



Universiteit
Leiden
The Netherlands

Comparison of model-based and delineation-based target volume definition for ocular proton therapy

Klaassen, L.; Rasch, C.R.N.; Beenakker, J.W.M.

Citation

Klaassen, L., Rasch, C. R. N., & Beenakker, J. W. M. (2026). Comparison of model-based and delineation-based target volume definition for ocular proton therapy. *Physica Medica*, 148. doi:10.1016/j.ejmp.2026.105895

Version: Publisher's Version

License: [Creative Commons CC BY 4.0 license](#)

Downloaded from: <https://hdl.handle.net/1887/4310408>

Note: To cite this publication please use the final published version (if applicable).



Technical Note

Comparison of model-based and delineation-based target volume definition for ocular proton therapy

Lisa Klaassen^{a,b,c,d,*}, Coen R.N Rasch^{c,d}, Jan-Willem M. Beenakker^{a,b,c,d}

^a Dept. of Ophthalmology, Leiden University Medical Center, Leiden, the Netherlands

^b Dept. of Radiology, Leiden University Medical Center, Leiden, the Netherlands

^c Dept. of Radiation Oncology, Leiden University Medical Center, Leiden, the Netherlands

^d HollandPTC, Delft, the Netherlands

ARTICLE INFO

Keywords:

Ocular proton therapy
Target volume definition
Tumour models
Delineation

ABSTRACT

Background: In recent years, eye-specific, high-resolution MRI protocols have become available for ocular tumours, enabling 3D tumour delineation. Despite these advances, ocular proton therapy typically still relies on model-based target volume definition. Therefore, the aim of this research was to compare model-based and delineation-based target volume definition for ocular tumours.

Methods: Tumours were delineated for 70 uveal melanoma patients. From the delineated tumour base, polynomial models of different degrees were generated. Additionally, model variations with expanded base and added thickness were generated. Models were considered acceptable at a coverage level of 98% or a maximum underestimation of 0.4 mm. The best model for each patient was defined as the acceptable model with the smallest volume.

Results: For 69/70 patients, an acceptable tumour model could be generated, out of whom 12/69 needed an expansion of the tumour base or added tumour thickness to produce at least one acceptable model. At a coverage level of 98%, tumours were overestimated with 20.5% (5th-95th percentile: 5.7%-59.7%), corresponding to a median absolute surface distance of 0.42 mm. Irregularly shaped tumours showed larger overestimations than dome-shaped tumours (16.4% vs 36.6%, $p < 0.001$).

Conclusion: Tumour models as used in ocular proton therapy treatment planning systems can achieve acceptable tumour coverage. However, to achieve this coverage, the tumour models overestimated the delineated tumour volume.

1. Introduction

Ocular proton therapy (PT) is one of the main treatment options for intra-ocular tumours such as uveal melanoma, especially for larger lesions or those located near the optic nerve [1–3]. In ocular proton therapy, most treatment planning systems, such as EyePlan, Eclipse Ocular Proton Planning (EOPP), RayOcular and Octopus offer a model-based approach for definition of the eye and the tumour [3–8]. In this approach, the user defines a tumour base on the fundus view (a map-like representation of the inside of the eye) and annotates the location of the tumour apex. Subsequently, a polynomial function is then used to model the three-dimensional tumour-vitreous interface. The degree of the polynomial is manually selected by the user to achieve the best possible correspondence to the observed tumour shape.

However, several imaging modalities, such as B-scan ultrasound and magnetic resonance imaging (MRI), reveal that up to 30% of ocular tumours can occur in complex shapes that are not easily captured by mathematical models [9]. For example, mushroom-shaped, multilobular, asymmetrical, and overhanging tumours have been described [2,10–12]. In previous work, we evaluated simple ellipsoid tumour models, generally used for prognosis, which do not offer sufficient tumour coverage for radiotherapy purposes, highlighting the need to assess the more flexible polynomial models with a delineated tumour base that are used in ocular PT [9].

In many other tumour sites, tumour delineation based on 3D imaging has long been the standard of care. In recent years, eye-specific, high-resolution MRI protocols have become available for ocular tumours as well [10,13,14], enabling geometrically accurate tumour delineation

* Corresponding author at: Postal Zone J3-S, P.O. Box 9600, 2300 RC Leiden, the Netherlands.

E-mail address: l.klaassen@lumc.nl (L. Klaassen).

<https://doi.org/10.1016/j.ejmp.2026.105895>

Received 30 September 2025; Received in revised form 26 June 2026; Accepted 13 July 2026

Available online 17 July 2026

1120-1797/© 2026 Associazione Italiana di Fisica Medica e Sanitaria. Published by Elsevier Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

with sub-millimetre interobserver variation [15,16]. A shift towards volumetric imaging in ocular proton therapy is visible in the latest survey of ocular proton centers, where 14 out of 19 centers use MRI, CT or both [17]. Furthermore, the three model-based treatment planning systems that were historically used most, have become obsolete and are not maintained [3]. Currently, many ocular proton therapy centers are in the process of implementing modern treatment planning systems which allow for incorporation of 3D imaging and tumour delineation, but also support a model-based approach of target definition [17]. Given the expertise in model-based target definition and the possibility of adopting a new delineation-based workflow in ocular proton therapy, the aim of this research was to compare model-based and delineation-based target volume definition for ocular tumours.

