Video training to replace sedation for pediatric patients

The PROMISE grant funded by the Cancer Prevention and Research Institute of Texas (CPRIT) aims to reduce the risk of treating cancer patients under age 7.
Currently, most pediatric cancer patients under age 7 receive daily general anesthesia during radiation treatment to ensure they remain still. The long-held consensus has been that children, being naturally active, are not able to self-regulate their movements long enough to receive a radiation treatment that depends on precise targeting. “This is not ideal, as a child can be sedated as many as 30 times in succession, which could potentially have side effects, both short- and long-term,” says Steve Jiang, Ph.D., Professor and Vice Chair of Radiation Oncology and director of the Medical Physics and Engineering Division. Dr. Jiang was recently the recipient of a $900,000 CPRIT grant for his project, "Pediatric Radiation Oncology with Movie-Induced Sedation Effect (PROMISE).” PROMISE proposes to enable non-sedated pediatric radiotherapy using a combination of behavior training and motion monitoring. "If you’ve ever watched a child watching television, you’ll notice how an active, restless kid can suddenly become immobile when they’re watching something they’re interested in," says Dr. Jiang. PROMISE principal investigator. “This gave us the idea to incorporate video into the treatment process.” Prior to receiving treatment, the young patients will be trained to remain still by watching a training video projected onto the ceiling of the treatment room. A surface coordinate video surveillance system (Vision RT) that beams a grid of light on the patient will monitor patient motion and provide feedback by pausing the movie when the patient moves. If the child reverts to his or her treatment position within a predetermined period of time (such as one minute), the movie resumes. The idea is to create a sort of game for the patients, with increasing levels of time spent in stillness based on both positive feedback (tokens for different levels achieved) and negative feedback (the movie cut off). Once a child successfully undergoes training and is deemed eligible to receive radiation without anesthesia, he or she will be allowed to watch an age-appropriate movie during treatment. Vision RT will continue to monitor patient motion and shut off the beam automatically if the patient moves outside of defined parameters. Video feedback is not new in radiation therapy and has previously been useful for coaching adult patients in how to breathe for breast and lung cancer treatments. The PROMISE proposal calls for an initial 20 patients, ages 3 to 7, to be treated with this method within the framework of a clinical trial. “If proven successful, PROMISE could eliminate the safety risk of giving multiple episodes of anesthesia for pediatric patients.”

Single-fraction CyberKnife for breast cancer

UT Southwestern has opened a clinical trial to offer a single treatment of CyberKnife for patients with early-stage breast cancer. The trial is part of an ongoing effort at UT Southwestern Radiation Oncology to find alternative strategies for partial-bread irradiation. An earlier study (presented last year at the American Society of Clinical Oncology annual meeting) used the CyberKnife in five treatments to deliver 40 Gy to patients. “Results have been promising thus far in our five-fraction trial,” says Asal Rahimi, M.D., Assistant Professor of Radiation Oncology and the study’s principal investigator. “There were no recurrences and cosmetic results were good to excellent in a majority of patients, so this served as a guide for us to further extend the principal with a single-treatment regimen.”

The additional benefits of SBRT include convenience (when compared to a three- to six-week course of standard radiation), wide-scale availability among different providers in various practice settings (over intraoperative therapy), ability to prescribe full prescription doses to the clinical target volume, and non-invasiveness. The dose escalation study will begin at 22.5 Gy and increase incrementally to 30 Gy.

Research shows 98% cure rate for prostate cancer using SBRT

A five-year study shows that stereotactic body radiation therapy (SBRT) to treat prostate cancer offers a higher cure rate than more traditional approaches, according to researchers here. The study found a 98.6 percent cure rate with SBRT, a form of radiation treatment that involves high-dose radiation beams entering the body through various angles and interacting at the desired target. “The high cure rate is striking when compared to the reported five-year cure rates from other approaches such as surgery or conventional radiation, which range between 80 to 90 percent, while the side effects of this treatment are comparable to other types of treatment,” says Raquibul Hannan, M.D., Assistant Professor of Radiation Oncology and lead author of the study.

UT Southwestern served as the lead site for the multi-institutional clinical trial, which involved first-time prostate cancer patients diagnosed with stage I or stage II prostate cancer. A total of 91 patients were treated prospectively and followed for five years, with only one patient experiencing a recurrence of his cancer. The findings are published in the European Journal of Cancer.
Faculty awards

* UT Southwestern researchers have been awarded $3.6 million in NASA funds to study how space radiation would affect the cancer risk of astronauts taking part in deep space missions to Mars.

