Local tumor control and treatment related toxicity after plaque brachytherapy for uveal melanoma: A systematic review and a data pooled analysis

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Abstract

Uveal melanoma (UM) represents the most common primary intraocular tumor, and nowadays eye plaque brachytherapy (EPB) is the most frequently used visual acuity preservation treatment option for small to medium sized UMs. The excellent local tumor control (LTC) rate achieved by EPB may be associated with severe complications and adverse events. Several dosimetric and clinical risk factors for the development of EPB-related ocular morbidity can be identified. However, morbidity predictive models specifically developed for EPB are still scarce.

PRISMA methodology was used for the present systematic review of articles indexed in PubMed in the last sixteen years on EPB treatment of UM which aims at determining the major factors affecting local tumor control and ocular morbidities. To our knowledge, for the first time in EPB field, local tumor control probability (TCP) and normal tissue complication probability (NTCP) modelling on pooled clinical outcomes were performed.

The analyzed literature (103 studies including 21,263 UM patients) pointed out that Ru-106 EPB provided high local control outcomes while minimizing radiation induced complications. The use of treatment planning systems (TPS) was the most influencing factor for EPB outcomes such as metastasis occurrence, enucleation, and disease specific survival, irrespective of radioactive implant type. TCP and NTCP parameters were successfully extracted for 5-year LTC, cataract and optic neuropathy. In future studies, more consistent recordings of ocular morbidities along with accurate estimation of doses through routine use of TPS are needed to expand and improve the robustness of toxicity risk prediction in EPB.

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Uveal melanoma (UM) represents the second most common form of melanoma and the most common primary intraocular tumor with an occurrence, in both the U.S. and Europe, of about 5–7.5 cases per million people per year [1–4].

UMs typically appear as dome shaped mounds, which involve primarily the choroid (90%) and to a lesser extent the ciliary body and the iris (6% and 4%, respectively) [5]. According to UM size and location, diverse treatment choices exist such as enucleation, stereotactic radiotherapy, charged particle irradiation and eye plaque brachytherapy (EPB) [6]. Up to ‘80s, the treatment of choice for UMs was enucleation. However, for small and medium sized UMs, a large trial from the Collaborative Ocular Melanoma Study (COMS) established no differences in survival between patients undergoing enucleation compared to EPB treatment [7]. With EPB, an eye applicator (the plaque) containing a radioactive source (gamma or beta emitter) is surgically affixed beneath the tumor base in direct contact with the ocular bulb for the time necessary for the prescribed dose to reach the tumor apex. In clinical practice, different radioisotopes are used including low-energy gamma radioisotope (I-125 and Pd-103) seeds along with the beta-emitting Ru-106 and Sr-90 plaques. Traditionally, the most common treatment in North America is I-125 EPB while Ru-106 is the isotope of choice in Europe and Asia [8,9], Ir-192, Cs-131, Au-198 and miscellaneous loaded plaques are also used worldwide [10]. The excellent tumor control rate of over 90% achieved by EPB [11,12] can however be associated with severe complications and adverse events. A wide
range of radiation-related ocular toxicities, including retinopathy, maculopathy, optic neuropathy, neovascular glaucoma and cataract, may affect visual outcome and patient quality of life [9,13–16]. Hence, for more effective treatments, the EPB endpoint should be not just to achieve local tumor control, but also to spare the healthy adjacent structures so as to improve patient’s quality of life.

In EPB dosimetry, the ophthalmic information (tumor apex height, tumor basal dimensions and ophthalmic structures at risks – OARs) were commonly obtained by a two-dimensional (2D) representation using ultrasound (US) and/or fundus images [10]. A central axis-point-dose calculation approach, i.e. one-dimensional (1D) dose calculations, was then applied to define the plaque implantation time required to deliver the tumor apex prescription dose neglecting tumor asymmetry or eccentricity corrections [10]. Even though 1D calculation method assured the tumor coverage with the required dose, the only OAR for which the dose can be estimated is the sclera. Recently, with the goal of reducing OARs toxicity, different treatment paradigms have been proposed to improve EPB dosimetry by including treatment planning systems (TPS), Computed Tomography (CT) or Magnetic Resonance (MR) imaging to create accurate 3D eye models and quality assurance procedures [17–19].

Several clinical and treatment related risk factors for the development of EPB-related ocular morbidity may be identified, such as tumor size and location, comorbidities and delivered radiation doses to OARs. Higher radiation doses to OARs are expected to be related to higher risk of toxicity. However, morbidity predictive models specifically developed for EPB are still scarce [20,21].

The purpose of our research is to perform a systematic review of the current literature on EPB treatment for UM in order to highlight the major factors affecting local tumor control and ocular morbidity. To meet a recognized need for quantitative analysis in modern EPB, tumor control probability (TCP) and normal tissue complication probability (NTCP) modelling were also performed on pooled clinical data.

