest study in this review period, from Loma Linda Medical Center [7], examined the effect of 70 Gy relative biological effectiveness (RBE) PBT in 78 patients with mostly (77%) medium-sized tumours, using the definitions set forth by the COMS. At a median follow-up of 34 months, 5 year local control was 90.5% and metastasis-free survival (MFS) was 76.2%. Five year overall survival was 70.3% and disease-specific survival (DSS) was 75.6%. Toxicities were relatively high, with an enucleation rate of nearly 25%, in part due to high numbers (26%) of anteriorly located tumours, which on further analysis was a significant factor associated with enucleation. Thirty-eight percent of patients experienced retinal detachment, as well as glaucoma (18%), rubeosis (13%), ocular pain (17%) and vitreous bleeding (9%). Visual acuity outcomes showed that for the patients in the highest visual acuity group, acuity decreased by 36%, whereas for those in the lowest visual acuity group, acuity actually improved by 36%.

The Swiss experience included two large studies separately assessing survival outcomes in 2435 patients [8] and ophthalmological outcomes in 2645 patients [9], followed up for 40 and 44 months, respectively. Both studies had similarly high proportions of anterior tumours, nearly 32%. Although neither study defined size according to COMS, and changed definitions between studies, tumours in this cohort were predominantly large, and larger than in the previously discussed study. Ninety-six percent of patients received 60 Gy (RBE). Similar to the previous study, high local control rates of 95.8 and 94.8% were attained at 5 and 10 years, respectively. Ten year overall survival was 72.6% for non-recurrent tumours and 47.6% for recurrent tumours. The enucleation rate was lower than the previous study at 8.2%.

The earliest centre to use PBT for uveal melanomas was Harvard, starting PBT in 1975. The first major analysed report by Gragoudas *et al.* [10] encompassed 1922 patients, 94% treated to 70 Gy (RBE) (the dose was decreased over time when data from the same group showed no outcome differences between 70 Gy (RBE) and 50 Gy (RBE), in a randomised trial [11]). Consistent with previous data, with a median follow-up of 62 months, the 5 year local control was 96.7%; this remained high at 95.1% at 15 years. Although the authors did not report ophthalmological complications, previous data in 241 patients [12], albeit with a short follow-up of 15 months, showed an enucleation rate of 4.1%. The subsequent study by this group [13] reported on the largest cohort to date, 3088 patients. Both studies from this group also had a high proportion of anterior tumours (27%). However, it is notable that unlike the Loma Linda and Swiss

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