Uncertainties in ocular proton planning and their impact on required margins

Jörg Wulff\textsuperscript{a,b,c,*}, Benjamin Koska\textsuperscript{a,b,c}, Dalia Ahmad Khalil\textsuperscript{a,b,c,d}, Ronald Richter\textsuperscript{a,b,c,d}, Claus Maximilian Bäcker\textsuperscript{a,b,c}, Christian Bäumer\textsuperscript{a,b,c,e,f}, Andreas Foerster\textsuperscript{b,g}, Nikolaos E. Bechrakis\textsuperscript{b,c,g}, Beate Timmermann\textsuperscript{a,b,c,d,e}

\textsuperscript{a} West German Proton Therapy Centre Essen (WPE), Essen, Germany
\textsuperscript{b} University Hospital Essen, Essen, Germany
\textsuperscript{c} West German Cancer Centre (WTZ), Essen, Germany
\textsuperscript{d} Department of Particle Therapy, Essen, Germany
\textsuperscript{e} German Cancer Consortium (DKTK), Essen, Germany
\textsuperscript{f} Department of Physics, TU Dortmund University, Dortmund, Germany
\textsuperscript{g} Department of Ophthalmology, University Hospital Essen, Essen, Germany

\textbf{ARTICLE INFO}

Keywords:
Proton Therapy
Margins
Funduscopy

\textbf{ABSTRACT}

\textbf{Purpose:} To review required margins in ocular proton therapy (OPT) based on an uncertainty estimation and to compare them with widely used values. Further, uncertainties when using registered funduscopy images in the 3D model is investigated.

\textbf{Methods:} An uncertainty budget in planning and delivery was defined to determine required aperture and range margins. Setup uncertainties were considered for a cohort of treated patients and tested in a worst-case estimation. Other uncertainties were based on a best-guess and knowledge of institutional specifics, e.g. range reproducibility. Margins for funduscopy registration were defined resulting from scaling, rotation and translation of the image. Image formation for a wide-field fundus camera was reviewed and compared to the projection employed in treatment planning systems.

\textbf{Results:} Values for aperture and range with margins of 2.5 mm as reported in literature could be determined. Aperture margins appear appropriate for setup uncertainties below 0.5 mm, but depend on lateral penumbra. Range margins depend on depth and associated density uncertainty in tissue. Registration of funduscopy images may require margins of >2 mm, increasing towards the equator. Difference in the projection may lead to discrepancies of several mm.

\textbf{Conclusions:} The commonly used 2.5 mm aperture margin was validated as an appropriate choice, while range margins could be reduced for lower ranges. Margins may however not include uncertainties in contouring and possible microscopic spread. If a target base is contoured on registered funduscopy images care must be taken as they are subject to larger uncertainties. Multimodal imaging approach in OPT remains advisable.

1. Introduction

Ocular proton therapy (OPT) for uveal melanoma dates back to 1975 at the Harvard Cyclotron Laboratory and up to date more than 45,000 patients have been treated worldwide with exceptional success rates [1]. Although technical improvements occurred mainly with respect to treatment planning and imaging, the general concept has stayed more or less the same: a geometric eye model is constructed and the positioning of the target relative to the beam isocenter is achieved by means of orthogonal X-rays, which show the radio-opaque tantalum markers sutured to the outer eyeball.

Despite different beam properties and input to target definition at treating institutions, there appears a worldwide consensus on the required treatment margins, often universally termed “safety margin”. Typically a 2.5 mm aperture margin, representing the distance from the target to the lateral 50% isodose at isocenter, is used and 2–2.5 mm are
added up to the distal/proximal 90% isodose line [2–11]. Although some centers reduced margins to 1 mm, this reduction was identified as a risk-factor for local recurrences and hence reversed [2,12]. This heritage leaves clinicians with a general “don’t mess with margins” approach [13] and different centers may adopt the same margin for different reasons. Some centers explicitly include the microscopic tumor extent in the margins [14], others prescribe treatment to a clinical target volume (CTV) and the margin is equivalent to creating a planning target volume (PTV) [4,15]. In Seibel et al. [12] a 1 mm PTV margin is considered for setup uncertainties, while another 1.5 mm in proximal/distal direction is added for range uncertainties. In ICRU Report No. 78 the possible microscopic extent is considered part of the distal range/aperture margin and acknowledges that neither a CTV nor a PTV is explicitly drawn in this specialized treatment [16].

