SUPPLEMENTARY MATERIAL

Excluded patients

One patient died immediately after treatment, before any follow-up was performed, and was thus excluded from the analysis. Six patients were lost to follow-up, as their local ophthalmologist maintained the regular control visits due to logistical and/or physical conditions. These were used in the analysis until the transfer of care and censored afterwards.

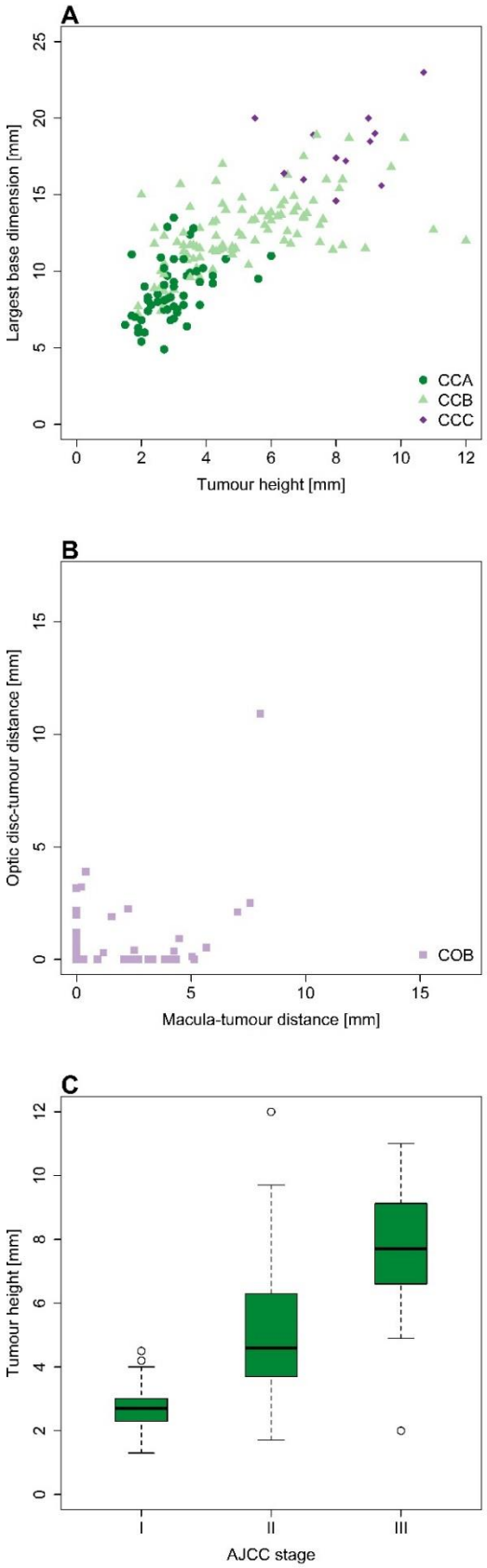
Correlation analysis

Correlation analysis showed a clear relationship between tumour height and tumour largest base dimension (Figure 4A). Based on clinical evaluation we kept tumour height in the model.

Tumour height, largest base dimension and plaque type all correlated closely, with the CCC plaque type used for the largest tumours, the CCA primarily used for smaller tumour sizes, and the CCB and the COB used for the remaining tumour sizes, depending on location within the globe. We chose to keep tumour height in the model.

Plaque type also correlated with optic disc-tumour and macula-tumour distance (Figure 4B). The COB plaque was used only for tumours within approximately 2 mm from each of the structures, while the remaining plaques were used for all distances. Based on clinical evaluation, we kept the optic disc-tumour distance in the model.

As expected, the AJCC stage and tumour height correlated strongly (Figure 4C). We performed the analyses separately with tumour height and stage since both were of clinical interest.



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23 Figure 4: Correlation between clinical variables. A) Tumour height, tumour largest base dimension and

type of plaque correlated. CCA and CCB plaques were used for smaller and medium sized tumours, while the CCC plaque was used only for large tumours. B) Macula-tumour distance correlated with optic disc-tumour distance and plaque type with the COB plaque being used only for small distances (primarily <2 mm from each of the structures). C) Tumour heights divided by AJCC stage.