Methods and materials

Search strategy

The main objectives of our search was to analyze reports focusing on EPB treatment for UM in order to describe the major factors affecting the local tumor control and ocular morbidities as well as to predict dose–effect relationship.

A keyword search in PubMed for “brachytherapy or plaque therapy” and “uveal melanoma or choroidal melanoma” was performed using the filter: published in the last 16 years (from January 1, 2005). The last update of the data search was October 31, 2020.

Selection process

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [22,23] methodology was used for study selection based on the eligibility/exclusion criteria described as follows. Only papers published in English were considered. Articles relating to eye re-treatment were specifically excluded. Each publication was assessed to determine the treatment modality, the number of patients and whether tumor response or at least one ocular complication was reported. Studies with less than 10 patients and including patients treated by external beam therapy were excluded. More details are shown in Supplementary Fig. S1.

The above inclusion criteria were assessed by two reviewers who independently screened titles and abstracts and, in case of controversial judgment, the papers were evaluated by a third author. The bibliographies of the selected articles were also reviewed to identify additional reports. No automation tools were used in the process.

Data collection process

From each study, patients (age, gender) and tumor features (stage, position, height and basal dimension), treatment strategies and planning related variables – such as radioisotope type, delivery time, imaging-based contouring for eye geometry modelling, dose calculation protocol followed and TPS use – were extracted and summarized.

As to outcomes, from each study, the reported data on tumor response and ocular morbidities were collected alongside the dose to the tumor and OARs whenever possible. When feasible, biologically effective dose (BED) to tumor apex was estimated as a function of the chosen radioisotope, implant duration time, source half-time, tumor half-time (corresponding to μ = 0.45 h⁻¹) and tumor α/β (11.5 Gy) [24].

For Local Tumor Control (LTC), defined as no local progression at the primary tumor site, the crude incidence and the actuarial rate of LTC at 5 years were extracted. For the studies where results were presented in Kaplan–Meier and actuarial figures, the corresponding data were drawn from figures. When reported in the literature, the incidence of metastasis, disease specific survival and enucleation after EPB were also collected in this review.

Synthesis method: statistical analysis and outcome modelling

Study features were summarized using median and range for continuous variables and percentage for categorical ones. The relationships between study outcomes and categorical study features were tested by non-parametric Mann–Whitney U test or its extension Kruskal–Wallis H test with Dunn test for post hoc analysis, when appropriate. Relationships between continuous variables were tested by Spearman’s rank correlation. A p value of 0.05 was considered statistically significant.

Local TCP and NTCP modelling for OARs were investigated assuming a logistic dose–response function correlating the probability (p) of the outcome with the dose (D) [25–28]

\[
p = \frac{e^{\gamma \frac{D}{D_{50\%}}}}{1 + e^{\gamma \frac{D}{D_{50\%}}}}
\]

where \(D_{50\%}\) is the dose required for a 50% probability of the considered outcome and \(\gamma\) is the normalized dose response gradient [27].

As for tumor response, to ensure consistency of TCP modelling, it was focused on actuarial 5-year LTC. The weighted least chi-square (\(x^2\)) method was used to fit the data and the reduced \(x^2\) was used for goodness of fit testing. Each study was weighted by the number of patients included.

Statistical analysis was performed with SPSS 18.0 statistical software (SPSS Inc., Chicago, IL) and with OriginPro 9.0 software (OriginLab corporation Northampton, MA).

Results

A reference list of 662 records was identified from the initial PubMed search. After screening and after applying the exclusion criteria (Supplementary Fig. S1), the two reviewers agreed to include 103 studies [1,8,9,11–16,29–122] for data collection and
modelling of outcomes. Full details of the included studies are reported in Supplementary Materials Table 1.

In 10 reports [11,15,16,30,36,37,51,52,75,76], 5 different cohorts were described (i.e., two reports were published on the same cohort). In 8 reports [12,31,32,40,47,48,102,112], each report was based on two patient’s cohorts treated with different EBRT strategies and accordingly they were analyzed as two separated cohorts. Finally, at the end of the selection process, 106 different cohorts including 21,263 UM patients treated with EBRT were selected. The range of the number of patients per cohort was 10–3,703.

 Studies characteristics

Tumor characteristics and EBRT treatment strategies are described in Supplementary Table S.1. Patients and treatment details, as well as absorbed doses and related tumor response and radiation-induced toxicities are presented in Supplementary Tables S2–S4. A summary of relationships among study features and outcomes are described in Table 1.

Patients and tumor characteristics

Reviewed studies reported UM occurrence between the ages of 40 and 70; a slight preponderance of UM in women was observed (median percentage of treated female 52%).

