Ocular Oncology: Advances in Retinoblastoma, Uveal Melanoma and Conjunctival Melanoma

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Abstract

Introduction/background: Retinoblastoma, uveal and conjunctival melanomas are important malignancies within the remit of ocular oncology. Outlined are the diagnostic features and management principles, as well as advancements in the field and current challenges.

Sources of data: Original papers, reviews and guidelines.

Areas of agreement: Most eyes with retinoblastoma (International Intraocular Retinoblastoma Classification (IIRC) group A-D) are salvaged, whereas advanced cases (group E) remain a challenge. Despite a high rate of local tumour control in uveal melanoma, metastatic spread commonly occurs. Conjunctival melanoma is treated by complete resection, but high rates of local recurrence occur, with the possibility of systemic relapse and death.

Areas of controversy: Use of the IIRC in retinoblastoma, and systemic screening in melanomas.

Growing points: Utilization of novel treatment modalities in retinoblastoma and an increasing understanding of the genetic basis of melanomas.

Areas timely for developing research: Improvements in chemotherapy delivery in retinoblastoma and prognostic tests in melanomas.

Keywords:

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Introduction

Tumours of the eye comprise intraocular, ocular surface, orbital and adnexal lesions. In this review, we concentrate on the intraocular cancers retinoblastoma and uveal melanoma, and on the ocular surface cancer conjunctival melanoma. These are rare compared to non-ocular malignancies, but are an important branch of ophthalmology, within the subspecialty of ocular oncology.

Retinoblastoma is the most common intraocular malignancy of childhood worldwide, with approximately 50-60 new cases per year in the UK and 300-400 in the USA. A variety of treatments are employed to combat retinoblastoma and these are highlighted, including novel modes of delivery. There are challenges in treating advanced intraocular retinoblastoma and controversies in the current International Classification.

Uveal melanoma is the most common primary intraocular malignancy in adults worldwide. In the UK, approximately 500-600 new cases are diagnosed each year. There has been much recent work on prognostication genetics, to identify those at high risk of metastatic spread. Screening for systemic relapse, usually in the liver, following control of the primary intraocular tumour, varies with no consensus for the preferred modality or frequency.

Conjunctival melanoma is a potentially fatal malignancy. It is considered rare, even in terms of ocular tumours, but thought to be increasing in incidence. Current management involves surgical resection, but emerging areas include the role of sentinel lymph node biopsy, genetic studies as prognostic factors and potential treatment targets.

Retinoblastoma

Introduction

Retinoblastoma, the most common intraocular cancer in children, occurring in approximately 1 in 18,000 live births, is a disorder initiated in the majority of cases by mutation of the *RB1* gene.[1] The cancer, which is thought to originate in a photoreceptor precursor cell, develops in early childhood, may be heritable or non-heritable, and involves one or both eyes. Nearly 3% of unilateral non-heritable retinoblastoma cases lack the *RB1* mutations, however show high-level of MYCN oncogene amplification.[2] Intracranial involvement, mainly of the pineal gland, known as trilateral retinoblastoma, occurs in less than 5% of inherited cases, and has decreased in the era of intravenous chemotherapy for intraocular disease. Untreated retinoblastoma is generally fatal by spread to the central nervous system (via the optic nerve) and haematogenous spread. However, rare cases of spontaneous regression are known to exist. A “white pupillary reflex” and strabismus are the most common presenting symptoms. In developed countries the prognosis for children with retinoblastoma is good, with 5-year survival rates greater than 95%. In countries without established specialist centres, primary care infrastructure and educational strategies, the survival rate can be as low as 20%.

Paradigm shift and reclassification

Early diagnosis and treatment of intraocular retinoblastoma are key features in combating the disease. New treatment modalities have evolved and currently a wide armamentarium is available to treat various manifestations of intraocular retinoblastoma. In the majority of the 20th century the main conservative treatment modality was external beam radiotherapy (EBRT) but was associated with an

