Guest Editorial

Radiation therapy for exudative choroidal hemangioma

A case of exudative circumscribed choroidal hemangioma successfully treated with CyberKnife® stereotactic radiosurgery is presented in this issue.[1] It was reasonable to assume Cyberknife ® would be effective because ionizing radiation causes a progressive, obliterative vasculitis secondary to destruction of vascular endothelial cell and pericytes.[2] At least 15 exudative circumscribed choroidal hemangiomas have been successfully CyberKnife® irradiated.[3-8] In each case, both the tumor and its exudative retinal detachment have regressed. Most reported no significant complications with relatively short follow up. However, this issues' CyberKnife® report prompted me to abstract what we know about radiation therapy for exudative choroidal hemangioma, compare it to laser therapies and comment on how we may decide which treatment is the "best" treatment.

Pathophysiology of Choroidal Hemangioma

It is important to consider the pathophysiology of the targeted tissue.[9] Uveal hemangiomas (circumscribed and diffuse) are typically comprised of combinations of capillary proliferations and cavernous vascular components. Circumscribed hemangioma margins also demonstrate tissue compression with non-reactive melanocyte proliferation seen as a ring of pigmentation at its margins. The tumor also has a tendency to blend into the adjacent normal appearing uvea. The choriocapillaris commonly appears as sclerotic, obliterated and in some cases calcified (ossified). The overlying retinal pigment epithelium can demonstrate atrophy, sclerosis, proliferation and drusen formation. Breakdown of Bruch's membrane and the retinal pigment epithelium has been associated with findings of lipofuscin deposition, intraretinal fluid (cystoid degeneration), and subretinal fluid (exudative retinal detachment).[9] This analysis points out that hemangiomas offer innumerable vascular targets for both focal laser treatments and the more generalized obliterative vasculitis typically induced by radiation therapy.

Laser versus Radiation Therapy

Thermal Laser

Over the last six decades, thermal ophthalmic xenon-arc, argon, krypton, and infrared "TTT" laser have been used to treat uveal hemangiomas and their secondary retinal detachments.[10-14] However, there exists many weaknesses to this approach: each laser has a relatively small spot size and variable ability to penetrate tissue. Further, penetration is dependent on tissue pigmentation, tissue sclerosis and calcifications as found in choroidal hemangiomas.[9] These tissues (particularly pigment) blocks and absorbs the light and prevents treatment of subjacent tissues. Last, no laser can effectively address tumor invasion of the sclera.

Thermal laser side-effects have been reported to include: large scotomas, choroidal neovascularization, vascular occlusions, retinal hemorrhage, pre-retinal fibrosis, and cystoid macular edema.[10-14] Thermal laser has been reported to be effective in treatment of 50% of circumscribed choroidal hemangiomas and retreatment increases the incidence of the aforementioned complications.[10-14]

PDT Laser

Photodynamic therapy (PDT) was the next generation of laser therapy.[11-13] Unlike the prior "thermal" lasers, this procedure utilizes cold laser beam to photo-activate a systemically administered, light sensitive dye within the tumor. Limited to transpupillary delivery, the cold-laser is directed through a dilated pupil into the dye-laden choroidal hemangioma to create singlet oxygen to destroy tumor blood vessels. Reports on its use suggest 73–100% resolution of exudative retinal detachments.[11-13] However, like prior thermal laser therapies, PDT requires transpupillary laser delivery. Such delivery works best for small to moderately sized, posteriorly located (easily visualized) choroidal tumors in eyes with clear media (cornea, lens and vitreous) and no overlying retinal detachment. Visualization of the tumor is a requirement for all lasers (hot and cold).

Radiation Therapy

In contrast, the most widely available linear accelerator (LINAC) generated radiation therapy treatment volume can uniformly include the entire tumor and a free-margin.[15-19] External beam radiation therapy (EBRT) does not require real-time tumor visualization as does laser. LINAC-generated EBRT can uniformly treat sections of or the entire eye as needed for circumscribed or diffuse uveal hemangiomas, respectively.[15]

Another difference includes the speed of treatment. In The New York Eye Cancer Center a low dose of 16–20 Gy is typically used to treat uveal hemangiomas. Thus, at 200 cGy per day, 6MV photon LINAC-based radiation can be completed within 8–10 days. In my experience, such irradiations typically result in permanent regression of exudative retinal detachments, thinning of the hemangioma and no vision limiting side effects. In contrast, PDT-laser typically involves multiple monthly sessions with generally slower resolution of tumor-related retinal detachments.

Radiation: Ready, Shoot, Aim?