2. Methods

2.1. Patients

For this study, data from two existing cohorts were analysed retrospectively. The first cohort consisted of 56 uveal melanoma patients who received an MRI as part of clinical care or a scientific study between May 2019 and March 2021, receiving either brachytherapy, proton therapy or enucleation. The second cohort consisted of 14 patients who underwent MRI scans before proton therapy in the context of a prospective scientific study between November 2022 and February 2024, resulting in a total of 70 included patients. Both cohorts are described in more detail in a previous paper [9] and both studies were conducted after approval of the local ethics committee (METC Leiden-Den Haag-Delft, NL73433.058.20 and NL57130.058.16).

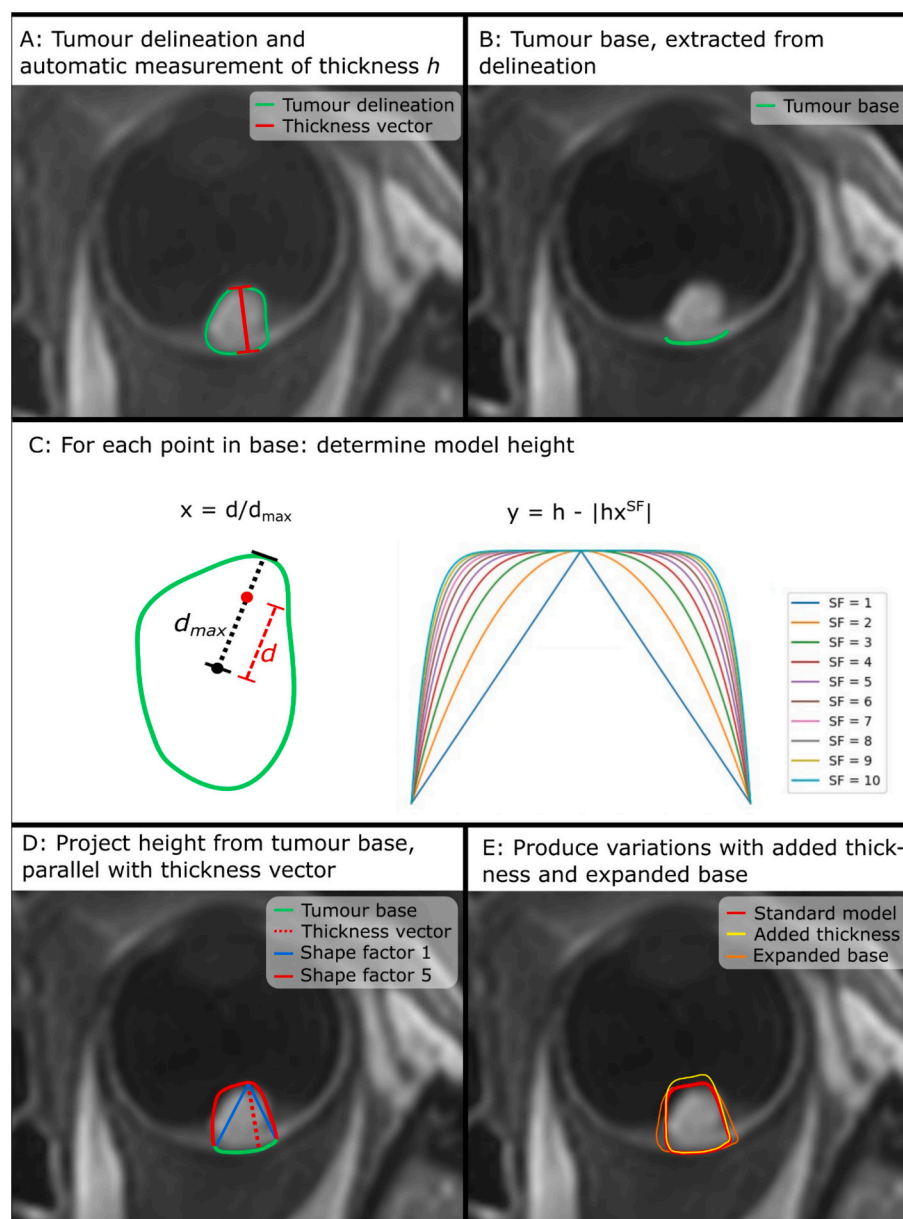


Fig. 1. Generation of a geometric tumour model from a delineated tumour. (A) Tumours were delineated (green contour) and the thickness (red line) was determined automatically; (B) the tumour base (green line) was extracted from delineation; (C) for each point in the tumour base, model height was determined based on distance d from base centre to the point, distance $d_{\max}$ from base centre to outer contour in the same direction, thickness h and shape factor SF ; (D) model height was projected from tumour base (green line), parallel to the thickness vector (dashed red line); (E) variations of the standard tumour model (red line) with added thickness (yellow line) and expanded tumour base (orange line) were produced as well.

2.2. MRI acquisition and analysis

Tumours were delineated on the 3D contrast-enhanced T1-weighted scans (Fig. 1A), with the 3D non-contrast-enhanced T1-weighted scan and 3D T2-weighted scans used as a reference to distinguish the tumour from surrounding structures. These MRI scans were acquired with a 3 T MRI scanner (Ingenia Elition, Philips Healthcare, the Netherlands) with a 4.7 cm surface receive coil (Philips Healthcare), using an earlier described protocol [13,14]. The MRI scans had an acquisition voxel size of $0.8 \times 0.8 \times 0.8 \text{ mm}^3$, a reconstruction voxel size of $0.4 \times 0.4 \times 0.4 \text{ mm}^3$ and the contrast-enhanced T1-weighted scan was acquired in 2 min and 7 s.

Tumour delineation was performed by one observer (LK) and the contours were verified and, if necessary, corrected by an ophthalmic MRI expert (JWB) with 12 + years of experience. For overhanging tumours, the projection of the tumour top on the retina was also included, similar to the clinical workflow.

