UT Southwestern

THE TARGET

News from the Department of Radiation Oncology

SUMMER 2016

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.

What's Inside

Page 1 story Video training to replace sedation for pediatric patients

Steve Jiang, Ph.D.

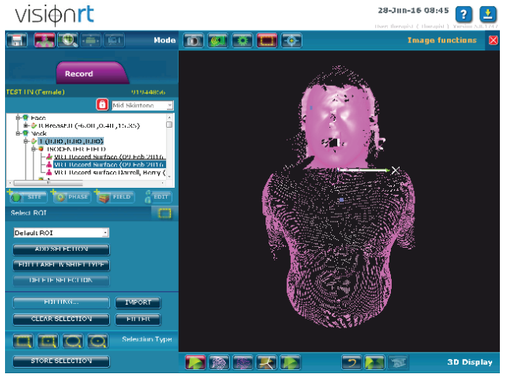
Currently, most pediatric cancer patients under age 7 receive daily general anesthesia during radiation treatment to ensure they remain still. The long-held consensus has been that children, being naturally active, are not able to self-regulate their movements long enough to receive a radiation treatment 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 strong 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 on 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.



Reference image acquired with Vision RT

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 cancer patients while also considerably lowering treatment costs," Dr. Jiang says.

UT Southwestern Radiation Oncology is a leading provider of cancer care to children in North Texas and serves as the primary treatment center for patients of Children's Medical Center in Dallas. Co-investigators in the PROMISE trial include Xuejun Gu, Ph.D.; Manish Vaidya, Ph.D.; Michael Folkert, M.D., Ph.D.; Ramzi Abdulrahman, M.D.; and Betsy Kennard, Psy.D.

Single-fraction CyberKnife for breast cancer

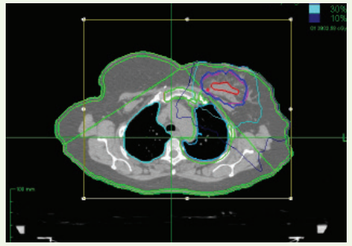
UT Southwestern has opened a clinical trial to offer a single treatment of CyberKnife for patients with early-stage breast cancer.

The trial is part of an ongoing effort at UT Southwestern Radiation Oncology to find alternative strategies for partial-breast 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.

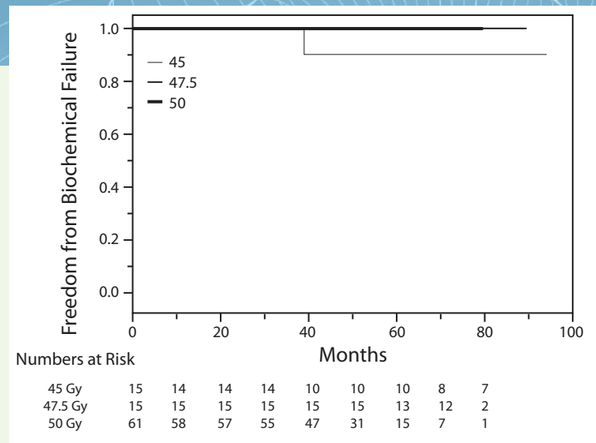
"Results have been promising thus far in our five-fraction trial," says Asal Rahimi, M.D., Assistant Professor of Radiation Oncology and the study's principal investigator. "There were no recurrences and cosmetic results were good to excellent in a majority of patients, so this served as a guide for 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 practices (over intraoperative therapy), ability to prescribe full prescription doses to the clinical target volume, and noninvasiveness.

The dose escalation study will begin at 22.5 Gy and increase incrementally to 30 Gy.



CyberKnife breast plan



A single biochemical failure was observed in the 45 Gy arm after 3 years

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 intersecting 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*.

Select Publications

Bhattacharya S and **Asaithamby A**. Ionizing radiation and heart risks. *Semin Cell Dev Biol*. 2016 Feb 2.

Hutchinson R, Sundaram V, **Folkert M**, **Lotan Y**. Decision analysis model evaluating the cost of a temporary hydrogel rectal spacer before prostate radiation therapy to reduce the incidence of rectal complications. *Urol Oncol*. 2016 Mar 30. (Epub)

Laine AM, **Pompos A**, **Timmerman R**, **Jiang S**, **Story MD**, Pistenmaa D, **Choy H**. The role of hypofractionated radiation therapy with photons, protons, and heavy ions for treating extracranial lesions. *Front Oncol*. 2016 Jan 11;5:302.