increased risk of cancers in patients with genetic retinoblastoma.[3] Currently EBRT is used to salvage eyes failing other treatments,[4] but is regarded by many authorities as tantamount to treatment failure. Systemic chemotherapy ("chemoreduction") supplanted EBRT as the main treatment for intraocular retinoblastoma in the 1990s after initial work in London, UK. This shift from radiotherapy to chemotherapy required a reclassification of intraocular disease from the Reese-Ellsworth classification,[5] which predicted the globe salvage after EBRT to the International Intraocular Retinoblastoma Classification (IIRC), which was more relevant to chemotherapy outcomes.[6] Eyes manifesting the tumour were classified into 5 groups from A to E (**Figure 1**) according to size, presence and extent of tumour seeds (vitreous or sub-retinal), and development of secondary complications (e.g. neovascular glaucoma). The disadvantages have included the inability to use historical EBRT outcomes to compare against emerging treatments and the fact that several versions of the IIRC have emerged. There is some variation in the definition of tumours in groups B and C, but mainly in respect to groups D and E eyes.[7] These discrepancies were thought to affect the prognostic value of the IIRC, leading to both over- and undertreatment.[8]

Management

IIRC Group A eyes are often amenable to treatment by focal methods, such as cryotherapy or laser therapy, with very high success rate. Groups B, C and D eyes are treated in many centres with systemic chemotherapy, with or without additional focal consolidating treatments (plaque radiotherapy in addition to the abovementioned).[9] Chemotherapy is best given according to a scheduled intense protocol. The most commonly used drugs include carboplatin, etoposide, and vincristine given every 3 weeks through central venous access line, although variations exist with number of drugs and cycles used and in the use of additional cyclosporine.[10] Globe salvage with chemotherapy is achieved in 100% of group A, 93% of group B, 90% of group C, and 47% of group D cases.[9] Systemic chemotherapy can treat potential metastases, reduces the risk of second non-ocular cancers compared to radiotherapy,[11] improves visual acuity,[12] and presumably reduces pinealoblastoma formation.[13] In regard to the latter, it is not clear whether intravenous chemotherapy is the sole factor responsible for this beneficial effect, the lack of radiotherapy or a combination of both.

Most advanced intraocular retinoblastoma, or group E eyes, are enucleated (removal of the eye). Prompt surgery is usually advised. Giving a trial of chemotherapy prior to enucleation may mask pre-existing pathologic adverse factors that would have necessitated post-operative adjuvant chemotherapy. In a retrospective analysis by Zhao et al., none of 37 group E patients that underwent primary enucleation died, but 4 out of 45 group E patients that received chemotherapy prior to enucleation died.[14] Advanced bilateral group E retinoblastoma, or patients in whom one eye is already enucleated and the fellow eye cannot be controlled by conservative means, are very challenging cases and no consensus exists regarding their management. While some centres would perform bilateral enucleations, in some chemotherapy with or without EBRT would be the treatment of choice.[15]

Novel treatments for intraocular retinoblastoma

With improved survival rates in developed countries, there has been an impetus to treat retinoblastoma without removal of the eye and to preserve vision. Advances in ocular drug delivery over the last 10 years are revolutionising this cancer– recent developments have delivered chemotherapy into the ophthalmic artery or directly into the vitreous cavity.

Local treatment of retinoblastoma with chemotherapy is an attractive idea to avoid potential systemic complications, such as neutropaenic sepsis or cumulative organ toxicities. In 2004, Yamane et al. described a system of selective ophthalmic arterial infusion of melphalan to treat intraocular retinoblastoma.[16] In 2006, Abramson and colleagues modified the Japanese approach by using direct intra-ophthalmic artery catheterisation (IAC) in patients with advanced retinoblastoma.[17] Reported results were encouraging with high eye salvage rates and acceptable side effect profile. Indications for use soon expanded for IAC to be utilized as primary and salvage treatments,[18] and additional chemotherapeutic agents were added to include melphalan, topotecan and carboplatin.[19] Some centres abandoned the use of systemic chemotherapy as first line therapy for retinoblastoma in favour for IAC. Where the tumour burden is mainly retinal or subretinal, there is no doubt that this is a very effective treatment. Initial enthusiasm for IAC was tempered by complications, including third cranial nerve palsy, orbital oedema, vitreous haemorrhage, retinal pigment epithelium changes and permanent retinal detachment resulting with loss of vision.[20,21] In addition there is wide variation between centres in the number of times the IAC is administered. There is a learning curve in being able to successfully cannulate the ophthalmic artery, which cannot be performed in neonates and very young babies. The involvement of anterior intraocular structures in eyes that had failed IAC as well as other treatments can be detected clinically and in higher rates on histopathologic analysis after enucleation.[22] Since the trabecular meshwork is an outflow from the eye, this is considered a high-risk feature and requires adjuvant systemic chemotherapy after enucleation.