A heterogeneity of data reporting on melanoma classification was found, with several studies adopting the American Joint Committee on Cancer staging system [123] while few studies classify melanomas according to the COMS staging system [124], which is based on height and the largest basal dimension of the tumor. According to COMS, in order to standardize the data for further analysis, the staging was grouped in small, medium and large. A prevalence (79%) of medium size treated melanomas was found in the reviewed literature (Table 1).

In the analyzed literature, 25 cohorts were characterized by patients treated for posteriorly located tumors (recorded according to the position of the tumor posterior margin); in 21 of the cohorts, patients were predominantly (>50%) treated for posteriorly located tumors; a heterogeneous distribution of tumor position among anterior, posterior and equatorial was described in 30 of the cohorts (Table 1). In the remaining 30 series, the position was not reported or not classifiable according to the above schematizations.

Treatment and planning strategies

The distribution of the plaque sources utilized in the reviewed literature was presented in Fig. 1a. In 14 cohorts, patients were treated using a variety of plaque sources including I-125, Ru-106, Co-60, Ir-192, Cs-131 (hereinafter referred to as “miscellaneous”). In one cohort the plaque source was not described.

The plaque shape was reported in only 62% of the cohorts, the used shape depends on the tumor base dimension and on tumor position with respect to that of the optic disc. When the perimeter of the tumor overlaps or lies adjacent to the optic disc, a plaque with a notched perimeter instead of a rounded one was often employed for treatment. Notched or rounded plaques were used in 37% of cohorts, while in the remaining cohorts the use of different shape (finger-type slotted, eccentric, rectangular, COMS design, etc.) was reported.

The plaque dimension was generally selected in order to include the entire tumor base with a safety margin of 2–3 mm to the basal dimension. The plaque sizes ranged between 4 mm and 25 mm, with 4 mm sized plaque used for treating patients with peri- and juxtapapillary very small choroidal melanomas (<2.4 mm of apical height) (Supplementary Table S.1). In one study custom-made eye plaque size was adopted. Transpupillary thermotherapy (TTT) can be used in combination with EPB as primary treatment or to treat residual or recurrent tumors after the brachytherapy treatment (i.e., during the follow-up) [96]. In the revised series, a combined EBRT-TTT treatment was performed in 25 cohorts. In 12 out of 25, only a small subset (<15%) of patients received EPB in combination with TTT (Table 1).

A wide variety of prescription doses to the tumor apex were reported in the reviewed literature, ranging from 40 Gy to 150 Gy (Supplementary Table S.1), according to different plaque sources and following different available recommendations [125,126]. As regards the tumor apex mean dose (median 85 Gy, range [62.5–157.0] Gy), a significant correlation was found between the type of radioisotope and the tumor apex dose (p = 0.002). In particular, the lower tumor apex dose was reported for Pd-103 (median 81.0 Gy, range [68.9–87.0] Gy) compared with Ru-106 (median 100 Gy, range [67.0–157.0] Gy) (Fig. 1b). Furthermore, a median dose rate to tumor apex of 0.8 Gy/h (range [0.1–4.1] Gy/h) and a delivery time ranging between 1 and 12 days were described.

The use of TPS was reported in 27 cohorts (Fig. 1a), in most of them the Eye Plaque Simulator (PS) software (version 5 and earlier versions Bebig Gmbh, Berlin, Germany or version 6 Eye Physics LLC, Los Alamitos, CA [127]) was used. In Vonk et al. [70] a Pinna-Cle® TPS brachytherapy module (v 9.0; Phillips Medical Systems, Madison, WI) coupled with an in-house MATLAB code (release 2012b, The MathWorks, Inc, Natick, MA) was adopted. Imaging by CT, MR and US for eye structures and tumor dimension modelling was not a clinical routine in the reviewed literature and was reported in 15 cohorts only.

A significant correlation between tumor height and type of radioisotope was found (p = 0.017), with the thickest tumors treated by I-125 plaques (median height 5.0 mm, range [2.1–10.4] mm) compared with Pd-103 (median height 3.4 mm, range [2.1–8.6] mm) (Fig. 1c). The height of tumors treated by Ru-106 was not significantly different from that of tumor treated by I-125 or Pd-103.

Disease outcomes

The crude incidence of LTC was described in 76% of all cohorts and was evaluated on average over a follow-up of 57 months (range [16–305] months). The actuarial rate of LTC at 5 years was available from 38% of the cohorts. Median LTC and median actuarial 5-year LTC over the analyzed cohorts were 94% (range [54–100] %) and 91% (range [59–100] %), respectively. The incidence of metastasis and data on enucleation following EBRT treatment were reported in 65% and 86% of the cohorts with a median incidence of 8.0% (range [0–45] %) and 7% (range [0–35] %), respectively. Disease specific survival (DSS) data were available in 44% of the cohorts with a median rate of 92% (range [78–100] %). Notably, the reported crude and actuarial rates were pooled together for metastasis, DSS and enucleation (Table 1). Local and distant disease outcomes data after EBRT treatment from the analyzed cohorts were detailed in Table S.2.