Skinner HD, Giri U, Yang L, Woo SH, **Story MD**, et al. Proteomic profiling identifies PTK2/FAK as a driver of radioresistance in HPV negative head and neck cancer. *Clin Cancer Res*. 2016 Apr 1. (Epub)

Westover KD, Jänne PA, Gray NS. Progress on covalent inhibition of KRASG12C. *Cancer Discov*. 2016 March 1;6:233.

Department News

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.

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

Sandeep Burma, Ph.D.

"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) made two more awards to radiation 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.

A majority of patients undergoing chest radiotherapy during adolescence and young adulthood develop fibrosis in the cardiac muscle and are six times more likely to develop heart failure. Dr. Aroumougame's lab has developed a novel method to study muscle cell turnover in the heart, to determine for the first time whether these late side effects are related to retarded muscle cell turnover.

Associate Professor Benjamin Chen, Ph.D., is co-PI of a $900,000 grant titled "DNA Damage-Induced Small Non-Coding RNAs: Mechanism and Their Role in Cancer Development."

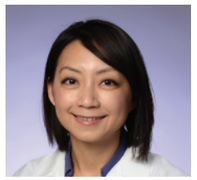
The study will examine how DNA damage triggers the production of small RNAs and how these small RNAs function to facilitate the DNA repair process.

* Assistant Professor Raquibul Hannan, M.D., has been awarded a four-year American Cancer Society Research Scholar Grant of $701,000 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.

New physics faculty

Mu-Han Lin, Ph.D., has joined the department faculty as Assistant Professor in the Division of Medical Physics and Engineering.

Dr. Lin earned her Ph.D. in medical physics at National Tsing Hua University, Taiwan, and completed her medical physics residency at Fox Chase Cancer Center. An award winning educator, her research has also received recognition at national meetings including American Society for Radiation Therapy (ASTRO) and the American Association of Physicists in Medicine (AAPM).



Mu-Han Lin, Ph.D.

Dr. Lin will serve as coordinator of treatment planning in the clinic, helping to bridge research and development with routine treatment planning. In addition to clinical implementation of new treatment technologies, her research interests include stereotactic radiotherapy and Monte Carlo-based simulation.

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" Gabriel O. Sawakuchi, M.D., Ph.D., MD Anderson Cancer Center
- "Analysis and Preprocessing of Single Proton/Ion Tracks for Clinical Imaging" Keith Schubert, Ph.D., Baylor University
- "Prompt gamma imaging for range verification and dose monitoring of carbon ion therapy" Mingwu Jin, Ph.D., UT Arlington
- "Preliminary study of PET image-based on-line beam range-verification and delivery" Yiping Shao, Ph.D., UT Southwestern Medical Center
- "Neutron detector array for monitoring neutrons generated during heavy ion therapy" Bruce E. Gnade, Ph.D., UT Dallas

Clinical Trials

BRAIN

022015-106 A phase I dose-escalation study of stereotactic radiosurgery for brain metastasis without whole brain radiation

NRG BN001 Randomized phase II trial of hypofractionated dose-escalated photon IMRT or proton beam therapy versus conventional photon irradiation with concomitant and adjuvant temozolomide in patients with newly diagnosed glioblastoma

042011-075 Interstitial radioactive iodine implants for the treatment of pan-invasive pituitary macroadenomas

042011-050 Phase II trial of hippocampal-avoiding whole brain irradiation with simultaneous integrated boost for treatment of brain metastases

BREAST

New– 052015-047 Intra-patient comparison of active breathing coordinator-based vs. Vision RT-based deep inspiration breath-hold for left chest wall irradiation, a pilot study for breast cancer

New– 062015-085 Phase I dose-escalation trial of single fraction adjuvant stereotactic body partial-breast irradiation (SB-PBI) for early-stage breast cancer

New– 112014-004 The IDEA study (Individualized Decisions for Endocrine therapy Alone): A prospective, single-arm cohort study of patients receiving endocrine therapy alone (without radiotherapy) after breast-conserving surgery for early-stage, post-menopausal breast cancer

GASTROINTESTINAL

032012-025 Phosphatidylserine-targeting antibody bavituximab in combination with capecitabine and radiation therapy for the treatment of stage II and III rectal adenocarcinoma

GENITOURINARY

New– NRG-GU001 Randomized phase II trial of postoperative adjuvant IMRT following cystectomy for T3/pT4 urothelial bladder cancer

