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U C L A

Clinical Update

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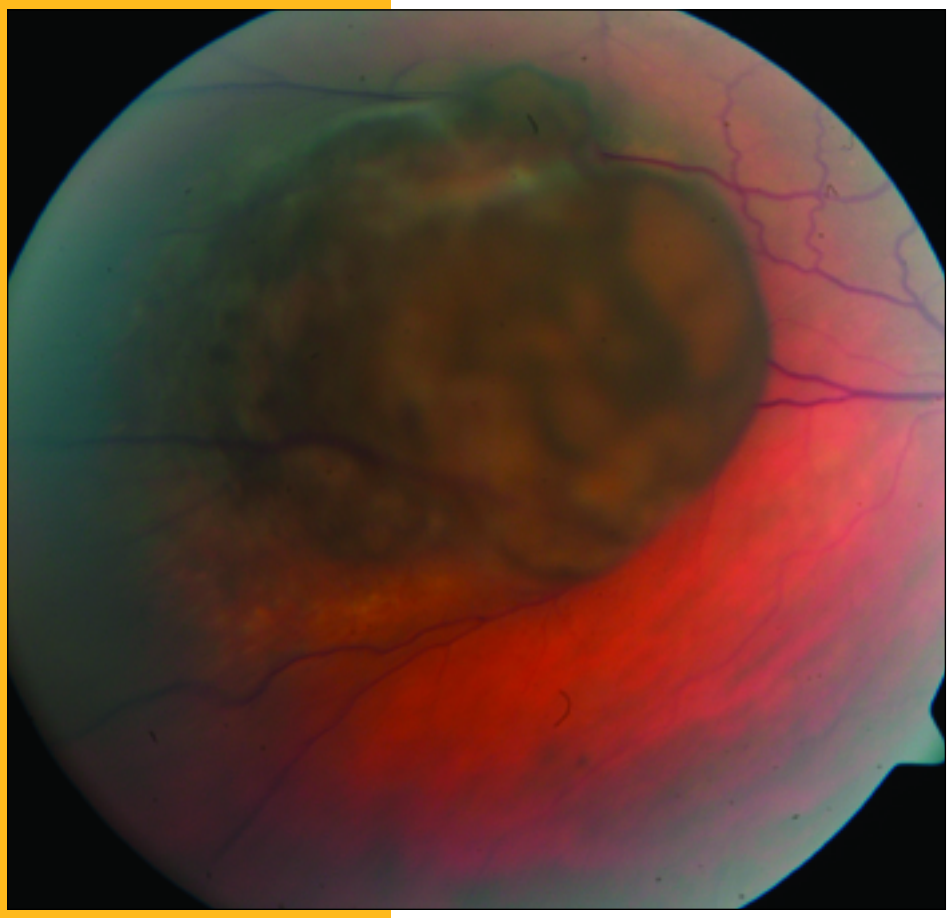
New Biopsy Procedure: A Valuable Tool for Prognosis and Research in Choroidal Melanoma



Choroidal Melanoma. A new cytogenetic test at the Ophthalmic Oncology Center at Jules Stein Eye Institute can predict a patient's prognosis for metastasis.

Choroidal melanoma is the most common primary malignant ocular tumor. Although relatively rare — roughly six cases per one million population per year in the United States — it carries serious consequences, both for sight and for mortality. Approximately half of patients diagnosed with choroidal melanoma develop fatal metastatic disease.

The affected eye is typically treated with a standard regimen of radiation. Until recently, though, ophthalmologists who made the diagnosis of choroidal melanoma had no way of distinguishing the patients who have the more aggressive form — which is more likely to cause metastasis and death — from those who are much less likely to experience metastasis.

A new procedure developed and studied at the Jules Stein Eye Institute uses specific genetic information about the cancer. JSEI researchers have developed a pioneering technique to biopsy tissue from the living eye to predict which tumors carry high metastatic risk. Their findings were published in the November 15, 2006, online edition of the journal *Ophthalmology*.

"We have demonstrated that it's safe and feasible to perform a biopsy in the living eye to obtain information about whether a tumor has high-risk metastatic potential or not," explains Tara A. Young, M.D., Ph.D., assistant professor of ophthalmology and co-director of JSEI's Ophthalmic Oncology Center. "Identifying patients at high risk for metastasis is an important first step toward reducing the death rate of this cancer."