Target definition involves various sources of information for the extent of the malignant growth [1] and funduscopy as a standard modality in diagnosis of uveal melanoma [17,18] is frequently employed for treatment planning. This is typically achieved in a projection of the 3D eye model, i.e. an anterior pole centric, azimuthal equidistant view, overlaid with a registered funduscopy image [19–22]. The resulting overlay is however subject to uncertainties, given by the registration itself but also by the process of image formation. The latter is affected by the eye and the employed fundus camera [23,24] and can introduce significant deviations.

Hence, it is obvious that the definition of a target volume and the appropriate margins are affected by uncertainties in modeling of the eye and tumor and in delivery of the proton fields. Although the general approach of OPT is the same at different treating institutions, technical details of the delivery and planning differ. Margins should thus be deducible from an analysis of contributing uncertainties, e.g. following the concepts of van Herk et al. [25]. To the authors’ knowledge, this approach has not been reported in literature on OPT.

The Westdeutsches Protonen-Therapiezentrum Essen (WPE) in Germany started ocular treatments in 2021, utilizing the RayOcular treatment planning system (RaySearch Laboratories, Sweden) as the first clinical user [26]. In the frame of the current study, the 3D image based workflow with RayOcular was reviewed and an uncertainty estimation was established to deduce aperture/range margins. Additional uncertainties associated with the usage of funduscopy images were estimated from reviewing the registration and image formation process, with the aim to understand limitations for target delineation. The overall aim of this study was to justify the use of (or any deviation from) commonly applied margins for our center and to describe a methodology for margin definition that could be potentially adopted by others.

2. Materials and methods

2.1. 3D based treatment workflow with the RayOcular TPS at WPE

A parametric model of the individual patient eye is constructed and fitted to available 3D data, i.e. computed tomography (CT) and magnetic resonance imaging (MRI). The free parameters of the model include the size of the actual ellipsoidal eye globe, anterior chamber, position/rotation within the CT and position/rotation of the optical nerve. The latter is matched to the visible structures in CT/MRI and is crucial for the definition of landmarks for funduscopy image registration (see section 2.2.3). The locations of tantalum fiducials are directly determined in the CT image set. Fig. 1a shows an example of a 3D model registered to the CT of a patients left eye with a calculated dose distribution.

The target is defined within this 3D model and also based on the visible tumor in the registered MRI. The delineation is accomplished in the anterior pole centric, azimuthal equidistant projection, i.e. the polar 2D representation on or below the inner surface of the eye globe, proportional to the arc length in radial direction. This view is a commonly used representation of the retina and called “polar view” in EyePlan, OCTOPUS and RayOcular and allows the overlaying of fundus images (see section 2.4). Tumor dimensions and (Euclidean) distances can be measured in this fundus view and compared to available ophthalmologic information, including clip-to-target distances measured during surgery, extension in ultrasonic images and optical coherence tomography (OCT). The target is modelled with a two-dimensional polygon base-shape and a polynomial of selectable order with a defined apex-height in the third dimension, forming an analytical representation of the actual volume. Fig. 1b shows the polar fundus view in the RayOcular

---

Fig. 1. A) Example slice for a registered 3D model of the left eye on patient CT. The broken lines indicate the equator (EQ), ora serrata (OS) and limbus (LI). The optic disc (OD) is located on top of the optical nerve (solid yellow) and with correspondence to the macula (MA). The optic nerve is additionally shown with a variation of -2.5° (orange contours). The target is shown as filled red contour, covered by the 50% (light-blue) and 90% isodose (yellow) of a proton field. The arrows indicate the lateral and distal margins. B) Fundus representation of the model with registered wide-field funduscopy image (Zeiss Clarus). The broken circles represent tantalum clips with three clips located around the target base (red solid line). The blue cross indicates the posterior pole. Both figures are based on screenshots from the RayOcular TPS (v12B). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
TPS with the tumor base in relation to the model clips, which were located in the CT.

The density information of the underlying CT is not taken into account during dose calculation in RayOcular. Instead an enclosing volume overrides the whole model by a user-chosen material and the individual structures, e.g. lens can additionally be assigned a material in terms of atomic composition and excitation energy. At WPE the lens is assigned a density of 1.06 g/cm³, while the whole eye model is approximated with properties of water and uniform density of 1.04 g/cm³. The latter is motivated by ICRP Report No. 110, assigning a density of 1.05 g/cm³ to the whole human eye [27], and using a ratio of stopping powers between muscle and water in the range of 20–80 MeV with 0.992.