Sandep Burma, Ph.D. Associate Professor of Radiation Oncology, will examine the increased risk of glioblastoma following exposure to particle radiation.

“We’ve known for a long time that exposure to radiation causes cancer, but the radiation we have experience with here on Earth is different from that in space,” said Dr. Burma. “It’s a long haul to Mars – three years there and back – and astronauts would be exposed to a lot of space radiation, so it’s important that we understand how this exposure would affect them.”

* The Cancer Prevention and Research Institute of Texas (CPRIT) has awarded two more grants to radiology oncology faculty this spring.

Assistant Professor Asaithamby Aroumougame, Ph.D., is co-principal investigator of the project “Effect of Chest Radiation Therapy on Cardiomyocyte Turnover, ” which was funded with $897,570.

Assistant Professor Raquelb Hanann, M.D., has been awarded a four-year American Cancer Society Research Scholar Grant of $971,000 for his project “Image-guided Stereotactic Radiation Therapy of Primary Renal Cancer.” The funds will be used to support a Phase II clinical trial that uses innovative motion modeling and imaging for tumor targeting.

Department announces heavy ion seed grants

The Department of Radiation Oncology has awarded five, two-year seed grants of $100,000 to Texas researchers to facilitate research related to heavy ion therapy. The seed grants are part of UT Southwestern’s effort to launch a National Particle Therapy Research Center here.

The selected projects include:

- “Exploiting hadron therapy differential DNA damage for radioprotection and radiosensitization” by Gabriel O. Sawakuchi, M.D., Ph.D., MD Anderson Cancer Center
- “Analysis and Preprocessing of Single Proton/ Ion Tracks for Clinical Imaging” by Keith Schubert, Ph.D., Baylor University
- “Prompt gamma imaging for range verification and dose monitoring of carbon ion therapy” by Mingjun Jin, Ph.D., UT Arlington
- “Preliminary study of PET image-based on-linear beam range-verification and delivery” by Yiping Shao, Ph.D., UT Southwestern Medical Center
- “Neutron detector array for monitoring neutrons generated during heavy ion therapy” by Bruce. E. Ginade, Ph.D., UT Dallas

Clinical Trials

**BRAIN**

022015-106 A phase I dose-escalation study of stereotactic ablative radiotherapy for brain metastases with whole brain radiation

032015-001 Randomized phase II trial of hyperfractionated-dose stereotactic radiosurgery (SRS) for newly diagnosed glioblastoma

042011-071 Interstitial radiotherapy implants for the treatment of recurrent glioblastoma multiforme

043011-050 Phase II trial of Hyperfractionated whole brain irradiation with simultaneous integrated boost for treatment of brain metastases

**Chest Radiation Therapy**

Bruce E. Gnade, Ph.D., is co-PI of a $900,000 grant to study how this exposure would affect them.

**GASTROINTESTINAL**

032012-025 Polypholganilide-targeting antibody bispecific in combination with capecitabine and cetuximab for treatment of stage II/IIO rectal adenocarcinoma

**GENITOURINARY**

032014-004 The DTA study randomized Decisions for Endorsement Therapy (AD) prospective, single-arm cohort study of patients receiving endocrine therapy alone (without radiotherapy) after breast cancer surgery for early-stage, post-menopausal breast cancer

**SPINE**

072013-038 A phase III trial of stereotactic body radiation therapy (SBRT) plus maintenance chemotherapy for stage IV non-small cell lung cancer (NSCLC).

072013-023 A phase III trial of stereotactic body radiation therapy (SBRT) plus maintenance chemotherapy for stage IV non-small cell lung cancer (NSCLC).

072013-012 A phase III trial of stereotactic body radiation therapy (SBRT) plus maintenance chemotherapy for stage IV non-small cell lung cancer (NSCLC).

For more information, please contact Clinical Research Manager Jean Wu at 214-633-1753 or jean.wu@utsouthwestern.edu
Management of Choroidal Melanoma

By Michael R. Folkert, M.D., Ph.D., Assistant Professor of Radiation Oncology, UT Southwestern Medical Center

After completing this activity, the participant should be better able to:

• Identify the types of patients at risk for developing choroidal melanoma and describe the necessary workup and staging for choroidal melanoma.

• Understand the basis for conservative (eye-preserving) management of choroidal melanoma.

