INTRODUCTION

The Collaborative Ocular Melanoma Study (COMS) was the largest study ever to be funded and performed in ocular oncology. With 43 participating centers and hundreds of investigators, more than 2000 patients enrolled, 28 numbered studies published over a period of 16 years and almost innumerable editorials, letters, comments, and review articles generated by its findings, the breadth and depth of the knowledge produced by the COMS is unparalleled in ophthalmic oncology.

To develop a sense of the legacy of the COMS and its effect on clinical practice in ocular oncology, Retina Today interviewed Timothy G. Murray, MD, MBA, FACS, who was the Principal Investigator for the COMS at Bascom Palmer Eye Institute at the Miller School of Medicine of the University of Miami.

The impressive bibliography of the COMS is available on the Internet at:
http://www.jhu.edu/wctb/coms/general/publicat/pubs.htm

Retina Today: As the name tells us, the COMS was a collaborative undertaking. What were the effects of that experience in ophthalmology?

Timothy G. Murray: One of the things you learn in a collaborative clinical trial is what it truly means to collaborate. Prior to the COMS, the vast majority of patient care for ocular melanoma took place at a small number of centers, and there were a handful of other centers involved. With the COMS we suddenly had more than 40 centers, all of which had to be expert in the delivery of care to the study patients, including diagnostic evaluation and accuracy, appropriate imaging studies—particularly with the standardized echography that was used—and the ability to provide the different types of treatments employed in the study. These included enucleation, which was the standard surgical procedure at the time for ocular melanoma; brachytherapy using iodine-125 plaques, which was potentially new to many institutions; and for patients with large melanomas who were randomized to the group that received radiation before enucleation, a radiation service that could provide external beam radiation therapy.

The COMS taught all of us that you can establish standards, and through the use of that standardization you can broaden access to care, from a few outstanding centers to multiple centers across the United States.

Another lesson was that, in a collaborative clinical trial, the investigator must be capable of adopting the concept of equipoise. That is to say, there are 2 treatments, and the investigator has to be confident that he or she does not know which is better. In this case, in the medium-sized tumor trial, the treatments were very
different—enucleation to remove the cancer along with the eye vs radioactive plaque to cure the cancer and leave the eye in place. In a normal clinical situation, the patient looks to us to tell him or her which is the best option. We had to be comfortable not knowing the right answer. When the patient was randomized, we lost the ability to choose the therapy. Accepting that situation required real collaborative effort from the investigators.

In addition, in a collaborative clinical trial, the protocols are not promulgated by an individual; they are group endeavors. We were already performing iodine-125 brachytherapy at Bascom Palmer for patients who were not included in the COMS. The COMS protocol was dictated by the study. Therefore, what I thought was the best care delivery for a patient who was not in the study may have differed from what I did in the study. So the investigators had to be comfortable enough with the study-defined treatment strategies and how they were determined to be willing to participate in the trial.

The underlying fact, therefore, is that patient care in a collaborative trial differs from standard clinical care. Your interaction with the patient is different in unique ways, the treatments you provide may differ from treatments you would offer outside the clinical trial, and you must be willing to accept the potential that you really are at equipoise—you really don’t know the answer and you’re going to investigate it so that we all can learn what that is. Although the answer may not be what is best for the individual patient in the clinical trial, we hope that it will benefit patients in the future. Therefore, there must also be an altruistic commitment from the patients participating in such clinical trials.

RT: Did you have trouble recruiting for the medium-sized tumor trial because of the difference between the treatments?

Murray: Yes. I think there was difficulty recruiting for the medium-sized tumor trial because the treatments were so disparate. I do not think there was difficulty recruiting for the large tumor trial because we were going to offer enucleation to both randomized groups. One arm would get preenucleation radiation, and that did not have a significant impact for the patient, so it was easier to recruit. The difficulty with recruiting to the medium tumor trial was that brachytherapy was already widely touted to be an outstanding therapy. Those few groups that had used brachytherapy had already published enough of their results from nonrandomized clinical trials that it was seen as a viable treatment option. Therefore, patients who wanted to keep their eye had a treatment option outside the trial.

If the trial had begun at the advent of brachytherapy, it would have been easier to recruit patients. If the only way to receive brachytherapy was by enrolling in the trial, more people would have been willing to participate. But in the COMS, patients who were eligible had the opportunity to be treated outside of the clinical trial with the ability to select either of the treatments used in the trial. The greatest difficulty in the medium tumor trial was how long recruitment took. If all of the eligible patients in the United States over the period of recruitment had participated in the trial, it would have been finished in half the time.

RT: How did the COMS change practice?