Local control estimates stratified for clinical factors

Figure 5 illustrates Kaplan-Meier curves stratified for several different clinical factors.

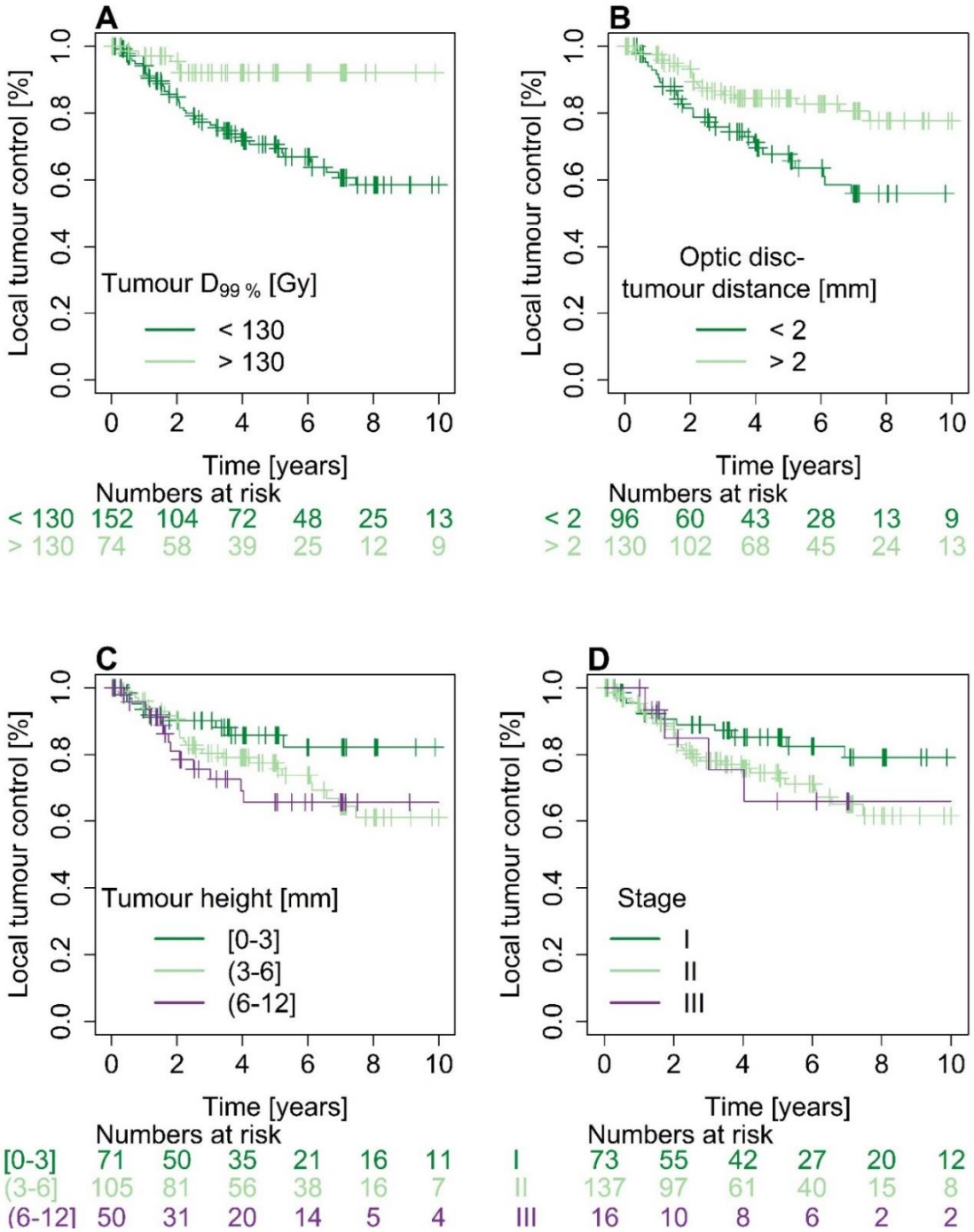

Figure 5: Kaplan-Meier curves showing probability of local tumour control for the population divided into groups based on A) tumour doses, B) optic disc-tumour distances, C) tumour heights and D) stages. Crosses represent censored patients.