Diagnosis and Treatment of Choroidal Melanoma

Earlier studies discovered that choroidal melanoma patients who are missing one copy of chromosome 3 in their tumor tissue are more likely to have highly aggressive cancers. Using this genetic marker as the starting point for their research, Dr. Young, along

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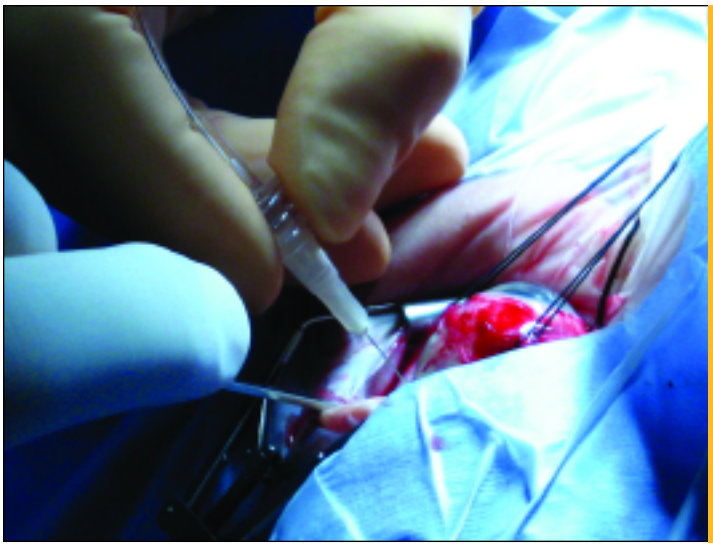
CHOROIDAL MELANOMA (*continued from page 1*)



Intra-Operative Fine-Needle Aspiration Biopsy during Iodine-125 plaque placement surgery for Choroidal Melanoma. The biopsy is performed with a 30-gauge needle directly through the sclera at the site of the tumor. Following the biopsy, the plaque is sutured to the sclera and its placement confirmed with intra-operative ultrasonography.

with Bradley R. Straatsma, M.D., co-director of JSEI's Ophthalmic Oncology Center, Nagesh P. Rao, Ph.D., associate professor of pathology and laboratory medicine, and colleagues studied a group of patients who had been newly diagnosed with the disease. Each patient was scheduled for eye surgery to temporarily implant a small disc designed to treat the tumor with radiation and preserve the eye.

An ultra-fine needle was used to collect cells from the cancer at the time of surgery. The cells were analyzed to determine whether they were missing a copy of chromosome 3. Pioneered by Ben J. Glasgow, M.D., director of JSEI's Ophthalmic Pathology Laboratory, the technique of fine-needle aspiration for collecting cancer cells from the living eye has been the standard of care for patients with choroidal melanoma at the Institute since 2005. Of the nine patients in the study who underwent biopsy and cytogenetic studies, four had tumors identified as high-risk for aggressive metastasis, and five were identified as low-risk.

"Until now, there has been little we could do but radiate the eye and wait for the possibility of metastasis to develop," says Dr. Young. "When physicians know which patient has a poor prognosis, they will monitor the person more closely to detect metastasis earlier and consider more aggressive treatments to increase the patient's chance of survival. Knowledge of metastatic risk will also help patients and their physicians decide whether to pursue clinical trials of experimental therapies that target metastasis. This is a critical starting point for new discoveries in the molecular biology of this cancer."