After model creation, the optimal gaze angle is defined and verified during simulation and treatment by comparing the expected location of tantalum fiducials’ projections to their location on planar X-ray images. Range and modulation are defined in a single proton beam with lateral field dimensions limited by the target projection.

The delivery of the created treatment plan as well as the outlined eye modelling process is subject to several uncertainties that need appropriate aperture and range margins. Delineation uncertainties and possible microscopic tumor spread are considered implicitly included in the target contour. Hence, the resulting contour is treated as a CTV with an extra delineation margin, depending on the available information for an individual patient. The overlay of a funduscopy image is an important source of information for refinement of the target contour, especially if the location of clips and provided distances to the target are ambiguous, but requires separate margin consideration.

2.2. Derivation of margins

2.2.1. General approach

To define a target margin, the concepts by van Herk [25,28] were followed with estimated systematic Σ and random σ contributions. Due to the limited number of fractions N, the effective standard deviations were calculated with [29,30]

\[
\sigma_{\text{eff}}^2 = \frac{\sigma_{\text{sys}}^2}{N} + \frac{\sum \sigma^2}{N} \left( 1 - \frac{1}{N} \right)
\]

(1)

The margins were calculated using the formulations of Gordon et al. [29] for the van Herk concept with a target coverage c of 90 % and N = 4 for a 415 Gy(RBE) prescription in OPT, i.e.

\[
M = M_t + \text{norminv} \left( c, 0, \sqrt{\sigma_{\text{sys}}^2 + \sigma_{\text{org}}^2} \right) - \text{norminv}(c, 0, \sigma_r)
\]

(2)

In the above equation norminv is the inverse normal distribution and σr the standard deviation for a lateral penumbra (LP) described by an error-function. For LP between the 80 % and 20 % isodose it follows \(\sigma_r \geq \text{LP}_{80/20} = 0.59\). The margin contribution accounting for the systematic uncertainties

\[
M_t = a \cdot \Sigma_{\text{org}}
\]

was considered differently in lateral and proximal/distal direction. The coverage factor for a confidence level of 90 % in 1D was used for proximal/distal margins with \(a = 1.64\) and in 2D lateral margins with \(a = 2.15\) (see e.g. Table 2 in Ref. [28]).

2.2.2. Aperture and range margins

Similar to a previous investigation [31], uncertainties in delivery and eye modelling were identified as machine-, model- and setup-related. The influence quantities by the machine included manufacturing of the aperture, the co-incidence of proton beam and X-ray system and difference in range. The size/shape, the positions of clips and the assignment of densities to the 3D-model were considered. Potential translation and rotation of the eye were included in setup-related uncertainties. All contributions were used to define a combined uncertainty estimate, following the concepts of “Guide to the Expression of Uncertainty in Measurement” (GUM) [32]. Hence, a probability distribution was assigned to each contributing quantity to reflect the most appropriate way to characterize them. All quantities were considered uncorrelated and thus added in quadrature and used in equation (1) either as random or systematic.

The required aperture margin depends on the LP of the beam, defined as the distance between the 80 % and 20 % isodose. The aperture margin defines the 50 % isodose at isocenter and – given the aimed coverage with 90 % of the prescription dose – the target margin needs to be extended by the distance from 90 % to 50 %. The latter can be calculated from modelling the lateral beam profile with an error-function and yields \(\text{LP}_{90/50} = \text{LP}_{80/20} 	imes 0.76\). The final aperture margin was calculated for different values of LP between 0.5 and 2.5 mm. The total required proximal/distal range margin is proportional to the prescribed range, caused by the relative range uncertainty in the material assignment (see section 2.1). Thus, the range margin was calculated as a function of prescribed range, taking different density uncertainties between 1–5 % into account.

2.2.3. Target delineation margins for registration of funduscopy images

The registration includes a possible translation, scale and rotation of the funduscopy image when overlaid to the fundus projection [20–22]. These effects were considered by simple geometric relationships for a simplified eye ball with 24 mm diameter. Each effect was assumed as standard uncertainty (\(k = 1\)) and following a normal probability distribution.

The optic disc (OD) and the macula serve as anatomical landmarks and the optic disc location is considered as the extension of the optic nerve. The manual localization of the latter in the CT/MRI is subjective to a certain degree. The rotation of the nerve by 2.5° shown in Fig. 1 corresponds to ~ 0.5 mm for a 24 mm diameter eye and was considered as standard deviation, independent of the position within the fundus view.