062014-027 Phase I clinical trial of stereotactic ablative radiotherapy (SABR) of pelvis and prostate targets for patients with high-risk prostate cancer

022015-058 Safety lead-in phase II trial of neo-adjuvant SABR for IVC tumor thrombus in newly diagnosed RCC

092013-013 Phase II study of stereotactic ablative radiotherapy (SABR) for low-risk prostate cancer with injectable rectal spacer

RTOG 924 Androgen deprivation therapy and high-dose radiotherapy with or without whole-pelvic radiotherapy in unfavorable intermediate or favorable high-risk prostate cancer: A phase III randomized trial

122013-030 A phase II trial of stereotactic ablative body radiation therapy (SABR) for patients with primary renal cancer (RCC)

12013-041 A phase II trial of high-dose IL-2 and stereotactic ablative body radiation (SABR) for patients with metastatic clear cell renal cell cancer (mRCC)

102012-026 A phase II trial of sipuleucel-T and stereotactic ablative body radiation (SABR) for patients with metastatic castrate-resistant prostate cancer (mCRPC)

GYNECOLOGIC

082013-064 A phase II study for image-guided hypofractionated radiation boost therapy for definitive treatment of locally advanced cervical cancer

HEAD AND NECK

New– 062013-052 A phase I CyberKnife accelerated hemilarynx stereotactic radiotherapy study for early-stage glottis larynx cancer

052014-085 A phase I trial of stereotactic HYpofractionateD RadioAblative (HYDRA) treatment of advanced laryngeal cancer

112013-007 A phase I study of reduced-volume hypofractionated, PET-directed intensity modulated radiotherapy concurrent with weekly cisplatin chemotherapy for T1/NO-2 squamous cell carcinoma of the head and neck

NRG-HN001 Randomized phase II and phase III studies of individualized treatment for nasopharyngeal carcinoma based on biomarker Epstein Barr virus (EBV) deoxyribonucleic acid (DNA)

RTOG 0920 A phase III study of postoperative radiation therapy (IMRT) /- cetuximab for locally advanced resected head and neck cancer

LUNG

Small Cell Lung Cancer

CALGB 30610/RTOG 0538 A phase III comparison of thoracic radiotherapy regimes with cisplatin and etoposide in limited small cell lung cancer

Non-Small Cell Lung Cancer

022015-069 JoLT-Ca A randomized phase III study of sublobar resection (SR) versus stereotactic ablative radiotherapy (SABR) in high-risk patients with stage I non-small cell lung cancer (NSCLC), the Stablemates Trial

92013-070 Maintenance chemotherapy versus consolidative stereotactic body radiation therapy (SBRT) plus maintenance chemotherapy for stage IV non-small cell lung cancer (NSCLC): A randomized phase II trial

RTOG 1306 A randomized phase II study of individualized combined modality therapy for stage III non-small cell lung cancer (NSCLC)

062012-53 A randomized phase I/II study of nab-paclitaxel, or paclitaxel, plus carboplatin with concurrent radiation therapy followed by consolidation in patients with favorable-prognosis inoperable stage IIIA/B NSCLC

052011-093 Phase III randomized study of standard versus accelerated hypofractionated image-guided radiation therapy (IGRT) in patients with stage II/III non-small cell lung cancer and poor performance status

SPINE

New– 072015-013 Evaluation of targeted radiofrequency ablation and vertebral augmentation prior to or following radiation therapy to treat painful metastatic vertebral body tumor(s) (The STARTT Study)

072010-134 A phase II study of stereotactic body radiation therapy and vertebroplasty for localized spine metastasis

RTOG 0631 A phase II/III study of image-guided radiosurgery/SBRT for localized spine metastasis

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

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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 orbit in 2016 and 210 deaths from eye diseases;[1] of these, the most common primary intraocular malignancy is uveal melanoma, a malignancy arising from melanocytes of the uveal tract, accounting 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 often 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; these all suggest a malignant lesion. Ocular ultrasound is a key diagnostic study: A-scans are one-dimensional scans that identify material/acoustic properties, 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).[5] 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.[6]

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.[7]

