Article:
Espensen, CA, Kiilgaard, JF, Appelt, AL orcid.org/0000-0003-2792-9218 et al. (5 more authors) (2021) Dose-response and normal tissue complication probabilities after proton therapy for choroidal melanomas. Ophthalmology, 128 (1). pp. 152-161. ISSN 0161-6420

https://doi.org/10.1016/j.ophtha.2020.06.030

Supplementary material

Appendix A: Treatment details

Each patient had four tantalum clips surgically sutured onto the sclera surrounding the tumour borders. The surgeries were performed under general anesthesia, and transillumination was used to visualize the tumour. The thickness and diameter of the tumour were reported from subsequent ultrasound scan.

Tumour contouring was based on pre-treatment retinographies including a 2.5 mm margin surrounding the tumour. The retina, macula, optic disc, globe, ciliary body, cornea and lens were all contoured as well. Tumour coverage was highest priority during all treatments. When possible and without compromising tumour coverage, macula and optic nerve sparing were prioritized by carrying out proton plan optimization using gazing angle, margins and/or filter.

The proton therapy treatment was carried out two to four weeks after clip placement. During treatment, the patients were seated with the head immobilized by a specially designed facemask and bite block. Orientation of the eye in the correct angle was achieved by a light-emitting diode. X-ray images was used to position the clips (and thus the tumour) correctly in the beam during dosimetry. The position and movement of the eye was observed by video camera during treatment, which was disrupted if eye movements occurred.

Appendix B: Analysis plan

Complication/outcome	Dose to structure*	Clinical factors	Analysis	Patients
Visual acuity deterioration i. Pre-treatment VA better than 0.5 logMAR. Post-treatment VA increase of 0.3 logMAR compared to initial ii. All patients regardless of initial visual acuity. Post-treatment VA increase of 0.3 logMAR compared to initial	Retina (surface) Macula (volume) Optic disc (surface) Globe (volume) Ciliary body (volume) Cornea (surface) Lens (volume)	Age, gender, tumour height, tumour-optic disc distance, pre-treatment VA and follow-up time	**Logistic regression**	i. 551 ii. 1020
Maculopathy Includes both ischemia and edema in the macular region as defined in the database	Retina (surface) Macula (volume) Optic disc (surface) Globe (volume) Ciliary body (volume)	Age, gender, tumour height, tumour-optic disc distance	**Cox regression analysis**. Censoring: death from any cause, lost to follow-up, relapse or enucleation	991
Optic neuropathy An oedemic, atrophic, undelimited and/or pale	Retina (surface) Macula (volume) Optic disc (surface) Globe (volume)	Age, gender, tumour height, tumour-optic disc distance	**Cox regression analysis**. Censoring: death from any	991

optic disc as defined in the database	Ciliary body (volume)		cause, lost to follow-up, relapse or enucleation	
Cataract Includes only the radiation induced cataracts as defined in the database	Globe (volume) Ciliary body (volume) Cornea (surface) Lens (volume)	Age, gender, tumour height, tumour-optic disc distance	**Cox regression analysis**. Censoring: death from any cause, lost to follow-up, relapse or enucleation	991
Neovascular glaucoma Includes the neovascular glaucomas as defined in the database	Retina (surface) Optic disc (surface) Ciliary body (volume) Cornea (surface) Globe (volume)	Age, gender, tumour height, tumour-optic disc distance	**Cox regression analysis**. Censoring: death from any cause, lost to follow-up, relapse or enucleation	991
Dry eye Includes all with dry eye as defined in the database	Globe (volume) Cornea (surface)	Age, gender, tumour height, tumour-optic disc distance	**Cox regression analysis**. Censoring: death from any cause, lost to follow-up,	991