Like laser, therapeutic radiation has a long history of innovation leading to many types of sources and methods of radiation delivery. In ophthalmology, ophthalmic irradiation most commonly involves the use of a LINAC generated photon-based EBRT

for uveal metastasis and radioactive plaque implants for choroidal melanoma.[15] However, consider that there exists: electrons, X-rays, photons, charged-particles, neutrons as well as ruthenium-106, iodine-125, palladium-103, cesium-131, iridium-192, strontium-90, and others.[15-22]

In the absence of medical evidence suggesting differential toxicity or case-matched efficacy, most of these types of radiation therapy have been randomly employed to treat exudative circumscribed choroidal hemangiomas.

The Ophthalmic Oncology Task Force that developed consensus guidelines for plaque brachytherapy of uveal melanoma and retinoblastoma for the American Brachytherapy Society decided to suggest comparative radiation dosimetry studies for each patient prior to selection of radiation modalities.[23] So let's take a moment to compare the more generalized dose distribution characteristics of commonly used radiation therapy modalities.

Teletherapy versus Brachytherapy

Teletherapy involves delivering radiation from an external source, as to transit the eye to the tumor. In contrast, brachytherapy involves inserting the radiation source within the patient into or next to the tumor.[20] However, I prefer LINAC generated teletherapy 6 MV photons for posterior choroidal hemangiomas because this modality offers the most homogeneous dose to the eye, tumor and orbit. In that the dose required to control hemangiomas is low (<20 Gy), LINAC generated photons are unlikely to cause significant side-effects (other than cataract and a mild dry eye). If possible, techniques exist to avoid irradiating the lens. Lastly, for younger patients there exists a very small, long-term risk of radiation oncogenesis.

Other forms of teletherapy (e.g., charged particles, Cyberknife®) deposit higher doses of radiation as it enters the eye (entry dose) and travels toward and into the tumor.[15] These high dose rate forms of teletherapy are analogous to fixed and more focused columns of radiation traversing the eye into the tumor. While in theory these more focused forms of teletherapy should limit dose to normal ocular structures, in practice we must take into account that the relatively strong beams are more susceptible to mis-application caused by eye-movements during treatment.[9,10,15]

In contrast, episcleral brachytherapy plaques are surgically attached to the eye beneath the tumor.[23] As the eye tumor moves, so does the eye plaque, making the radiation less susceptible to eye movement induced geographic miss. In addition, unlike teletherapy, the entry dose is through (limited to) the radiation resistant sclera. However, plaques sources are characterized by their base to apex "dose-gradient" where the base of the tumor (and surrounding tissues) can receive many times the apex dose."[23] Thus, the dose gradient is important in treatment of posterior intraocular tumors where the choroid, retina, and optic nerve are in close proximity to the eye plaque.

As compared to LINAC-based EBRT, plaque treatment of posterior choroidal hemangioma may increase the patients' risk for radiation retinopathy or optic neuropathy. Conversely, in treatment of anterior tumors, the posterior segment may receive less. This is one example where pre-treatment comparative dosimetry will clarify which modality offers the least risk.

Conclusion

Exudative circumscribed choroidal hemangioma are poor candidates for thermal laser treatment. PDT and radiation therapy are more likely to induce sustained regression of secondary retinal detachments and do not typically cause the aforementioned thermal laser-associated, vision-risking chorioretinal complications. PDT requires one or more systemic injections of a photosensitizing dye and the PDT-laser requires visualization of the tumor. In comparison, the literature suggests that the <20 Gy radiation doses required to effectively treat leaking choroidal hemangioma are likely to be both effective and well tolerated. However, each radiation therapy source is characterized by a unique ocular, periocular, and orbital dose distributions. In that we do not (as yet) have comparative evidence from clinical trials or side-effects registries, eye tumor specialists should perform comparative dosimetry studies to determine which offers the best dose to critical ocular, adnexal, and orbital structures.

Paul T Finger

The New York Eye Cancer Center, New York City, New York, USA.
E-mail: pfinger@eyecancer.com

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About the author

Paul T. Finger, MD, NYU Clinical Professor and Director of The New York Eye Cancer Center and Ocular Tumor Services at New York University and The New York Eye and Ear Infirmary of Mt. Sinai in the USA. He has served 2 terms as Ophthalmic Oncology Chair of the American Joint Committee on Cancer (AJCC-UICC) which developed the first and most widely used consensus staging system for ocular cancers. He Chaired The American Brachytherapy Society (ABS) Committee that provided consensus guidelines for ophthalmic plaque brachytherapy and was on the American Association of Physicists in Medicine (AAPM) Task Group-129 for ophthalmic brachytherapy dosimetry and quality assurance.