Murray: The COMS was a critically important trial; it changed the way ocular oncology is practiced in the United States, and elevated the level of care in many centers.

First, the trial documented the high degree of accuracy of clinical diagnosis based on ultrasound, photography, fluorescein angiography, and clinical assessment. In a field that does not biopsy routinely for confirmation of tumor cell type, the investigators had a diagnostic accuracy, based on evaluations of all the enucleated eyes, of about 99%. It is still amazing to me that a diagnostic accuracy of 99% could be achieved in a multicenter, national clinical trial.

Second, the trial established a shift in parameters for treatment. When the COMS started, the smallest tumor that was eligible for the medium tumor trial was 3 mm in height. That was reevaluated, and the eligibility criterion was lowered to 2.5 mm in height. There was a concern that there would be less diagnostic accuracy for these smaller tumors. But when the smaller tumors were included, the diagnostic accuracy did not change from the diagnostic accuracy with larger tumors. That shift in the protocol and the documentation of the diagnosis of those eyes treated with enucleation was supportive that the clinical evaluation of patients with tumors as small as 2.5 mm in height was accurate.
Third, before the trial, many practitioners believed that the only way to treat eyes with medium-sized tumors was with enucleation. Although the top ocular oncology centers had moved away from enucleation and toward radiation therapy in these eyes, the other centers were still focused on enucleation. The results showed that brachytherapy was as successful as enucleation at controlling the tumor, with equivalent survival outcomes. The COMS said that we no longer had to remove those tumors. We could feel comfortable that, without removing the tumor and using brachytherapy within the confines of the study protocol, patients would have the same outcome course and survival. That was a huge change. We moved to an eye-sparing therapy, and we documented that leaving the eye and treating the cancer with radiation was as effective as removing the eye.

Fourth, there was a belief before the trial that in eyes with large tumors, removing the eye might disseminate the tumor. The study indicated that this hypothesis was incorrect, and it also suggested that using radiation to try to decrease surgery-related complications was not beneficial. The findings showed that we don’t need to give patients radiation to have outcomes as good as enucleation alone. In the large tumor subset, the results did indicate a statistically significant decrease in orbital tumor recurrence in eyes that received preenucleation radiation therapy. However, recurrence happened rarely—in fewer than 1% of cases. The lesson many ocular oncologists have taken from this finding is that if we think there is a significant risk of orbital recurrence, we discuss with the individual patient that in this case radiation may be beneficial. That is, the clinical pearl was that with large tumors there is no benefit to routine use of enucleation plus radiation, but for the select patient with a high concern for orbital recurrence there may be some benefit to radiation therapy—not to enhance the survival outcome, but to lower the possibility of tumor recurrence in the orbit.

In addition to improving care in ocular oncology, the COMS improved some of the events that occurred around this care. For example, ultrasound at many of the participating institutions became much better than it had been because of the standards employed in the clinical trial; the technology platforms were standardized, and the techniques for the utilization of the technology were also mandated. This benefitted every patient who needed an ultrasound, whether for a retinal detachment, a nonmalignant tumor, or other issues.

The structure of the trial included an ultrasound study center, a photography reading center, and a radiation physics center, and these centers were charged with oversight of the clinical centers, review of the information that was captured and submitted, and site visits to clear the center before it entered into the trial. This provided significant assurance that participating centers could meet the standards of the clinical trial. If they were not up to the standard before the trial, they purchased new equipment, trained to the standards, adopted new techniques, and became a better center.

The trial also helped us to understand some of the long-term results of brachytherapy in the medium-sized tumor subset. The COMS data established, in a national multicenter clinical trial framework, the rate of visual loss, the rate of enucleation for complications of radiation, and the rate of failure for radiation to control the tumor at 3 years after brachytherapy. Those are important pieces of information for physicians considering use of brachytherapy.

Many people might look at a trial negatively if it shows that 2 treatments being compared have similar outcomes. It’s disappointing because 1 was not found to be better than the other. However, as with the recent CATT trial comparing ranibizumab and bevacizumab for the treatment of neovascularization in age-related macular degeneration, the COMS showed that both treatments—both in the medium-sized and large tumor subsets of the trial—were very good. This has allowed clinicians to have a discussion with patients with much broader understanding of the options available.

For these reasons, the COMS was a critically important trial in ocular oncology that advanced clinical practice and elevated the standard of care in centers all over the country.

RT: At present, the last numbered publication from COMS—No. 28, the 12-year mortality results with brachytherapy—was published 5 years ago, in 2006. What was the significance of that publication, and what has changed since that time?

