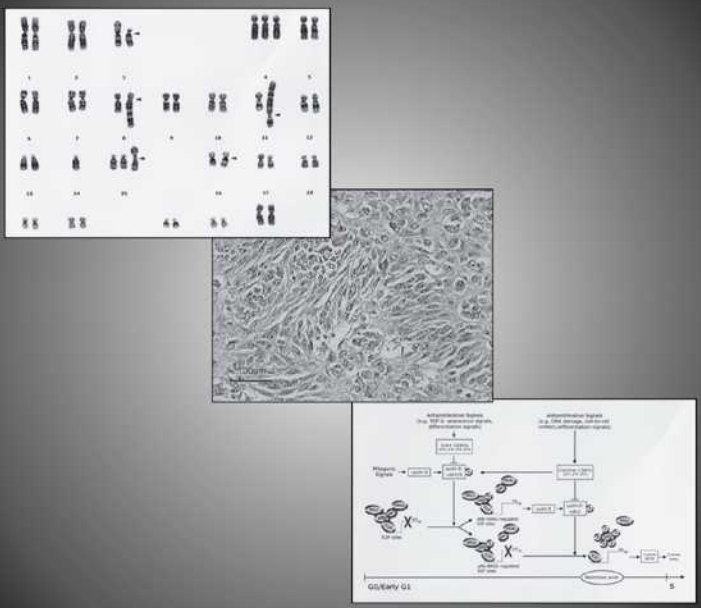
OCULAR ONCOLOGY



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To the scientists and clinicians who have labored and continue to labor to determine the causes, pathogenesis, and effective treatments of eye tumors.

Preface

Ocular tumors are unique among the diseases of the eye, threatening both sight and life. Prior texts in oncology and ophthalmology have focused primarily on providing physicians with information about the treatment of eye tumors. *Ocular Oncology* differs in that it is our objective to present a comprehensive account of the most current basic and clinical science related to eye tumors, and to offer new ideas about innovative treatments derived from recent genetic, biochemical, and immunological studies. In addition, this book discusses the current status of clinical trials in ocular oncology, as well as provides an up-to-date review of risk and prognostic factors associated with eye tumors. Finally, current findings are presented from studies of animal models and their use to assess the efficacy of novel treatment modalities with potential for human treatment.

Ocular Oncology focuses on uveal melanoma and retinoblastoma, the principal tumors originating in the eyes of adults and children, respectively. Although considered uncommon diseases, we need to acknowledge that rare and uncommon diseases often provide insights into fundamental biological processes and advance the development of innovative treatments of more prevalent diseases. There is perhaps no better example in science than retinoblastoma, a rare childhood ocular tumor with an incidence of only 300 to 400 cases per year in the United States. Studies of retinoblastoma, however, funded by the National Eye Institute, led to the identification of the first tumor suppressor gene. Prior to these studies, cancer was considered solely a "gain of function" phenomenon; studies of retinoblastoma instigated a fundamental change in thinking and scientific approach. In addition, studies of retinoblastoma led to the identification of further genes and pathways involved in one of the most fundamental processes in biology, namely the molecular control of cellular growth. Likewise, while much attention has been focused recently on anti-angiogenic strategies for the treatment of solid tumors, new studies of uveal melanoma have revealed a form of non-endothelial-based tumor microcirculation, owing to the dedifferentiation of tumor cells, that may compromise anti-angiogenic treatments. The relevance of such an alternative circulatory pathway during the growth and progression of other types of cancer is now an active area of investigation, instigated by studies of a rare eye tumor.

What is evident from recent technological advances, encompassed in new cytogenetic methods and the use of DNA chip arrays, is that ocular tumors, like eye diseases such as retinitis pigmentosa, are really a composite of different sentinel mutations that lead to the alteration of very different cellular pathways. Ultimately, the phenotype is unrestricted growth, a fairly limited description that likely undervalues the variety of causes leading to an eye tumor. This diversity and the ensuing complexity at a molecular level eventually will require methods of diagnosis and treatment that are tailored on a more individual level.

We would like to thank all of the contributors who thoughtfully considered the complexities of their particular scientific subdiscipline of ocular oncology, who fairly presented the controversies and candidly acknowledged the limitations of our knowledge, and who speculated boldly on what we need to accomplish before we can hope to successfully treat or prevent eye tumors and their metastases.

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1

Clinical Overview of Uveal Melanoma: Introduction to Tumors of the Eye

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I. INTRODUCTION

A. Background

Melanoma of the uveal tract is the most common primary intraocular cancer in humans and accounts for about 12% of all melanomas [1]. Over 90% of uveal melanomas arise from the ciliary body and/or choroid and are referred to as posterior uveal melanomas; whereas about 5–8% of uveal melanomas arise in the iris [2]. Iris melanomas are generally much smaller, have a better prognosis, and are managed somewhat differently than posterior uveal melanomas.

B. Epidemiology/Demographics

Uveal melanoma occurs in about 5–7 persons per million persons annually (1200–1700 new cases per year) in the United States [1,3]. Uveal melanomas can arise from pre-existing uveal nevi or de novo. Based on earlier prevalence estimates for choroidal nevi (3.1% in persons over 30 years old), it was calculated that about 1 in 4000–5000 nevi transform into melanomas [4]. However, more recent studies, including a prospective analysis from our group, suggest that the prevalence of choroidal nevi may be as high as 18% in Caucasian populations, which would indicate that the proportion of nevi that convert to melanomas may be even smaller than previously assumed.

There is now convincing evidence that solar ultraviolet (UV) light plays an etiological role in cutaneous melanoma through induction of DNA damage in dermal melanocytes [5]. However, the relationship between uveal melanoma and UV irradiation remains controversial. Several studies found a link between uveal melanoma and increased UV exposure, sensitivity to UV light, ancestry from northern latitudes, light skin color, residence at lower latitudes, sunlamp use, and a history of intense sunlight exposure [6–9]. Light iris color has also been linked to uveal melanoma [6,9,10]. However, other studies have failed to support an association between uveal melanoma and UV exposure [1,11]. If there is an etiological link between UV light and uveal melanoma, it is probably much weaker than that for cutaneous melanoma.

Uveal melanoma has been linked to a variety of occupational and environmental factors, such as indoor working conditions, exposure to chemicals, and radiofrequency radiation [6,10,12,13], but the epidemiological significance of these associations has not been established.

C. Clinical Genetics

Uveal melanoma is usually a nonheritable, sporadic tumor. In fact, the world literature contains only a few families in which uveal melanomas were documented in more than two members in a bona fide Mendelian inheritance pattern [14–16]. There is little evidence for a hereditary uveal melanoma syndrome, which might include such features as the development of melanoma at an early age, bilateral ocular tumors, or predisposition to other second primary cancers [15]. Aside from rare patients with the familial atypical nevus-melanoma syndrome, there is a weak association between uveal and cutaneous melanoma. The systemic disorder most commonly linked to uveal melanoma is oculo(dermal) melanocytosis [17]. Uveal melanoma has also been reported in association with neurofibromatosis type 1 (NF1), but there does not appear to be a predisposition to uveal melanoma among NF1 patients, and we have shown that NF1 mutations are rare in uveal melanoma. The lack of hereditary pattern or association with an inherited condition has greatly hampered the search for causative genes in uveal melanoma, since genetic linkage analysis is not possible. This situation stands in contrast to retinoblastoma, where the hereditary pattern led to discovery of the first tumor suppressor gene [18,19]. Efforts to identify causative genes in uveal melanoma will rely on other approaches, such as the study of cytogenetic changes and mutations in known cancer genes [20,21].

II. DIAGNOSIS

A. Clinical Features

The clinical appearance, size, and location of uveal melanomas are highly variable (Fig. 1). Many other lesions can simulate uveal melanoma [22]. However, clinical examination and ancillary testing can accurately diagnose most uveal melanomas. Iris melanomas usually present as a variably pigmented, elevated mass that replaces the iris stroma (Fig. 1). The color of the tumor can vary from light tan to dark

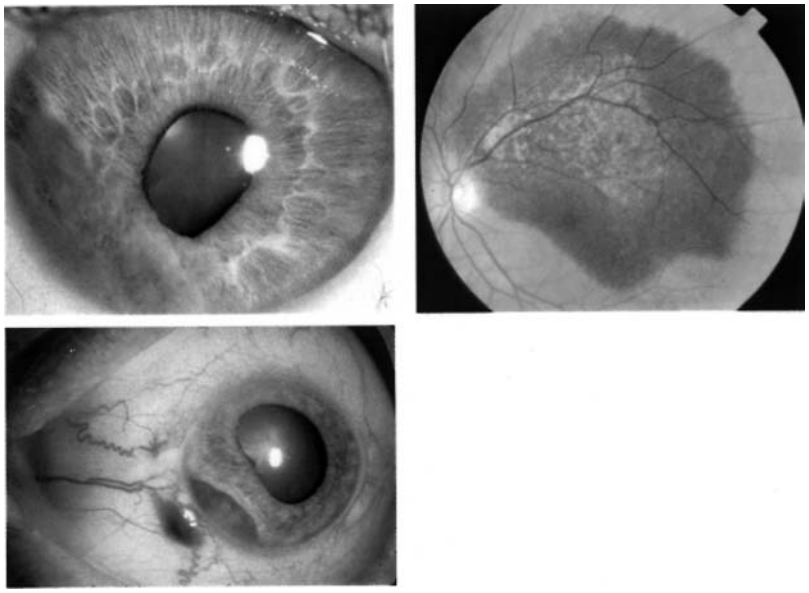

Figure 1 Uveal melanoma can involve the iris (top, left), choroid (top, right), and/or ciliary body (bottom).

brown, and intrinsic tumor vessels can often be identified in lightly pigmented tumors. Distortion and contraction of the iris stroma may lead to pupillary peaking or ectropion uveae. Shedding of tumor cells onto the iris surface and into the anterior chamber angle can lead to satellite lesions, hyperpigmentation of the trabecular meshwork, and secondary glaucoma. Lenticular touch may lead to focal cataract formation. About 6.5% of small iris melanocytic lesions will grow over a 5-year period; the clinical features most predictive of growth and malignancy include increased size and thickness, pigment shedding, secondary glaucoma, intrinsic tumor vessels, and visual changes [23].