The macula is not visible in CT or MRI, but the individual OD-macula distance (typically ~ 4.6 mm [33]) can be measured in OCT and used to match the scale of the image. An uncertainty in this measured distance and the identification of the macula in the funduscopy image translates into an uncertainty, increasing with distance from the registration point. A scaling effect with 5 % was considered, assuming the funduscopy image is registered to the posterior pole.

The funduscopy/OCT imaging is performed with a chin-rest of the camera systems, but a rotation of head and eye respectively may remain. The 3D based eye-model on the other hand is registered to the CT and the impact of a rotation in the polar dimension increases with distance from the posterior pole. The rotation was considered as the vector length for a point on the tumor base contour, rotated by 5° around the posterior pole. The resulting chord length \(l\) on a certain distance (in terms of arc length) from the posterior pole was thus calculated with

\[
l = 2a \sin (y/2)
\]

(3)

where \(y\) is the rotation angle and \(a\) the arc length from posterior pole for a spherical eye.

2.2.4. Further uncertainties in fundus representation

In general, the matched 3D model has to be projected in an appropriate representation of the fundus view. Different concepts exist that ideally match the actual fundus image generation. According to Dobler et al. [22], the projection of arc length is a suitable description of the imaging properties of fundus cameras. However, a fundus image is generally distorted by the projection of the curved eye fundus onto a planar image [34]. Reasonable agreement of measured and actual distances in a registered funduscopy image within the RayOcular TPS up to ~60° from posterior pole was found [35]. RayOcular allows the funduscopy overlay in “polar mode”, i.e. simply proportional to arc length
for an eye angle θ and “camera mode”, mimicking properties of the camera. In camera mode the projection is a function of the visual angle β (see Fig. 2), depending on a nodal point, i.e. the point in the eye where light rays are passing as a straight line [36], and an optics fit-factor. The latter corrects for possible refraction, compressing the image towards the center, although no clear reference is given for its value. If left at zero, the formed view is simply proportional to angle β and after applying the aforementioned scaling of the funduscopy image to macula-OD distance (see section 2.2.3), both polar and camera modes agree.

It has become clear that both the Zeiss Clarus (Zeiss, Germany) as well as the Optos Optomap (Optos, UK) wide-field fundus cameras display the retina in a stereographic projection centered on the macula [37,38]. This type of projection exhibits an increased pixel distance towards the equator and thus differs from arc length. The Optos system adheres to the DICOM standard, which defines the properties of a stereographic projection [39]. For a spherical eye in stereographic projection, the length on the retina a' can be calculated as

\[ a' = 2r \cdot \tan \left( \frac{\theta}{2} \right) \]  

(4)

with r as radius and θ as the angle relative to the eye center. For the Zeiss system the stereographic projection is based on the visual angle β at the pupil of the eye and proportional tan(\(\frac{\beta}{2}\)) [37]. The conversion between angle θ and β can be calculated following Doelemeyer et al. [34] with

\[ \beta = \arctan \left( \frac{r \cdot \sin(\theta)}{d + r \cdot (\cos(\theta) - 1)} \right) \]  

(5)

with d as distance from the retinal surface to the point where β is defined. This distance may differ and depends on the positioning of the patient in front of the camera.

To investigate the possible impact on target delineation, the difference between the projection proportional to arc length (i.e. polar mode in RayOcular) and stereographic projections proportional to θ and β was calculated in 1D, i.e. along the radial dimension of the fundus representation. For this purpose the cross section of the eye was simplified as a circle with 24 mm diameter and the angle θ converted to distance from the posterior pole. The distance d (see Fig. 2) was varied between 19 and 23 mm, i.e. angle β defined at pupil positions between 1 mm and 5 mm below the surface of the simplified model eye. Mimicking the registration process in the TPS, the single projections were scaled to match a distance between macula and optic disc of 4.5 mm, i.e. at \(\theta = 21.5^\circ\).

2.3. Determination of setup uncertainties and impact on target coverage

The contribution from setup uncertainties for equation (1) and (2) respectively were deduced from an analysis of treated patients. At WPE a setup tolerance of <0.3 mm is aimed for as in other OPT centers [40]. This is achieved by an iterative position correction, matching fiducial projections in two orthogonal X-ray images to their predicted positions from the CT-based model. The deviation is manually determined by the therapist. The position correction may include a rotation of the fixation light and the tolerance for this adjustment is set to 4’’, which results in the approximate equivalent to a shift of ~0.3 mm (see Appendix 6.1).

The X-ray image pairs acquired after last position correction for four fractions were analyzed in 20 patients, to determine the deviation of each of the four clips in the two radiographs. The resulting systematic and random contributions for the margin were calculated as the mean population-based standard deviation in the three dimensions and as mean of individual standard-deviations per considered patient, respectively [25].