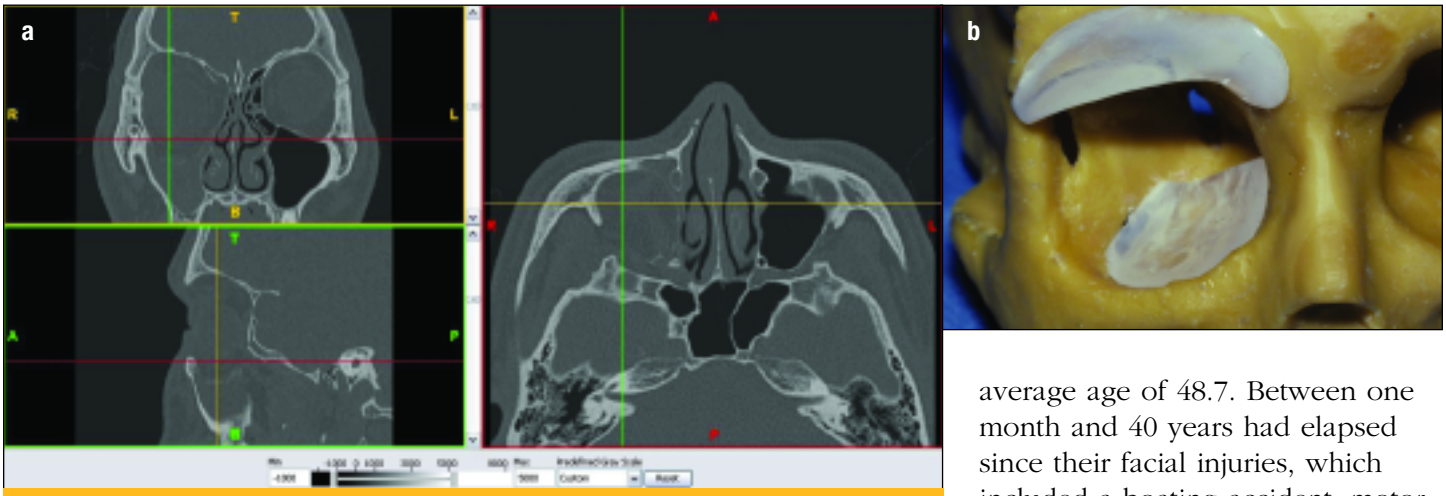
Tissue Useful for Patients and Scientists Alike

Although there is no life-saving treatment for metastatic choroidal melanoma patients who get metastasis at this time, Dr. Young believes it is still important to identify patients at high risk, both as a scientific starting point to better understanding this cancer and because the information may be of great value to patients. In collaboration with Annette Stanton, Ph.D., professor of psychology at UCLA, Dr. Young has been conducting a study on whether previously treated patients would have wanted the prognostic information had it been available. "If the risk is low, it's a relief," she says. "If the risk is high, it enables patients to plan for their families, and make the most of each day." All Ophthalmic Oncology Center patients receive psychological counseling and support.

The biopsied tissue also helps the center's researchers as they seek to understand the abnormalities associated with high-risk choroidal melanoma. In addition to the chromosome 3 test, researchers are studying other molecular and cytogenetic characteristics of choroidal melanoma, and correlating these characteristics with the patient outcomes. "We are discovering new scientific information in the laboratory, which may be important," Dr. Young explains. "Because this is such a rare cancer, new information and discoveries will be critical toward developing a treatment to detect and treat metastasis."

With just a few micrograms of tumor tissue, she notes, it is possible to obtain the genetic signature of the cancer. With that information, researchers can conduct a myriad of experiments designed to learn more about the disease and, ultimately, to tailor treatments to the individual tumors. At the Ophthalmic Oncology Center, a multidisciplinary team of researchers and clinicians is taking management of choroidal melanoma to a new level. "In the future, we expect to have more than just this one genetic test," says Dr. Young. "We will have several tests that can tell us about a patient's tumor tissue so that we can decide well ahead of time which treatments would help the patient the most."

High-resolution CT Scan Modeling for Creating Orbitofacial Implants



(a) CT scan showing all three dimensions (sagittal, coronal, and axial) of orbitofacial defect as a preliminary step in the formation of a biomodel. (b) Photograph showing CT biomodeling of the patient's anatomical defects with PMMA implants placed over the defect. Two separate PMMA implants were constructed for superior and inferior bony defects.

A recent study by members of the Orbital and Ophthalmic Plastic Surgery Division at the Jules Stein Eye Institute and their associates reports the successful use of high resolution computer tomography (CT) modeling in reconstruction of complex orbitofacial defects secondary to trauma. The study reported in the November/December 2006 issue of *Archives of Facial Plastic Surgery* demonstrates that custom-design polymethyl methacrylate (PMMA) implants using such technology offer excellent aesthetic results and are well-tolerated over the long term.

The accurate replication of complex human anatomy has been long sought for patients with severe orbitofacial defects that may result from trauma, congenital defects or iatrogenic defects, such as tumor removal. The main objective of orbitofacial defect reconstruction is to restore anatomic integrity, providing proper eyelid and facial function in addition to cosmetic improvement. Severe trauma and resultant multicontoured disruption of tissues causes extensive scarring, loss of anatomical landmarks and loss of functional tissue, which make secondary reconstructions a challenge to the surgeon. Typically, autologous and alloplastic materials, which are modeled intraoperatively, have failed to create ideal three-dimensional facial and orbital contours. High resolution pre-operative modeling facilitates precise implant construction and placement providing improved facial contour, but concerns have been raised about the long-term stability and risk of infection associated with plastics and other non-organic materials.

