Review Article

Uveal melanoma: epidemiology, pathogenesis, diagnosis and treatment

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Uveal melanoma is a life-threatening intraocular malignancy and is also the most common primary intraocular tumor in adults. These tumors arise from the uveal tissue which consists of the iris, ciliary body, and the choroid.

Epidemiology

Statistically, although retinoblastoma is the most common eye cancer the world over, uveal melanoma is the most common ocular cancer in Europe and the United States, exceeding retinoblastoma by a factor of 6.[1] In the United States, one study stated that the mean incidence of uveal melanoma was 4.3 cases per million population. A higher rate was observed in males (4.9 cases per million) as opposed to females (3.7 cases per million). Uveal melanoma is more commonly seen in an older age group. The age-specific incidence rate peaks at the age of 70 years (24.5 cases per million in males and 17.8 cases per million in females)[2].

Ethnically, people of European descent showed a higher incidence. An American study reported the annual age-adjusted incidence (per million population) of uveal melanoma as 0.31 in black patients, 0.38 in Asian patients, 1.67 in Hispanic patients, and 6.02 in non-Hispanic white patients[1,3].

Shields' report of 8033 patients with uveal melanoma from a single tertiary referral center in the United States over a 4-decade period, the division of uveal melanoma was as follows: choroid (90%), ciliary body (6%), or iris (4%).[4] The tumor affected men (51%) or women (49%), and primarily occurred in Caucasians (98%) compared with African American (<1%), Hispanic (1%), and Asian, Native American, Middle Eastern, and Asian Indian (each <1%). In this report, the reported mean patient age at detection was 58 years, with range from 3 to 99 years. The tumor was detected in children 20 years or younger (1%), mid-adults 21 – 60 years (53%), and older adults over 60 years (45%)[4,5].

Recent reports have pointed to several host factors being associated with an increased risk for uveal melanoma. Among those, congenital ocular and oculodermal melanocytosis (also known as Nevus of Ota) and uveal nevus are known predisposing factors for uveal melanoma. However, the observed lifetime risk to develop uveal melanoma from Nevus of Ota is low at 1 in 400 individuals[6]. Light skin color,[7,8] blond hair[9] and blue eyes[7-12] are specific host risk factors that have been reported. Choroidal nevi, although extremely common in the white population, show a low rate of malignant transformation: 1 in 8845[13]. A population-based study showed choroidal nevus prevalence in 4% of Caucasians, 1% of Hispanics, less than 1% of Blacks, and less than 1% of Chinese[14].

Size of the nevi, however is an important feature: choroidal nevi that are10 mm or more in diameter were estimated to transform into melanoma in 18% over 10 years[15]. The role of sunlight exposure in the etiopathogenesis of uveal melanoma is at best, weak and contradictory[16]. Other risk factors include atypical cutaneous nevi, common cutaneous nevi, cutaneous freckles, and iris nevi[17].

Pathogenesis

Although histologically, the melanocytic origin of cutaneous melanomas and intraocular melanomas share the same melanocytic origins; the clinical course, the molecular mechanisms and the treatment modalities are different[16].

The molecular pathogenesis of uveal melanoma was not known until the past decade when molecular diagnostics and techniques in biochemistry evolved enough to unravel the sequence of events that lead to the development and the proliferation of uveal melanoma. There are early occurrences that disturb cell cycle and apoptotic control that eventually lead to malignant transformation and subsequent proliferation of uveal melanocytes[18]. Slowly the tumor increases in size and eventually, the growing tumor encounters a critical bifurcation point, where it advances along one of two possible genetic pathways that possess very distinct genetic signatures (monosomy 3 vs. 6p gain) and metastatic propensity.