Modelling using AJCC stage

The results from the analysis using AJCC stage as an alternative to tumour height but with all other factors retained are listed in Table 3 and illustrated at 3 and 7 years after primary treatment in Figure 6A and Figure 6B. In the reduced model, $D_{99\%}$ remained the most significant variable emphasizing the robustness of $D_{99\%}$ on the effect on local tumour control. Combined TTT and Ru-106 and sex also remained significant.

Table 3: Cox proportional hazards from the reduced model using stage instead of tumour height

Variables in full model	**HR (95% CI)**	**p-value**
Age	1.02 (1.00-1.05)	0.09
Sex (male relative to female)	2.32 (1.22-4.43)	0.01
Eye (left relative to right)	0.99 (0.56-1.75)	0.97
Tumour height	-	-
Optic disc-tumour distance	0.92 (0.82-1.04)	0.19
Stage II+III (relative to I)	3.73 (1.77-7.89)	0.0006
$D_{99\%}$	0.86 (0.80-0.92)	$<10^{-4}$
Combined TTT and Ru-106	2.67 (1.35-5.26)	0.005
Variables in reduced model	**HR (95% CI)**	**p-value**
$D_{99\%}$	0.85 (0.80-0.91)	$<10^{-4}$
Stage II+III (relative to I)	3.11 (1.50-6.44)	0.002
Combined TTT and Ru-106	2.86 (1.49-5.51)	0.002
Sex (male relative to female)	1.97 (1.07-3.63)	0.03

HR=hazard ratio, CI=confidence interval, $D_{99\%}$=minimum physical tumour dose, TTT=transpupillary thermotherapy, Ru-106=Ruthenium-106. HRs for a 10 Gy increase in $D_{99\%}$