Posterior uveal melanomas can involve the ciliary body, choroid, or both (Fig. 1). Tumors involving the ciliary body and/or peripheral choroid tend to grow to a larger size before detection, whereas tumors in the posterior pole tend to be detected when they are smaller, due to earlier visual changes. Posterior uveal melanomas can vary in color from light tan to dark brown. They are usually dome- or mushroom-shaped, which indicates that the tumor has broken through Bruch's membrane (mostly in tumors $\geqslant 5$ mm thick). Exudative retinal detachment is often present. Subretinal or vitreous hemorrhage may occur, especially in larger tumors. Choroidal neovascularization may occur in chronic, dormant lesions [24]. Small melanocytic lesions under 2.5–3 mm in thickness are often followed for evidence of growth prior to treatment, since many of these lesions will prove to be dormant. In a group of patients with small tumors that were observed in the Collaborative Ocular Melanoma Study (COMS), 31% of the tumors grew within 5 years [25], which is similar to the 26–36% growth rate reported in earlier retrospective studies [26,27]. Clinical features associated with growth of small choroidal melanocytic lesions

include increased thickness and diameter, subretinal fluid, orange lipofuscin pigment overlying the tumor, juxtapapillary location, visual changes, internal quiet zone on B-scan ultrasonography, and hot spots on fluorescein angiography [25–27]. Features associated with lower risk for lesion growth include drusen and retinal pigment epithelial atrophic changes around the tumor [25].

B. Diagnostic Modalities

For posterior uveal melanoma, ultrasonography is generally the most useful ancillary diagnostic test. Uveal melanomas usually demonstrate low to medium internal reflectivity on standardized A-scan ultrasonography (Fig. 2). B-scan mode demonstrates the overall shape and topography of the tumor (Fig. 2). These features usually allow melanomas to be distinguished from simulating lesions such as choroidal metastases, which tend to have high irregular reflectivity, and choroidal hemangiomas, which usually demonstrate high and relatively uniform reflectivity [2]. The recent development of high-frequency (20- to 50-MHz) ultrasound units for examining the anterior segment have aided greatly in determining the size, location, extent, internal characteristics, and growth of iris and ciliary body lesions (Fig. 2) [28].

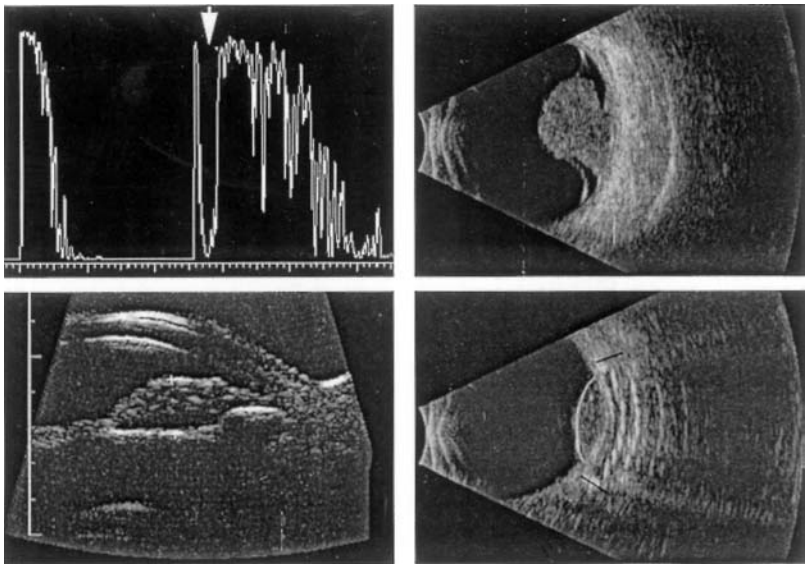

Figure 2 Ultrasonography can be very helpful in diagnosing uveal melanoma. Low internal reflectivity within the tumor on A scan (arrow) is characteristic of melanoma (top, left). Tumor topography, such as the mushroom shape, can be seen using B-scan ultrasonography (top, right). Iris melanomas can be evaluated with high-frequency anterior segment ultrasonography (bottom, left). Intraoperative ultrasonography is extremely useful for localizing radioactive plaques (bottom, right). The white line indicates the tumor and the black lines indicate the edges of the plaque, demonstrating excellent localization of the plaque over the tumor.

Fluorescein angiography can be useful but is not diagnostic in the evaluation of choroidal melanoma [29]. In particular, fluorescein angiography can help to distinguish between a melanoma, which often has intrinsic hyperfluorescence and vascularity, and a hemorrhagic lesion such as a ruptured retinal arterial macroaneurysm or peripheral choroidal neovascularization, which generally blocks fluorescence. Indocyanine green (ICG) angiography can be useful in detecting choroidal neovascularization and ruling out a choroidal hemangioma, which usually displays a characteristic late "washout" of dye [30]. Magnetic resonance imaging (MRI) is occasionally useful for distinguishing between uveal melanoma and other lesions [31]. MRI is most useful when performed with surface coils and fat suppression to maximize the sensitivity for evaluating intraocular masses. Melanomas characteristically demonstrate hyperintensity compared to vitreous on T1 weighting and hypointensity on T2 weighting [32].

The COMS reported a diagnostic accuracy rate of 99.7% for posterior uveal melanomas using the noninvasive techniques described above [33]. This high accuracy rate is due in part to the collective experience gained in the clinical evaluation of intraocular tumors but also to the fact that tumors with atypical features were excluded from the COMS for the specific purposes of the study. Therefore, the COMS results do not account for a significant proportion of melanomas (approximately 10% in our institution) with atypical features that can only be diagnosed with certainty by tissue biopsy. Intraocular fine-needle aspiration biopsy is most commonly used for tumors with atypical clinical features in which the biopsy will determine treatment. Fine-needle biopsy can be performed by transscleral, transvitreous, or transcorneal approaches, depending on the size and location of the tumor. When performed by an experienced surgeon and interpreted by an experienced ocular cytopathologist, intraocular biopsy yields a high percentage of positive cytopathological diagnoses, is relatively safe, and poses an extremely small risk of extraocular tumor dissemination [34,35].

III. TREATMENTS

A. Observation

Although there is general agreement among ocular oncologists that most uveal melanomas should be treated to minimize the risk of metastatic disease, there has never been a clinical study proving that treatment improves survival. Ethical and practical concerns will probably preclude such a trial from ever being performed. However, the rationale for treating uveal melanomas is based on several well-established observations, including the following. Patients who undergo enucleation or plaque radiotherapy for small melanomas have a much lower risk of metastasis than those with large melanomas [36,37], suggesting that treatment may prevent the further accumulation of risk that accompanies tumor enlargement. Conversely, local tumor recurrence following plaque radiotherapy greatly increases the risk of metastasis [9,38], suggesting that successful radiotherapy significantly reduces the risk of metastasis, as opposed to unsuccessful radiotherapy. Nevertheless, there are circumstances where observation is appropriate, as in patients with small

indeterminate lesions that may be dormant or in those who may have a limited life expectancy.

B. Enucleation

Enucleation, or surgical removal of the eye, was the primary form of treatment for many years and is still the best option in many patients. Contemporary indications for enucleation include (1) large tumor size, (2) tumor invasion of the optic nerve head, (3) lack of access to other treatment options, (4) inability to return for follow-up, and (5) patient choice. Macular tumor location is a relative indication for enucleation, since radiotherapy in this location will usually result in poor vision. However, quality-of-life studies are needed to determine whether patients with macular tumors are more satisfied with enucleation or radiotherapy. Although pre-enucleation radiotherapy reduces the viability and replicative capacity of uveal melanoma cells [38–40], the COMS recently determined that external-beam radiotherapy prior to enucleation does not improve the survival of patients with large uveal melanomas (thickness greater than 10 mm or diameter greater than 16 mm) [41], confirming earlier retrospective studies [42,43].

In the 1970s, Zimmerman and colleagues raised the possibility that enucleation may hasten the development of metastatic disease, possibly by disseminating tumor emboli [44]. The ''Zimmerman hypothesis'' was based on certain statistical assumptions that are now questioned, but there is still evidence from animal models that enucleation may promote metastatic disease. Primary tumors that produce angiostatin, an inhibitor of endothelial cell proliferation, may suppress the vascularization and growth of metastatic deposits; therefore, removal of the primary tumor may allow metastases to grow [45]. Since some uveal melanomas produce angiostatin and appear to suppress metastasis in animal models [46], further work is needed to investigate this mechanism in humans and to determine whether angiostatin therapy may be beneficial in uveal melanoma patients at high risk for metastasis.

C. Radiotherapy

Conventional external-beam radiotherapy is not often used for uveal melanoma, because the high radiation doses required to treat this radioresistant tumor would lead to severe ocular and periocular complications. Brachytherapy allows much higher radiation doses to be delivered locally with acceptable complications. Although ocular brachytherapy for intraocular tumors had been attempted earlier in the twentieth century, it was not until the 1970s that interest in brachytherapy intensified as a result of the Zimmerman hypothesis (see above). Typically, ocular brachytherapy involves attaching radioactive seeds to a lead or gold ''plaque'' that is sewn to the sclera overlying the tumor. Currently, iodine 125 (^{125}I) is the most common radioisotope used in the United States [47], whereas ruthenium 106 (^{106}Ru) is commonly used in Europe [48]. Other isotopes, such as palladium 103 (^{103}Pd), have also been used [49]. Typically, 80–100 Gy is delivered to the tumor apex over 4–5 days, with a 2-mm plaque margin around the tumor base [47]. While the dosimetric characteristics of ^{125}I allow treatment of tumors up to 10–12 mm in thickness, ^{106}Ru has much weaker penetration and can be used only to treat tumors up to about 5 mm

in thickness [48]. This fact has probably contributed to the more rapid development of other treatment modalities in Europe, such as local resection and stereotactic radiosurgery (see below).

In a prospective, multicenter trial conducted by the COMS to compare enucleation versus ^{125}I radiotherapy for medium-sized tumors (2.5 to 8 mm in thickness, diameter no greater than 16 mm), no significant difference in survival was identified [50], confirming previous impressions from retrospective studies [51]. An initial quality-of-life study from several COMS centers showed that patients undergoing radiotherapy scored higher on vitality and mental components of the Medical Outcome Study Short Form than patients treated by enucleation, but no other significant differences in quality of life were detected [52]. Additional outcomes studies of patient subgroups (e.g., tumor location and size, patient age and health status) are needed to guide the optimal treatment choice for a given patient.