Tumour thickness and largest basal diameter were computed automatically based on the 3D tumour delineations according to a previously published method [18].

2.3. Tumour models

Tumour models were generated using Python (version 3.12.7). The tumour thickness was determined automatically [18] and the tumour base was extracted from the delineated tumour (Fig. 1B). For each point on the tumour base, the height of the model was calculated by taking into account the tumour thickness, the distance from that point to the edge of the base and a shape factor. That shape factor defined the degree of the polynomial used to model the tumour's vertical profile, where a value of 1 resulted in a pyramidal shape and a value of 10 approximated a cylindrical shape (Fig. 1C). The calculated heights were then projected from the corresponding points in the base, parallel with the vector of the tumour thickness, resulting in a three-dimensional reconstruction of the tumour geometry (Fig. 1D).

We expect that some tumours, for example asymmetrical or overhanging tumours, may be more accurately described with a larger base or a larger thickness. Therefore, for each patient, variations of the standard model were created: one with 0.5 mm added thickness, one with an expansion of the base contour of 1.0 mm, and a combination of both.

For all four tumour variations (standard model, with added thickness, with expanded base and with added thickness and expanded base), models were created with shape factors ranging from 1 to 10 in increments of 0.1. The code to generate these tumour models is available on GitHub: github.com/MREYE-LUMC/OPT_tumourmodels.

2.4. Model evaluation

All models were compared to the tumour delineation and evaluated based on volume and surface distance metrics.

2.4.1. Volume and surface distance metrics

Tumour coverage and volumes of overestimation and underestimation, relative to the delineated tumour volume, were determined. Additionally, signed surface distances were determined between the top of the delineated tumour and the top of each model, as at the tumour base both contours were identical by definition. Here, negative distances corresponded to model contours that were inside the delineated tumour contour and vice versa. Minimum and median surface distance, as well as the 5th and 95th percentiles, were determined. Additionally, the median absolute surface distance was determined to quantify overall deviation regardless of direction.

2.4.2. Selection of best models

Models were considered acceptable if they either had a coverage larger than 98% or a minimum surface distance of greater than -0.4

mm, meaning the model contour was allowed to lie at most 0.4 mm inside of the delineated contour, corresponding to the MRI reconstruction voxel size and the size of the dose grid used in the treatment planning system at our centre. The best model was then selected from all acceptable models and was defined as the model with the lowest volume.

2.4.3. Sensitivity to varying thresholds and shape factors

The sensitivity of the results for different acceptance thresholds was investigated: in addition to the previously mentioned threshold of 98% coverage or a maximum underestimation of 0.4 mm, three other thresholds were evaluated: (1) a more lenient threshold with a coverage of 95% or a maximum underestimation of 0.4 mm; (2) a threshold of the coverage of 95% and a maximum underestimation of 0.4 mm; and (3) a stricter threshold with a coverage of 98% or a maximum surface distance of 0.2 mm.

Furthermore, as the optimal shape factor was selected with a precision of one decimal, a level of accuracy that may be challenging to achieve in clinical practice, the sensitivity of the results to variations in the shape factor was evaluated. For each overall best model (i.e. one per patient), the analysis was repeated using three alternative shape factor values: the shape factor rounded down, rounded up, and rounded up plus one.

2.5. Statistics

For each variation, the number of patients with an acceptable model was reported. Median and 5th and 95th percentiles of all volume and surface distance metrics were calculated for all best models.

Additionally, tumour shape was assessed visually by two observers (LK, JWB) and classified as regular (dome-shaped or flat lesions) or irregular (mushroom-shaped, bilobular or other asymmetrical shapes) [9]. Differences in tumour overestimation, 95th percentile surface distance and shape factor between regularly and irregularly shaped tumours were evaluated with an unpaired *t*-test or Mann-Whitney *U* test, depending on the results of the Shapiro-Wilk test for normality.

3. Results

Average tumour thickness and largest basal diameter were $6.4 \pm 3.0 \text{ mm}$ (range 1.3–12.9 mm) and $15.0 \pm 3.7 \text{ mm}$ (range 7.2–22.4 mm). AJCC 8th edition TNM staging [19] was as follows: T1: 13%, T2: 14%, T3: 50%, T4: 23%. 50/70 tumours had a regular shape and 20/70 had an irregular shape.

For 69/70 patients, an acceptable tumour model could be produced with either the standard model or one of the expanded variations, out of whom 12/69 needed one of the variations to produce at least one acceptable model (Table 1). However, for an additional 25 patients, one of the expanded variations produced a model with a smaller overestimation than the standard model, due to a lower shape factor that resulted in an acceptable model.

For one patient, no acceptable tumour model could be produced with the threshold of coverage of 98% or maximum underestimation of 0.4 mm. This patient had a very flat tumour with a large diameter and acceptable models could only be produced with the more lenient threshold of 95% coverage.

With the best models, an average coverage of 98.1% was achieved (5th–95th percentile: 94.2% – 98.7%), corresponding to a relative overestimation of the delineated tumour volume of 20.5% (5th–95th percentile: 5.7% – 59.9%, Table 1, Fig. 2). For the entire group, the median 5th percentile surface distance was -0.23 mm (Fig. 2C), with the lowest values observed in the largest tumours. Similarly, median 95th percentile surface distance was 1.10 mm, with larger tumours exhibiting higher values (Fig. 2D). This effect likely occurred because the models, despite larger surface distances, still adhered to the 98% coverage threshold, due to their large volume. Examples of patients with

Table 1

Volume and distance metrics for all variations of tumour models. Median and 5th-95th percentiles are shown. The overall best model was the model with the lowest overestimation.