To further test the impact of setup uncertainties, sixteen clinical treatment plans were recalculated in the RayOcular 12B TPS. The robust evaluation workspace of RayOcular allows the calculation of the voxel-wise minimum dose for a series of dose calculations with variations in the isocenter position scenarios. Using end-points of Cartesian axes and diagonals of the cuboid defined by the uncertainty, a total of 14 distributions was considered for isotropic position uncertainties between 0.2 and 1 mm. The voxel-wise minimum dose was evaluated for a structure encompassing the clinical target. An additional margin was derived as outlined in the previous section 2.2.1, but excluding the contribution by setup uncertainties. The average, minimum and maximum loss in D99.9, i.e. dose to 99.9 % volume, for the target including this margin was calculated.

3. Results

3.1. Aperture and range margins

Table 1 summarizes the estimated uncertainties in the OPT planning and delivery process, as identified specific to WPE. Some quantities were assumed to affect both the lateral and the distal/proximal dose.

<table>
<thead>
<tr>
<th>influence quantity</th>
<th>uncertainty/mm</th>
<th>distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>proton beam/X-ray co-incidence</td>
<td>0.4</td>
<td>systematic</td>
</tr>
<tr>
<td>manufacturing tolerance</td>
<td>0.1</td>
<td>systematic</td>
</tr>
<tr>
<td>aperture</td>
<td>0.3</td>
<td>normal</td>
</tr>
<tr>
<td>3D model size &amp; shape</td>
<td>0.6</td>
<td>systematic</td>
</tr>
<tr>
<td>clip positions in model</td>
<td>0.1</td>
<td>normal</td>
</tr>
<tr>
<td>setup (translation/rotation)</td>
<td>0.3</td>
<td>random</td>
</tr>
<tr>
<td>range difference to TPS</td>
<td>0.2</td>
<td>systematic</td>
</tr>
<tr>
<td>reproducibility in distal range density</td>
<td>0.5</td>
<td>normal</td>
</tr>
<tr>
<td>material assignment eye</td>
<td>1</td>
<td>systematic</td>
</tr>
</tbody>
</table>

\(\text{a}^*\) value here for 4 % density uncertainty and range of 25 mm.

![Fig. 2. Schematic model of an eye with radius r. The arc length a for eye angle \(\theta\) corresponds to a stereographic projection with length a’. \(\beta\) is the visual angle defined at a nodal point (NP) with distance d from the retina.](image-url)
distribution, while e.g. range uncertainties are obviously only relevant for the distal/proximal margin.

The values for the coincidence between proton and X-ray beam were determined as worst result from measurements at WPE for the dedicated IBA eye treatment nozzle [15] and includes the mechanical play of the collimator in the snout/nozzle. The value is comparable to the median quality assurance checks of treating OPT centers [1]. Without further knowledge, a rectangular distribution was assumed and converted to standard uncertainty by multiplying with $1/\sqrt{3}$. The aperture manufacturing tolerance was given by the vendor certificate of the milling machine in use at WPE.

The CT-based model dimensions are estimated to agree within 0.3 mm, governed by eye-length measurements. The value was estimated from experience in creating an eye-model in CT and comparing to registered MRI and the tolerance given in distance between the model sclera and clips. The underlying distribution was set to normal ($k = 1$). The contribution for distal/proximal direction was doubled given the fact that the exact location of the target with respect to the sclera and/or sclera thickness is more difficult to define. The clips in the 3D eye model are based on the visible image contrast in CT. Despite significant artefacts, the center of gravity is expected to represent the clip center. This location can automatically be calculated within the RayOcular treatment planning system and was estimated to be within 0.1 mm standard deviation.

The setup translation/rotation uncertainty was estimated from the analysis of patients treated at WPE (see section 2.3 and 6.1) and provided as the standard uncertainty of a normal distribution with 0.2 mm for systematic and 0.3 mm for random contributions, respectively. The latter strongly depends on the individual clinical case. Some patients tend to have an unstable gaze which may further change during the treatment. It will be shown below (section 3.2), how the final aperture location can automatically be calculated within the RayOcular treatment planning system and was estimated to be within 0.1 mm standard deviation.

