Radiation compromised survival of patients with heritable retinoblastoma (H1): what will be the long-term consequences of current eye salvage therapies?

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Temming and colleagues (1) present important data from the German national retinoblastoma reference center (University Hospital Essen) confirming the previously observed (2) long-term very serious consequence of radiation treatment to save vision for children with heritable retinoblastoma: second cancers. The long-term overall survival of 633 patients with heritable retinoblastoma diagnosed between 1940 and 2008 was studied. Heritable retinoblastoma is initiated by constitutional mutation in the RB1 tumor suppressor gene, indicated as “H1” in the 8th edition of the TNMH cancer staging for retinoblastoma (3).

Most of the children (93%) had bilateral disease, while 7% were unilaterally affected and shown to be H1 by a close relative or genetic testing. No child with heritable unilateral retinoblastoma died as a result of a second cancer, compared to 9% of bilaterally affected patients. This may suggest that carriers of a reduced expressivity/penetrance RB1 mutation also have fewer second cancers.

Survival was significantly worse for persons with heritable retinoblastoma (93% at 5 years and 80% at 40 years) than for those with unilateral, non-familial retinoblastoma. With overall median follow-up from diagnosis to last clinical appointment or time of death of 21.5 years, 110/633 H1 patients died. Within 5 years of retinoblastoma diagnosis, 44/633 children died due to retinoblastoma related deaths (metastasis or treatment related). However, 53 patients died later from second cancers, and 13 died of other causes.

Most of the second cancers were sarcomas in patients who had received external beam radiotherapy (EBRT) to salvage an eye(s). EBRT was significantly associated with an all-cause mortality hazard ratio of 2.96. Compared with enucleation or focal therapy, overall survival was decreased significantly following EBRT and even more following EBRT combined with chemotherapy. There was no significant difference in overall mortality for patients treated with enucleation or focal therapy, versus chemotherapy alone. However, systemic chemotherapy to treat intraocular retinoblastoma is not adequate to completely control intraocular retinoblastoma, and these patients likely had both systemic chemotherapy and focal therapy, although not mentioned in the paper. Eye salvage was 63% for eyes treated with chemotherapy (presumed with focal therapy), compared with focal treatment only (53%), EBRT (56%), and worst for EBRT plus chemotherapy (48%).

The title “How eye-preserving therapy affects long-term overall survival in heritable retinoblastoma survivors” is ambiguous and dangerously might be interpreted to suggest that eye-preserving therapy improves overall long-term survival.

The patients included in this retrospective analysis were predominantly treated with EBRT, starting in the
1960’s when Ellsworth promoted radiotherapy as the best therapy: “Radiotherapy is by far the most valuable weapon against retinoblastoma” (4). EBRT was replaced by systemic chemoreduction with focal consolidation (5), in the 1990’s, when the epidemic of second cancer in H1 retinoblastoma patients was finally recognized. Temming et al. show that systemic chemotherapy (with focal therapy consolidation) is not associated with shortened survival.

Today, in 2017, we are faced with a new therapy, intra-arterial chemotherapy (IAC), not available in the time frame of Temming’s study (6). However, IAC is burdened with a confusing literature of widespread duplicate publication of individual patients and conflicting systems to stage intraocular retinoblastoma (3,7). Without interpretable data for safety or efficacy, IAC is now widely promoted to replace enucleation for many children: “Intra-arterial chemotherapy has transformed the treatment of intraocular retinoblastoma...” (8). The potential long-term outcomes of IAC for long term survival and vision are rarely discussed.

Temming et al. state well the major issue for retinoblastoma children: “…in determining eye-preserving therapy for children with heritable retinoblastoma, long-term adverse effects and the negative impact on overall survival need to be balanced with the decision to preserve vision and the choice of eye-preserving treatment.” The long-term impact on survival of patients with heritable retinoblastoma is important to evaluate prospectively, since the excitement of a new therapy to attempt eye salvage may lead to future harm. Saving life is the priority of retinoblastoma treatment, followed by vision salvage; the least important is eye salvage. The child deserves the opportunity to enjoy a healthy life, and the many procedures and their complications that may span years for at best a 50% chance to save a blind eye with risk of tumor spread, are poorly justified, and can endanger life and compromise quality of life socially, economically and psychologically, especially when the other eye is normal (9,10).

Often missing from choices in the complex care of children with retinoblastoma are the truly informed parents. In the absence of a strong evidence base for retinoblastoma treatment, essentially the doctors decide what treatment they “feel” is best, and offer little else to parents and guardians. There are many undocumented and usually ignored true “costs” of each treatment: the burden of invasive therapies and potential undiscovered complications; the imposition of hours and days in hospitals and feeling ill on the child, whose real job in those critical, irreplaceable years, is play; the true financial costs including time off work, uncertainties; and the burden of “false hope” in the absence of real evidence. There are imminent solutions on the horizon, such as DePICTRB (11) encompassing the whole medical record for a lifetime with retinoblastoma, viewable on line by the family and patient, and the burgeoning field of patient reported outcomes. New attitudes and tools may in the future empower good choices by parents for their child and family.

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Footnote

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