• Describe the treatment options available for choroidal melanoma, including external photon beam, brachytherapy, and charged particle options.

Introduction

It is estimated that there will be 2,810 new cases of malignancy of the eye and 1,910 deaths from eye diseases1 of these, the most common primary intracocular malignancy is uveal melanoma, a malignancy arising from melanocytes of the uveal tract, account for approximately 60-80 percent of new presentations each year. Choroidal melanoma is the largest subsite of uveal melanoma, which also includes melanoma malignancies arising from the iris or the ciliary body. The choroid is a pigmented layer of the eye. Melanoma arising from the choroid is a relatively rare disease that previously was treated with enucleation, or removal of the eye.2 The mean age of diagnosis for ocular melanoma is 60, and men and women are equally affected. There is a predilection for occurrence in fair-skinned and light-eyed (blue irides more than brown irides) patients, and the disease is almost always unilateral. Dysplastic nevi syndrome may predispose to melanoma. The majority of choroidal melanomas present with painless loss or distortion of vision, but lesions that cause detachment of the retina may be associated with visual symptoms such as flashing lights, and eye pain can rarely be a presenting symptom.3 The diagnosis of choroidal is primarily clinical, made by an experienced ophthalmologist. With direct or indirect ophthalmoscopy, subretinal fluid or orange pigment may be noted, and serial exams may document growth; therefore, all suspect a malignant lesion. Ocular ultrasound is a key diagnostic study. A-scans are one-dimensional scans that identify material structure of the globe, and low internal reflectivity is associated with malignant melanoma; B-scans are two-dimensional scans that document shape and size factors, such as the oft-described “collar button” or mushroom appearance that indicates disruption of Bruch’s membrane and is associated with malignant melanoma. Additionally, B-scans can identify retinal detachment and the presence of subretinal fluid and detect orbital extension. Any lesion ≥3 mm in height is most likely a melanoma. The official staging systems by the Collaborative Ocular Melanoma Study (COMS) and American Joint Committee on Cancer (AJCC) are presented in Table 1.4 Choroidal melanoma is usually localized to the globe on presentation. All patients with choroidal melanoma must undergo cross-sectional imaging of the abdomen, not just liver function tests, as the primary site of spread for the disease is to the liver (>90 percent of all metastases). Liver function tests (LFTs) and abdominal ultrasound do not have sufficient sensitivity to detect small lesions in the liver. FDG-PET imaging is reasonable due to the avidity of melanoma but may miss small lesions; either triphasic contrast-enhanced CT or MR imaging is optimal for metastasis screening.5

Treatment by stage

The COMS Group conducted a series of studies from 1986-2003 to find the optimal treatment for ocular melanomas at various points in the disease process. The COMS Medium trial was a pivotal study that proved conservative eye-preserving therapy is a viable treatment option for patients presenting with relatively early-stage choroidal melanomas.6 In that trial, 1,317 patients with unilateral choroidal melanoma 2.5-10 mm in height and up to 16 mm in diameter were randomized to enucleation or iodine-125 (125I) plaque brachytherapy. Outcomes at 12 years showed no significant difference; mortality was 41 percent in the enucleation group and 43 percent in the 125I plaque group, and 17 percent had developed distant metastases in the enucleation group vs. 21 percent in the 125I plaque group. In the companion quality-of-life study, 125I plaque brachytherapy was associated with better visual function for driving peripheral vision, although increased anxiety was present.7 The final report did not provide details on local control, but an earlier report provided an enucleation rate of 12 percent at five years, due to recurrence and/or symptoms.8 Outcomes for multiple institutional studies using epidermal plaque brachytherapy were summarized in the American Brachytherapy Society (ABS) report on brachytherapy for uveal melanoma,9 five-year local control for 125I-based plaque brachytherapy ranged from 81-92 percent. For patients with larger lesions, the role of radiation therapy is less clear. In the COMS Large Choroidal Melanoma trial,10 1,003 patients with larger lesions (either ≥16 mm in basal diameter or ≥10 mm in height, or ≥8 mm in height and ≥2 mm of the optic disc) were randomized to enucleation or enucleation plus external beam radiation therapy (a prescribed dose of 20 Gy in 5 daily fractions of 4 Gy per fraction). Outcomes were not improved with additional radiation therapy; 10-year mortality was 61 percent for both arms, and rates of metastases were unchanged. It should be noted that the doses used in this study were very low, and doses above 4 Gy per fraction are generally recommended as melanoma is considered to be relatively radiation-insensitive.11 Adjuvant dosing schedules for melanoma are generally much higher (on the order of 48 Gy in 20 fractions, or 30-36 Gy in 5-7 fractions).12,13 While an increased dose theoretically may have yielded superior outcomes, such high doses would likely result in unacceptable toxicity when administered to the orbit. Small lesions (1-3 mm in height and at least 5 mm in basal diameter) are generally enucleated. In the COMS Small Choroidal Melanoma Observational Study, 204 patients were followed and were noted to have only a 1 percent metastasis-specific survival rate in 12 years.14 These patients can be followed with periodic photos of the fundus and ultrasound imaging. Patients with orange pigment, absence of drusen (yellow, lipid-rich deposits between Bruch’s membrane and the retinal pigment epithelium [RPE] of the eye) or absence of changes in RPE near the lesion, and larger size are associated with increased likelihood of growth.15 Several risk factors for progression have been identified, including tumor thickness ≥2 mm, the posterior margin touching the optic disc, visual symptoms, orange pigment, or subretinal fluid.16 The presence of even one of these symptoms predicts growth in 36 percent of patients, increasing to 50 percent for patients with three factors.