			relapse or enucleation	
Retinal detachment (post-treatment) Includes all the retinal detachments that occur after treatment as defined in the database	Retina (surface)	Age, gender, tumour height, tumour-optic disc distance	**Logistic regression**	991
Ocular hypertension Includes all the patients with hypertension that occurs after the treatment as defined in the database	Retina (surface) Optic disc (volume) Ciliary body (volume) Cornea (surface)	Age, gender, tumour height, tumour-optic disc distance	**Cox regression analysis**. Censoring: death from any cause, lost to follow-up, relapse or enucleation.	991
Vasculopathy	Retina (surface) Macula (volume) Optic disc (volume) Globe (volume) Ciliary body (volume)	Age, gender, tumour height, tumour-optic disc distance	**Cox regression analysis**. Censoring: death from any cause, lost to follow-up, relapse or enucleation.	991

Table B1: Analysis plan

*Dose to specific volumes/surface of the structure ($D_{2\%}$, $D_{20\%}$, $D_{50\%}$, $D_{98\%}$) will be used in the model. Furthermore, we will include volume/surface that receives a specific dose (V/S_{5Gy}, V/S_{10Gy}, V/S_{26Gy}, V/S_{42Gy}, V/S_{52Gy}).

Appendix C: Model performance

Hosmer-Lemeshow was used to evaluate the model performance of the logistic regressions. Figure C1 illustrates the results. The p-values of p=0.27 for pre-treatment visual acuity loss and p=0.05 for visual acuity deterioration indicate that there was no significant difference between the observed and expected risk for pre-treatment visual acuity loss and visual acuity deterioration, respectively.

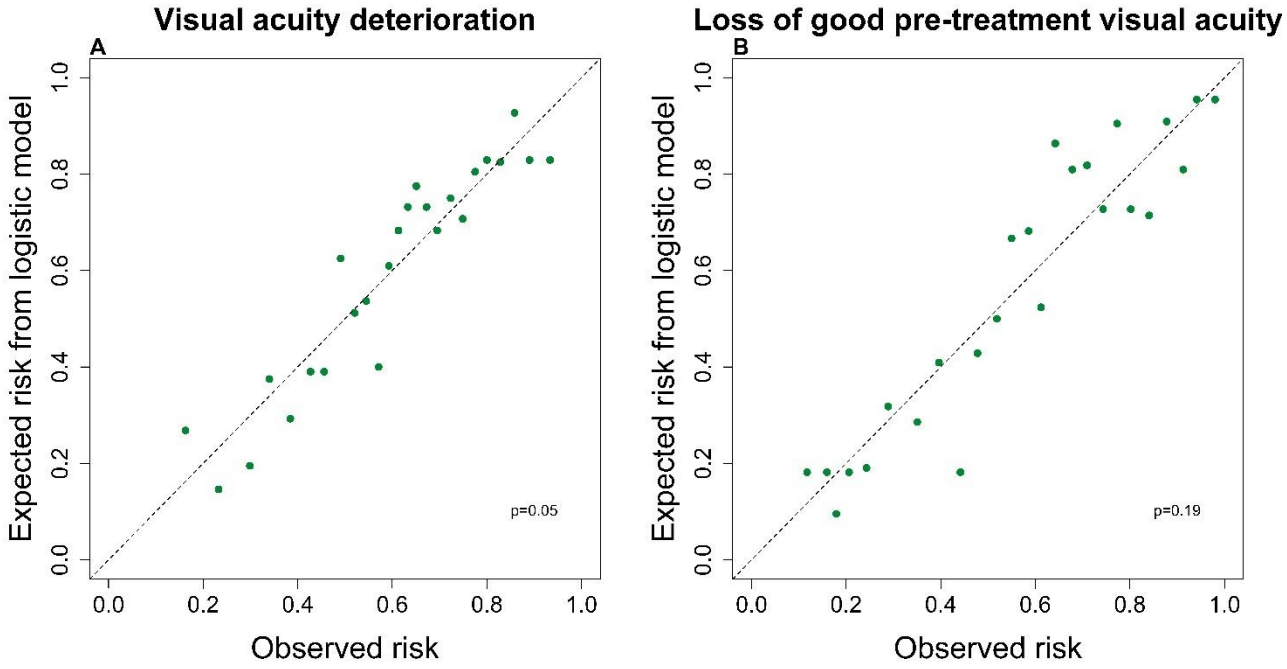

Figure C1: A) Hosmer-Lemeshow calibration comparing the observed risk of visual acuity deterioration group with the fitted probabilities expected from the logistic model (group 1, analysis 1). Number of groups was set to 25. B) Same for loss of good pre-treatment visual acuity (group 1, analysis 2).