One of the most difficult features of retinoblastoma is the control of vitreous seeding, with many eyes requiring EBRT or enucleation.[23] Recent attempts have been made to inject chemotherapy drugs directly into the vitreous cavity. Previously this route of delivery was prohibited, due to the risk of retinoblastoma seeding outside the eye. However, Munier *et al* overcame this risk by describing a safety enhanced technique, where the intraocular pressure was lowered by paracentesis of the anterior chamber, the intravitreal chemotherapy injection delivered by a 32G needle given in a tumour free area – confirmed via ultrasound biomicroscopy, and cryotherapy applied at the needle entry point as it was removed from the eye.[24] In 2014, Munier further described the phenotypic variability of retinoblastoma seeds and classified them into 3 subtypes, namely dust, spheres and clouds.[25] The vitreous seed classification can be predictive in regard to time to regression and number of intravitreal melphalan injections required: median time to regression was 0.6, 1.7, and 7.7 months for dust, spheres, and clouds, respectively, and median number of injections required to reach regression was 3, 5, and 8 injections, respectively.[26] In terms of tumour spread, Smith and Smith performed a systematic review in which they included 14 studies and more than 1,300 intravitreal injections, and concluded it is a rare occurrence.[27]

Discussion

During the last half century, the management of retinoblastoma has been revolutionized with the advent of novel therapeutic modalities. The shift from EBRT to systemic chemotherapy improved survival. The further shift to intraophthalmic artery and more recently the intravitreal delivery of chemotherapy has allowed eyes and vision to be retained that would otherwise be lost. Until the long-term efficacy, side effect profile and spectrum of benefits are understood, these should be used with caution. Enucleation remains an important treatment for advanced cases, in which attempts to salvage the eye might pose the patient to risk of metastasis and death. The need for international multi-

institutional prospective studies to better define indications and complication profiles is self-evident in this rare but important cancer (ClinicalTrials.gov Identifier: NCT02097134 and NCT00335738).

Uveal melanoma

Introduction

Among all melanoma cases, only 5% arise from the ocular and adnexal structures. Uveal melanoma is the most common primary intraocular malignancy in adults, occurring in approximately 6 individuals per million population annually.[28] Of these, 5% originate from the iris, 10% from the ciliary body, and the majority, 85%, are choroidal (**figure 2**). Uveal melanoma mainly affects light-skinned individuals, though it can occur less frequently in dark-skinned. There is a slight male preponderance. It is considered to be a sporadic event, although associated with dysplastic naevus syndrome and ocular melanocytosis.

Historically, uveal melanoma was treated by primary enucleation. However with advances in radiation delivery most centres now use radiotherapy by proton beam or plaque brachytherapy if tumour size allows, with high local tumour control rates and more than 90% eyes salvaged.[29] However vision is often compromised or lost due to radiation damage to the retina and optic nerve. A more exploratory treatment for small uveal melanoma is photodynamic therapy (low frequency laser),[30] a modality under debate, not universally accepted, and which awaits long-term results.

Uveal melanoma metastasizes via haematogenous spread primarily to the liver, and is believed to occur early in the course of the disease, despite successful treatment of the eye.[31] In a retrospective analysis by Shields et al. of more than 8,000 patients, 33% and 25% of ciliary body and choroidal melanoma patients, respectively, were diagnosed with metastatic spread at 10 years.[32] Iris melanoma had a more favourable prognosis. Size of the primary tumour at time of detection was important in determining the chances for secondary spread: at 10 years, metastasis were diagnosed in 12% of small melanoma (elevation ≤3.0mm), 26% of medium melanoma (elevation 3.1-8.0mm) and 49% of large melanoma (elevation >8.0mm).

Despite the improvements in treatment of the primary tumour, a corresponding decrease in metastatic death has not been documented, with5-year relative survival rate of 70-80%.[33,34] To date, metastatic uveal melanoma is a major challenge for physicians to treat although many new targeted immune modulatory treatments are now available such as PD1 inhibitors and MEK inhibitors in addition to targeted hepatic chemotherapy.