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 and peripheral vision, although increased anxiety was present.[8] 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.[9] Outcomes for multiple institutional studies using episcleral plaque brachytherapy were summarized in the American Brachytherapy Society (ABS) report on brachytherapy for uveal melanoma;[10] 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,[11] 1,003 patients with larger lesions (either ≥16 mm in basal diameter or ≥10 mm in height, or ≥8 mm in height and within 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 radiation 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.[12] 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).[13-15] 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 observed. In the COMS Small Choroidal Melanoma Observational Study, 204 patients were followed and were noted to have only a 1 percent melanoma-specific mortality at five years.[16] 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.[17] 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.[18] 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 brachytherapy plaques, a variety of radioactive isotopes 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). Plaques are fabricated to deliver a dose of 75-85 Gy to the apex of the intraocular 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 0.6-1.05 Gy/hour when using an 125I-based plaque.[10] Patients with gross extrascleral extension, ring melanoma, involvement of the irides, and significant involvement of the ciliary body (>½) are not suitable for plaque brachytherapy.

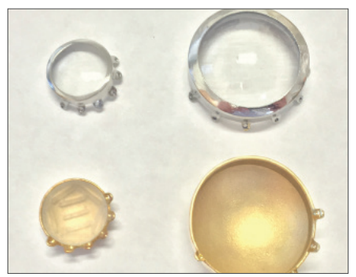

Figure 1. Example of "dummy plaques" (top row) and treatment plaques (bottom row) used for choroidal melanoma. Plaque on bottom left shows the silastic insert used to hold the 125I seeds.

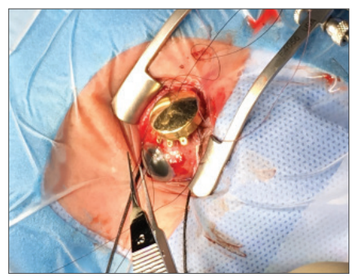

Figure 2. Treatment plaque secured in place.

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). (Figure 2) It may 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 extraocular 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 extraocular 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.[9]

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, photon-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 data for 3,088 patients with uveal melanoma treated with proton beams from 1975 to 2005.[19] 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 local control rates of >90 percent at five years, five-year enucleation rates between 7-10 percent, and good visual outcomes, with most patients retaining purposeful vision.[20] Proton beam radiation therapy has also been shown to be useful for salvage reirradiation.[21]

Photon-based stereotactic radiosurgery is a treatment option available at many centers that have specialized technology such as the Gamma Knife or CyberKnife for treating other diseases of the central nervous system. These techniques are helpful for treatment of lesions near the optic nerve or anterior eye, as plaque brachytherapy may have less utility in these anatomic subsites. Single fraction treatments with marginal doses of <25 Gy can be delivered with Gamma Knife radiosurgery (GK-SRS), with local control rates above 90 percent.[22]

While no direct comparison exists between GK-SRS and plaque brachytherapy, in a single-institution experience in the UK, 170 patients treated with GK-SRS (doses ranging from 35-70 Gy in a single fraction) were compared to 620 patients treated with enucleation.[23] No difference was found in survival, and in the least toxic treatment group receiving 35 Gy in a single fraction, only 6.5 percent proceeded to post-radiation enucleation. High-dose single fraction radiation therapy can be associated with acute swelling, which may require steroid management post-treatment.

Other nonradiation-based methods include transpupillary thermotherapy (TTT) using an infrared diode laser, photodynamic therapy (PDT), and laser photocoagulation.[24]

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 pleomorphic nucleoli, high mitotic rate, Ki-67 positivity, lymphocytic infiltration, monosomy of chromosome 3, additional copies of chromosome 8q, and codeletions in chromosome 1 and 3 are also poor prognostic factors.[27-29]

Thus far, no adjuvant treatment has had any success. Interferon-α, 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.[6]

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.

COMS Stage	Apical height	Basal Diameter
Small	<3 mm	5 - 16 mm
Medium	3 - 10 mm	5 - 16 mm
Large	>10 mm	>16 mm
Diffuse	Flat growth, thickness <20% basal dimension	
Metastic	Any N1 or M1	

