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Hypofractionation in retinoblastoma: an increased risk of retinopathy†

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Abstract

Forty-four eyes in 38 children were treated between 1963 and 1991 by external radiotherapy for retinoblastoma. Treatment modalities varied widely during this period; in addition to radiotherapy there was chemotherapy (16/44), photocoagulation (14/44), and laser therapy or cryotherapy (14/44). Treatment technique and dose fractionation also varied widely; lateral beam technique (39/44) versus anterior or anterior/lateral beam; doses per fraction ranged from 1 to 4.5 Gy, total doses from 30 to 61.5 Gy, and overall times from 22 to 49 days. Patients were followed at 3-month intervals, and actuarial survival at 10 years was 88%, with 62% local control. Ten eyes showed clinical evidence of retinopathy. A multivariate analysis of factors associated with increased risk of retinopathy was carried out using the Cox proportional hazards model and the mixture model of Farewell. The estimated latent time was 17 months (95% confidence interval, 14–20 months). The only factors found to be significantly associated with retinopathy were total dose multiplied by dose per fraction, or total dose normalized to the equivalent total dose in 2-Gy fractions as estimated from the LQ model, and these gave equivalent descriptions. There were trends (not significant) for increased risk of retinopathy when treatments included chemotherapy or photocoagulation, and for decreased risk (also not significant) when cryotherapy was used in conjunction with radiotherapy. No significance could be attached to any of the following: number of sites per eye, Reese–Ellsworth stage, and family history. We conclude that hypofractionation carries a significant risk for retinopathy in the treatment of retinoblastoma.

Key words: Retinoblastoma; Retinopathy; Linear-quadratic model; Radiotherapy; Fractionation

1. Introduction

External radiotherapy can be generally considered as a sight-saving treatment procedure in retinoblastoma. It can be applied alone or in combination with other treatment modalities especially in bilateral cases. Although radiotherapy is known to be effective in eradicating retinoblastoma cells, there are different treatment-related complications that may result in visual loss. If eye-saving can be considered an important endpoint in the treatment of retinoblastoma, assessment of the effects of changing radiotherapy parameters is mandatory. We report a retrospective analysis of 44 eyes treated by radiotherapy or a combination of treatment modalities including radiotherapy. The aim of this retrospective study was to analyse the importance of dose per fraction and other factors in the appearance of retinopathy.

2. Patients and methods

Forty-four eyes in 38 children were treated between 1963 and 1991. The patients were eligible for this retrospective analysis if there was a minimum follow-up of 12 months. The follow-up ranged from 14 months to 17 years with a median follow-up of 35 months. Treatment modalities were very different from one treatment period to another, and radiotherapy was not the only treatment modality involved (see Table 1). In 29 eyes radiotherapy was associated with chemotherapy (16/44), photocoagulation (14/44), laser therapy or cryotherapy

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Table 1
Patient and treatment characteristics: 38 children (44 eyes), treated from 1963 to 1991

Patient characteristics			
Male/female ratio	0.65		
Bilateral/unilateral	6.6		
Family history	21%		
		Range	Median
Follow-up*		14 months–17 years	35 months
Age at diagnosis		2–68 months	17 months
Treatment characteristics			
Dose/fraction (Gy)		1–4.5 Gy	2 Gy
Total dose		30–62 Gy	45 Gy
Total elapsed time (days)		22–49	34

*Minimum follow-up for inclusion in the present analysis: 12 months.

(14/44). Moreover, there was a variation of treatment techniques and dose per fraction over this treatment period. Thirty-nine eyes of 44 were treated by a lateral beam technique. From 1986 on, the eye immobilisation technique described by Schipper was used for the lateral beam technique [13]. Five eyes were treated by an anterior beam or a combination of an anterior and lateral beam. The dose per fraction ranged from 1 to 4.5 Gy (see Table 2), and total doses from 30 to 62 Gy (median, 45 Gy). The number of fractions per week ranged from 3 to 6 (median, 4). The median total elapsed treatment time was 34 days (range, 22–49 days). For some of these patients different doses per fraction were used for the same patient, probably illustrative of the problems encountered during anesthesia resulting in a tendency towards hypofractionating the treatment. The total dose was prescribed at the center of the eye. The heterogeneity within the target volume was at most 5% compared to the prescription point.