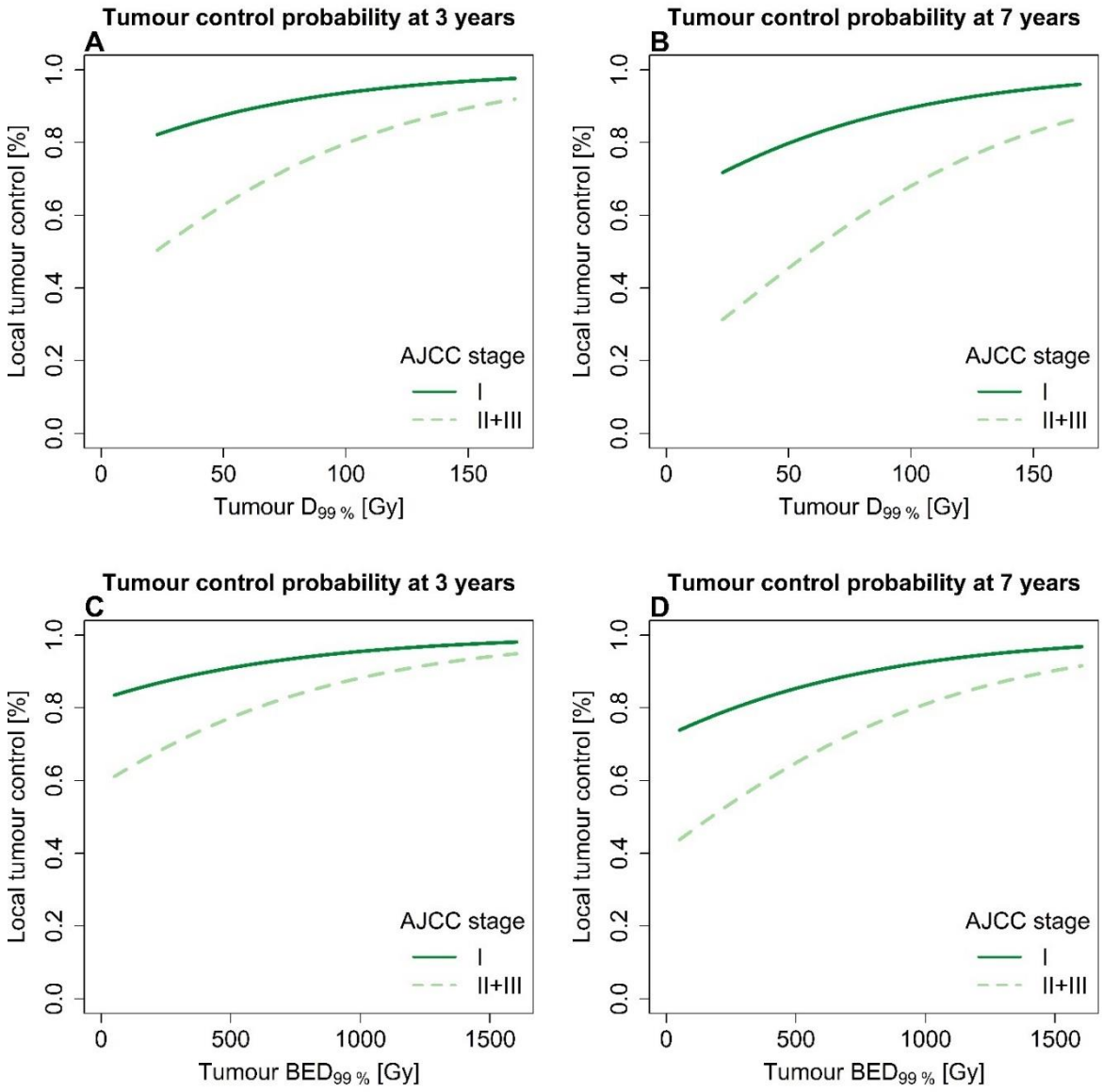

Figure 6: A) Tumour control probability (TCP) curves at 3 years divided into two groups based on AJCC stage (AJCC stage I and AJCC stage II+III). B) TCP curves at 7 years divided into the same staging groups. The TCP curves in A) and B) were built from Cox proportional hazard regressions, using age of 62 years (median age of cohort), and male sex (the most frequent sex in the cohort). C) TCP curves using $BED_{99\%}$ at 3 years divided into the three tumour heights. D) TCP curves using $BED_{99\%}$ at 7 years divided into the three tumour heights

Modelling using Biologically Effective Dose

Results from the $BED_{99\%}$-based TCP analyses for the models with tumour height and AJCC stage are listed in Table 4. The latter is illustrated at 3 and 7 years after primary treatment in Figure 6C and Figure 6D, respectively. Higher AJCC stage had larger risk of local tumour recurrence relative to smaller stage.

Table 4: Cox proportional hazards using BED instead of physical dose

	Model with tumour height		Model with stage	
Variables in full model	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Age	1.02 (1.00-1.05)	0.08	1.02 (1.00-1.05)	0.08
Sex (male relative to female)	2.44 (1.29-4.61)	0.006	2.35 (1.23-4.49)	0.009
Eye (left relative to right)	0.94 (0.54-1.66)	0.84	0.96 (0.55-1.70)	0.89
Tumour height	1.17 (1.02-1.33)	0.02	-	-
Optic disc-tumour distance	0.92 (0.81-1.04)	0.19	0.92 (0.81-1.04)	0.16
Stage II+III (relative to I)	-	-	2.91 (1.41-6.00)	0.004
$BED_{99\%}$	0.99 (0.98-1.00)	0.003	0.98 (0.97-0.99)	0.0005
Combined TTT and Ru-106	1.77 (0.89-3.52)	0.10	2.30 (1.18-4.49)	0.01
Variables in reduced model	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
$BED_{99\%}$	0.99 (0.98-0.99)	0.0005	0.98 (0.97-0.99)	0.0001
Sex (male relative to female)	2.26 (1.24-4.11)	0.007	1.95 (1.06-3.58)	0.03
Stage II+III (relative to I)	-	-	2.36 (1.18-4.72)	0.02
Combined TTT and Ru-106	2.25 (1.18-4.31)	0.01	2.48 (1.29-4.74)	0.006