Eye plaque brachytherapy procedure

While the COMS study used 125I-based plaques, a variety of radioactive isotoes may be used. “High energy” plaques include 60Co (which emits 1.17 and 1.33 MeV gamma rays) and 106Ru (which emits 36 keV beta-particles). “Low energy” plaques include the standard 125I source (which emits 35 keV photons) and the 103Pd source (which emits 21 keV photons). Plaque material is fabricated to deliver a dose of 75-85 Gy to the apex of the intracocular tumor, with a 2 mm margin all around the tumor (such that a 10 mm diameter tumor would be treated with a 14 mm diameter plaque). (Figure 1) Per American Brachytherapy Society (ABS) recommendations, the minimum dose to the apex of the tumor should be 85 Gy, with a dose rate of 0.6-0.85 Gy/hour when using a 125I-based plaque.17 Patients with gross extracocular extension, ring melanoma, involvement of the irides, and significant involvement of the ciliary body (>3) are not suitable for plaque brachytherapy. Plaque placement is generally performed under general anesthesia. After the conjunctiva is reflected, the choroidal lesion is localized by intraoperative ultrasound, transillumination (most effective for pigmented lesions), and/or indirect ophthalmology. Many practitioners first place a nonradioactive “dummy” plaque of identical size and shape to the brachytherapy plaque over the site to confirm coverage and then place sutures that can be used to quickly secure the actual plaque in position (reducing radiation exposure to the ophthalmic surgeon). The plaque can be necessary to sever the lateral rectus muscles or other extraocular muscles to ensure adequate placement. The plaque remains in position for three to seven days (generally three). Shorter placement times are associated with increased toxicity while longer placement times are inconvenient to the patient, increase the risk of infection, and potentially compromise successful reimplantation of extracocular muscles if severed for placement. Adequate treatment is defined as no tumor growth or reduction in size. Surveillance following treatment includes regular ophthalmic follow-up, imaging of the liver (CT or MRI), and LFTs at scheduled intervals. The complications of plaque brachytherapy are well-characterized. Early complications include bleeding, infec-
tion, and diplopia (especially if an extracocular muscle such as the lateral rectus is temporarily severed). Late complications include radiation retinopathy (42 percent at five years), cataracts, optic neuropathy, and keratitis. For all patients treated with COMS-style 125I-based plaque brachytherapy, regardless of baseline visual acuity, five-year visual acuity was <20/200 in 63 percent of treated patients, and <5/200 in 45 percent of treated patients. Five years after 125I-based plaque brachytherapy, the rate of enucleation is 12 percent due to recurrence and/or ocular toxicity.12

**Alternative eye-preserving therapy options for choroidal melanoma**

While plaque brachytherapy is considered the standard of care, other therapies have been employed to good effect, including charged-particle therapy, proton-based stereotactic radiosurgery (Gamma Knife or CyberKnife), and ophthalmic interventional techniques for eye preservation. Proton beam radiation therapy for ocular melanoma also has a long history. In one of the largest series reported, Lane et al. presented long-term outcomes for 3,088 patients with uveal melanoma treated with proton beam from 1975 to 2005.13 At 15 years, all-cause mortality was 49 percent with melanoma-specific mortality of 24.6 percent. A recent review by Verma and Mehta examined 14 original investigations at 10 institutions utilizing proton beam therapy (dose ranges 50-70 CGE) for uveal melanoma and noted consistent findings across from the Harold C. Simmons oncology building under construction remarks given by UT Southwestern Comprehensive Cancer Center is going installed in the building, and in March a topping-out ceremony was held, with remarks given by UT Southwestern Medical Center President Daniel K. Podolsky, M.D.