The setup translation/rotation uncertainty was estimated from the analysis of patients treated at WPE (see section 2.3 and 6.1) and provided as the standard uncertainty of a normal distribution with 0.2 mm for systematic and 0.3 mm for random contributions, respectively. The latter strongly depends on the individual clinical case. Some patients tend to have an unstable gaze which may further change during the treatment. It will be shown below (section 3.2), how the final aperture location can automatically be calculated within the RayOcular treatment planning system and was estimated to be within 0.1 mm standard deviation.

The setup translation/rotation uncertainty was estimated from the analysis of patients treated at WPE (see section 2.3 and 6.1) and provided as the standard uncertainty of a normal distribution with 0.2 mm for systematic and 0.3 mm for random contributions, respectively. The latter strongly depends on the individual clinical case. Some patients tend to have an unstable gaze which may further change during the treatment. It will be shown below (section 3.2), how the final aperture location can automatically be calculated within the RayOcular treatment planning system and was estimated to be within 0.1 mm standard deviation.

The setup translation/rotation uncertainty was estimated from the analysis of patients treated at WPE (see section 2.3 and 6.1) and provided as the standard uncertainty of a normal distribution with 0.2 mm for systematic and 0.3 mm for random contributions, respectively. The latter strongly depends on the individual clinical case. Some patients tend to have an unstable gaze which may further change during the treatment. It will be shown below (section 3.2), how the final aperture location can automatically be calculated within the RayOcular treatment planning system and was estimated to be within 0.1 mm standard deviation.

The setup translation/rotation uncertainty was estimated from the analysis of patients treated at WPE (see section 2.3 and 6.1) and provided as the standard uncertainty of a normal distribution with 0.2 mm for systematic and 0.3 mm for random contributions, respectively. The latter strongly depends on the individual clinical case. Some patients tend to have an unstable gaze which may further change during the treatment. It will be shown below (section 3.2), how the final aperture location can automatically be calculated within the RayOcular treatment planning system and was estimated to be within 0.1 mm standard deviation.

To determine the lateral margin, the values of Table 1 were combined to a total systematic uncertainty $\Sigma = 0.44$ mm and random uncertainty $\sigma = 0.3$ mm. By applying equation (2) the lateral margin was calculated yielding $M = 1.3$ mm for $LP_{80/20} = 1.5$ mm. Without the contribution of random setup uncertainties in Table 1 this margin reduced to $M = 0.95$ mm. The final aperture margin was increased for the contribution of different values of LP. Fig. 3a shows the aperture margin as a function of the random contribution and for different values of the LP. The required aperture margin is increasing with a larger contribution of random setup uncertainties, i.e. by ~0.5 mm for setup uncertainties between 0–0.5 mm. The constant contribution of the LP corresponds to a vertical shift of the required aperture margin in Fig. 3a, with larger margins the larger the LP. Assuming a typical LP = 1.5 mm, the commonly value of ~2.5 mm aperture margin appears reasonable.

Using the values of Table 1 for the proximal/distal uncertainties the range margin was deduced. Fig. 3b shows the calculated range margin as a function of a prescribed depth in the eye for different values of the expected uncertainty in density. With increasing depth the contribution of the relative range uncertainty increases, leading to a continuous increase of the required range margin. According to Fig. 3b, a value of 2.5 mm occurs appropriate for 5 % uncertainty and ~23 mm range. However, for lower ranges and/or lower uncertainties in the assigned density, a margin of 2 mm would be sufficient.

As can be concluded, for the uncertainty estimates in Table 1 the 2.5 mm margin is “consumed” by setup and general model uncertainties and thus the target delineation needs to be handled separately.

3.2. Impact of setup uncertainties on target coverage

Fig. 4 shows the calculated worst case reduction in the target coverage as a function of the considered position offset. The calculation of reduction in target coverage was based on the voxel-wise minimum for the whole treatment course, i.e. applies to all fractions. As can be concluded for the investigated clinical cases, up to ~0.4 mm may lead to a reduction of <5 %. Hence, the aperture margin of 2.5 mm appears reasonable to ensure a coverage well above 90 % with the LP and setup tolerances at WPE for typical cases treated.

3.3. Target delineation margins for registration of funduscopy images

Fig. 5 shows the estimated uncertainties for registration of a funduscopy image in the polar view as a function of angle to the posterior pole. The single contributions were taken as uncorrelated and the combined effect as systematic uncertainty $\Sigma$. If extended with $\alpha = 2.15$ (see section 2.2.1), it yields the corresponding margin $M_{\text{fundus}}$. 