	Standard model	With added thickness	With expanded base	With added thickness and expanded base	Overall best model
Number of patients with acceptable model	57	58	68	69	69
Median shape factor	2.5 (1.8 – 4.7)	2.2 (1.7 – 4.6)	1.8 (1.1 – 4.3)	1.4 (1.1 – 3.3)	2.3 (1.2 – 4.3)
Volume metrics					
Coverage [%]	98.1 (94.4 – 98.4)	98.1 (92.8 – 98.6)	98.3 (94.5 – 99.1)	98.5 (98.0 – 99.2)	98.1 (94.2 – 98.7)
Overestimation [%]	17.5 (5.5 – 51.5)	20.1 (7.7 – 51.7)	28.8 (14.0 – 84.6)	30.9 (12.6 – 63.3)	20.5 (5.7 – 59.9)
Distance metrics [mm]					
5th percentile surface distance	−0.23 (−0.38 – 0.10)	−0.21 (−0.46 – 0.20)	−0.17 (−0.44 – 0.31)	−0.22 (−0.39 – 0.14)	−0.23 (−0.46 – 0.06)
Median surface distance	0.45 (0.18 – 1.14)	0.56 (0.25 – 1.10)	0.44 (0.15 – 1.53)	0.42 (0.12 – 1.09)	0.41 (0.14 – 0.87)
95 th percentile surface distance	1.31 (0.53 – 3.00)	1.35 (0.61 – 2.90)	1.22 (0.58 – 3.57)	1.08 (0.54 – 3.16)	1.10 (0.53 – 2.71)
Median absolute surface distance	0.45 (0.19 – 1.14)	0.56 (0.26 – 1.10)	0.47 (0.19 – 1.53)	0.42 (0.15 – 1.09)	0.42 (0.18 – 0.88)

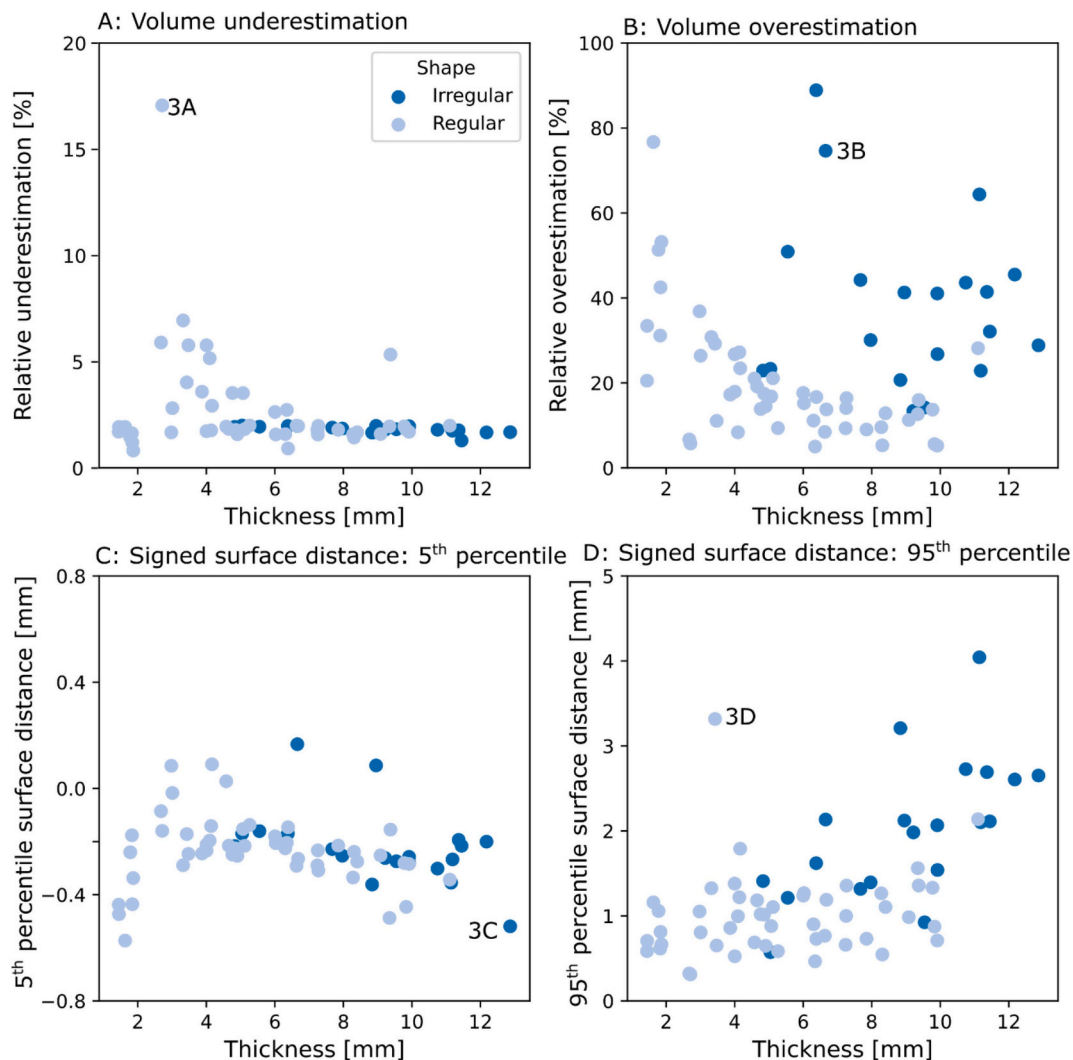


Fig. 2. Relationship between model performance and tumour thickness: (A) underestimation, (B) volume overestimation, (C) 5th percentile of signed surface distance, (D) 95th percentile of signed surface distance. Negative signed surface distance corresponds to a that model contour is inside the delineated tumour contour. Regularly shaped tumours are shown in light blue, irregularly shaped tumours in dark blue. Annotated points are shown in detail in Fig. 3.

relatively high underestimation or overestimation are shown in Fig. 3.