HR=hazard ratio, CI=confidence interval, $BED_{99\%}$=minimum biologically effective tumour dose, TTT=transpupillary thermotherapy, Ru-106=Ruthenium-106. HRs for a 10 Gy increase in $BED_{99\%}$

Choice of dose metric

The p-values from the reduced Cox model for the full range of dose metrics are plotted in Figure 7. $D_{99\%}$ and $BED_{99\%}$ had the strongest correlation, although most high dose metrics showed good correlation with outcome.

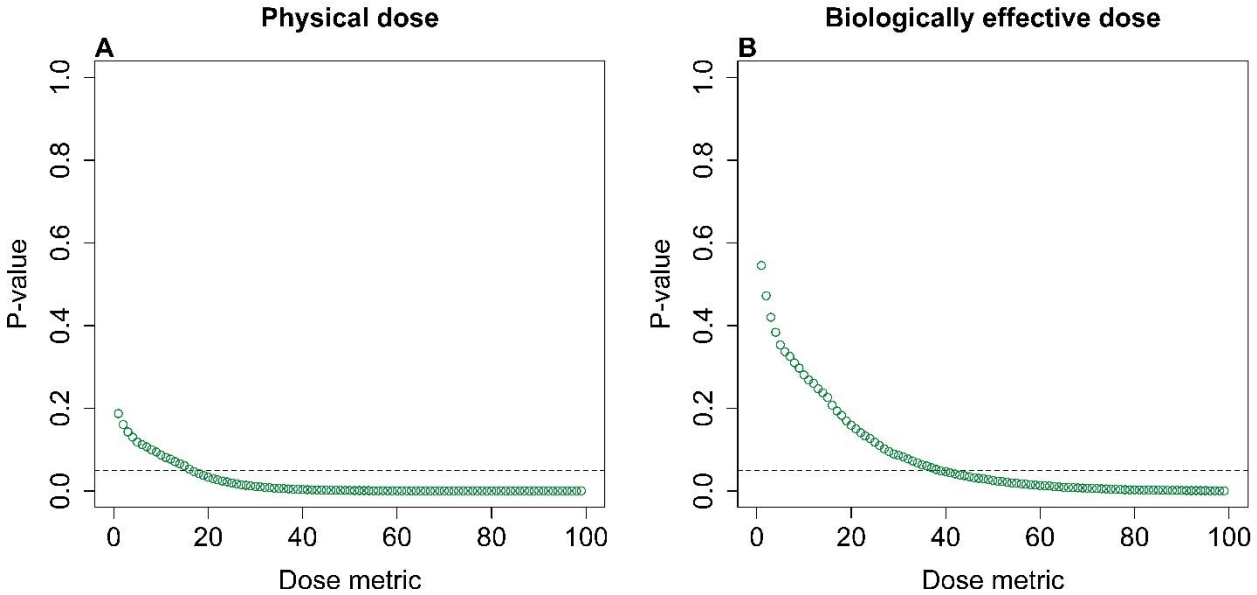

Figure 7: Significance of each dose metric ranging from $D_{1\%}$-$D_{99\%}$ (A) and $BED_{1\%\text{-}99\%}$ (B). Dotted line indicates p=0.05.

Competing risk analysis

Competing risk analysis was performed to account for death and TTT during follow-up. The cumulative incidences are illustrated in Figure 8.