Prognostic factors

Several clinical and histopathological variables of primary uveal melanoma were found to be associated with metastatic death.[35] These include increasing patient age, increasing tumour size (tumour elevation and independently tumour diameter), ciliary body involvement, extraocular extension, epithelioid cell type, lymphocytic infiltration, presence of fibrovascular loops and several biomarkers, including human leukocyte antigen (HLA) molecules, and others, by immunohistochemical methods. Some variables are used in practice more than others. However, advances over the past two decades have expanded our understanding of the molecular biology of the disease, and genetic studies more accurately predict chances for metastatic disease.

In 1996 Prescher et al., using karyotyping and genomic hybridization techniques, found that monosomy of chromosome 3 predicted mortality in greater than 50%, whereas disomy of chromosome 3 had 100% survival.[36] Additional abnormalities were found in chromosomes 8, 6 and 1, but loss of chromosome 3 and increased tumour size were found to be the most significant predictors of patient survival.[37] Further studies with more advanced techniques confirmed these findings – Damato et al., using multiplex ligation-dependent probe amplification to detect chromosomal abnormalities, found that ten-year disease-specific mortality was 0% in tumours with disomy 3, 55% in tumours with monosomy 3, and 71% in tumours showing chromosome 3 loss and 8q gain.[38] Later, using oligonucleotide microarrays, Tschentscher et al. determined gene expression levels in 20 uveal melanoma tumours and concluded that there are two distinct entities, or classes, of uveal melanoma, that correlate one to monosomy and the other to disomy 3.[39] Onken and colleagues used hierarchical cluster analysis of gene expression and demonstrated that class 1 lesions have better prognosis and are associated with disomy 3 and a gain of chromosome 6p, whereas class 2 lesions predict more likely melanoma-related mortality and are associated with a loss of heterozygosity of chromosome 3.[40] Recently, Walter et al. found that class 2 uveal melanomas had better prognosis when the largest basal tumour diameter was less than 12mm at the time of treatment.[41] Nearly all uveal melanomas harbour oncogenic mutations in the Ga_q stimulatory subunit GNAQ.[42] Harbour et al. found that mutations in BAP1, encoded by a gene on chromosome 3p21, and which is important for tumour suppression, were associated with increased risk of distant metastatis.[43]

From a clinical perspective, tumour aspirates for genetic analysis are taken prior to plaque or proton beam radiotherapy or after eye removal. Patients found at high risk for systemic spread are considered candidates for intensive screening and for adjuvant targeted molecular therapy, currently under investigations in clinical trials.[44]

Surveillance and treatments for metastatic disease

Rarely in patients with uveal melanoma is metastatic spread detected concurrently with the diagnosis of the ocular tumour. Despite being treated for their primary tumour, these patients are at lifetime risk of developing metastasis. The role of screening tests for distant disease remains controversial within the ophthalmic and oncologic communities, as there is no serum biomarker that can be utilised and the evidence for imaging modality and frequency is conflicting. While some investigators advocate the use of screening tests for metastatic spread once every 4-6 months,[31] others, relying on findings that early detection of metastatic disease is not associated with better survival rates,[45] are reluctant to perform any tests whatsoever.

Commonly used imaging techniques to detect distant spread, mainly to the liver, are ultrasonography, computed tomography (CT), positron emission tomography/CT (PET/CT) and magnetic resonance imaging (MRI). The National Guidelines for the Management of Uveal Melanoma in the UK state that all patients should be offered metastatic surveillance with non-ionising imaging of the liver (ultrasound or MRI) to prevent unnecessary radiation of the patient.[46] Marshall et al. in a prospective study in 188 high risk uveal melanoma patients found that, by performing biannual MRI liver scans, 92% of metastatic patients were diagnosed by imaging 6 months prior to experiencing any symptoms.[47] In a comparative study, Orcurto and colleagues found that MRI is superior to PET/CT in detecting early hepatic metastasis, however PET/CT has a possible role in assessing early therapy response.[48] Liver function tests, which were commonly used as a screening tool in the past, are often normal when liver metastasis are found early, and are considered an inadequate tool for surveillance when used alone.[46]