Many uveal melanomas do not meet the COMS criteria for plaque radiotherapy but may nevertheless benefit from this treatment. In many centers, larger tumors up to about 18 mm in diameter and 10–12 mm in thickness are often treated with plaque radiotherapy with acceptable results, albeit with higher radiation complication rates. Some centers have been reluctant to treat juxtapapillary tumors with plaque therapy, due to a higher risk of local recurrence and metastasis. However, the success rate for treating these tumors appears to be improved by using notched plaques, intraoperative ultrasound to guide plaque placement, and adjuvant transpupillary thermotherapy (Fig. 3) [53–56]. In addition, selected iris melanomas appear to respond favorably to plaque radiotherapy [57,58]. Further prospective, controlled studies will be needed to determine the indications for plaque therapy other than those addressed in the COMS.

Complications of plaque radiotherapy include radiation complications (e.g., cataract, retinopathy, papillopathy, and neovascular glaucoma) and local tumor recurrence, which is a strong risk factor for metastatic disease [38,59,60]. The incidence of radiation complications are dose-dependent and begin to increase sharply over about 40 Gy [61], which is below the minimum threshold thought to be necessary for local tumor control. Therefore, pharmacological interventions that render the tumor more radiosensitive could greatly improve visual and ocular outcomes after plaque therapy. Local tumor relapse, which may occur in up to 15% of patients, is most common in posterior tumors near the optic nerve and macula [62–64]. One explanation for these local failures in posterior tumors may be inaccurate plaque placement due to limited surgical access and obstruction by extraocular muscles, optic nerve sheath, and other structures. Recent studies have shown that intraoperative ultrasonography is very helpful for localizing plaques accurately and identifying plaques that are tilted away from the sclera (Fig. 2) [54,65]. Preliminary studies have further shown that routine use of intraoperative ultrasonography may reduce the rate of local tumor recurrence [56].

Charged particle therapy, usually from a proton beam or helium ion source, is a means of delivering highly focused radiation to treat uveal melanomas. The indications and complications are similar to those for plaque radiotherapy except that anterior segment complications and neovascular glaucoma are more common with charged particles [62]. Reported rates of local tumor recurrence are lower for charged particles than plaque radiotherapy (especially for juxtapapillary tumors) [38,59,62], but results with plaque therapy may be substantially improved by the use

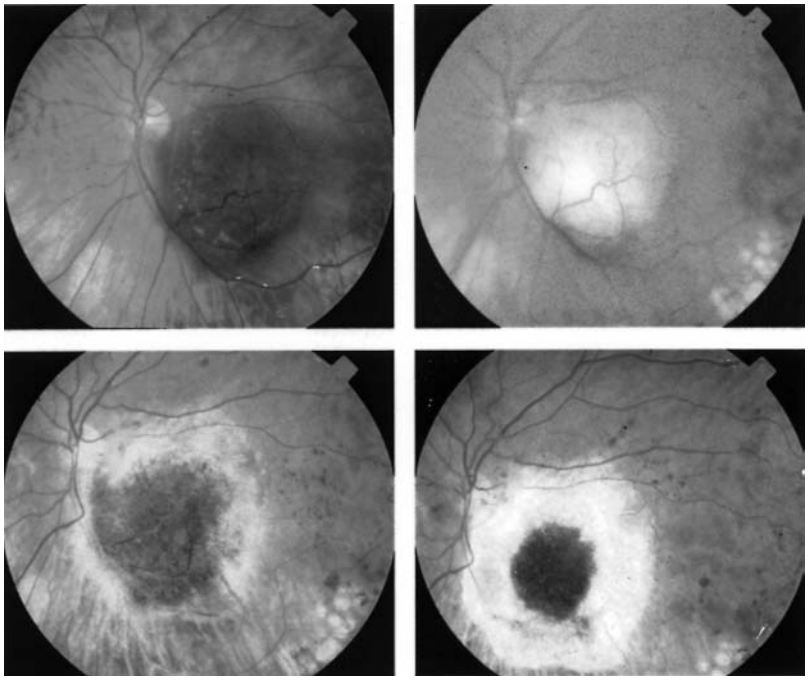

Figure 3 Plaque radiotherapy and transpupillary thermotherapy have a synergistic effect on uveal melanoma regression. A juxtapapillary tumor did not shrink significantly at 12 months following plaque radiotherapy (top, left). Therefore, adjunctive transpupillary thermotherapy was applied (top, right). Within 6 weeks, the tumor began to respond (bottom, left), and after 6 months the tumor was markedly regressed (bottom, right). Local control has been maintained on long-term follow-up. The retinal hemorrhages are due to a branch retinal vein occlusion.

of intraoperative ultrasonography for plaque localization and adjuvant laser thermotherapy (see above) [54–56]. In addition, charged particle therapy is more expensive than plaque therapy and is available at only a limited number of centers. Therefore, the situations where charged particle therapy is clearly preferable to plaque therapy remain unclear. Stereotactic radiosurgery is another modality that allows a radiation source to be focused from an external source in order to minimize radiation complications to the eye and periocular tissues [65]. Most experience with this technique had been in Europe, and it remains unclear what role it will have in the treatment armamentarium.

D. Local Resection

Iridocyclectomy is widely performed for melanomas involving the iris and ciliary body [66]. Cyclochoroidectomy is occasionally used in some centers for more posterior tumors [67]. Complications may include retinal detachment, proliferative vitreoretinopathy, intraocular hemorrhage, and local tumor recurrence, for which prophylactic scleral buckling, vitrectomy, hypotensive anesthesia, and postoperative

plaque radiotherapy, respectively, have been advocated [68]. However, these interventions carry their own risks and must be weighed against potential benefits compared to other treatments such as plaque radiotherapy. Melanoma-containing eyes that were enucleated as part of the COMS demonstrated frequent invasion of local structures such as the retina, vitreous, and blood vessels [33], suggesting that tumor cells may often be left in the eye following local resection. On the other hand, most of the melanomas in this study were large, advanced tumors that may not have been candidates for local resection.

A matched-group, retrospective study by Augsburger and colleagues comparing local resection to cobalt-60 (^{60}Co) plaque radiotherapy found no significant difference in survival between the two treatments [69]. Interestingly, local resection was associated with a much higher risk of vision loss (<20/200) immediately following treatment, but the risk leveled off after about 1 year. In contrast, plaque therapy resulted in a slower but relentless loss of vision. The visual survival curves appeared to cross at about 7 years posttreatment, suggesting that the rate of long-term visual loss may actually be higher in the radiated patients. Based on these findings, the authors suggested that the optimal indications for local resection may include younger patient age, anterior tumor location, greater tumor thickness, and smaller tumor base.

In the absence of a prospective, randomized clinical trial to examine patient outcomes after local resection, ocular oncologists will continue to be guided by their training experience, familiarity, and skill with this challenging surgical technique as well as the availability of alternative treatments. ^{125}I plaque radiotherapy would appear to provide superior visual potential and local control in many situations, but ^{125}I is not uniformly available. Where only ^{106}Ru is available, combining local resection with plaque therapy may be a reasonable approach to avoid enucleation. A well-designed clinical study is needed to determine the optimal surgical technique and the appropriate indications for local resection.

E. Transpupillary Thermotherapy

Hyperthermia acts synergistically with radiation to induce regression of tumors [70]. Various techniques have been used for ocular hyperthermia, including microwaves, localized current field, ferromagnetic seeds, and ultrasound [71–74]. More recently, Oosterhuis and colleagues introduced "transpupillary thermotherapy" (TTT) as a less invasive and more convenient technique for delivering heat to intraocular tumors [75]. The Oosterhuis group established the current parameters for TTT, including 810-nm infrared diode laser, a large spot size (2–3 mm), 1-min exposures, and low energy, with the goal of creating a light-gray discoloration of the tumor at the end of each application. For uveal melanoma, TTT is usually administered via a slit-lamp attachment, but it can also be delivered through the operating microscope or indirect ophthalmoscope. Using this technique, TTT increases the temperature of the tumor above 45°C but below the threshold for photocoagulation; it can cause tumor necrosis to a depth of 3.9 mm [75].

The Oosterhuis group has advocated the use of TTT in conjunction with plaque therapy [55]. Nevertheless, it has been adopted in the United States largely as primary therapy for small melanomas [76–78]. Although early reports from United States centers have been favorable, these results must be interpreted with the

following cautions in mind. First, TTT can cause significant vision-threatening complications such as macular traction, retinal vascular occlusion, macular edema, macular pucker, retinal or vitreous hemorrhage, and visual field defects [77,78]. Therefore, it remains unclear whether visual outcomes following TTT are superior (or even equivalent) to plaque therapy. Second, although the available data from the literature indicate a low local recurrence rate for TTT, these reports included very short follow-up. With longer observation, most centers are now seeing more local recurrences with TTT. Since local recurrence is a risk factor for metastasis after plaque radiotherapy [38], incomplete treatment with TTT may not have a neutral effect on survival. Third, many of the tumors treated with TTT that have been reported in the literature were very small with little or no documented growth [76–78], raising the question of whether some of these lesions may actually have been nevi. Further, if these studies used indications for treatment that differed substantially from those generally accepted for plaque therapy and other modalities, comparisons will be difficult to make between TTT and these other modalities. Thus, the role of TTT as primary therapy for uveal melanomas must be viewed with caution until there is a well-designed prospective study that provides treatment guidelines and meaningful estimates of visual outcome, local control, and metastatic risk.

Despite these reservations, TTT may still be appropriate in some situations (e.g., in patients that cannot undergo surgery), and TTT is likely to play an important role as an adjunct to plaque radiotherapy. TTT following plaque therapy causes melanomas to regress more rapidly and completely [55,79], indicating a possible synergistic interaction (Fig. 3). Combination therapy may be particularly useful in tumors with a high risk of local recurrence, such as juxtapapillary tumors. Radioresistant tumors are often responsive to plaque radiotherapy when combined with TTT (Fig. 3) [55]. Limited areas of local tumor recurrence often can be treated successfully with TTT, thereby avoiding enucleation. Although attitudes toward TTT continue to vary widely, the appropriate role of this modality will remain unclear until a properly designed clinical study is performed.

IV. PROGNOSIS AND SURVIVAL

Metastasis occurs in a substantial proportion of patients with uveal melanoma. In a metanalysis of patients enucleated for uveal melanoma, 5-year mortality rates were 16% for small tumors, 32% for medium-size tumors, and 53% for large tumors, with most mortality due to metastatic disease [36]. The most common metastatic sites include liver (87–93%), lung (24–46%), bone (16–29%), and skin (11–17%) [80,81]. The median time from ocular diagnosis to metastasis is about 2 years [82]. Median survival following clinical detection of metastasis is about 5–9 months [81–83]. Patients diagnosed with metastatic disease during routine screening examinations have a longer survival than those who become symptomatic prior to detection [82], supporting the practice of periodic systemic screening. Based on estimates of growth rates of metastatic tumors, an interval of 4–6 months has been suggested for systemic screening, although many centers perform this testing on an annual basis [84].