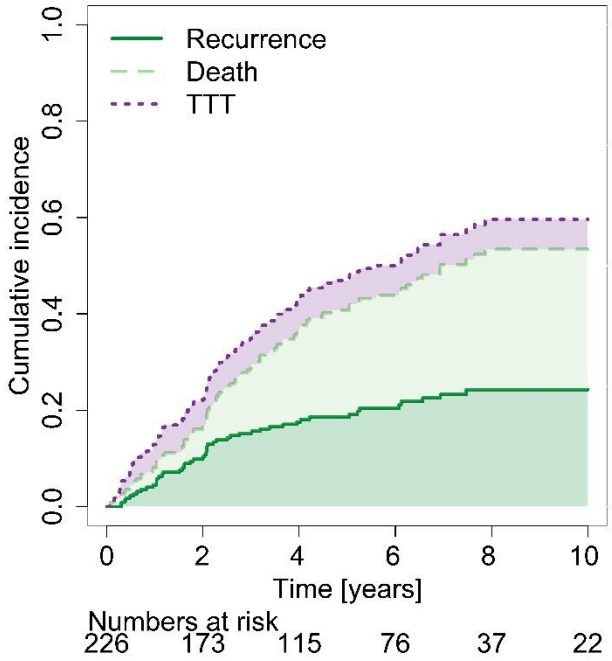

Figure 8: Cumulative incidences with death (light green), tumour recurrence without TTT (green), and recurrence with TTT (purple) as competing events.

Taking competing risks into account did not change the overall model estimates. The hazard ratios and corresponding p-values from the competing risk analysis are listed in Table 5.

Table 5: Reduced Cox proportional hazards accounting for competing risks.

Variables in reduced model	HR (95% CI)	p-value
$D_{99\%}$	0.87 (0.82-0.92)	$<10^{-4}$
Tumour height	1.11 (0.99-1.25)	0.08
Combined TTT and Ru-106	2.35 (1.26-4.37)	0.007
Sex (male relative to female)	1.53 (0.88-2.65)	0.02

HR=hazard ratio, CI=confidence interval, $D_{99\%}$=minimum physical tumour dose, TTT=transpupillary thermotherapy, Ru-106=Ruthenium-106. HRs for a 10 Gy increase in $D_{99\%}$

Considering marginal and central tumour recurrence (separating the two types of recurrence) as well as death and TTT in follow-up as competing risks, the results appear to be driven primarily by central recurrences. The cumulative incidences are illustrated in Figure 9. The hazard ratios and corresponding p-values from the competing risk analysis are listed in Table 6 and Table 7.

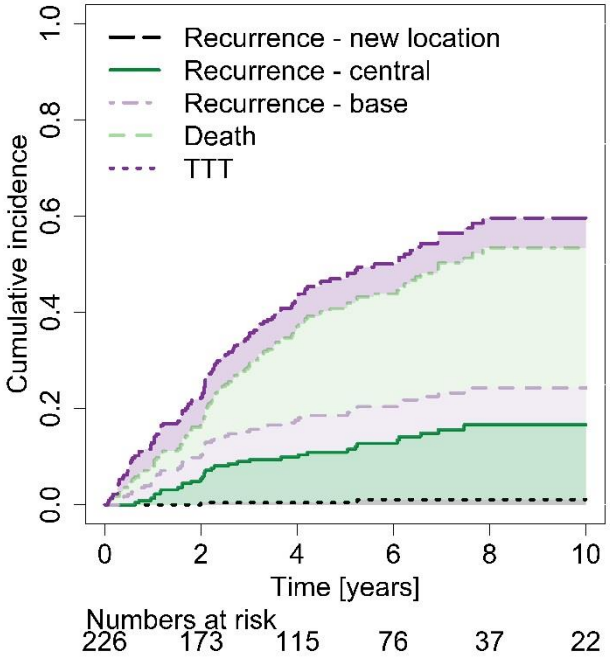

Figure 9: Cumulative incidences with tumour recurrence without TTT in a new location (black), marginal tumour recurrence without TTT (dark green), death (light green), central tumour recurrence without TTT (light purple), death (light green), and recurrence with TTT (dark purple) as competing events.