Using the data extracted from the reviewed literature, we studied the potential factors affecting disease outcomes (Table 1). For reason of uniformity, the actuarial rate of LTC at 5 years was used in the subsequent analysis and modelling. Age was the only patient related factor positively correlated with 5-year LTC. The employed radioisotope was the treatment related factor impacting on 5-year LTC with Ru-106 showing a reduced LTC (median 86%, range [59–97] %) compared to I-125 (median 93%, range [83–100] %) (Fig. 2a), likely due to a suboptimal use of Ru-106 plaque affecting target dose distribution. Our analyses support that both metastasis occurrence and enucleation were correlated with increasing tumor occurrence. 
### Table 1
Summary of study features and clinical outcomes extracted from the revised literature (106 cohorts) and their correlations.

<table>
<thead>
<tr>
<th>Study features</th>
<th>Median (range)</th>
<th>N of cohorts</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LTC 5 years</strong></td>
<td>(91.0–100.0)</td>
<td>40</td>
<td>–</td>
</tr>
<tr>
<td><strong>Metastasis</strong></td>
<td>(8.0–45.0)</td>
<td>64</td>
<td>0.025</td>
</tr>
<tr>
<td><strong>Enucleation</strong></td>
<td>(7.0–35.0)</td>
<td>91</td>
<td>0.048</td>
</tr>
<tr>
<td><strong>DSS</strong></td>
<td>(92.0–100.0)</td>
<td>34</td>
<td>–</td>
</tr>
<tr>
<td><strong>Cataract</strong></td>
<td>(20.0–62.5)</td>
<td>57</td>
<td>–</td>
</tr>
<tr>
<td><strong>RON</strong></td>
<td>(10.3–100.0)</td>
<td>37</td>
<td>–</td>
</tr>
<tr>
<td><strong>RM</strong></td>
<td>(23.8–100.0)</td>
<td>34</td>
<td>–</td>
</tr>
<tr>
<td><strong>RR</strong></td>
<td>(38.9–100.0)</td>
<td>48</td>
<td>–</td>
</tr>
<tr>
<td><strong>NVG</strong></td>
<td>(6.0–36.0)</td>
<td>45</td>
<td>–</td>
</tr>
</tbody>
</table>

#### Study features

<table>
<thead>
<tr>
<th>Feature</th>
<th>Median (range)</th>
<th>N of cohorts</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61.3 (41.6–71.1)</td>
<td>95</td>
<td>0.025</td>
</tr>
<tr>
<td>Male (%)</td>
<td>48.2 (10.0–73.9)</td>
<td>87</td>
<td>0.048</td>
</tr>
<tr>
<td>Tumor height (mm)</td>
<td>4.6 (1.9–10.4)</td>
<td>90</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tumor basal diameter (mm)</td>
<td>11.0 (7.0–20.0)</td>
<td>84</td>
<td>–</td>
</tr>
<tr>
<td>Tumor apex dose (Gy)</td>
<td>85.0 (62.5–157.0)</td>
<td>81</td>
<td>–</td>
</tr>
<tr>
<td>Tumor base dose (Gy)</td>
<td>293.4 (105.0–989.6)</td>
<td>21</td>
<td>–</td>
</tr>
<tr>
<td>Tumor apex BED (Gy)</td>
<td>140.7 (102.2–314.4)</td>
<td>41</td>
<td>–</td>
</tr>
<tr>
<td>Lens dose (Gy)</td>
<td>14.5 (0.7–53.6)</td>
<td>25</td>
<td>–</td>
</tr>
<tr>
<td>Optic disc dose (Gy)</td>
<td>42.8 (9.2–111.2)</td>
<td>31</td>
<td>–</td>
</tr>
<tr>
<td>Sclera dose (Gy)</td>
<td>327.0 (184.0–1438.0)</td>
<td>31</td>
<td>–</td>
</tr>
<tr>
<td>Delivery time (days)</td>
<td>5.1 (2.2–8.0)</td>
<td>55</td>
<td>–</td>
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<tr>
<td>Tumor position</td>
<td>76</td>
<td>–</td>
<td>0.019</td>
</tr>
<tr>
<td>Posterior</td>
<td>32.9</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Posterior &gt;50% pts</td>
<td>27.6</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Tumor &lt;50% pts</td>
<td>39.5</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Imaging use</td>
<td>106</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>No</td>
<td>85.8</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Yes</td>
<td>14.2</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>TPS use</td>
<td>106</td>
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<td>0.023</td>
</tr>
<tr>
<td>No</td>
<td>74.5</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Yes</td>
<td>25.5</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Radionuclide</td>
<td>105</td>
<td>–</td>
<td>0.001</td>
</tr>
<tr>
<td>Ru106</td>
<td>34.3</td>
<td>–</td>
<td>0.05</td>
</tr>
<tr>
<td>1129</td>
<td>42.9</td>
<td>–</td>
<td>0.008</td>
</tr>
<tr>
<td>Pd103</td>
<td>9.5</td>
<td>–</td>
<td>0.003</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>13.3</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Combined TTT and EPB</td>
<td>106</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>None</td>
<td>76.4</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>≤15% pts</td>
<td>11.3</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>15–50% pts</td>
<td>8.5</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>&gt;50% pts</td>
<td>3.8</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>COMS staging</td>
<td>90</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Small</td>
<td>12.2</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Medium</td>
<td>78.9</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Large</td>
<td>8.9</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