![Fig. 3. A) Required aperture margin as a function of random uncertainty $\sigma$ (for values of systematic uncertainties in Table 1). The single solid lines are results for different lateral penumbra values $LP_{80/20}$. B) Required range margin as a function of depth in water. The solid lines represent results for different values of density uncertainty. The horizontal broken line in both figures indicates a commonly used value of 2.5 mm.](image-url)
This margin increases with distance from the posterior pole and amounts to more than 2 mm at the equator. Ignoring other image distortions, a contour drawn on a registered funduscopy image would thus require an additional margin as shown as broken line in Fig. 5.

### 3.4. Further uncertainties in fundus representation

Fig. 6 shows the deviation in arc length of a spherical eye, when different stereographic projections are considered. As can be concluded from the figure, any stereographic projections overlaid in the polar view of the TPS will appear larger. At 90° from the posterior pole, i.e. at the equator, the difference could reach more than 4 mm according to this model. Fig. 6 also shows how even a small change of the spherical eye model affects the calculated arc length. For a 1 mm change in length, the projection is changed by more than 1 mm at 90°, indicated by the shaded area in Fig. 6.

### 4. Discussion

Despite the high tumor control rates in OPT, margins should be justified by the underlying uncertainties. To our knowledge no other work demonstrated the rationale for the commonly used margin values following the calculation approach from van Herk. The present work applied this concept and aperture and range margins were based on an estimation of uncertainties at WPE. This estimation depends on the judgment of related uncertainties in treatment planning, especially the modelling of the treatment eye and the radiation delivery. The generally accepted and widely used 2.5 mm margins appear reasonable for our institution. Other centers may come up with different contributions, magnitude and shape of probability distributions. In fact, in a previous analysis slightly different values were reported by our group [31] and this is a matter of interpretation. In the present work we considered each contribution as uncorrelated, which may not always be the case. As was shown, the aperture margin is a function of LP and the distal/proximal margin a function of range and density uncertainty. The dependence holds only if the estimations for systematic and random contributions are valid.

The range margin of 2.5 mm was shown appropriate for a 5 % density uncertainty and a maximum range of 23 mm in water. One may thus consider to reduce the range margin to 2 mm for lower prescription ranges and/or smaller density uncertainties. In fact, some centers use a 2.0 mm range margin [5]. There is no unique information on the exact composition of the human eye. ICRP Report No. 23 provides a mean density of ~1.026 g/cm³ for all structures [41], while ICRP Report No. 110 assigned 1.05 g/cm³ to the whole human eye [27], which is used by most centers [42–45]. The extreme case with smallest impact of material uncertainty would be a target located in the anterior part of the eye, i.e. iris melanoma. In this case however, the assumptions on the target and eye modelling as presented here may not be applicable. Some centers treat iris-melanoma without clips to guide the generation of the eye model and positioning of the patient [46]. Further, the 3D based eye model in the TPS may not perfectly reflect the exact anatomy of the
anteriour chamber and the location of the iris. The commonly used margins in OPT of iris melanoma could be reviewed following the scheme as used in this work.

Margins may need to be adjusted on a case-by-case basis. For instance, if a patient is known to suffer from poor sight, the aperture margins may be increased to allow for larger setup tolerances. It needs to be remembered that the contributions are added up in quadrature, which leads to the relationship as illustrated in Fig. 3a. This figure also demonstrates how the lateral margin depends on the LP, which is typically defined at isocenter plane, but changes with depth and/or for different positions w.r.t. isocenter. The RayOcular TPS takes the source-to-axis distance effects due to angular variance in its beam-model into account and the LP due to multiple scattering in medium is modelled [26] and the appropriate margin may be checked by inspecting the complete dose distribution.

In this work we demonstrate that the “standard” margins are appropriate, when delineation uncertainties are separated from the classical concept of a PTV, i.e. target delineation uncertainties are not part of the budget. Uncertainties in the target size are typically considered as an intrinsic part of the drawn target contour, but may also be handled by an increase of the aperture margin. As described by Desjardins et al. the lateral margin may be increased up to 3.5 mm if necessary [47].

The margin calculation considered model based planning as currently used in OPT. Future planning tools could completely rely on fully segmented MRI images without need for a model and/or clips [44]. Although a similar magnitude of margins can be expected, the proposed calculation could be applied to such planning approaches.

Although MRI in OPT planning will most likely be the standard method of choice in the future [48], the use of funduscopy remains obvious as this is one of the most used diagnostic modalities for uveal melanoma. The registration and more importantly the image formation itself is subject to uncertainties, jeopardizing the quality of drawn contours. We found that the registration of the image alone could make an extra margin necessary, reaching more than 2 mm at equator. On the other hand, the target contour is not solely based on a funduscopy image. In practice all available information is taken into account to ultimately define the target, and tantalum clips are typically placed defining its shape. It needs to be considered that this clip location is also subject to uncertainty and one could argue that it should be considered by a corresponding delineation margin.