Numerous treatments have been proposed for metastatic uveal melanoma, including systemic chemotherapy, hepatic intra-arterial chemotherapy, chemoembo-

lization, interferon, cytotoxic immunotherapy, and surgical resection [85–90]. Even though these therapies are rarely curative, they may reduce the growth rate of metastatic tumors and prolong survival [82,84]. Accurate prediction of metastatic risk may allow appropriate patients to be identified for prophylactic systemic therapy. Clinical risk factors for metastasis include advanced age, male gender, larger tumor size, anterior location, and extrascleral extension [91–95]. Pathological risk factors for metastasis include epithelioid cell type, nuclear and nucleolar pleomorphism, and intratumoral vascular patterns [86,92,95–98]. Nonrandom cytogenetic abnormalities have also been linked to metastasis and poor survival, including loss of chromosome 3, loss of chromosome 6q, and gain of chromosome 8q [99–102]. Further studies are needed to determine how clinical, pathological and molecular characteristics of a tumor can be combined to provide highly accurate prognostic information.

V. UNANSWERED QUESTIONS

Despite significant advances in the diagnosis and treatment of uveal melanoma over the past decades, many important questions remain unanswered. When should small melanocytic lesions be treated? The consensus has been to observe small, indeterminate lesions for growth prior to treatment, but this response raises other questions. What is the appropriate definition of a small, indeterminate lesion? Most ocular oncologists consider lesions over 2.5–3 mm in thickness to be highly suspicious for melanomas. The COMS initially defined tumors up to 3.0 mm in thickness to be small tumors to be observed, but this definition was later changed arbitrarily to 2.5 mm [103]. More objective data are still needed to identify which small tumors are melanomas that should be promptly treated. Does observation until growth is documented increase the risk of metastasis? Augsburger and Vrabec found no difference in mortality in a case-matched, retrospective survival study comparing patients who were promptly treated versus those who were treated only after tumor growth was documented [104]. In contrast, Shields and colleagues determined from a retrospective study that documented growth was a risk factor for metastasis in small melanocytic choroidal tumors $\leqslant 3$ mm in thickness [105]. These contradictory results, and the other unanswered questions discussed above, point out the need for a prospective, randomized study of small tumors to compare prompt treatment versus observation.

VI. FUTURE ADVANCES

Future advances in diagnosis, prognosis, and treatment may improve survival in uveal melanoma patients. Current diagnostic techniques are highly accurate in differentiating melanoma from simulating lesions [33], but future advances in imaging and molecular diagnostic techniques may yield therapeutic and prognostic information that could allow management to be customized for individual patients. High-resolution ultrasonographic and angiographic imaging techniques, such as confocal ICG angiography, may allow the delineation of histological characteristics and vascular patterns within the tumor [106]. Noninvasive molecular imaging may allow the expression of cancer genes to be monitored [107]. Minimally invasive fine-

needle aspiration biopsy can yield sufficient tumor material for molecular and genetic testing [108]. For example, a small biopsy specimen could be screened using microsatellite markers, gene expression microarray analysis, and other techniques to examine genetic abnormalities known to have prognostic significance [109]. Current metastatic screening with liver function studies and conventional imaging modalities have a relatively low sensitivity for detecting metastasis, but new molecular diagnostic techniques may allow the detection of early micrometastasis at a stage where systemic intervention would be more effective. One such technique utilizes the reverse transcriptase polymerase chain reaction to detect melanocyte-specific genes in patient serum [110].

Effective treatment for metastatic uveal melanoma is one of the most recalcitrant and challenging areas for research. Most experimental approaches focus on immune modulation, such as interferon therapy [86], cytotoxic T-cell immunotherapy [89], and vaccination [111]. In light of animals studies linking angiostatin production by the primary tumor with suppression of metastasis [46], further studies are needed to test the efficacy of angiostatin or other antiangiogenic agents in metastatic disease. Some investigators are searching for molecular characteristics of melanoma cells that account for their profound chemoresistance. Melanoma cells express transport proteins that lead to multidrug resistance by pumping chemotherapeutic agents out of the cell, and expression of these genes has been linked to poor survival [112,113]. Agents that block these proteins could render melanoma cells more sensitive to chemotherapy. Radioresistance in melanoma cells may be may be due in part to defective signaling in the p53 pathway [114], suggesting that reactivation of p53 may render melanomas more radiosensitive. As our molecular understanding of uveal melanoma increases, molecular phenotyping of individual tumors may allow therapy to be individualized for each patient [115].

Looking into the future, a patient diagnosed with a uveal melanoma may undergo a series of noninvasive and/or minimally invasive studies to generate an array of clinical, pathological, and molecular data that indicate the optimal therapy for the intraocular tumor, the risk of metastatic disease, and other prognostic and therapeutic information. The intraocular tumor will then be treated, and prophylactic systemic therapy may be initiated if the metastatic risk is high. Vision loss from plaque radiotherapy may be significantly reduced by the use of adjunctive molecular agents that render the melanoma more radiosensitive, thereby allowing lower radiation doses to be used. The patient subsequently will be screened at regular intervals using sensitive molecular assays for micrometastasis. Metastatic disease will be detected much earlier than by conventional screening, allowing systemic therapy to be more effective. Molecular phenotyping may indicate the optimal of combination of immunotherapy and highly selective molecular agents for systemic treatment.

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2

Clinical Overview: Retinoblastoma

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Retinoblastoma is the most common and most important malignant intraocular tumor of childhood. It is important for the ophthalmologist to make a prompt and accurate diagnosis and to refer the patient to an ocular oncologist and/or other specialists for appropriate treatment. This chapter considers general aspects and clinical features of retinoblastoma. For completeness, it briefly alludes to pathology and management of retinoblastoma, but these are discussed in greater detail in other chapters. The subject of retinoblastoma is also covered in more detail in the authors' textbooks on the subject of intraocular tumors [1–3].

I. GENERAL CONSIDERATIONS

Retinoblastoma is second to uveal melanoma as the most common primary intraocular malignancy in humans. In parts of the world where uveal melanoma is rare, such as Africa and Asia, retinoblastoma is the most common primary malignant intraocular tumor. Although estimates vary, it occurs with a frequency of approximately 1 in 15,000 to 1 in 23,000 live births [4]. Approximately 6% of newly diagnosed retinoblastoma cases are familial and 94% are sporadic. All patients with familial retinoblastoma are at risk to pass the predisposition for the development of the tumor to their offspring. The details of the genetics of retinoblastoma are discussed in Chap. 3.

There is no apparent predisposition of retinoblastoma for race or sex and no predilection for the right or left eye. The tumor occurs bilaterally in 25–35% of cases. In the multicentric or bilateral cases, the average number of tumors per eye is five, with a random distribution between the two eyes. The tumor is diagnosed at an

average age of 18 months, with the bilateral cases being recognized at an average age of about 12 months and the unilateral cases at 23 months. In rare instances, the tumor is first recognized at birth, in the teens, or even in adulthood [1,5].

II. CLINICAL FEATURES

The clinical features of retinoblastoma vary with the stage of the disease at the time of diagnosis.

A. Early Signs

1. Strabismus

When retinoblastoma arises in the foveal region, it can cause loss of central fixation, which can lead to strabismus, either exotropia or esotropia. Although most children with strabismus do not have retinoblastoma, it is important that every child with this finding have a comprehensive fundus examination to exclude the possibility of retinoblastoma or other organic cause for visual loss [1].

2. Leukocoria

As retinoblastoma grows, it eventually causes leukocoria (white pupillary reflex). When the tumor is small, the leukocoria may be apparent only in certain fields of gaze. When the tumor is large enough to fill more than one-third of the globe, the white reflex becomes apparent in all fields of gaze (Fig. 1) [1].

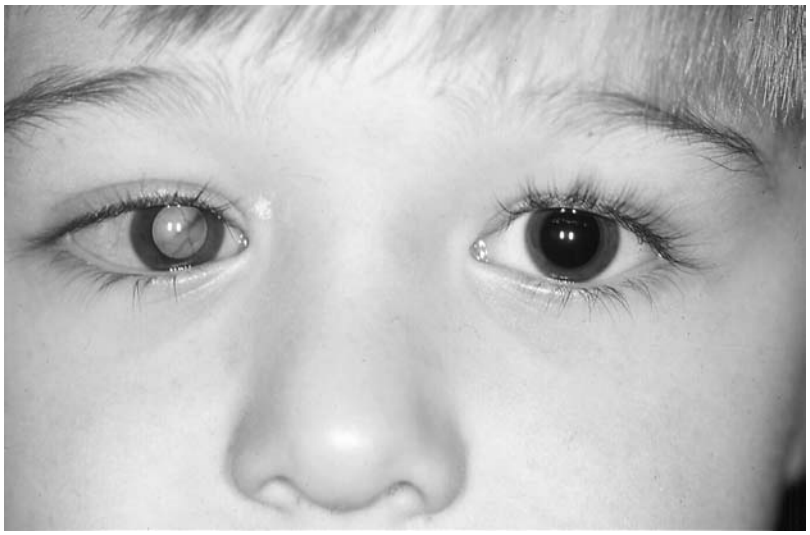

Figure 1 Leukocoria in a child with retinoblastoma.

B. Growth Patterns

1. Intraretinal Lesions

Retinoblastoma begins as a transparent lesion in the sensory retina. As it enlarges, it becomes opaque white (Fig. 2). With further tumor enlargement, dilated tortuous retinal arteries and veins develop to supply and drain the tumor (Fig. 3). Some untreated retinoblastomas show foci of chalk-like calcification that has been likened to cottage cheese (Fig. 4). More characteristically, retinoblastoma is larger at the time of presentation and it assumes either an endophytic or an exophytic growth pattern. Such larger tumors almost always cause leukocoria.

2. Endophytic Growth Pattern

Some retinoblastomas are associated with seeding of tumor cells into the overlying vitreous. Such an endophytic growth pattern is characterized by a white hazy mass over which no retinal vessels can be visualized (Fig. 5). Because of their friable nature, endophytic tumors can eventually seed the entire vitreous cavity and simulate endophthalmitis. An endophytic retinoblastoma can also seed into the anterior chamber and produce multiple nodules at the pupillary margin. With time, the cells may settle into the inferior portion of the anterior chamber angle and resemble a hypopyon [1].