**Abbreviations:** LTC: Local Tumor Control, DSS: Disease Specific Survival, TTT: Transpupillary Thermotherapy, RON; Radiation Optic Neuropathy, RM: Radiation Maculopathy, RR: Radiation Retinopathy, NVG: Neovascular Glaucoma, pts: patients.

* Spearman’s rank test for continuous variables and Mann–Whitney U test or its extension Kruskal–Wallis H test with post hoc Dunn test for categorical variables.

* Evaluated over the N cohorts in which the feature was reported.
height. The TPS use was instead associated to lower metastasis occurrence and enucleation events as well as with higher DSS.

Physical dose TCP modelling of 5-year LTC (Fig. 3) resulted in an estimated \( D_{50\%} = 63.1 \) Gy (95%CI 59.9–66.2 Gy) and \( \gamma = 2.8 \) (95%CI 2.4–3.3), with a reduced \( x^2 \) of 1.28. In patients treated with Ru-106 plaques, a separate TCP model led to a \( D_{50\%} = 63.7 \) Gy (95%CI 56.6–70.9 Gy) and \( \gamma = 3.2 \) (95%CI 0.5–5.9), with a reduced \( x^2 \) of 1.40. Modelling data using BED values was not feasible owing to the reduced number of data points for which BED values could be estimated.

Radiation-induced morbidity

Morbidities to the eye structures following EPB therapy, including cataract, radiation-induced optic neuropathy (RON), radiation-induced maculopathy (RM), radiation-induced retinopathy (RR) and retinal detachment (RD), were variously described in the reviewed literature (Supplementary Table S.3). In addition, EPB therapy was associated with a range of other ocular complications including neovascular glaucoma (NVG), keratitis, vitrectomy, corneal opacity and papillopathy (Supplementary Table S.4). Results on study features affecting ocular morbidities were summarized in Table 1.

Cataract rates were reported with a median incidence of 20% (range [0–90] %) in response to a median lens dose of 14.5 Gy (range [0.7–53.6] Gy) over the reviewed cohorts. None of the analyzed tumor features correlated with the incidence of cataract. Plaque source type was correlated with lens dose \( (p = 0.047) \) as well as with the incidence of cataract \( (p = 0.001) \): patients treated with Ru-106 and Pd-103 showed a reduced incidence compared with patients treated with I-125 or with miscellaneous radioisotope treatments (Fig. 4a).

RON after EPB was reported with a median incidence of 10% (range [0–62.5] %) in response to a median optic disc dose of 42.8 Gy (range [9.2 and 111.2] Gy). Plaque source type was correlated with both optic disk dose \( (p = 0.013) \) and RON incidence \( (p = 0.05) \). A reduced morbidity occurrence, although not statistically significant, was observed with Ru-106 compared with both I-125 and Pd-103 (Figure 4b). RON incidence was also affected by tumor position \( (p = 0.019) \), being posterior position a higher risk factor (Fig. 4c). Of note, no statistical difference was found in the distribution of tumor position among the different type of plaques \((x^2, p = 0.713)\).

Posterior segment complications as RM, RR and RD occurred with a median incidence of 24% (range [0–100] %), 39% (range [0,100] %) and 4% (range [0,42] %), respectively. Of note RD was described in only 18 cohorts. Radiation doses delivered to retina, macula and fovea have been reported to be related to posterior segment complications. However, in the reviewed cohorts, only one study reported a mean dose to the retina of 30.2 Gy [106]. Doses to macula and fovea were also scarcely reported (12% and 16% of cohorts) and were 53.4 Gy (range [19.1–94.9] Gy) and 56.8 Gy ([39.9–157.7] Gy), respectively. The literature analysis did not find specific factors significantly associated with RM. The type of plaque source \( (p = 0.008) \) was the treatment study feature associated with RR and the incidence of RR was significantly higher for those cohorts where a miscellaneous plaque sources were used compared with Ru–106 (Fig. 4d). A male prevalence in the cohort was positively correlated with RR.