In irregularly shaped tumours a larger amount of overestimation of the tumour was required for an acceptable model: medians for relative overestimation were 16.4% and 36.6% (<0.001), with 95th percentile surface distances of 0.99 mm and 2.08 mm for regularly shaped and

irregularly shaped tumours, respectively (Fig. 4A,B). Differences in shape factor between regularly and irregularly shaped tumours were not significant (2.3 for regular shape and 2.2 for irregular shape, $p = 0.66$). However, variations to make the tumour model larger were used more often in irregularly shaped tumours (41% of regularly shaped tumours

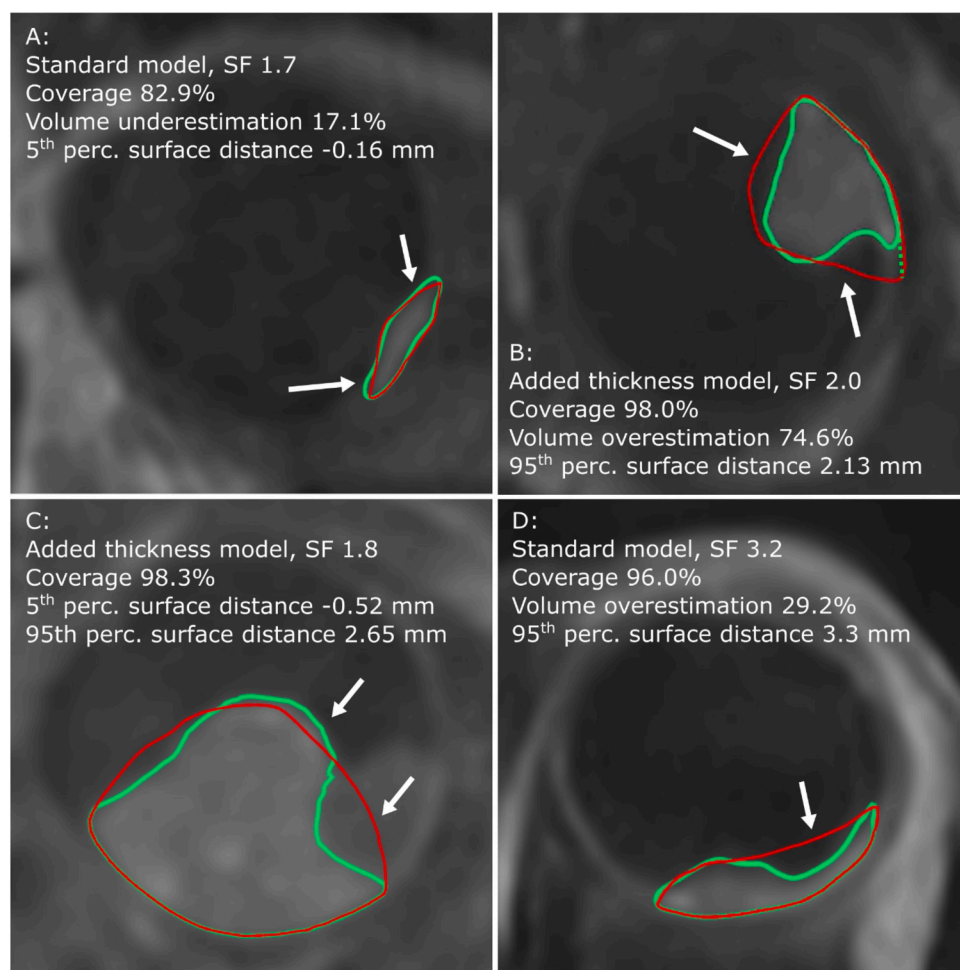


Fig. 3. Examples of delineated tumours (green) with their best-performing tumour model (red). (A) Small tumour with a relatively large volume underestimation of 17% (arrows). This model was accepted because the maximum underestimation was still within 0.4 mm. (B) Asymmetrical (overhanging) tumour that required a manual expansion of the tumour base (dashed green line) to achieve an acceptable coverage, resulting in a large overestimation of 74.6%. The area at the white arrow was not covered by the standard model. (C) Large mushroom-shaped tumour with relatively large areas of over- and underestimation (white arrows) but with a coverage of over 98%. (D) Dome-shaped tumour with flat extension (white arrow), which is overestimated by the tumour model, resulting in a relatively large 95th percentile surface distance of 3.3 mm.

and 85% of irregularly shaped tumours, Fig. 4C,D).

At the more lenient threshold of 95% coverage, all patients had an acceptable tumour model, with a median overestimation of 10.6%. The stricter thresholds resulted in a decreasing number of patients meeting the requirements ($n = 61$ for the 95% coverage *and* maximum underestimation of 0.4 mm threshold) or an increasing overestimation (22.2% for the maximum underestimation of 0.2 mm). All results for the different thresholds are shown in [Supplementary Table 1–4](#).

In the analysis for robustness to variation in shape factors, each step of 1.0 in shape factor corresponded to an increase of overestimation of approximately 15 percentage points and approximately 0.3 mm in the 5th percentile surface distance ([Supplementary Table 5](#)). Rounding down to the nearest shape factor resulted in a decrease in coverage to a median of 94.9%, corresponding to a 5th percentile surface distance of -0.44 mm.