High Resolution CT Biomodeled Custom PMMA Implant

In the current study, researchers assessed long-term outcomes following the use of PMMA implants in nine patients with complex facial and orbital defects caused by facial trauma. The five men and four women were between the ages of 28 and 63 years, with an average age of 48.7. Between one month and 40 years had elapsed since their facial injuries, which included a boating accident, motor vehicle crashes, falls and a snowboarding accident. All patients had previously undergone unsatisfactory primary reconstructive procedures elsewhere.

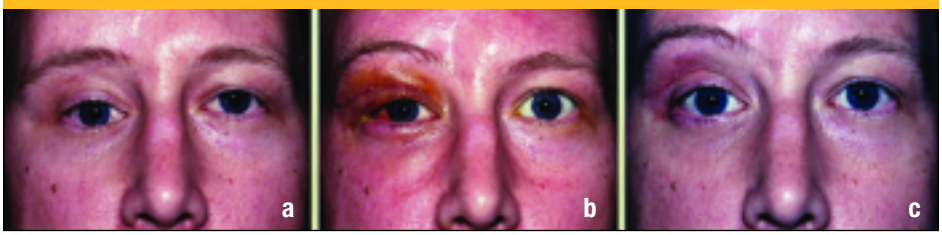
Study patients underwent three-dimensional high-resolution CT scanning of the face and head. Data acquisition by CT, and evaluation of patient data were carried out according to principles established in preliminary studies on geometrically standardized models and the production of implants for bony models. Generation of a physical model from CT data required several basic steps: acquisition of CT data by specified protocols, the delineation of a CT data subset, which described the model itself, and data translation into a rapid prototyping machine to form the 3D model. CT data then was used to generate a physical model from which a prefabricated customized PMMA implant was cast. High resolution CT biomodeling and prefabrication of implants provided an exact fit. During reconstruction of the orbitofacial defects, care was taken to ensure precise implant placement. The implant's placement was surgically fixed using screws. All of the screws were counterfitted

(buried below the bony level) so they could not be palpated.

Results

Long-term data demonstrates that placement of orbital implants achieves reliable stability and long-term improvement in function with minimal risk of extrusion or implant infection. During an average of 4.3 years of follow-up, none of the patients in the study developed significant complications including infection, extrusion or displacement of the implant. Patients had minimal postoperative pain and none developed hematoma or seroma. No surgical drains were used. All patients had a routine follow up of complete ophthalmologic evaluation once a week for a month followed by once every two months and quarterly annual visits thereafter. "In all of the patients, wound healing was uneventful, with antibiotics given perioperatively," the authors write. "All of the patients demonstrated long-term sustained improvement of facial deformities," including facial symmetry and eyelid function.

(a) Photograph showing significant post traumatic hypoglobus,restrictive strabismus, enophthalmos and orbital volume defect of right eye.The patient underwent multiple reconstructive surgeries of face and orbit but still complained of diplopia and facial asymmetry before undergoing reconstructive surgery with implantation of prefabricated custom made PMMA implant. (b) Early postoperative photograph of patient showing minimal orbital inflammation with sutures at superior lid crease and lateral canthal angle following reconstructive surgery. (c) One-year follow-up demonstrating improvement of hypoglobus, superior sulcus deformity and enophthalmos.



The authors conclude that reconstruction with custom biomodeled implant offers a practical alternative in complex cases of orbitofacial bone defects secondary to trauma. It requires a preoperative CT according to specific parameters and can be accomplished in almost all radiology centers. Model construction is straightforward with reduced operative time. All patients in the current study demonstrated long-term, sustained improvement of facial deformities, confirming that PMMA biomodeled implants are well tolerated in the long term. The authors believe the advantages of customization and long-term efficacy reported in the study far outweigh potential complications in complex orbital reconstruction, which require precise implant customization to provide function improvement.

RECENT PUBLICATION

Groth MJ, Bhatnagar A, Clearihue WJ, Goldberg RA, Douglas RS. Long-term efficacy of biomodeled polymethyl methacrylare implants for orbitofacial defects. *Arch Facial Plast Surg 2006;* 8:381-9.

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