Scleral necrosis or thinning were described in few studies (18 out of 106) with a median incidence of 2% (range [0–100] %). The dose received by the sclera was correlated with the employed radioisotope \( (p = 0.017) \) (Fig. 4e) and the highest scleral dose was related to the use of Ru-106 (570 Gy, range [226.4–1438.0]).

Study factors affecting RD or scleral morbidity occurrences were not analyzed owing to the low amount of available data.

Finally, in 42% of cohorts, NVG has a median occurrence of 6% (range [0,36] %) while, in 13% of cohorts, median papillopathy appearance was 18% (range [0, 50] %). The lowest incidence of NVG was observed in patients treated with Ru-106 \( (p = 0.003) \) compared with the other plaque sources (Fig. 4f). NVG occurrence was also associated to male prevalence, tumor dimensions (height and diameter) and, accordingly, to COMS staging.

Anterior segment complications, such as keratitis and corneal opacity were reported in only one study. Vitrectomy was often the fatal outcome for a severe RR in patients receiving EPB treatment. Eight cohorts reported vitrectomy rates ranging from 3% to 100%.

By NTCP modelling for cataract as function of lens dose values retrieved from the literature review (Fig. 5a), we estimated a \( D_{50\%} = 39.6 \) Gy (95%CI 27.3–51.9 Gy) and \( \gamma = 0.39 \) (95%CI 0.20–0.57) \((x^2 = 2.27)\). In the same way, NTCP modelling for RON as function of optic disc dose values (Fig. 5b) provided a
D50% = 107.7 Gy (95% CI 70.6–144.7 Gy) and $c = 0.98$ (95% CI 0.64–1.33), reduced $x^2 = 1.59$. A separate model for RON in posteriorly located tumors compared with other positions was not possible owing to the sparsity of the data. NTCP logistic modelling for other ocular morbidities such as RM or RR resulted in poor model fits.

Discussion

Plaque brachytherapy is the most frequently used visual acuity preservation treatment option for small to medium sized UM lesions [7]; larger tumors should be offered this treatment modality in selected cases [128]. Although EPB avoids enucleation, the risk of vision loss is still about 50% resulting from high radiation doses to the optic structures [16]. This is particularly critical for the posteriorly located tumors due to their proximity to the optic disc and fovea, in which the approach to reduce toxicity often implies a tradeoff between the tumor coverage and the OAR sparing.

The choice of radioactive plaque, prescription dose, new eye plaque designs, better imaging, new treatment planning techniques are all crucial to evaluate the therapeutic index of the EPB treatment [128]. Our systematic review was intended to gather information from the current knowledge on EPB for UM in order to help the clinical practice and to design future clinical trials.

Reviewing the literature from the last 16 years, we could observe that the most common radioisotopes used in EPB treatments are the gamma emitter I-125 and the beta emitter Ru-106, irrespective of tumor thickness. Apart from European vs United States traditions, the use of Ru-106 eye plaques has been traditionally the treatment of choice for small to medium sized ocular melanomas because of electrons limited depth penetration. However, Ru-106 was reported as a good treatment option also for tumor with a depth of more than 5 mm [8] or even thicker than 7 mm [59], while larger tumors have typically been treated with I-125 plaques [35]. Disease outcomes were not affected by the choice of the radioisotope, with the exception of the 5-year LTC rate which was lower for Ru-106 than for I-125, but still above 86%. This observed significant difference in 5-year LTC rate between Ru-106 and I-125 was however due to one single study on a small cohort of patients treated with Ru-106 [72] where the frequency of local tumor recurrence was found to be higher than expected. The authors associated the higher rate of local tumor recurrence to a low radiation dose at the edge of the Ru-106 plaque not correctly accounted for during the brachytherapy planning. It is indeed

Fig. 2. Effect of eye plaque brachytherapy (EPB) characteristics on disease outcomes. Boxplots of group cases (EPB radioisotopes) for 5-year local tumor control (LTC) rate (a). Boxplots of group cases (treatment planning system (TPS)) for metastasis rate (b); enucleation rate (c); disease specific survival (DSS) rate (d).

Fig. 3. Local Tumor Control (LTC) rate as a function of tumor apex dose and logistic Tumor Control Probability (TCP) model fitting curve. Each study was weighted by the number of patients included. (1) = Ru-106, (2) = I-125, (3) = Pd-103, (4) = miscellaneous. N = Number of cohorts.

$D_{50\%} = 107.7 \text{ Gy (95\% CI 70.6–144.7 Gy)}$ and $c = 0.98$ (95% CI 0.64–1.33), reduced $x^2 = 1.59$. A separate model for RON in posteriorly located tumors compared with other positions was not possible owing to the sparsity of the data. NTCP logistic modelling for other ocular morbidities such as RM or RR resulted in poor model fits.
important to underline that the observed results regarding a given isotope might not be ascribed to the isotope itself, but to an incorrect use of the selected plaque and, accordingly, to a suboptimal intraocular radiation distribution.