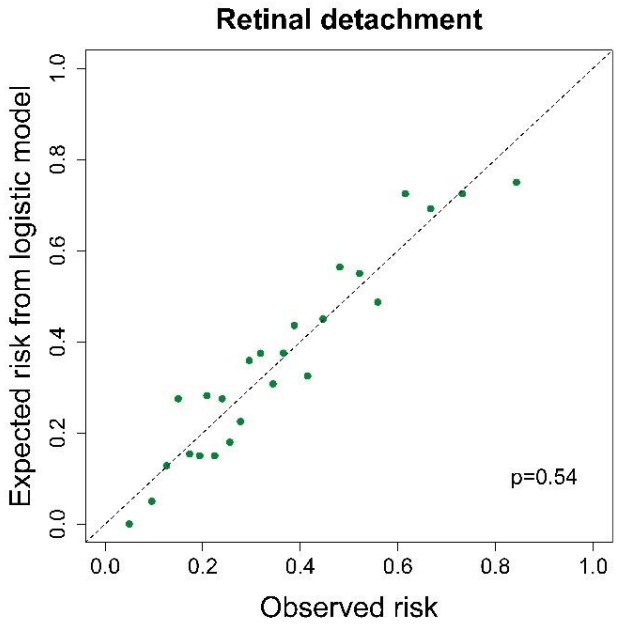

Figure C2: Hosmer-Lemeshow calibration comparing the observed risk of loss of pre-treatment visual acuity with the fitted probabilities expected from the logistic model. Number of groups was set to 25.

Concordance index was calculated for all Cox regression models to evaluate the model performance.

Complication	**5-year c-index**	**5-year Brier score**
Maculopathy	53.8 %	0.164
Optic neuropathy	76.9 %	0.109
Neovascular glaucoma	83.8 %	0.082
Cataract	63.2 %	0.196
Ocular hypertension	80.1 %	0.062

Table C1: Concordance index for each complication at 5-years

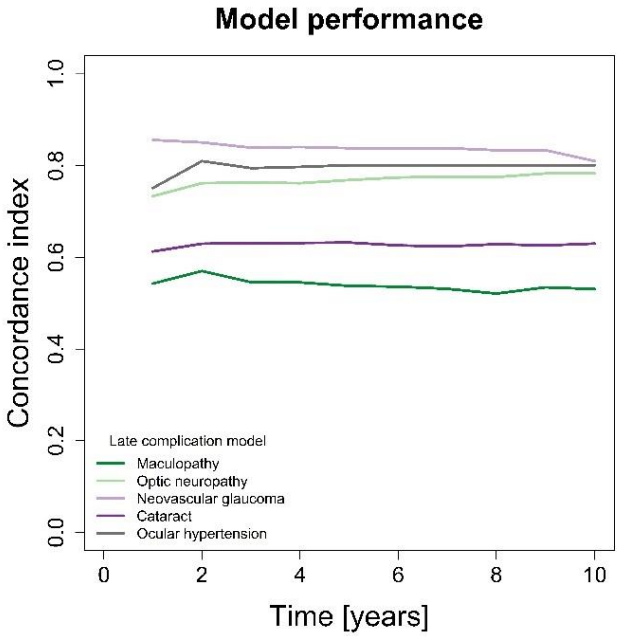

Figure C3: Concordance index plotted for each of the late complications for a 10-year period.