Murray: Long-term follow-up is important because melanoma is not like some other cancers; for instance in breast cancer, women who survive 5 years after diagnosis have a good chance of remaining cancer-free. Melanoma has a rapid increase in mortality rate early, but it also continues to have unusual late deaths from melanoma metastasis. That is not well understood.

It is important for clinicians to know the 5-, 10-, and 12-year melanoma-specific mortality rates in the COMS. It is often said that the mortality rate from melanoma has not changed in the last 50 years, that it’s 50%. It is not.
The melanoma-specific mortality rates at 5 years were 1% in the small tumor trial, less than 10% in the medium tumor trial, and less than 30% in the large tumor trial. According to the 2006 paper, the histopathologically confirmed melanoma-specific rate in the brachytherapy arm was 10% at 5 years, 18% at 10 years, and 21% at 12 years, compared with 11% at 5 years, 17% at 10 years, and 17% at 12 years in the enucleation arm. Those are pretty encouraging numbers because the average patient age at trial entry was in the early 60s. So we can counsel patients that they have an 80% chance of being alive 10 years from now without having died from this cancer.

Of course, all-cause mortality is higher—43% in the brachytherapy arm and 43% in the enucleation arm at 12 years. But I tell patients that my job is to treat their cancer, and I can only affect that. It is important for us to know those numbers and remember that they are better than what many seem to think.

Since 2006, there have been advances in technology and changes in the adjunctive treatments available to us. Ultrasound technology has also improved. This does not so much affect diagnostic accuracy for melanoma, which was high in COMS. But it does help us in identifying the pathology in patients who would not have been eligible for COMS because we did not think they had a melanoma.

There have been advances in how to treat the complications associated with radiation therapy, and there have been advances in how to improve the success rate of radiation therapy. At our institution, we now use adjunctive bevacizumab at the time of surgery in brachytherapy; this has changed the outcomes for our patients. That drug was not available to be evaluated in the COMS.

We have started imaging patients after brachytherapy with high-resolution optical coherence tomography (OCT), which was not available when COMS was designed. We find that this technology allows us to better evaluate and predict visual outcomes for patients. OCT also detects radiation complications earlier, and earlier detection has allowed us to treat patients who in the COMS essentially were untreatable. So there has been a significant decline in visual loss from radiation complications at our institution and others. The ability to look for these complications and to treat with these pharmacologic agents did not exist.

Another recent development is an ongoing evaluation of the genetics of these tumors. Investigators have suggested that we can perform fine-needle biopsy of melanomas before radiotherapy and achieve a classification of the tumor that may be predictive of high and low risk for metastatic disease. What has not come along with the ability to classify, however, is the ability to treat the patients who have high-risk disease in a way that has been shown to decrease their risk. So we have a test that may be important, but it hasn’t been associated—yet—with a treatment option for high-risk patients that has been shown to be effective. Therefore, one of the ongoing controversies is: What is the role for the biopsy? What does it mean to classify these tumors, and what should we do with that information once we have it? I have not been performing fine-needle biopsy because I don’t yet see a positive answer for my patients.

The controversies in our field that remain unaddressed include the treatment of very small tumors, which were excluded from the COMS; treatment of tumors around the optic nerve, which were also excluded from the COMS; and treatment with radiation therapy for very large tumors. Since 2006, there has not been another multicenter clinical trial similar to COMS, but superb smaller studies have shown that radiation can be used for small tumors, for tumors around the optic nerve, and for large tumors. Other controversies include, as mentioned above, what is the role for genetic testing, and which of the available genetic tests is the best? How to best treat radiation complications to preserve vision is a subject of ongoing debate. And after patients have been treated, how should the medical physician or oncologist follow them? Some clinicians are minimalists, and some believe you should spend $20 000 a year testing. No one knows the right answer.

Finally, as much as the collaborative work of COMS was important, it is clear that specific oncology centers can achieve better results than those seen in such large, multicenter clinical trials. Centers that maintain expertise in ocular oncology have continued to report outcomes better than those obtained in the COMS. Why? Data suggest that the more often one performs a surgical procedure, the lower the complication rates for that procedure are, and potentially, the better the outcomes. So it is important for us to have high-volume centers that maintain an expertise in oncology. Still, the COMS was a landmark event in ocular oncology and ophthalmology, and it provides and will continue to impart many important lessons for clinicians.

Timothy G. Murray, MD, MBA, FACS, is a Professor of Ophthalmology with a Secondary Appointment in Radiation Oncology at Bascom Palmer Eye Institute at the Miller School of Medicine of the University of Miami. He is also a member of the Retina Today Editorial Board. Dr. Murray may be reached at +1 305 326 6166; or via email at tmurray@med.miami.edu.