Several prognostic variables for UM outcome have been described in the literature. These include the size of the tumor, patient older age, tumor location [37,129]. As expected, tumor thickness was the study factor influencing EPB outcomes such as metastatic risk, in line with the analysis by Shields et al. [44] in which each millimeter of increasing tumor thickness and diameter contributed to the risk for metastatic disease. In our analysis, older patient age was an additional clinical factor impacting both the 5-year LTC and metastasis occurrence, in agreement with a previous study reporting increasing patient age as a clinical factor predictive of metastasis [129].

In the analyzed series, there was a slight increase in the number of females treated (52%). There is no previous evidence of gender-based survival differences in primary UM when prognostic variables such as tumor size are fully corrected for [38]. Similarly, gender-based differences in radiosensitivity are not reported. In the present analysis, male gender was correlated with retinopathy and NVG. Interestingly, male gender has been reported as a risk factor for retinopathy in a non-diabetic population and thus a sex difference in the pathogenesis leading to retinopathy has been hypothesized [130]. However, the reasons for male–female differences identified in this review are unknown.

As regards the EPB treatment related toxicity, the analyzed literature suggested that Ru-106 EPB has on the whole a lower risk for ocular morbidity than other plaque sources consistently with Ru-106 favorable dosimetric characteristics. Reduced radiation-related morbidity occurrence with Ru-106 compared with I-125 was observed for pooled rate of cataract, optic neuropathy, and NVG. On the contrary, the scleral dose, the most important risk factor for scleral necrosis, resulted to be considerably higher for Ru-106 compared with I-125 and Pd-103 gamma seeded plaques [131].

Notably, in our analysis, no difference in the dimension of tumor treated by I-125 or Ru-106 was observed and, hence, the lesion dimension itself might not be the cause of the reduced toxicity with Ru-106.

Fig. 4. Effect of eye plaque brachytherapy (EPB) characteristics on ocular morbidities and ocular structure dose. Boxplots of group cases (EPB radioisotopes): for cataract occurrence (a), Radiation Optic Neuropathy (RON) occurrence (b). Boxplots of group cases (tumor position) for RON occurrence (c). Boxplots of group cases (EPB radioisotopes): for Radiation Retinopathy (RR) occurrence (d), sclera dose (e) and Neovascular Glaucoma (NVG) occurrence (f).
TCP and NTCP models for EPB of uveal melanoma

On the whole, both I-125 and Ru-106 EPB are hereby confirmed as an effective treatment for uveal melanoma providing good tumor control and a high rate of survival. Ru-106 offers the benefit of high local control outcomes while minimizing radiation induced complications. Pd-103 equally succeeded in reducing cataract risk compared with I-125 in agreement with the superior control rates and visual acuity outcome reported in the nonrandomized phase I clinical evaluation of Pd-103 by Finger et al. [107]. However, randomized trials between radioisotopes controlling for tumor size, tumor location, and potentially different surgical techniques should be performed to confirm the potential benefits of Ru-106 or Pd-103 over I-125 [69].

As to dose prescription, different dose levels were prescribed with apical doses ranging from 63 to 157 Gy in order to adequately treat the tumor. In the reviewed literature, we found the COMS and ABS recommended minimum dose of 85 Gy to the tumor apex to be widely used as a standard for I-125 and Pd-103 EPB treatments. Unlike gamma emitters, for Ru-106 EPB, there was no internationally accepted standard prescription. Owing to the limited penetration depth by the emitted beta-particles, the most widely adopted recommendation was 100 Gy to the tumor apex for UM less than 5 mm in thickness according to GEC ESTRO guidelines [126], while other authors suggested 120 Gy prescribed at a depth of 5 mm for tumors with a thickness >5 mm [117,132]. Nonetheless, despite GEC ESTRO recommendations, a number of reviewed studies using Ru-106 EPB reported a prescription dose of 85 Gy according to the ABS and COMS rationale. Although conflicting results exist [72], some authors have even suggested that the standard therapeutic dose of 85 Gy could be reduced for all types of plaques without compromising tumor control [47,59,133].

In order to shed light on this issue, dose–response relationship for LTC was modelled using a two-parameter logistic model (Fig. 3). The logistic model is an alternative to Poisson statistics for TCP modelling, which usually produces less steep dose–response curves characteristic of tumor populations, probably due to inter-tumor heterogeneity [26]. A TCP logistic model for all types of plaques was first drawn and, subsequently, a separate TCP model was specifically devised for Ru-106 based treatments obtaining comparable radiobiological parameters. Subject to the uncertainty inherent to the data extraction and modelling process, the estimated TCP suggests that 95% of 5-year LTC could be already obtained at a tumor apex dose of 80 Gy in agreement with the conclusion by Kowal et al. [37] and Echegaray et al. [134] that the gold standard empirically derived 85-Gy prescription dose for the treatment of UM should be tested in a randomized study; A correct management of the dose at the edge of the plaques, lower for Ru-106 than for a similarly designed I-125 plaque, should be nonetheless accounted for in brachytherapy planning protocols.