3. Exophyic Growth Pattern

An exophytic retinoblastoma is one that grows from the retina outward into the subretinal space. In contrast to an endophytic tumor, the retinal vessels are apparent with ophthalmoscopy. Such tumors produce a progressive retinal detachment, with the retina often displaced anteriorly behind the clear lens and a white mass

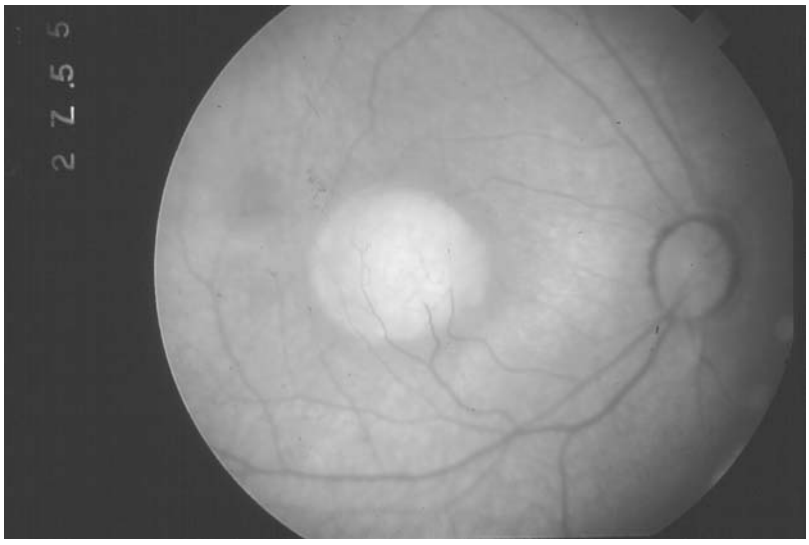

Figure 2 Small retinoblastoma showing white color of tumor.

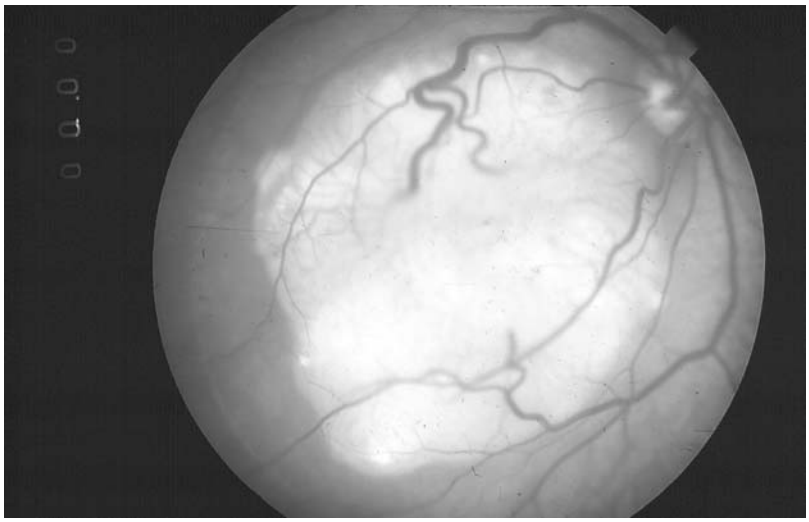

Figure 3 Retinoblastoma with dilated, tortuous retinal blood vessels.

immediately behind the detached retina (Fig. 6). An exophytic retinoblastoma can clinically resemble Coats disease or other forms of exudative retinal detachment [1].

4. Diffuse Infiltrating Growth Pattern

Diffuse infiltrating retinoblastoma is a less common form of retinoblastoma, characterized by a relatively flat infiltration of the retina by tumor cells [6,7]. Because an obvious mass is not present, there is often a delay in diagnosis and sometimes

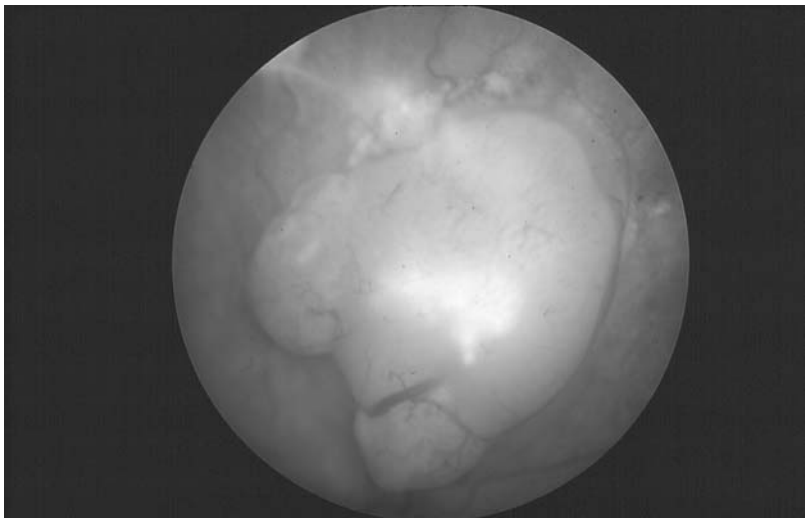

Figure 4 Retinoblastoma with foci of calcification.

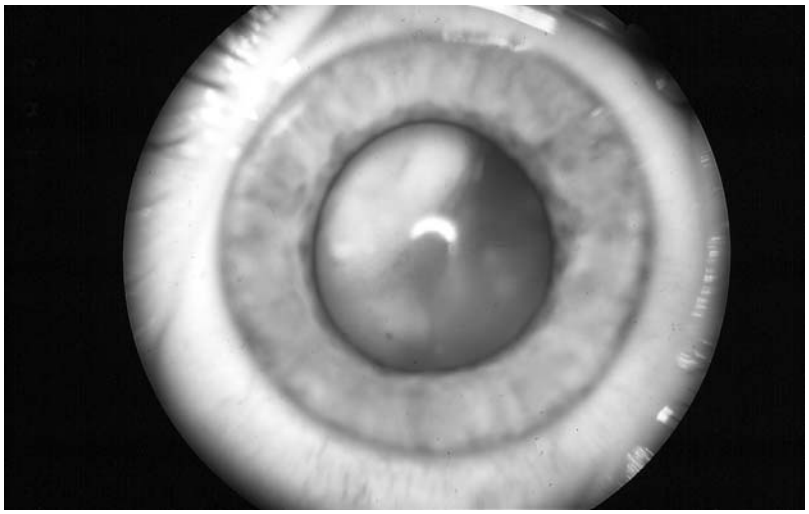

Figure 5 Endophytic retinoblastoma.

misdirected intraocular surgery [8]. Therefore, diffuse retinoblastoma is usually recognized clinically at an older age than typical cases of retinoblastoma. These lesions frequently produce vitreous and anterior chamber seeding, which may cause diagnostic confusion with intraocular inflammation (Fig. 7). Fortunately, almost all reported cases of diffuse infiltrating retinoblastoma have been unilateral sporadic cases with a negative family history. Because of the extensive intraocular seeding in most instances, enucleation has been considered to be the best management.

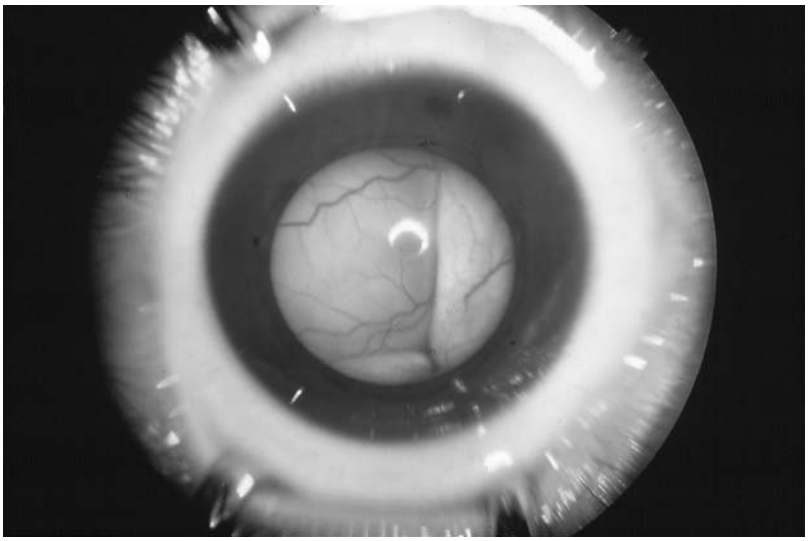

Figure 6 Exophytic retinoblastoma.

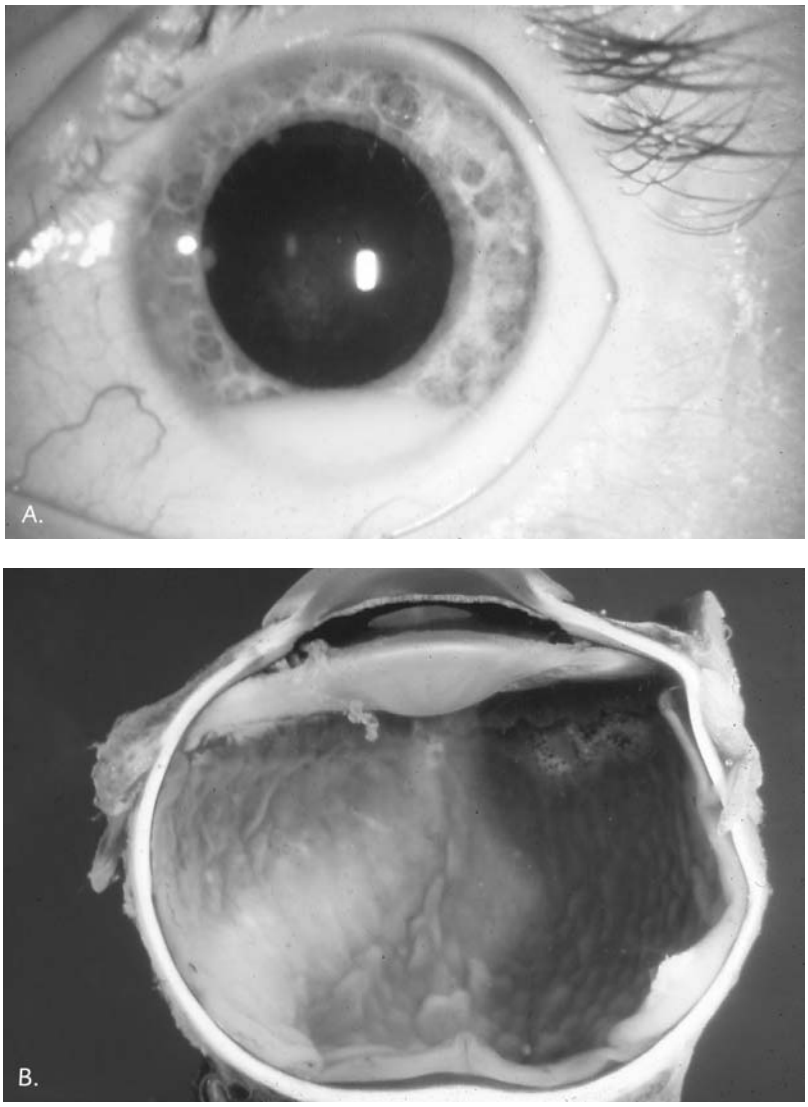

Figure 7 Spontaneous pseudohypopyon secondary to diffuse infiltrating retinoblastoma. A. Anterior segment, showing white pseudohypopyon. B. Section of enucleated eye through main calotte, showing flat diffuse retinoblastoma with not elevated mass and no calcification.