4. Discussion

This study compared geometric tumour models used in treatment planning systems for ocular PT to delineated ocular tumours. The results show that acceptable tumour models could be generated for almost all patients, although especially irregularly shaped tumours often needed expansion of the tumour base, extra thickness, or both. Furthermore, at

this coverage level, tumours were overestimated by approximately 20%. Our observation that geometrical tumour models are larger than the delineated tumour volume is consistent with the findings reported by Via et al. [20] and Marnitz et al. [21]. However, the comparison performed by Marnitz et al. resulted in an even larger difference, which may be explained by our use of automated optimisation of the shape factor.

Most of the overestimation occurred at the vitreous body, however, if a base expansion was required to adequately cover the tumour, the overestimation also occurred along the retina and choroid. Both coverage and overestimation of the tumour depended on the shape factor of the tumour model: with shape factors rounded down, coverage decreased to about 95%. However, depending on the tumour shape and location, the effect on the collimator size and therefore irradiated volume is likely smaller.

Few papers have addressed margin calculation in ocular PT. In the studies by Wulff et al. [22] and Björkman et al. [23], the tumour model itself is not considered. Our results show that an increase or decrease of 1 in shape factor resulted in about a 0.3 mm difference in the 5th percentile surface distance, i.e. a possible underestimation or overestimation of the tumour contour. It may be advisable to incorporate this variation in the margin recipe. Nevertheless, the margin of 2.5 mm has been widely used in clinical practice across multiple centres, resulting in high local control rates [24–28]. This suggests that the tumour models used in clinical

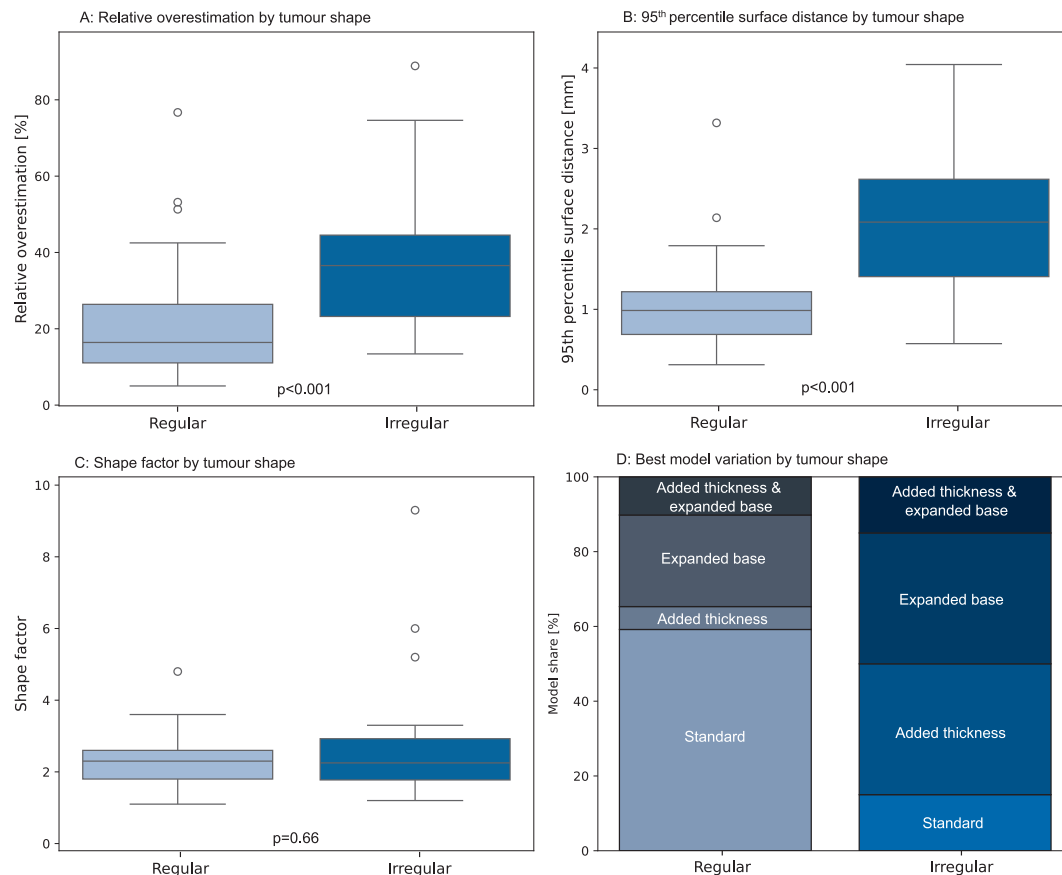


Fig. 4. The influence of tumour shape (regular shape: $n = 50$, irregular shape: $n = 20$) on model performance. (A) Irregular tumours show a larger relative overestimation; (B) and a larger 95th percentile surface distance; (C). Shape factors did not differ significantly; (D) Irregular tumours needed an expansion of the standard model more often.

practice provide sufficient coverage with the current radiation technique. It is likely that either the user already expands the tumour base during model creation – similar to the approach in this study – or that the single beam dose delivery used in ocular PT, inherently irradiates regions potentially uncovered by the tumour model.

The workflow in this paper uses the same tumour base for the ground-truth delineation and the tumour model, mitigating potential missed flat tumour components [29] and eliminating any effects from the base delineation typically performed in the fundus view in clinical practice. In practice, the difference between base delineation in a 3D imaging viewer and the fundus view, based on clip-tumour distances and tumour diameters, might be larger than the differences between model-based and delineation-based target volume delineation as described in this study. This is especially relevant because differences of about 1 mm in clip-tumour distances between different measurement modalities are not uncommon [12]. In this context, MRI-based delineation fused with fundus imaging [29,30] may improve the accuracy of base delineation.