Given that insulin-like growth factor-1 (IGF-1) receptor has been found to be highly expressed in metastatic uveal melanoma, Frenkel et al. assessed the role of serum IGF-1 in early diagnosis of uveal melanoma liver metastasis using enzyme-linked immunosorbent assays (ELISA) in 118 patients. This study revealed that serial IGF-1 measurements in 10-years' disease free patients were considerably lower compared to those in healthy controls, and higher compared to those with metastatic disease. The authors concluded that serial IGF-1 levels may have a role as a predictive biomarker for metastatic uveal melanoma when measured repeatedly in one individual.[49] Triozzi et al. studied 76 treated primary uveal melanoma patients and found a correlation between the presence of monosomy 3 and human leukocyte antigen-class-I-associated β-2 microglobulin ($P \leq 0.02$). Based on the strong association between monosomy 3 and development of metastatic disease, the authors concluded that the microglobulin may have a potential role as a screening tool for metastatic disease.[50]

Treatment options for metastatic uveal melanoma are limited. Surgical resection is considered the main strategy for a very highly selected population of patients with resectable disease.[51] Other modalities, including chemo-embolization, radio-embolization and administration of classic chemotherapeutic agents, have shown limited efficacy, if at all.[52] In the absence of classical modalities for metastatic disease, newly developed therapies have evolved lately, namely kinase inhibitors and immunotherapy, and these are currently evaluated.[53,54] In this regard, selumetinib, a selective kinase inhibitor, was found in a randomized clinical trial to improve progression-free survival and response rate in metastatic uveal melanoma patients, as compared to chemotherapy.[55] Interestingly, in this study, no improvement in overall survival was observed.

Discussion

For more than three decades eye preserving plaque radiotherapy is the mainstay treatment for primary uveal melanoma with high eye salvage rate in long-term follow-up. Although exceptions exist, overall, local tumour control is no longer a major concern, but future metastatic risk after eye treatment remains a challenge. Most centres now offer earlier treatment, when a melanocytic lesion starts to develop suspicious features rather than wait for growth in such lesions. In the past two decades a rapid evolution in our understanding of the molecular behaviour of uveal melanoma has occurred, resulting in the development of more accurate genetic prognostic tools to detect patients at high risk for metastatic spread. The main focus is currently on the development of immune modulatory therapy for established metastatic disease. Once the optimum treatment for metastatic disease is developed we will have an effective therapy to use in the adjuvant setting, which will lead to improved survival.

Conjunctival melanoma

Introduction

Conjunctival melanoma is an ocular surface cancer, and as so, it differs substantially in its features and management from the previously described intraocular tumours. It is a rare malignancy, accounting for 1-2% of all ocular melanomas. However incidence seems to be on an upward trend, analogous to increased incidence seen in cutaneous melanoma. As in cutaneous melanoma, exposure to solar radiation is considered an important risk factor and a suggested causative link.[56] Conjunctival

melanoma most commonly appears in middle aged or elderly white individuals, but can occur in African or African-Americans as well. The majority of conjunctival melanoma cases (75%) arise from primary acquired melanosis (PAM) with atypical cells, 20% from a pre-existing conjunctival naevus and only 5% de novo. Higher incidence of the disease is seen in several systemic conditions, including familial atypical mole and melanoma syndrome, xeroderma pigmentosum and neurofibromatosis.

Clinically, conjunctival melanoma appears as a fleshy, elevated lesion of variable pigmentation, commonly located on the nasal or temporal bulbar conjunctiva (**Figure 3**). Amelanotic or minimally pigmented conjunctival melanomas occur in approximately one fifth of cases.[57] The lesion can be well circumscribed or diffuse, the latter more frequently seen in cases arising from PAM. It may extend towards the eyelid margin or be contiguous with an eyelid margin melanoma, the globe or the orbit. It may also extend into the lacrimal drainage system or nose following tumour seeding at time of primary surgical resection, giving rise to epistaxis or epiphora as presenting signs of nasolacrimal recurrence.[58]