**Adjuvant therapy options**

The predominant mode of disease progression for choroidal melanoma is distant metastasis; therefore, adjuvant therapy following definitive treatment of the primary disease is an area of active research. Poor prognostic factors that have been used to guide additional therapy include larger tumor diameter and thickness, ciliary body invasion, lesions arising near the fovea/macula, tumor invasion through the sclera, optic nerve invasion, and older age. Tissue is rarely available at initial diagnosis, but mixed or epithelioid histology and/or plasmacytoid nuclei, high mitotic rate, Ki-67 positivity, lymphoepithelial infiltration, monosomy of chromosome 3, additional copies of chromosome 8q, and codela-chromosomes 1 and 3 are also poor prognostic factors.17,18 Thus far, no adjuvant treatment has had any success. Interferon-a, bacillus Calmette-Guerin (BCG), and infusional fotemustine (an alkylating agent) have all been explored without benefit in terms of overall or progression-free survival: A range of trials incorporating tyrosine kinase inhibitors (sunitinib), HDAC inhibitors (valproic acid), and ALK inhibitors (crizotinib) for patients with high risk disease are concluding or underway. Immune checkpoint inhibitors in particular have increasing application in the treatment of melanoma, and their utility in the management of choroidal melanoma is under investigation.9

**CONCLUSION**

For medium-sized choroidal melanomas, or small choroidal melanomas with adverse features, conservative treatment with eye preservation should be the standard of care. For most patients, plaque brachytherapy is the simplest treatment, requiring only two operative visits (one for placement and one for removal), with flexible treatment times ranging from three to seven days. For patients with lesions near the optic nerve or anterior eye, stereotactic radiosurgical techniques may provide superior dosimetry: Charged-particle techniques (proton, helium ion, and others) are well-established and provide an alternative treatment option, and they have additional application to larger and/or recurrent tumors. Management of distant metastases is an area that still needs a great deal of work because a significant portion of patients will develop distant metastases, even in the setting of adequately treated local disease. Therapies that perhaps augment the systemic immune response to the malignant lesion may help to prevent early micrometastases from taking hold.9

**Construction update**

The new state-of-the-art radiation oncology building under construction across from the Harold C. Simmons Comprehensive Cancer Center is going up quickly! All structural steel has been installed in the building, and in March a topping-out ceremony was held, with remarks given by UT Southwestern Medical Center President Daniel K. Podolsky, M.D.

**Table 1. COMS and AJCC 2010 staging for melanomas of the choroid and ciliary body**

<table>
<thead>
<tr>
<th>COMS Stage</th>
<th>Apical height</th>
<th>Basal Diameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1: Tumor size category 1</td>
<td>≤ 3 mm</td>
<td>5 - 16 mm</td>
</tr>
<tr>
<td>T1a: size category 1 without both ciliary body involvement and extraocular extension</td>
<td>≤ 3 mm</td>
<td>5 - 16 mm</td>
</tr>
<tr>
<td>T1b: size category 1 with ciliary body involvement</td>
<td>≤ 3 mm</td>
<td>5 - 16 mm</td>
</tr>
<tr>
<td>T3: Tumor size category 3</td>
<td>Any N1 or M1</td>
<td>Any tumor size category with extraocular extension &gt;5 mm in diameter</td>
</tr>
<tr>
<td>T3a: size category 3 without both ciliary body involvement and extraocular extension</td>
<td>Any tumor size category with extraocular extension &gt;5 mm in diameter</td>
<td></td>
</tr>
<tr>
<td>T3b: size category 3 with ciliary body involvement</td>
<td>Any tumor size category with extraocular extension &gt;5 mm in diameter</td>
<td></td>
</tr>
</tbody>
</table>

**Image:**

- **Figure:** Construction update.
- **Table:** COMS and AJCC 2010 staging for melanomas of the choroid and ciliary body.
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Physicians who would like to make a referral may call the Department’s main clinic number at 214-645-8525 or UT Southwestern’s physician referral line at 214-645-8300 (toll-free 866-645-5455) for adult patients, or 877-445-1234 for pediatric patients.

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