The difference in the representation of the fundus projection in stereographic and polar, i.e. arc length proportional views, could lead to a potential overestimation of the target size of up to a few mm. The estimated registration uncertainty may already be covered by this larger contour. Deformations and registration uncertainties increase towards the equator. In most beam configurations this coincides with the proximal part of the spread-out Bragg-peak where a considerably high dose exists. On the other hand, the larger the target contour extends towards the equator, the larger the modulation that has to be chosen, which in turn may lead to potentially higher risk of toxicities [8]. One could in principle compensate for the different projection modes. However, the underlying formation processes are more complex and depend on the camera used. Other cameras may exhibit different projection properties. For instance, Via et al. [49], demonstrated their camera following a Lambert azimuthal equal-area projection, which would show a negative difference to the arc length projection with increasing angle. Apart from the non-spherical shape of the human eye and its variable length, the projection may get further distorted e.g. by the shape of the cornea [50]. Even if a basic characterization of fundus cameras is described by ISO [51], further camera aberrations are not well known and would need to be corrected for. Hence, more work is needed to reduce uncertainties in target delineation with funduscopy images only. This may become even more important for clip-less OPT approaches.

In the discussion on required margins, the biologically effective dose in OPT deserves attention. Although the radio-sensitivity may vary for different cell-lines of uveal melanoma, a commonly used prescription is 4x15 GyRBE. If a biological effective dose (BED) of 100 Gy is assumed to be sufficient [52], the distance between the 90 % isodose of this prescription to the BED could reach a few millimeters (see Appendix 6.2). Hence, depending on the penumbra there already exists an additional radiobiology-driven margin for tumor control.

5. Conclusion

The commonly used margin concept of 2.5 mm in OPT can be confirmed for 3D model-based planning, following an uncertainty estimation in treatment planning and delivery, but may not cover delineation uncertainties. The use of funduscopy in the model based treatment planning should be used with caution and requires particular attention. More work is needed to understand the image formation in funduscopy and to have a robust registration in the treatment planning model. It is strongly recommended that all available data is used conservatively, to maintain the high success rates in OPT.

6. Ethics statement

Images shown belong to patients who were enrolled in a prospective registry study (“ProReg”, German Clinical Trial Register: DRKS00004384) covered by ethics approval and had provided written informed consent.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors thank Andrzej Kacperek for fruitful discussions on the topic. Sandija Plaude (WPE) is acknowledged for her review of this manuscript.
increase with applied rotation. As one can conclude from the figure, as long as the remaining rotation is kept below 4° and the average distance for all clips is minimized, the remaining maximum offset will be 0.2–0.3 mm on average.

Fig. A1. Calculated maximum offset for a point on a circle with 24 mm diameter as a function of rotation. The positions of three randomly placed points was minimized after rotation. The solid line is the average of randomly placed points on the sphere and the broken line is the standard deviation STDV.

6.2 Biological effectiveness considerations in margins for OPT

The most common prescription throughout all treating centers is 4x15 GyRBE [1]. This concept has been proven as effective with many thousand patients treated. There is a variety of uveal melanoma cell-lines with a variety of radio-sensitivity [53]. When applying the simple linear-quadratic BED-model [54], the biologically effective dose (BED) for most cell-lines with $\alpha/\beta$ values of 2–15 Gy is comparably high with 510–120 Gy, respectively. The underlying mechanisms may be more complex, but using this simple BED-model, one can determine the additional margin that results from the high BED in OPT. Assuming $B = 100$ Gy as sufficient for tumor control [46], the distance from 90 % of the prescribed 4x15 Gy can be calculated analytically for a given lateral penumbra of the single proton beam. Fig. A2a illustrates the general relationship exemplarily. Fig. A2b shows the additional distance to the $B = 100$ Gy isolines as a function of the $\alpha/\beta$ for a hypothetical tumor for different values of the (lateral) penumbra.

Even though the $\alpha/\beta$ may are not exactly known and the BED model is limited to sufficiently to describe the biological effects [55], for most cell-lines with alpha–beta of 10 Gy, an additional “buffer” may exist. On the other hand, for larger $\alpha/\beta$ values and/or required $B > 100$ Gy, the margins could even be too small.

References