T1: Tumor size category 1	T3: Tumor size category 3
T1a: size category 1 without both ciliary body involvement and extraocular extension	**T3a:** size category 3 without both ciliary body involvement and extraocular extension
T1b: size category 1 with ciliary body involvement	**T3b:** size category 3 with ciliary body involvement
T1c: size category 1 without ciliary body involvement with extraocular extension ≤5 mm	**T3c:** size category 3 without ciliary body involvement with extraocular extension ≤5 mm
T1d: size category 1 with ciliary body involvement and extraocular extension ≤5 mm	**T3d:** size category 3 with ciliary body involvement and extraocular extension ≤5 mm
T2: Tumor size category 2	**T4: Tumor size category 4**
T2a: size category 2 without both ciliary body involvement and extraocular extension	**T4a:** size category 4 without both ciliary body involvement and extraocular extension
T2b: size category 2 with ciliary body involvement	**T4b:** size category 4 with ciliary body involvement
T2c: size category 2 without ciliary body involvement with extraocular extension ≤5 mm	**T4c:** size category 4 without ciliary body involvement with extraocular extension ≤5 mm
T2d: size category 2 with ciliary body involvement and extraocular extension ≤5 mm	**T4d:** size category 4 with ciliary body involvement and extraocular extension ≤5 mm
	T4e: Any tumor size category with extraocular extension >5 mm in diameter

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

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.

Visit our webcam to watch real-time progress on the facility: oxblue.com/open/whitingturner/UTSRO.

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A kidney cancer cure with SABR

Ray Kebodeaux, 87, of Allen, Texas, is sitting on a black leather couch in his living room with a gray fox terrier settled against his legs. Across from him sits Dixie, his wife of 68 years. He jokes, "The two of us are about to get the kinks worked out. Maybe just another year or two and we'll finally get it."

A retired salesman, great-grandfather and avid reader with a fondness for humor, Ray is also a case study in cancer survival as one of the first patients at UT Southwestern Medical Center to receive a curative treatment of stereotactic ablative radiotherapy (SABR) for his renal cell cancer.

Mr. Kebodeaux had previously battled colon cancer in 2007, undergoing both chemotherapy and surgery to remove a portion of his colon. In 2012, during one of his regularly scheduled follow-up scans, doctors noted a new growth in his right kidney. After two years of observation, the spot began to grow rapidly and a biopsy determined that the growth was cancer.

While the good news was that his regular imaging studies caught the cancer early, the bad news was that Ray, because of his age and previous colon cancer treatment, was ineligible to have surgery, the option that normally cures early-stage, organ-confined renal cancer.

"Our doctor mentioned, almost as an afterthought, that there was a clinical trial open at UT Southwestern for SABR," recalls Mr. Kebodeaux. "He said, 'You might be a good candidate for that.'"

"We came home and discussed it with our kids and looked up SBRT on the internet," he continues. "I liked that it would exactly hit the cancer and not damage anything around it."

SBRT (also known as stereotactic body radiation therapy) uses advanced technology to target and track the tumor location, enabling physicians to give higher doses precisely to the target with greater curative potential than standard radiation.

The trial at UT Southwestern is one of the first in the U.S. to use SABR for the purpose of actually curing early-stage renal cancer. Kidney cancer is considered a radiation-resistant cancer, and therefore radiation has historically been used only rarely to relieve symptoms when surgery is unavailable or unsuccessful, rather than to cure. But evidence now suggests that the higher individual radiation doses given with SABR may overcome renal cell resistance to radiation therapy.

Ray Kebodeaux

"The main reason SABR hasn't been used in the past to treat kidney cancer is because the kidney moves with breathing – it's a moving target," says Raquibul Hannan, M.D., Ph.D., Assistant Professor of Radiation Oncology, principal investigator of the trial, and Mr. Kebodeaux's physician. "However, we have developed newer technology that allows us to hit this moving target. The purpose of this study is to generate some data that physicians can use to consider offering this to patients as a noninvasive treatment option."

The SABR treatment of 36 or 40 Gy is given in either three or five treatments, respectively, depending on whether any nearby structures (particularly the bowel) need to be accounted for by giving an increased number of more tolerable doses. The clinical trial is open to operable as well as inoperable patients, and the treatment is also available to patients outside the clinical trial setting.

"In addition to being noninvasive, because the radiation is so focused, the option for surgery afterward, if needed, is likely viable for most patients, so we're not closing any doors," Dr. Hannan says.

So far there has been no need. In the handful of patients who have been treated so far, all have seen their tumors shrink on radiographic imaging, and a recent grant from the American Cancer Society will fund biopsy testing to prove that the radiated cancer cells are no longer viable.

Mr. Kebodeaux says it was easy for him to come to the clinic five times, lay on a table each time for 30 minutes, and receive a completely painless treatment with no side effects.

"I was pretty well satisfied with the results," he says. "My tumor is getting smaller and smaller. I'm in good health for my age and fairly active."

There's more time left for him to finish working things out with that woman he's been seeing.

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