Furthermore, various projection methods are possible to generate the tumour top from the delineated tumour base. In this paper, we applied a curved projection where the height was projected relative to each point of the tumour base. An alternative method would project relative to plane perpendicular to the eye at the apex location. We compared these approaches for the standard, unexpanded, model and found that they resulted in tumour models with similar performance (Supplementary Fig. 1 and Supplementary Table 6).

Additionally, we limited the target volume to one geometric model. Although for tumours with a flat component, splitting it in multiple volumes might result in less overestimation, the added complexity would be similar to switching to a delineation-based target definition (Supplementary Fig. 2) [6,8].

In this study, the impact of the differences between model-based and delineation-based target volume definition on irradiated volume was not assessed. In most centres offering ocular PT, a single passive scattering beam with a patient-specific collimator is used, with patients gazing at a LED at a predefined gazing angle [3]. This workflow, which deviates from conventional external radiotherapy practices, results in an irradiated volume that is inherently significantly larger than the delineated volume. It is therefore possible that under- and overestimations observed in this study have a limited effect on irradiated volume. Moreover, in the case of overestimation, the effect on organs at risk might be limited, as overestimation primarily involves the vitreous body.

The acceptance threshold of a coverage of 98% and a maximum underestimation of the tumour contour of 0.4 mm is somewhat arbitrary. The 0.4 mm corresponds with the size of the dose grid used in the treatment planning system at our centre. To assess the robustness of these thresholds, we also evaluated both more lenient and stricter thresholds. Our results showed that overestimation decreased with the more lenient thresholds, whereas a stricter threshold led to fewer patients meeting the criteria for an acceptable model.

5. Conclusion

All tumour models as used in ocular proton therapy treatment planning systems can achieve acceptable tumour coverage. However, to achieve this coverage, the tumour models overestimated the delineated tumour volume.

Funding

This research was funded by Varian, a Siemens Healthineers company (HollandPTC-Varian Consortium grant ID (project 2020016)).

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: L. Klaassen reports financial support was provided by Varian, a Siemens Healthineers company. L. Klaassen, J.W.M. Beenakker reports a relationship with Philips that includes: non-financial support. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejmp.2026.105895>.

