Intraocular tumors of any type are uncommon. The most common primary malignant tumor of the eye, uveal melanoma, occurs in 7 persons per million population per year -- less than one tenth the incidence of lung cancer.\(^1\) Retinoblastoma occurs as a childhood disease approximately as frequently as hemophilia.\(^2\) These two intraocular tumors, related only by anatomic proximity, have very different histories.

Retinoblastoma was a uniformly fatal disease before the turn of the century, when clinical diagnosis occurred late and left little chance of cure. Long-term survival with retinoblastoma became feasible with the introduction of the ophthalmoscope, which permitted diagnosis when the tumor was confined to the eye, and with the acknowledgment of the concept that surgical removal of a globe that harbored retinoblastoma could prevent hematogenous dissemination. As retinoblastoma survivors reached adulthood, it was evident that some patients could transmit the tumor to their offspring in an autosomal dominant fashion. The clinical marker for hereditary retinoblastoma had a particularly gruesome manifestation: bilateral eye involvement. In 1971, Alfred Knudson proposed a two-hit mutational hypothesis based on the age of children diagnosed with sporadic and inherited tumors.\(^3\) His hypothesis suggested that the molecular basis of retinoblastoma resides in a set of recessive genes. The discovery of deletions in chromosome 13 in some children with inherited retinoblastoma was a major breakthrough.\(^4\) The race to identify the genetic trigger of retinoblastoma was in full force by the early 1980s.\(^5\) The retinoblastoma gene is now the most studied human suppressor cancer gene as well as a model for many other ostensibly unrelated types of cancer.\(^6\)

The history of uveal melanoma is not as glorious as that of retinoblastoma but is just as fascinating. There is little evidence that modern diagnostic and therapeutic techniques have substantially prolonged the lives of patients with uveal melanoma since enucleation was introduced early in this century as standard therapy. The role of enucleation in the management of uveal melanoma became the topic of an international debate in 1978 when Lorenz E. Zimmerman and colleagues from the Armed Forces Institute of Pathology postulated that this surgical technique may actually promote hematogenous dissemination of melanoma and may hasten death.\(^7\)

This hypothesis was supported by three clinical observations. First, it is unusual to detect metastatic disease in patients with uveal melanoma before treatment or during the first six months following enucleation. Second, the rarity of pretreatment metastases (approximately 1% per year) is independent of the size of the primary tumor. In other words, preoperative metastases are no more common in patients with large tumors than in patients with small or medium tumors. Third, annual mortality rates from metastatic melanoma (death density function) peak between two and four years for small, medium, and large tumors. The temporal relationship of enucleation and death suggested that as many as two thirds of tumor deaths may be related to enucleation.\(^7\) For several years, ocular oncologists struggled to find another (and better) explanation for these observations.\(^8\) Editorials questioned whether a moratorium on enucleation for uveal melanoma was needed until the safety of enucleation could be resolved.\(^9\) Once therapies have gained widespread acceptance, however, it is difficult (if not impossible) to go back and test their effectiveness.

The merits of the so-called Zimmerman hypothesis became academic after the National Eye Institute launched the Collaborative Ocular Melanoma Study (COMS) in 1986. This randomized clinical trial was designed to test two major null hypotheses: (1) no difference in mortality exists for patients with medium-risk choroidal and ciliary-body mel-anoma treated with iodine 125 plaque and enucleation and (2) no difference in mortality exists for patients with high-risk choroidal and ciliary-body melanoma treated with enucleation with or without preoperative external radiation.\(^10\) The principal endpoint for each group is time to death from metastatic melanoma. Several of the major uveal oncology centers in the United States initially decided not to participate in the study. Reasons were varied, but perhaps the most compelling argument was based on the low likelihood that the study could detect a clinically meaningful difference in treatment effect in the medium-risk melanoma group. Another concern was the prolonged time interval from treatment to endpoint, since it was possible that new, more promising therapies could be developed before the study ended.

The COMS was conceived and developed knowing that the natural history of choroid melanoma had never been adequately documented. The COMS addressed one aspect of this problem -- the natural progression of small melanoma (less than 3 mm in height and 5 mm to 16 mm in basal diameter) to the time in its natural history that warrants treatment. Several studies have shown that there is no increase in tumor-specific mortality in patients with small choroidal melanoma whose tumors are observed for growth.\(^11\) Participation in a nonrandomized, prospective, follow-up study within the COMS was offered to the subset of patients with small melanomas in order to determine the natural history of these tumors. As of 1997, 204 patients with small tumors were enrolled in the COMS, and 27 of these patients died.\(^12\) Six deaths were melanoma related and four occurred more than five years after enrollment. The mean age of patients with small melanomas was 60 years. The Kaplan-Meier five-year melanoma-specific mortality was 1% (95% CI: 0% to 2.5%). These results show that persons with a small choroidal melanoma have a much greater risk of dying from causes other than melanoma within five years of diagnosis.

Tumors other than retinoblastoma and melanoma occur in the eye, and they are often the harbingers of disease elsewhere. Choroidal metastasis is the most frequently occurring intraocular malignancy and can be the initial manifestation of systemic malignancy. Choroidal metastases resemble nonpigmented melanomas. They have a similar appearance to melanoma on fluorescein angio gram and show subtle echographic differences on ultrasonography. Choroidal metastases, however, grow more rapidly and are more likely to cause large exudative retinal detachments.

The iris is an uncommon site of metastasis. In general, the prognosis for survival is poor once metastatic disease is found in the eye. As survival in systemic cancer patients improves, however, successful treatment of ocular metastases has an increasingly important role in maintaining a good quality of life.
increased the yield of immuno-pathologic studies.  

The articles in this issue of Cancer Control describe some of the accomplishments, controversies, and failures in perhaps one of the most parochial areas of oncology. If one theme runs through each of these papers, it is the growing need of interdisciplinary collaboration. The solutions to problems in ocular oncology depend on an understanding of the unique clinical and biologic features of eye tumors.

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