C. Advanced Presentations

1. Neovascular Glaucoma

Iris neovascularization (rubeosis iridis) occurs in 17% of all children with retinoblastoma [9] and in about 50% of eyes with advanced retinoblastoma that require enucleation [10]. We believe that iris neovascularization usually accounts for the acquired heterochromia iridis that characterizes some cases of retinoblastoma.

Any infant with unexplained acquired heterochromia should be evaluated for possible retinoblastoma. Spontaneous bleeding form these vessels may cause a hyphema [11].

2. Orbital Cellulitis

Some necrotic retinoblastomas produce severe secondary periocular inflammation, resulting in a clinical appearance of preseptal cellulitis or endophthalmitis [12,13]. Computed tomography (CT) in such cases can reveal a large calcified intraocular mass with periocular soft tissue density suggesting extraocular extension of retinoblastoma.. However, these advanced cases usually do not have evidence of extraocular extension after enucleation of the affected eye. The periocular inflammation seen with appears to be secondary to necrosis within the tumor and not secondary to extraocular extension of the tumor.

3. Extraocular Extension

Although some retinoblastomas can exhibit extension into the optic nerve, it is usually a microscopic observation found on histopathological study of the eye following enucleation. However, it neglected cases, or when the parents or guardians refuse treatment, the tumor can eventually break out of the eye and exhibit massive orbital and extraorbital extension (Fig. 8). Such an advanced presentation is rare in countries with advanced medical care, but it is common in third-world countries where advanced medical care is not readily available.

D. Other Clinical Variations

1. Trilateral Retinoblastoma

In recent years it has been recognized that some children with the familial form of retinoblastoma can also develop a pinealoblastoma [14,15]. The pineal tumor has many similarities to retinoblastoma from embryological, pathological, and immunological standpoints. The pineal tumor is best detected with high quality CT or magnetic resonance imaging (MRI). The prognosis for life is guarded. Most children who die from retinoblastoma have some degree of intracranial involvement, usually secondary to direct spread through the optic nerve or subarachnoid space. It is quite likely that some earlier reported cases of presumed brain metastasis probably represented pinealoblastoma or other parasellar neoplasms (''trilateral retinoblastoma'') that were misdiagnosed as metastatic retinoblastoma before the entity of trilateral retinoblastoma was recognized.

2. Retinocytoma

Recent evidence has accumulated to support the existence of an uncommon benign variant of retinoblastoma that has been termed *retinoma* [16] or *retinocytoma* [17]. We believe that the term *retinoma* is too general, since it could be interpreted to mean any tumor of the retina. Although no terminology is perfect, there is a stronger argument for using either the term *retinocytoma* or *spontaneously arrested retinoblastoma* to define this condition [1]. A retinocytoma carries the same genetic implications as an active retinoblastoma [16].

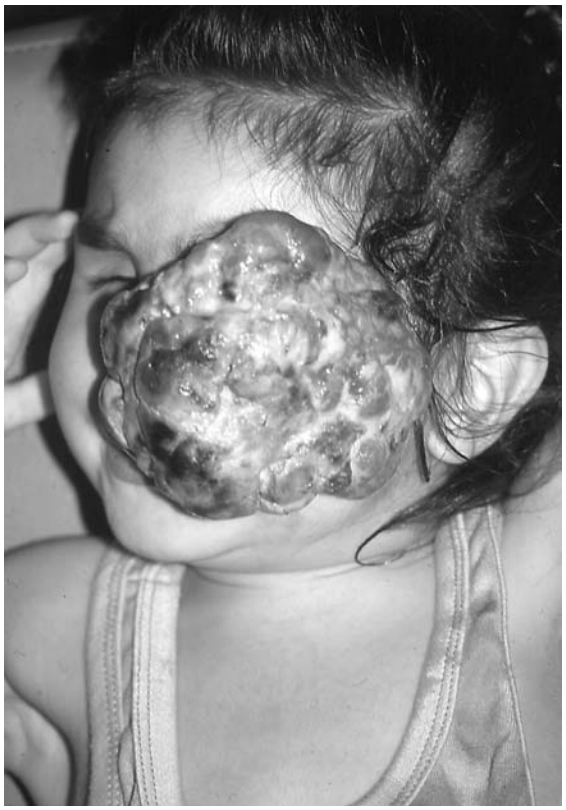

Figure 8 Advanced retinoblastoma with massive extraocular extension.

3. Spontaneously Regressed Retinoblastoma

Complete spontaneous necrosis leading to regression and a "cure" is a well-known phenomenon that is said to occur more frequently in neuroblastoma and retinoblastoma than with other malignant neoplasms [1]. It is characterized by a severe inflammatory reaction in the eye, sometimes followed by the development of phthisis bulbi. In cases of spontaneous regression of a smaller retinoblastoma, the eye may retain useful vision. (Fig. 9) It is not certain whether such tumor regression occurs secondary to vascular ischemia to the tumor or whether more complex immunopathologic mechanisms play a role. In any child with a phthisical eye of uncertain cause, the diagnosis of spontaneously regressed retinoblastoma should be considered. Spontaneously regressed retinoblastoma carries the same genetic implications as an active retinoblastoma.

III. DIFFERENTIAL DIAGNOSIS

There are a number of conditions that can simulate retinoblastoma, either by causing a small white fundus lesion or by producing leukocoria. In a series of 500 consecutive

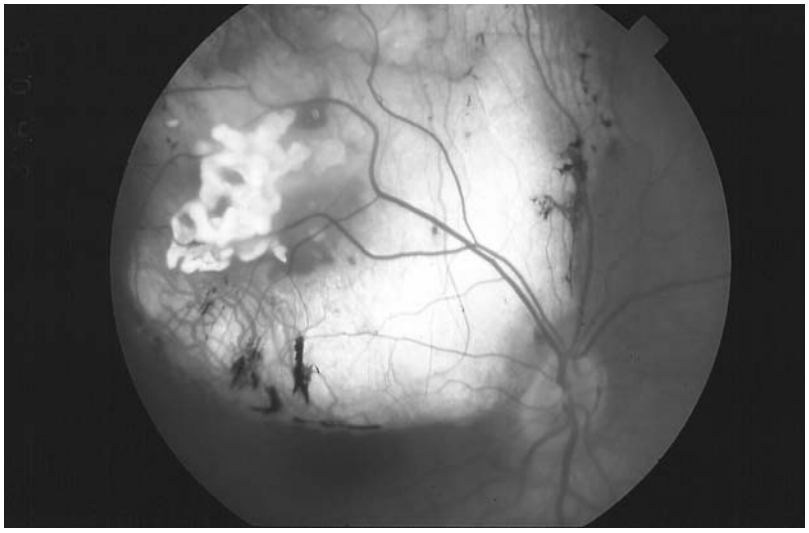

Figure 9 Spontaneously regressed retinoblastoma in an eye with useful vision. The margin of the regressed tumor barely spares the foveola.

patients referred with the diagnosis of possible retinoblastoma, 288 proved on subsequent evaluation to have retinoblastoma and 212 proved to have simulating lesions [18–20].

A. Other Intraocular Tumors

Other tumors are known to sometime simulate retinoblastomas. These include astrocytic hamartoma, medulloepithelioma, combined hamartoma, retinal capillary hemangioma, and sometimes amelanotic choroidal melanoma [18–20].

B. Other Nontumorous Conditions

In the above series, the conditions most often referred for suspected retinoblastoma were persistent hyperplastic primary vitreous (28%) Coats disease (16%) [21], and ocular toxocariasis (16%) [22]. Other nonneoplastic conditions included retinopathy of prematurity, retinopathy of prematurity, dominant exudative vitreoretinopathy, endogenous endophthalmitis, congenital cataract, congenital toxoplasmosis, chorioretinal coloboma, myelinated nerve fibers, and scar tissue secondary to surgical trauma [18–20].

IV. DIAGNOSTIC APPROACHES

A patient with suspected retinoblastoma should have a detailed history taken and receive general medical evaluation, external ocular examination, slit-lamp biomicroscopy, and indirect ophthalmoscopy to substantiate the diagnosis. In addition,

certain ancillary studies—such as fluorescein angiography, ultrasonography, CT, and MRI—can assist in the diagnosis.

A. Fluorescein Angiography

Fluorescein angiography can provide diagnostic and therapeutic information in selected children with discreet retinoblastoma [3,24]. Very small intraretinal tumors show only minimally dilated feeding vessels in the arterial phase, mild hypervascularity in the venous phase, and mild late staining of the mass (Fig. 10). Slightly larger intraretinal tumors show more intense hypervascularity and late staining. Moderate-sized tumors usually demonstrate markedly dilated feeding arteries and draining veins. Such tumors also show numerous fine capillary ramifications on the tumor surface.