Diagnosis

Full examination of the bulbar and tarsal conjunctiva is required. In addition, examination of the orbital rim is important because of the high rate of recurrence. If orbital involvement is suspected, imaging with CT or MRI is indicated. Occasionally, an intraocular melanoma with extraocular extension may have the appearance of a conjunctival melanoma, warranting detailed fundoscopy and ultrasonography. Regional lymphadenopathy can occur. Lymphatic spread to proximal nodes has been assessed with various approaches, including whole body PET/CT scan, MRI of the head and neck and ultrasonography and fine needle aspiration biopsy of suspicious lymph nodes. Micrometastatic disease to regional lymph nodes is accessed using sentinel lymph node biopsy (SLNB).[59,60]

Management

All lesions suspicious for conjunctival melanoma should be referred to a specialized centre, without undertaking an incisional biopsy, as this may shed malignant cells. Complete resection with clinically evident clear margins is necessary, which may include corneal alcohol epitheliectomy or for tumours fixed to the sclera, lamellar scleral dissection. Only the clear margins are surgically handled to avoid tumour seeding, resulting in the ‘no-touch’ technique. After the tumour resection, double or triple freeze-thaw cryotherapy is applied to clear margins to prevent recurrence. The conjunctival gap may be left to re-conjunctivalise, undergo primary closure or be lined with graft material (allograft from the fellow eye or amniotic membrane).

In cases of incomplete excision, adjuvant treatment with plaque brachytherapy (strontium or ruthenium) or topical chemotherapy (mitomycin C drops 0.02% or 0.04% in various protocols) is warranted to reduce chances of recurrence.[61] Strontium 90 beta radiotherapy application is a useful adjuvant treatment for incompletely excised conjunctival melanoma where the deep margin is involved.[62] Alternatively some centres used custom designed radioactive iodine plaques. If the tumour is incompletely excised from the fornix or caruncular area, proton-beam radiotherapy may be administered.[61] After local excision, close follow-up is advised and if local recurrence occurs, lesions should be re-excised. In advanced cases with extensive orbital involvement, exenteration of the orbital contents is necessary.[63]

Sentinel lymph node biopsy

Of the various ways to assess lymphadenopathy, SLNB has recently been under the spotlight.[59] Adapted from management of cutaneous melanoma, its use in the management of conjunctival melanoma is controversial.[64] Although up to 50% of patients with systemic spread of the disease show regional lymph node involvement, no consensus exists as to when SLNB should be performed or in which patients. In addition, this modality has not been proven to improve patient survival. The technique of SLNB involves pre-operative scintigraphic mapping of the afferent lymphatics using radionuclide imaging, followed by intraoperative localization of the sentinel node by methylene blue dye and/or radioactive tracer detected by a hand-held gamma probe. The selected sentinel nodes are dissected and submitted for histopathologic evaluation. In cases of positive sentinel lymph node biopsies, further regional lymphadenectomy is warranted. In an 8 year prospective study of ocular adnexal melanoma patients performed by Savar et al., SLNB has shown benefit in cases of tumours of 2 mm in thickness or more, but also in smaller tumours associated with ulceration.[65] The authors showed a significant decrease in the rate of false negative readings in the second half of the study, implying that the technique requires expertise, gained in a relatively shallow learning curve. In a retrospective analysis by Cohen et al., the authors concluded that SLNB should be considered when tumours are ≥2 mm thick and in cases of non-limbal location of the conjunctival melanoma.[66]

Prognosis

Our ability to explore the prognostic measures and outcomes of conjunctival melanoma is limited by the tumour's rarity. Nevertheless, existing figures point out that by 10 years up to 50% of patients will have experienced a local recurrence, with palpebral location of the primary lesion and excision without the use of adjuvant therapy, being significant risk factors.[61,67] Shields et al. investigated the outcomes of nearly 400 cases of conjunctival melanoma and found that for patients in which the melanoma originated from PAM – the majority of cases, metastasis occurred in 19% and death in 5% in 5 years. However, for patients for whom the melanoma originated de-novo, 5-years' outcomes were significantly worse: 35% melanoma related-metastases and 17% deaths. At 10 years, more than one third of patients have died. On a multivariate analysis, melanoma arising de-novo, in contrast to that originating from PAM or pre-existing naevus, indeed was found to be a significant risk factor for the development of metastatic disease and death.[57]