In the present study, we also evaluate the effect of TPS use as well as of imaging-based treatments on EPB outcomes. At present, very few image-based treatment-planning systems for ocular brachytherapy exist such as some in-house software solutions [135,136] and there is only one commercially available solution, the PS software [127], although it is not FDA approved. In addition, CT or MR imaging are not always available in the clinical EPB practice. Accordingly, a limited number of reviewed studies have documented the use of TPS (24%) or imaging (15%) in EPB. In the conventional dosimetric approach, the estimation of implant duration time was generally based on plaque central-axis-point dose calculation. Although the coverage of the tumor with the prescribed dose is guaranteed, an accurate evaluation of the doses received by OARs is not provided due to the lack of an image-based dose map calculation involving the ocular anatomy [20]. Interestingly, in the studies where a TPS was used, we observed a significant reduction of metastasis rate or enucleation events as well as an increased DSS. On the other hand, we were not able to demonstrate the impact of imaging on any outcome, probably due to the low numbers of studies reporting on its use.

In order to perform a dose–complication analysis, we performed a systematic study to analyze the pooled NTCP data after EPB treatment of UM. A substantial heterogeneity of reported data on OARs dosimetric parameters and morbidity risks across the studies was highlighted, thus hindering meaningful fitting results to logistic dose–response function except for cataract and RON incidence for which the NTCP model parameters were reasonably consistent. The obtained dose–response for cataract resulted in a reduced $D_{50}$ value of 40 Gy along with a reduced $x^2$ of 2.27, which indicates that the fit has not fully captured the data. The rate of cataract formation is highly variable across the studies. The formation of cataract is indeed multifactorial and, other than the radiation dose to the lens, it generally depends on multiple variables such as anterior tumor location, greater tumor height or basal dimension, increased patient age. In their retrospective study on 227 patients treated with Ru-106 EPB, Espensen et al. [30] proposed a three variable model for cataract risk prediction, which included lens dose, age and tumor base dimension. The model, adjusted for age at treatment of 62 years and a tumor base dimension of 11 mm, yields a 50% probability

![Fig. 5. Cataract rate as a function of lens dose and logistic Normal Tissue Complication Probability (NTCP) model fitting curve (a). Radiation optic neuropathy (RON) rate as a function of optic disc dose and logistic NTCP model fitting curve (b). Each study was weighted by the number of patients included. (1) = Ru-106, (2) = I-125, (3) = Pd-103, (4) = miscellaneous. N = Number of cohorts.](image-url)
of cataract for lens dose of 40 Gy in agreement with our findings. Of note, the present analysis did not allow to include those clinical dose modifying factors for the low number of studies reporting cataract rates and dosimetric correlates (22 cohorts). More consistent fitting results (reduced $\chi^2$ of 1.59) were obtained by NTCP modelling for RON, which suggested a $D_{50\%}$ value of 108 Gy and a $\gamma$ of 0.98. Interestingly, the obtained NTCP parameters are in agreement with those reported in Moiseenko et al. [137] for optic neuropathy after standard dose fractionation external radiation therapy.

Given the heterogeneity of the morbidity estimates extracted from the literature, with variability in reporting dosimetric data, the resultant model-based estimates should be considered with caution. Notably, because most of the analyzed data were not based on 3D EPB treatment planning, the relationship between the dose delivered to the ocular OARs may be strongly influenced by the method used in the reviewed articles for dose estimation. Another caveat concerns the few data points for BED estimations which might influence both tumor control probability and NTCP analysis. In addition, a limitation of the performed analyses is that it was based on retrospective studies due to lack of prospective, randomized trials for UM treatment, which hinders a formal meta-analysis.

In conclusion, these findings provided a coherent picture of the disease outcomes and morbidities in EPB for UM. Our analysis confirmed the effectiveness of EPB for UM as organ sparing treatment modality and, at the same time, its ability to achieve high control rates. Owing to the heterogeneity and insufficient data reporting of outcomes and dosimetric correlates, NTCP modelling results were limited to cataract and optic neuropathy. More rigorous and consistent reporting of clinical morbidities together with ocular structure doses is needed to implement robust NTCP models in EPB. Accurate dosimetry optimization by image-based 3D planning and inclusion of patients in well-designed clinical trials will help define better the optimal use of EPB in UM.

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**Data Sharing Statement**

All data generated and analyzed during his study are included in the manuscript.

**Conflict of Interest**

None.

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**Appendix A. Supplementary data**

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2021.11.007.

**References**