B. Ultrasonography

Retinoblastomas have ultrasonographic features that usually help to differentiate them from the pseudoretinoblastomas [3]. A-scan typically shows constant high internal echoes within the tumor and rapid attenuation of the normal orbital pattern. There is frequently an anechoic area in the basal portion of the tumor nearest the sclera. B-scan ultrasonography characteristically shows a rounded or irregular intraocular mass with numerous highly reflective echoes within the lesion. A characteristic feature of B scan is attenuation or absence of the normal soft tissue echoes in the orbit directly behind the tumor (Fig. 11). This occurs as a result of

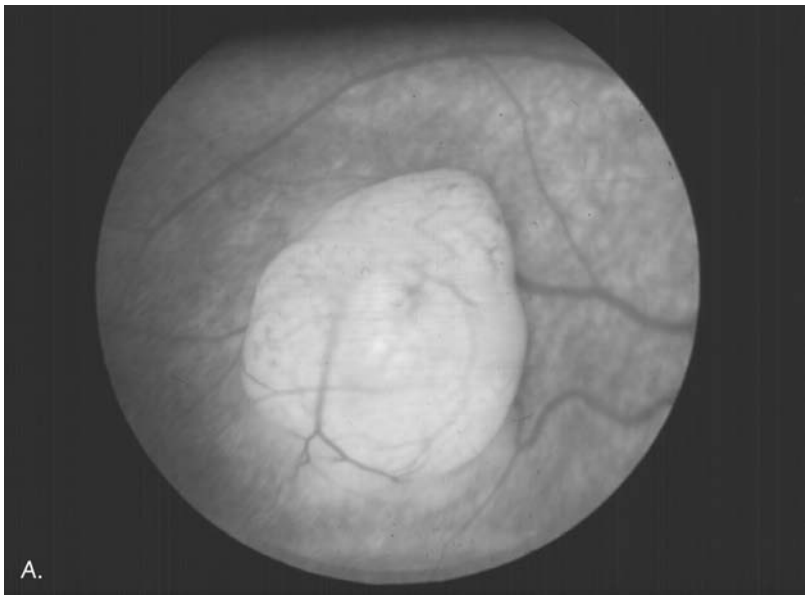

Figure 10 Fluorescein angiography of retinoblastoma. A. Clinical appearance of tumor. B. Arterial phase, showing two feeding arteries. C. Late angiogram showing continued hyperfluorescence of the mass.

attenuation and reflection of the sound by the calcification within the mass. These reflective focal echoes within the tumor persist after the soft tissues echoes of the eye have disappeared when the sensitivity of the ultrasound machine is lowered. Ultrasonography can be used to document tumor regression following radiotherapy.

C. Computed Tomography

Although both ultrasonography and CT can detect calcium in retinoblastoma, CT has the advantage over ultrasound in that it is better able to delineate extraocular

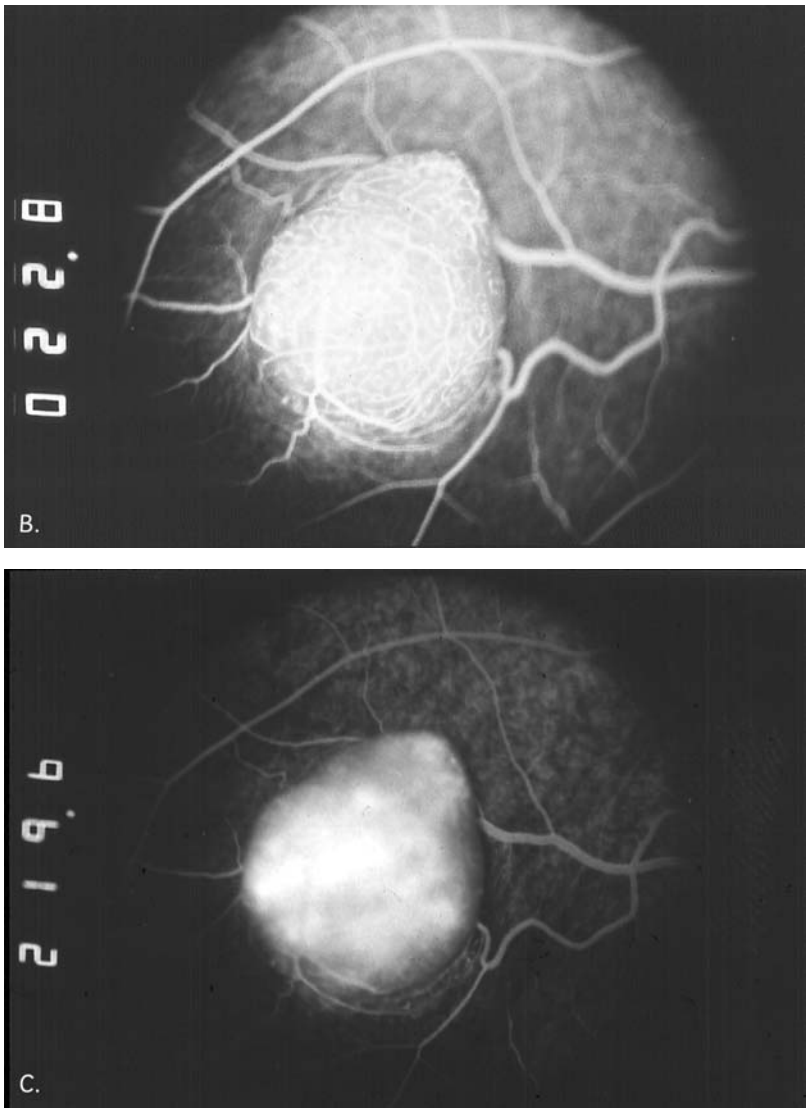

Figure 10 Continued.

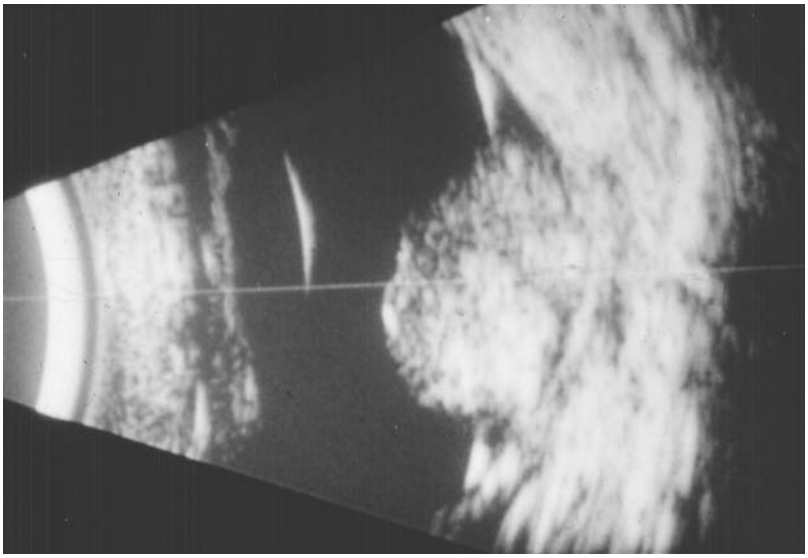

Figure 11 B-scan ultrasonography of retinoblastoma showing mass with calcification.

extension of tumor and to detect the presence of an associated pinealoblastoma (trilateral retinoblastoma).

With CT, retinoblastoma typically appears as an intraocular mass with foci of calcification within the tumor in greater than 80% of tumors [3] (Fig. 12). The presence of intraocular calcification with CT is suggestive of retinoblastoma but is not pathognomonic. Other conditions, such as retinal astrocytoma, advanced Coats disease, retinal angiomatosis, and ocular toxocariasis, can occasionally produce intraocular calcification or even ossification that can lead to misdiagnosis with ultrasonography or CT. Therefore, all of the clinical findings should be taken into account in making the diagnosis of retinoblastoma.

D. Magnetic Resonance Imaging

MRI may be of some diagnostic assistance in the evaluation of a child with suspected retinoblastoma [25]. A retinoblastoma is moderately hyperintense to vitreous on T1 weighted images and becomes hypointense in T2-weighted images. Areas of calcification are often accentuated on T2-weighted images. Some authorities have reported that associated hemorrhage and exudation appears markedly different from retinoblastoma tissue on T2-weighted images. Thus, MRI has potential value in evaluating patients prior to treatment and in monitoring their response to therapy by helping to differentiate between active tumor, hemorrhage, and exudation. However, more studies will be necessary to determine the value and limitations of MRI in the evaluation of children with suspected retinoblastoma.

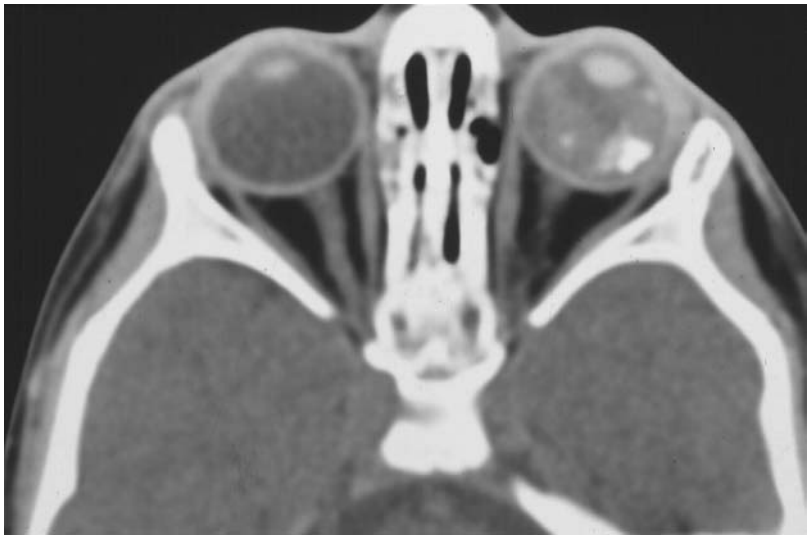

Figure 12 Computed tomography of retinoblastoma showing calcified intraocular mass.

V. PATHOLOGY

In most cases, retinoblastoma can be readily recognized in the sectioned eye by its typical appearance (Fig. 13). It is a chalky white, friable tumor with dense foci of calcification. An endophytic retinoblastoma usually produces seeding into the vitreous cavity An exophytic tumor tends to push the retina anteriorly and to occupy the subretinal space. Some tumors have both endophytic and exophytic components and others appear to be totally calcified as a result of marked necrosis [1]. The histopathological features of retinoblastoma are discussed in Chap. 9.

VI. MANAGEMENT

The management of retinoblastoma can be complex, and it is impossible to establish firm rules regarding treatment [26,27]. Each case must be individualized according to the entire clinical situation. Proper management necessitates the ability to use the various instruments, familiarity with the disease, and above all, experience in dealing with such problems [4]. There are several options available for the treatment of retinoblastoma, and the method selected should depend on the size and extent of the tumor(s), whether there is unilateral or bilateral involvement, and the patient's systemic status. The methods that we currently advocate include enucleation, external-beam irradiation, scleral plaque irradiation, photocoagulation, cryotherapy, chemotherapy, chemothermotherapy, and chemoreduction. In many cases it may be necessary to employ various combinations of treatment to achieve a satisfactory result [26–44]. These therapeutic modalities are considered in more detail in Chap. 8.