All patients were followed up at least every 3 months. No patients were lost to follow-up. Treatment-related retinopathy was routinely assessed at each follow-up. The diagnosis was made by clinical examination and photography, eventually confirmed by angiography. Retinopathy has been defined by Brown et al. as a vascular phenomenon characterized by the appearance of hard exudate, intraretinal hemorrhage, microaneurysms, cotton wool spots, telangiectases, vascular sheathing or any combination of these [3]. Only the vascular complications located outside the initial tumour volume or outside the region treated with laser or cobalt plaque therapy were considered in the present analysis as retinopathy related to external radiotherapy. It is noteworthy that none of the patients treated in part with cobalt plaque therapy developed retinopathy. Therefore, the total doses quoted in the present paper are the external doses only, not taking into account the dose delivered by cobalt plaque therapy.

A multivariate analysis of factors associated with retinopathy was performed using two methods: the Cox proportional hazards model [6] and Farewell mixture model [8]. With either model the endpoint was the time to occurrence of retinopathy or censorship (last follow-up). The former involves the assumptions that the hazard to experience the late effect, which depends on the covariates described below, is strictly proportional at all times (e.g. the ratio of hazards at two different radiation doses is independent of time) and that ultimately all patients would experience it. The latter model assumes the existence of a fraction of patients who will not experience the late effect, and assumes that latency is described by a standard failure-time model so that hazards may be proportional or not. These approaches have been compared by Taylor and Kim (in press, 1993).

The biological effect was calculated according to the LQ model, according to

$$\text{Effect} = \alpha D + \beta D d,$$

where D = total dose given in fractions of size d, or equivalent total doses in 2-Gy fractions (D_{eq}) were calculated according to

$$D_{eq}(d) = D(\alpha/\beta + d)/(\alpha/\beta + 2).$$

Overall treatment time was treated as a continuous variable in the analysis, and the actual values of the covariates 'number of tumor sites/eye' and 'Reese–Ellsworth stage' were used in the fits. The values 0 or 1

Table 2
Overview of the heterogeneity in treatment parameters

Number of eyes	Dose/Fr. (Gy)	Total dose (Gy)	Retinopathy	Chemotherapy
2	1.8	45	0	0/1
12	2	42–50	1	1/3
11	3	42–48	5	1/6
1	3.5	35	0	0/1
10	0.8–2.5	30–50.6	0	0/3
8	>2.5–4.5	35–61.5	4	2/2

*For these patients different doses per fraction have been used for the same treatment.

were used for chemotherapy, photocoagulation, and cryotherapy, according to whether these did not (0) or did (1) play a role in the treatment. The covariate "family history" was also given the values 0 (no) or 1 (yes).

3. Results

3.1. Survival

A total of 35 of 38 patients are alive, the 3 deaths having resulted from distant metastases. The actuarial survival at 10 years is 88%, which is comparable to published series [1,2,5,7,9,10–13,15].

3.2. Local control

There were recurrences in 15/44 treated eyes, for an actuarial local control of 62% at 10 years. Of the 15 eyes with recurrences, 10 were enucleated, and 5 were salvaged by cryotherapy, photocoagulation or cobalt plaque therapy.

A multivariate analysis with the Cox model was performed to identify factors associated with tumor recurrence. There was a marginally significant association ($p = 0.0524$) between increasing probability of local tumor control and increasing number of tumor sites per eye. This counterintuitive correlation may be due to the small number of events.

3.3. Retinopathy

Clinical evidence of retinopathy was found in 10/44 treated eyes (treatment details for these 10 are set out in Table 3).