Genetic studies

As for uveal melanoma, genetic studies have shed new light on the molecular basis of conjunctival melanoma. BRAF is a gene encoding to serine/threonine kinase mitogen-activated protein kinase (MAPK) pathway, which is involved in signal transduction. Mutations in BRAF were found in the majority of cutaneous melanoma, not at all in uveal melanoma, and in up to 50% of conjunctival melanoma.[68] Additional studies to characterize and understand the role of BRAF mutations, as well as other mutations, are currently underway.[64] In a study by Lake et al. BRAF V600E gene mutations were found in 50% of conjunctival melanoma and 75% of metastatic conjunctival melanoma.[69] Vemurafenib, a BRAF kinase inhibitor, was found in a phase 3 randomized clinical trial to prolong survival in metastatic cutaneous melanoma patients, [70] and first reports of its clinical use in the context of conjunctival melanoma are now emerging.[71]

Discussion

Conjunctival melanoma is a rare but deadly ocular surface cancer. Since the tumour is on the ocular surface, it is picked up at a smaller size compare to intraocular melanoma and survival figures are

better. Primary treatment includes surgical excision and application of cryotherapy with additional adjuvant treatments in cases of incomplete excision. Assessment of regional lymphadenopathy is essential, as lymphatic spread of the tumour is relatively a common occurrence, although distal metastatic spread without regional lymph node involvement has been reported in 25% of cases.[72] Further studies are warranted to better delineate the indications for use, advantages and disadvantages of each screening method, and specifically that of SLNB. Genetic studies on the molecular basis of conjunctival melanoma, and specifically BRAF mutations, are evolving, and will with no doubt be part of decision making in management and treatment of conjunctival melanoma.

Conclusion

Ocular tumours, in contrast to the majority of ophthalmic diseases, pose a threat not only to vision, but also to the integrity of the globe and moreover to life. Immense effort has been put in recent years into more accurate diagnosis, selective management with better side effect profile and useful screening tests for early detection of systemic spread of the ocular malignancies. Whereas survival rate in retinoblastoma in developed countries is very high, the main challenge is currently to salvage those eyes with advanced tumours. In contrast, in uveal and conjunctival melanoma, the major tasks are to further improve effective systemic treatment for metastatic disease and explore the role of adjuvant therapy in order to lower the rate of metastatic spread and death.

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Legends

Figure 1.

Fundus photographs of retinoblastoma tumour grouping according to the International Intraocular Retinoblastoma Classification,[6] and response to treatment. (A) Group A eye – tumours <3mm (arrows) confined to the retina, ≥3mm away from the foveola. (B) Same eye as in figure 1A after laser diode treatment. (C) Group B eye – a foveal tumour>3mm. (D) Same eye as in figure 1C after treatment with systemic chemotherapy – the tumour has shrunk and formed into a calcified inactive mass. (E) Group C eye – a retinal tumour with adjacent subretinal seeds less than 3 mm from tumour (arrow). (F) Same eye as in figure 1E after treatment with systemic chemotherapy and diode laser to the subretinal seeds. (G) Group D eye – a retinal mass and total retinal detachment. Intraocular pressure in this eye was within normal limits. (H) Same eye as in figure 1G after treatment with systemic chemotherapy. (I) Group E eye – a massive intraocular tumour occupying most of the posterior chamber, resulting with elevated intraocular pressure and neovascularization of the iris. The eye was enucleated.

Figure 2.

(A) Fundus photograph of a left eye choroidal melanoma. (B) Same eye 2 years after treatment with plaque radiotherapy – tumour significantly decreased in size (note chorioretinal atrophy surrounding the tumour).

Figure 3.

(A) Slitlamp photograph of a conjunctival melanoma (resected and confirmed on histopathological evaluation) encroaching the limbus and cornea. (B) Same eye after surgical resection, alcohol epitheliectomy and cryotherapy to conjunctival margins.