References

- Jager MJ, Shields CL, Cebulla CM, Abdel-Rahman MH, Grossniklaus HE, Stern MH, et al. Uveal melanoma. *Nat Rev Dis Primers* 2020;6:24. <https://doi.org/10.1038/s41572-020-0158-0>.
- Kaliki S, Shields CL. Uveal melanoma: relatively rare but deadly cancer. *Eye (Lond)* 2017;31:241–57. <https://doi.org/10.1038/eye.2016.275>.
- Hrbacek J, Kacperek A, Beenakker JM, Mortimer L, Denker A, Mazal A, et al. PTCOG Ocular Statement: Expert Summary of Current Practices and Future Developments in Ocular Proton Therapy. *Int J Radiat Oncol Biol Phys* 2024;120:1307–25. <https://doi.org/10.1016/j.ijrobp.2024.06.017>.
- Daftari I, Aghaia E, O'Brien JM, Dillon W, Phillips TL. 3D MRI-based tumor delineation of ocular melanoma and its comparison with conventional techniques. *Med Phys* 2005;32:3355–62. <https://doi.org/10.1118/1.2068927>.
- Daftari IK, Mishra KK, O'Brien JM, Tsai T, Park SS, Sheen M, et al. Fundus image fusion in EYEPLAN software: an evaluation of a novel technique for ocular melanoma radiation treatment planning. *Med Phys* 2010;37:5199–207. <https://doi.org/10.1118/1.3488891>.
- Dobler B, Bendl R. Precise modelling of the eye for proton therapy of intra-ocular tumours. *Phys Med Biol* 2002;47:593–613. <https://doi.org/10.1088/0031-9155/47/4/304>.
- Systems VM. Planning Reference Guide for Eclipse Ocular Proton Planning.; 2007.
- Wulff J, Koska B, Heufelder J, Janson M, Backer CM, Siregar H, et al. Commissioning and validation of a novel commercial TPS for ocular proton therapy. *Med Phys* 2023;50:365–79. <https://doi.org/10.1002/mp.16006>.
- Klaassen L, Ferreira TA, Luyten G, Beenakker JM. Estimating uveal melanoma volume with ellipsoid tumour models. *Acta Ophthalmol* 2025. <https://doi.org/10.1111/aos.17492>.
- Foti PV, Travali M, Farina R, Palmucci S, Spatola C, Raffaele L, et al. Diagnostic methods and therapeutic options of uveal melanoma with emphasis on MR imaging-Part I: MR imaging with pathologic correlation and technical considerations. *Insights Imaging* 2021;12:66. <https://doi.org/10.1186/s13244-021-01000-x>.
- Ramos-Davila EM, Dalvin LA. Clinical Implications of Ultrasound-based Morphology in Choroidal Melanoma. *Ophthalmol Retina* 2025;9:263–71. <https://doi.org/10.1016/j.oret.2024.09.010>.
- Jaarsma-Coes MG, Ferreira TA, Marinkovic M, Vu THK, van Vught L, van Haren GR, et al. Comparison of magnetic Resonance Imaging-based and conventional Measurements for Proton Beam Therapy of Uveal Melanoma. *Ophthalmol Retina* 2023;7:178–88. <https://doi.org/10.1016/j.oret.2022.06.019>.
- Ferreira TA, Grech Fonk L, Jaarsma-Coes MG, van Haren GGR, Marinkovic M, Beenakker JM. MRI of Uveal Melanoma. *Cancers (Basel)* 2019;11. <https://doi.org/10.3390/cancers11030377>.
- Ferreira TA, Jaarsma-Coes MG, Marinkovic M, Verbist B, Verdijk RM, Jager MJ, et al. MR imaging characteristics of uveal melanoma with histopathological validation. *Neuroradiology* 2022;64:171–84. <https://doi.org/10.1007/s00234-021-02825-5>.
- Jaarsma-Coes MG, Klaassen L, Verbist BM, Vu THK, Klaver YLB, Rodrigues MF, et al. Inter-Observer Variability in MR-Based Target volume Delineation of Uveal Melanoma. *Adv Radiat Oncol* 2023;8:101149. <https://doi.org/10.1016/j.adro.2022.101149>.
- Klaassen L, Haasjes C, Hol M, Cambraia Lopes P, Spruijt K, van de Steeg-Henzen C, et al. Geometrical accuracy of magnetic resonance imaging for ocular proton therapy planning. *Phys Imaging Radiat Oncol* 2024;31:100598. <https://doi.org/10.1016/j.phro.2024.100598>.
- Mortimer L, Slopesma R, Mazal A, Beenakker JW, Dendale R, Denker A, et al. PTCOG Ocular Survey - Perspective on Ocular Particle Therapy: Current Practices and Emerging Trends. *Int J Part Ther* 2026;19:101300. <https://doi.org/10.1016/j.ijpt.2026.101300>.
- Klaassen L, Jaarsma-Coes MG, Verbist BM, Vu THK, Marinkovic M, Rasch CRN, et al. Automatic Three-Dimensional magnetic Resonance-based measurements of tumour prominence and basal diameter for treatment planning of uveal melanoma. *Phys Imaging Radiat Oncol* 2022;24:102–10. <https://doi.org/10.1016/j.phro.2022.11.001>.
- Kivelä T SR, Grossniklaus HE, et al. Uveal melanoma. *AJCC Cancer Staging Manual*. 8th edition. New York: Springer; 2016. p. 805-17.
- Via R, Hennings F, Pica A, Fattori G, Beer J, Peroni M, et al. Potential and pitfalls of 1.5T MRI imaging for target volume definition in ocular proton therapy. *Radiother Oncol* 2021;154:53–9. <https://doi.org/10.1016/j.radonc.2020.08.023>.
- Marnitz S, Cordini D, Bendl R, Lemke AJ, Heufelder J, Simiantonakis I, et al. Proton therapy of uveal melanomas: intercomparison of MRI-based and conventional treatment planning. *Strahlenther Onkol* 2006;182:395–9. <https://doi.org/10.1007/s00066-006-1512-1>.
- Wulff J, Koska B, Ahmad Khalil D, Richter R, Maximilian Backer C, Baumer C, et al. Uncertainties in ocular proton planning and their impact on required margins. *Phys Med* 2024;121:103358. <https://doi.org/10.1016/j.ejmp.2024.103358>.
- Bjorkman D, Via R, Lomax A, De Prado M, Baroni G, Weber DC, et al. The effect of intra- and inter-fractional motion on target coverage and margins in proton therapy for uveal melanoma. *Phys Med Biol* 2024;69. <https://doi.org/10.1088/1361-6560/ad8297>.
- Egger E, Schalenbourg A, Zografos L, Bercher L, Boehringer T, Chamot L, et al. Maximizing local tumor control and survival after proton beam radiotherapy of uveal melanoma. *Int J Radiat Oncol Biol Phys* 2001;51:138–47. [https://doi.org/10.1016/s0360-3016\(01\)01560-7](https://doi.org/10.1016/s0360-3016(01)01560-7).
- Marinkovic M, Pors LJ, van den Berg V, Peters FP, Schalenbourg A, Zografos L, et al. Clinical Outcomes after International Referral of Uveal Melanoma patients for Proton Therapy. *Cancers (Basel)* 2021;13. <https://doi.org/10.3390/cancers13246241>.
- Bensoussan E, Thariat J, Maschi C, Delas J, Schouder ED, Herault J, et al. Outcomes after Proton Beam Therapy for Large Choroidal Melanomas in 492 patients. *Am J Ophthalmol* 2016;165:78–87. <https://doi.org/10.1016/j.ajo.2016.02.027>.
- Hussain RN, Chiu A, Pittam B, Taktak A, Damato BE, Kacperek A, et al. Proton beam radiotherapy for choroidal and ciliary body melanoma in the UK-national audit of referral patterns of 1084 cases. *Eye (Lond)* 2023;37:1033–6. <https://doi.org/10.1038/s41433-022-02178-0>.
- Papakostas TD, Lane AM, Morrison M, Gragoudas ES, Kim IK. Long-term Outcomes after Proton Beam Irradiation in patients with Large Choroidal Melanomas. *JAMA Ophthalmol* 2017;135:1191–6. <https://doi.org/10.1001/jamaophthalmol.2017.3805>.
- Via R, Pica A, Antonioli L, Paganelli C, Fattori G, Spaccapaniccia C, et al. MRI and FUNDUS image fusion for improved ocular biometry in Ocular Proton Therapy. *Radiother Oncol* 2022;174:16–22. <https://doi.org/10.1016/j.radonc.2022.06.021>.
- Haasjes C, Vu THK, Beenakker JWM. Patient-specific mapping of fundus photographs to three-dimensional ocular imaging. *Med Phys* 2025;52:2330–9. <https://doi.org/10.1002/mp.17576>.