There was a range of fraction sizes among the patients both with and without retinopathy, and the Cox and the mixture model were used to estimate the ratio of α/β in the LQ model. The results of the mixture model analysis, with 95% confidence limits, was $\alpha/\beta = -0.4$ (−2.2, 1.7) Gy. The negative value resulted from the negative estimate for $\alpha = -0.01$ (−0.06, 0.04) Gy^{-1}, and the fit with β alone was negligibly different. This corresponds to a small and positive, but uncertain, value for α, and therefore can be interpreted as indicative of a high fractionation sensitivity for retinopathy, with the value of α/β uncertain but bounded above by 1.7 Gy. The significance of the β term ($p = 0.0002$) was confirmed by analysis with the Cox model (which did not provide an estimate for α, since it was not significantly different from zero). The latent time to retinopathy was estimated from the mixture model with a logistic failure times at 17 months (95% confidence interval, 14–20 months).

Because of the very small α/β ratio, the significance of the β term is equivalent to the significance of the equivalent total dose in 2-Gy fractions, as calculated above. Using the mixture model and $\alpha/\beta = 1$ Gy (estimates of complication probability are insensitive to choices in this range), the long-term probability of retinopathy can be calculated using the parameter estimates (with 95% confidence intervals): b_0 (= constant) = 4.2 (1.35, 7.0) and b_1 (= coefficient of D_{eq}) = 0.074 (0.019, 0.13) Gy^{-1}. The estimated dose in 2-Gy fractions (D_{eq}) for long-term probability p of developing retinopathy is

$$D_{eq} = [b_0 - \ln(-\ln p)]/b_1.$$

For different values for p, the D_{eq} has been calculated and listed in Table 4.

Table 3
Treatment characteristics of the ten eyes with clinical manifestation of retinopathy

Case	Total dose (Gy)	Dose/Fr. (Gy)	No. fractions	Chemo-therapy
1	45	3	15	no
2	45	3	15	no
3	55.5	3.63–3.72	15	no
4	45.5	2.58–2.88	15	no
5	58	4–4.50	13	yes
6	61.5	3.50–4.50	14	yes
7	45	3	15	no
8	45	3	15	yes
9	45	3	15	no
10	44	2	22	yes

4. Discussion and conclusion

Conservative treatment of retinoblastoma can be applied by different treatment modalities. Cryotherapy, light coagulation and radioactive plaque applicators are usually chosen for localized treatment of tumor-bearing areas of the retina. Surgery, especially enucleation, has been considered a standard in unilateral cases (dependent on the size and localisation of the primary), and for one eye in bilateral cases. However, based on the eye-saving rate and excellent survival obtained with conservative procedures, external radiotherapy may be considered as one of the standard conservative treatment procedures. This is based on the current knowledge that the entire retinal surface is at risk of developing retinoblastoma [2,9,12,13,15]. Furthermore, the staging of this disease according to the Reese–Ellsworth classification clearly demonstrates the second most important endpoint after survival: risk of loss of visual function [12,13].

Table 4
Estimated dose in 2 Gy per fraction (D_{eq}) for a given long-term probability p of developing retinopathy

p	D_{eq} (Gy)
0.5	61.7
0.37	56.8
0.05	41.9

Table 5
Comparison of present data with recently published series

Centre	Ref.	Year	Total dose (Gy)	Dose/Fr. (Gy)	No. eyes	Σ enucl.	Σ enucl. Toxicity
Philadelphia	2	1990	40–45	1.5–2.0	42	17*	0
Mayo Clinic	9	1989	45	1.8	25	5*	0
MSKCC	10	1988	38.5–50	2.0	121	5*	0
Utrecht	12	1985	45	3.0	54	10	5
Lausanne		1992	30–62	1.0–4.5	44	12	2

*All the enucleations mentioned are for progressive disease.