Figure 1

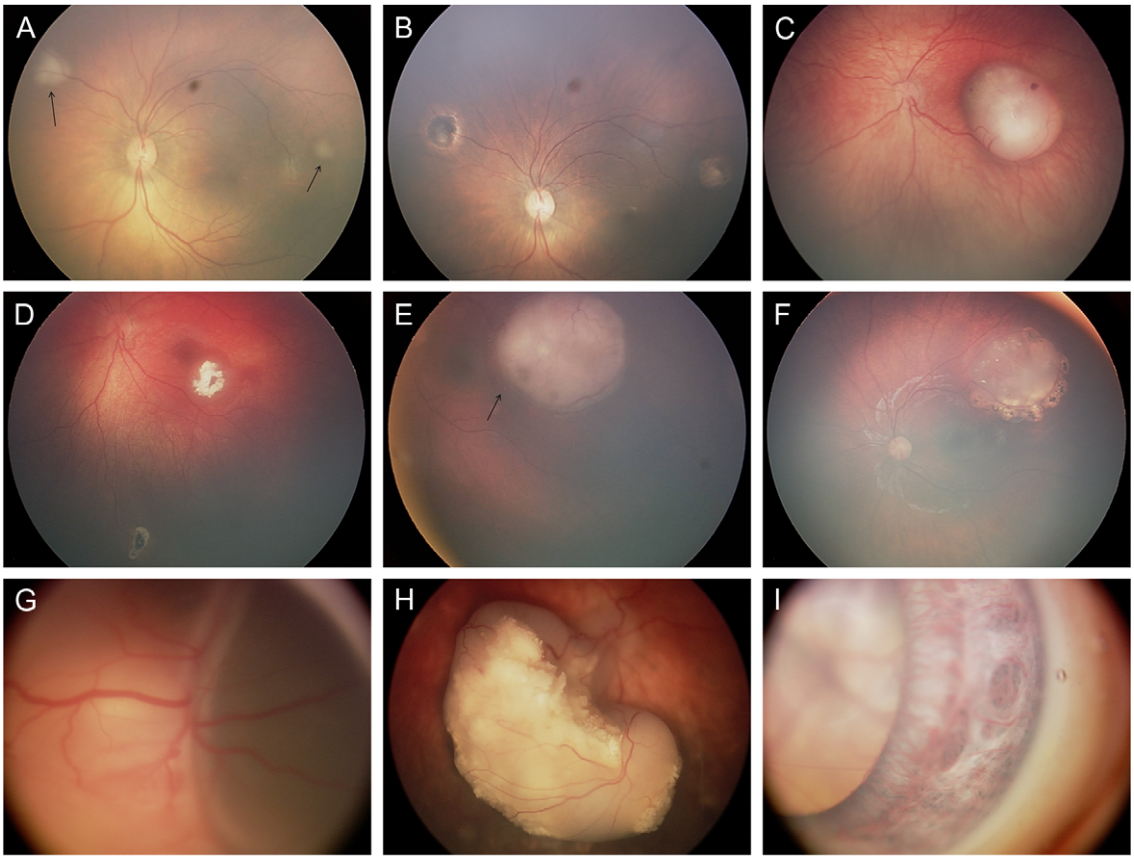

Figure 2

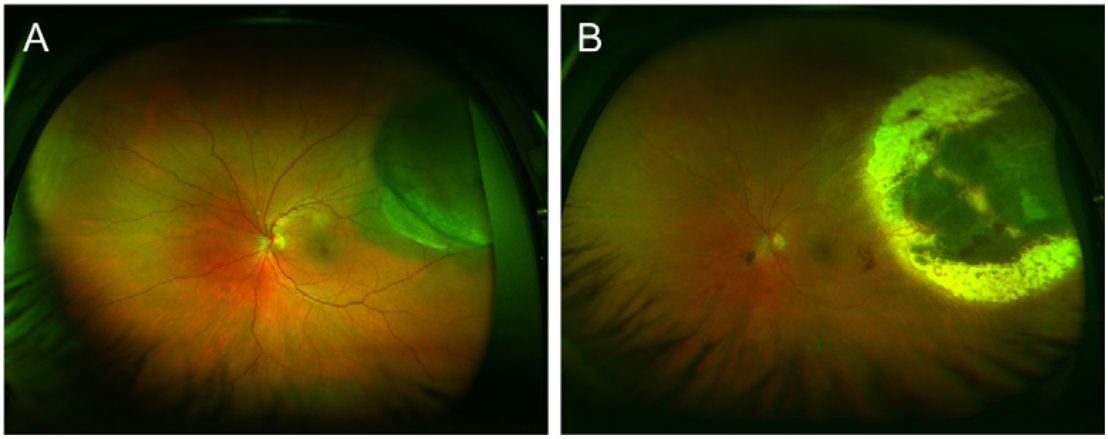

Figure 3