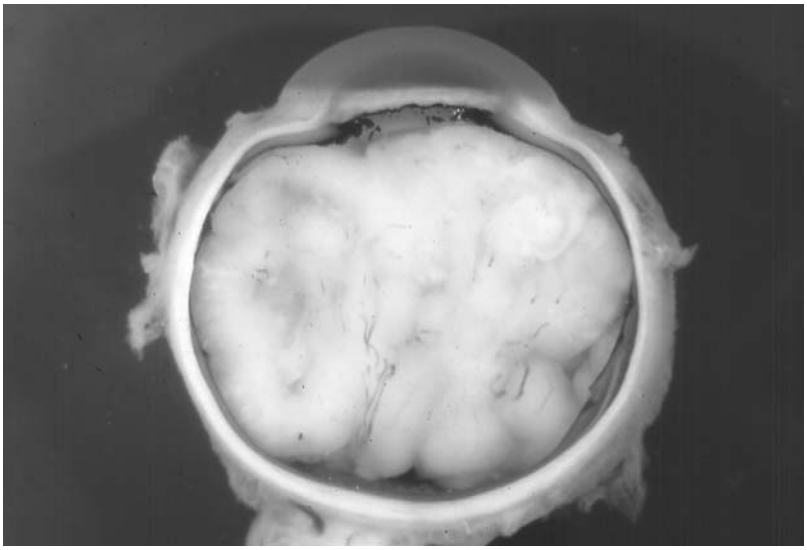

Figure 13 Grossly sectioned eye showing white retinoblastoma filling the interior of the eye. The massive white tumor correlates with the leukocoria seen clinically.

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3

Epidemiology of Uveal Melanoma: Patient Characteristics, Risk Factors, and Predisposing Elements

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Uveal melanoma is a rare disease but is the most common primary intraocular tumor and has a high potential for metastasis. The study of factors that determine the occurrence and distribution of this disease is critical in the understanding of its possible prevention. Previous knowledge of the epidemiology of uveal melanoma has been reviewed extensively [1–4], and we recommend these excellent readings. In the present chapter, we discuss the challenges associated with the epidemiologic study of uveal melanoma, review the current knowledge of its incidence and possible risk factors for diagnosis in light of new evidence, and outline future directions for epidemiologic research.

I. CHALLENGES ASSOCIATED WITH THE EPIDEMIOLOGIC STUDY OF UVEAL MELANOMA

Most of the current understanding of the epidemiology of uveal melanoma is based on surveys or registry data from many populations and on small observational studies in series of patients followed within clinical settings. The comparability of findings from these studies and generalizability to other populations are limited by

differences in study design and inconsistencies in the methods of disease classification, completeness of case ascertainment, and assessment of risk.

Definition and classification of uveal melanoma cases is central to any descriptive or analytic study. In developed countries, where access to state-of-the-art diagnostic tools is readily available, the accuracy of diagnosis is considered to be quite high [5,6]. However, considerable variability in inclusion criteria across published series complicates comparison. For example, some studies use "eye cancer" as a proxy for uveal melanoma in adults; this may be reasonable in the context of published series documenting that at least 70% of ocular neoplasms in adults comprise melanoma cell types [7]. Tumor stage and shape (usually inferred from basal dimension and/or apical height based on ultrasound), location within the uvea (choroid, iris, ciliary body, any or all sites), and cell type may represent subtypes of disease with differing etiology and prognosis; these subtypes may be distributed differently across populations or published studies. The advent of increasingly sophisticated diagnostic technology will permit more precise classification in future studies. Diagnostic accuracy and case definition may be less standard in older studies or those from the developing world; thus comparisons with other published studies must take these factors into account.

Comparison of incidence rates across populations and over time may be useful in generating etiologic hypotheses, but direct comparisons may be difficult due to variability in study design, including methods of adjusting for age. The incidence of uveal melanoma—i.e., the number of new cases occurring within a specified time period in a defined population—is generally derived from population-based registries. In countries with national systems of health care and central records, such as in northern Europe (e.g., Refs. 8,9), uveal melanoma registries are usually considered to be quite complete and the population base well defined. However, in all studies—and especially studies from societies with less structured or less universal health care systems—underascertainment is a concern. Methods of validating registry completeness exist [10] but have seldom been applied in uveal melanoma. Incidence estimates based on hospital-based case series are likely to be invalid due to lack of an appropriate population base.

In addition to documenting disease incidence, registries can be useful tools for conducting prospective or retrospective assessments of risk factors and prognosis [e.g., 11–14]. Retrospective, or case-control, studies are probably the most useful epidemiologic design for elucidating causative associations between risk factors and uveal melanoma because of the infrequent occurrence of this disease. This approach is subject to a number of inherent problems and biases that may complicate the interpretation of the results. Much has been written about selection of cases and controls, case definition, and potential difficulties with retrospective assessment of exposure (e.g., Refs. 15 and 16). Further complicating establishing etiologic associations in uveal melanoma is the presumed long latency period and the difficulty in quantifying exposures to hypothesized risks, such as to ultraviolet (UV) radiation [17]. For example, the literature contains many examples of case-control or cross-sectional investigations of the role of sunlight or UV exposure in causing uveal melanoma, with very mixed results. The inconsistencies in the findings may in part be due to variations in methods of defining and classifying exposure and the accuracy of retrospective assessment. Furthermore, it is generally very difficult in retrospective or cross-

sectional studies to establish the temporal sequence of presumed exposures and initiation of disease.

II. MAGNITUDE AND DISTRIBUTION OF CASES OF UVEAL MELANOMA

In the United States, the estimated incidence of intraocular malignancies has remained relatively constant over the last 30 years. The annual age-adjusted incidence estimate was 6 per million population based on the Third National Cancer Survey conducted from 1969 to 1971 [13]. Since that time, the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute has compiled the largest public-use database for cancer incidence in the United States. Nine regional SEER registries have reported all new cancer cases since 1973–1975; two registries were added in 1992. The annual age-adjusted incidence of noncutaneous melanoma was reported as 7 per million population during the period from 1973 to 1977 [18]. More recently, SEER data indicate that the age-adjusted incidence of eye and orbit cancer has remained relatively constant from 1992 through 1999 (7.6 cases per million population to 7.3 cases per million population [19]. Across the years 1992–1999, the overall age-adjusted incidence rate is 7.98 cases per million population; it should be noted that the U.S. population from the year 2000 is used as the standard population for these adjustments and represents a change from previous estimates. However, estimates based on population-based surveys conducted in the United States yield similar findings. In an incidence survey carried out from 1984 to 1989 in the six New England states, the annual incidence was 7.4 cases per million population [2].

Similar incidence rates have been reported from surveys conducted in Canada [20], Sweden [21], Finland [9], and Denmark [8]. In most populations, these rates have remained constant over the past several decades [22]. The incidence of uveal melanoma has appeared stable at 6 cases per million population over a 35-year period from 1961 to 1996 in Israel [23]. A higher incidence rate was observed in a population-based study in the United Kingdom using the General Practice Research Database; the estimated incidence rate was 11.6 cases per million person-years [24]. Age-adjusted incidence rates of up to 10 per million person-years have been reported in Europe [25]. An excellent source of worldwide cancer registry information is an electronic database compiled by the International Agency for Research on Cancer (IARC), which contains data from 149 population-based cancer registries covering 183 populations in 50 countries [26].

Based on the incidence rates from the NCI SEER program 1979–1998, the American Cancer Society estimated that about 2200 new cases of all primary intraocular cancers (eye and orbit) will be diagnosed in the United States in the year 2002; approximately 200 deaths will be due to these malignancies [27]. Assuming that at least 70% of all primary eye malignancies are uveal melanoma [28], this translates into at least 1600 new cases of uveal melanoma and approximately 150 deaths each year.

In contrast, the age-adjusted incidence between 1995 and 1999 for skin melanoma in the United States was 163 cases per million population [19], roughly 20 times higher than that of eye and orbit cancers. A recent report reviewed 84,836 cases

of cutaneous and noncutaneous melanoma in the United States [29] from the National Cancer Data Base from 1985 through 1994. This national cancer registry solicits all acute care hospitals to submit annually their cancer registry data. During this time period, 91.2% of cases were skin melanomas and 5.2% ($n = 4522$) were ocular melanomas. Of these 85% were uveal melanoma, 4.8% were conjunctival melanoma, and 10.2% occurred at other ocular sites.

III. PATIENT CHARACTERISTICS

Uveal melanoma occurs predominantly in individuals of Caucasian race, is associated with older age, and has been reported to occur more frequently in males than females. SEER data indicate increasing incidence with age in both males and females, with higher rates for males at all ages above 35 years [19]. The age-adjusted incidence rates by ethnicity are 8.9, 2.4, 3.9, 2.4, and 5.2 cases per million population for whites, blacks, American Indians/Alaskan Natives, Asian/Pacific Islanders, and Hispanics, respectively [19]. Recent statistics suggest that the age distribution of cases with new eye and orbit cancers is 32%, 24%, 22%, and 22% for individuals aged <50, 50–64, 65–74, and 75+ years, respectively [30]. Most studies suggest that the median age at diagnosis for the Caucasian population is approximately 60 years. In the review of ocular melanoma cases from the National Cancer Data Base, over 92% were white non-Hispanic, 52% were male, and the mean age at diagnosis was 60.4 years, with 75% aged 50 years or older [29]. This agrees with the mean age at diagnosis of 61 years obtained from the New England survey [2]. Similarly, a review of 184 Finnish patients with uveal melanoma diagnosed between 1994 and 1999 indicated that 47% were male and that the mean age at time of diagnosis was 60 years [31].

Race and ancestral origin appear to be associated with the development of uveal melanoma. Surveys among African and Asian populations indicate low risk of the disease [e.g., 32,33]. Similarly, in the United States, incidence in African Americans or other racial or ethnic groups is much lower than in Caucasians [2,34]. In a population-based study in Israel, there was considerable variation among ethnic groups; the highest incidence was observed in individuals with American- or eastern European-born parents [35]. Results from a previous case-control study suggest higher risk of uveal melanoma in individuals of northern European ancestry as compared to those of southern European or Mediterranean descent [36]. There appears to be ethnic variability in both incidence and age at diagnosis. The mean age at diagnosis of uveal melanoma in a series of Asian Indians was estimated as 46.1 years [37].

IV. RISK FACTORS FOR UVEAL MELANOMA AND PREDISPOSING ELEMENTS

A. Personal Characteristics

A number of personal characteristics have been associated with increased risk of uveal melanoma, including light irides [38–40], fair complexion [36] and melanocytic conditions such as ocular nevi [41], dysplastic nevus syndrome [42,43], and ocular