Treatment related complications after external irradiation of the eye in young children are bone growth retardation, cataract according to technique used and retinopathy [3,7,11]. The clinical picture of radiation retinopathy is characterized by the same features as diabetic retinopathy [11]. The pathological modification is an obstruction of small vessels with resulting ischemia, edema and neovascularisation of the optic disc [3,11]. Retinopathy never causes pain per se; however, if neovascularisation of the iris occurs, there will be some pain due to secondary angle closure. The delay of retinopathy after irradiation quoted from the literature, ranges from 17 months [3] to 2.5 years [11]. In our series the latency is shorter. In some of these cases of retinopathy, enucleation may be required. This can be considered a failure to reach the second most important endpoint in the treatment of retinoblastoma: conservation of visual function. Fortunately, enucleation for retinopathy is less frequent than enucleation for tumour recurrence [1,2,9,10].

The rather high frequency of enucleation for complications related to retinopathy in the present series (11% actuarial), raises the question of optimisation of treatment parameters (Table 5 for comparison with recently published data).

No enucleations for treatment-related complications were reported in the Philadelphia experience [2]. These patients were treated with a rather low dose (40–45 Gy) and a rather low dose per fraction (1.5–2 Gy). Enucleation for recurrence was done in 19 eyes. The same experience has been reported by the Mayo Clinic [9]. Ocular survival reached 80%. Enucleation was performed only for disease progression. However, visual acuity was impaired by cataract in 20% of the cases. The total dose and dose per fraction were, respectively, 45 Gy and 1.8 Gy. The 66 children (121 eyes) treated at MSKCC received a dose ranging from 38.5 to 50 Gy in 4–5 weeks at a daily dose of 2 Gy [10]. Enucleation was performed in 5 recurrences. It is noteworthy that there were no enucleations if patients were treated with lateral beam techniques. Enucleations were only performed for progressive disease, more frequently encountered if an anterior lens-sparing technique was used (local control rate 33% vs. 83%, $p = 0.006$).

It must be emphasized that some authors advocate enucleation if clinical evaluation of local control is impaired by lens opacification [7]. In the Utrecht series, 10 eyes of 54 were ultimately enucleated after radiotherapy. The radiotherapeutic treatment was applied by a lateral temporal technique with eye immobilisation [12,13]. The total dose was 45 Gy applied in 3 weekly fractions of 3 Gy per week. Fifty percent of those reported enucleations were done for extensive retinal detachment (5/10). Other reasons were rest tumor suspected at the optic disc (2/10), recurrent tumor (1/10) and a new tumor localisation outside previous irradiated area (2/10).

The dose per fraction effect is probably the only factor strongly enough related to retinopathy to be considered seriously, in view of the small number of events. No other patient- and treatment-related characteristics were significantly correlated with retinopathy. There was only a trend towards an increased complication ratio in cases of associated chemotherapy. This is probably due to the heterogeneity of the population and the variability of treatment parameters and the small number of events. Despite the small number (10) of events, the association between increasing biological effect from increasing fraction size, and probability of retinopathy, is considered significant. This corresponds to consideration of retinopathy as highly sensitive to change in fraction size, a characteristic of late effects illustrated by the small α/β [14]. For local recurrence as an endpoint the relationship with number of sites per eye brought out by the Cox analysis must be viewed together with the marginal p-values and small (15) number of events.

The 88% actuarial survival and the 62% actuarial local control at 10 years are in the range of published data [1,2,5,7,9,10–13,15]. However, optimisation is mandatory in order to reduce the incidence of treatment related retinopathy and hence frequency of enucleation for this late complication. The sigmoid dose-response curve being steep between 50 and 60 Gy [11], the recommended dose in our department is 50 Gy using a standard fractionation of 2 Gy per fraction, 5 fractions per week. However, according to the model for D_{eq} as a function of p (see above), the predicted probability of retinopathy for a standard schedule (50 Gy in 25 frac-

tions) would be 19%. In order to reduce this probability of late complications, a hyperfractionated schedule is discussed in our department. The main problem will be the repeated anesthesia and hence nutritional problems in these very young children.

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