Table 6: Reduced Cox proportional hazards accounting for competing risks and distinguishing between different recurrence phenotypes.
Endpoint: Central recurrence

Variables in reduced model	**HR (95% CI)**	**p-value**
$D_{99\%}$	0.82 (0.76-0.89)	$<10^{-4}$
Tumour height	1.15 (1.00-1.32)	0.05
Combined TTT and Ru-106	0.74 (0.33-1.66)	0.47
Sex (male relative to female)	1.20 (0.57-2.55)	0.63

HR=hazard ratio, CI=confidence interval, $D_{99\%}$=minimum physical tumour dose, TTT=transpupillary thermotherapy, Ru-106=Ruthenium-106. HRs for a 10 Gy increase in $D_{99\%}$

Table 7: Reduced Cox proportional hazards accounting for competing risks and distinguishing between different recurrence phenotypes.
Endpoint: Marginal recurrence

Variables in reduced model	HR (95% CI)	p-value
$D_{99\%}$	0.97 (0.91-1.04)	0.39
Tumour height	1.04 (0.83-1.32)	0.72
Combined TTT and Ru-106	8.94 (3.17-25.2)	$<10^{-4}$
Sex (male relative to female)	3.83 (1.43-10.2)	0.63

HR=hazard ratio, CI=confidence interval, $D_{99\%}$=minimum physical tumour dose, TTT=transpupillary thermotherapy, Ru-106=Ruthenium-106. HRs for a 10 Gy increase in $D_{99\%}$

Calibration

The calibration plots for predicted versus observed 3-year tumour control are illustrated in Figure 9 for both $D_{99\%}$ and $BED_{99\%}$. The calibration analyses showed good correlation between observed and predicted tumour control.

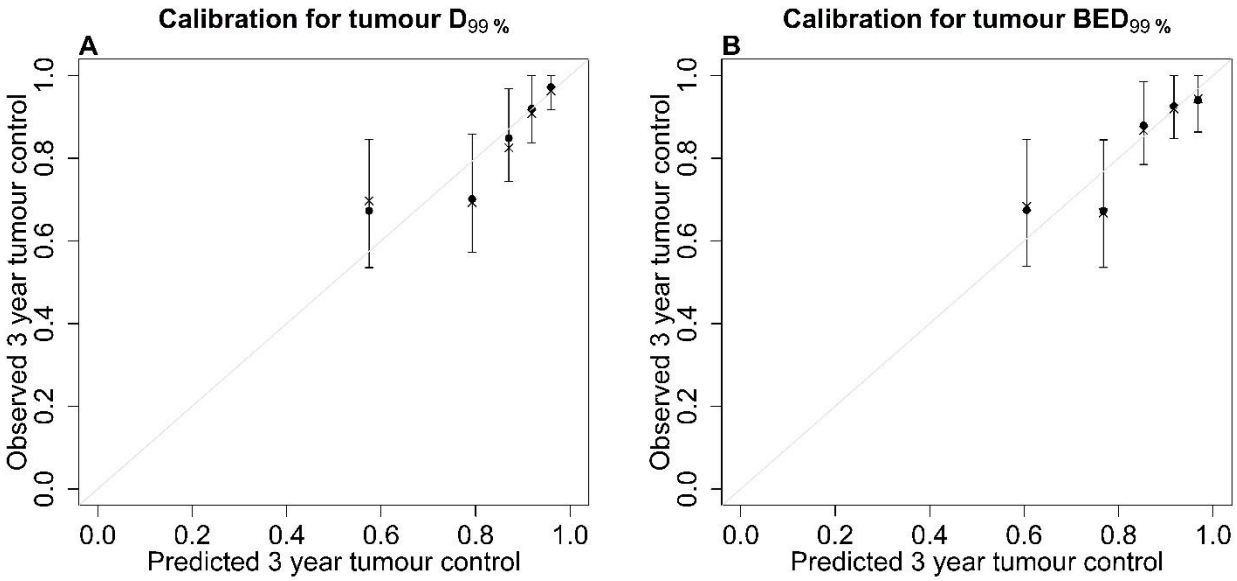

Figure 10: Calibration plots for predicted versus observed 3-year tumour control for the reduced Cox model with $D_{99\%}$ (A) and $BED_{99\%}$ (B). The grey line represents perfect prediction. Intervals with 40 patients in each was used (and resampled 500 times to produce 95 % confidence intervals).