There are various mechanisms proposed for the development of uveal melanoma. Deregulation of the cell-cycle is commonly seen in uveal melanomas. Disruption of the retinoblastoma tumor suppressor pathway is

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observed. The retinoblastoma protein inhibits cell-cycle progression through the G1–S phase transition point, so inactivation of retinoblastoma leads to unregulated proliferation.[18] Activating mutations in GNAQ gene occur in approximately half of all primary uveal melanomas and can activate the RAF/MEK/ERK pathway. These mutations lead to overexpression of cyclin D; which in turn inactivates the retinoblastoma protein.[18,19,20]

Usually tumor suppressor mechanisms help in removing damaged cells that have oncogenic mutations through senescence or apoptosis.[21] For a tumor to progress, the cells have to develop a mechanism whereby the tumor suppression apparatus is bypassed, thereby having unrestricted growth and multiplication. Uveal melanoma cells appear to exploit several pathways to avoid apoptosis and to promote survival.[18]

The p53 pathway and Bcl2 family are known control mechanisms that recognize and correct oncogenic insults by methods like regulating apoptosis, or triggering cell-arrest.[22,23] *p53* appears to be functionally inhibited by over expression of its inhibitor HDM2 – a finding present in many uveal melanomas.[24,25] The insulin-like growth factors (IGFs) often regulate cell proliferation, differentiation and apoptosis through their interaction with the IGF-1 receptor (IGF1R), which leads to activation of many pathways like RAF/MEK/ERK and PI3K–AKT.[26] The IGF1R is strongly expressed in many uveal melanomas.[18]

However, these molecular changes are seen across the board in metastatic and non-metastasizing tumors thereby suggesting that there are other late events that can decide whether a uveal melanoma metastasizes or not. Gain of chromosome 6p is seen largely in non-metastasizing tumors, as opposed to loss of one copy of chromosome 3 (monosomy 3) occurs mostly in metastasizing tumors. As discussed above, this suggests a bifurcation in the tumor progression.[27]

Certain genetic alterations have been associated with increased risk of metastasis of uveal melanoma: Monosomy 3 occurs in approximately half of uveal melanomas and has been strongly correlated with poor histopathologic factors and metastasis-related death.[28,29,30] Late chromosomal alterations in the cellular cycle, like the loss of chromosome 8p, can hasten the onset of metastasis in susceptible tumors.[18]

Gene expression profiling using microarray analysis suggests that uveal melanomas can be divided into two groups. "Class 1" tumors (low grade) are thought to have a much lower risk of distant metastasis than "class 2" tumors (high grade).[31]

Clinical features

The clinical presentation of uveal melanomas depends on the location, size, extent and associated secondary changes such as neovascularization, inflammation or bleeding.

Iris Melanoma

Iris melanomas may either present as a well defined, circumscribed mass or a diffuse lesion. In a single-centre analysis of 1611 cases of iris nevus, growth into melanoma occurred in 8% by 15 years. Shields et al. have suggested the mnemonic 'ABCDEF' to help identify the risk factors for progression of iris nevus to iris melanoma: Age young, Blood (hyphema), Clock hour inferior, Diffuse configuration, Ectropion uveae, and Feathery tumor margin.[32] Iris melanomas have a substantially lower incidence compared to choroidal melanomas. Their peak incidence is 10–20 years younger than choroidal melanoma patients, and most are detected because of an incidental finding or a cosmetic change.[33]

In most cases, slit lamp biomicroscopy, gonioscopy and ultrasound biomicroscropy (UBM) are sufficient to help diagnose iris melanomas.[33,34] Circumscribed iris melanomas are usually nodular, irregular and are seen in the inferior half of the iris. If lightly pigmented, blood vessels within the tumor may be visible. Iris melanomas may grow either anteriorly or posteriorly or both. Tumors that arise close to the angle can also invade the ciliary body which necessitates gonioscopy and UBM in order to delineate the complete extent of the mass. Such tumors can also push the lens posteriorly. As the tumor grows in size, lenticular touch and compression can present as cataract. Corneal decompensation, hyphema, secondary glaucoma due to pigment release, angle invasion or mechanical angle closure is other clinical features that may be seen.[35] Diffuse iris melanoma is seen as a result of either a primary melanoma arising from the stroma of the iris or secondary seeding from a ciliary body melanoma or a circumscribed iris melanoma. In these cases, the iris may not show any obvious nodule formation but only thicken diffusely. The onset of acquired hyperchromic heterochromia with ipsilateral secondary glaucoma should raise suspicion of a diffuse iris melanoma.[33]

Ciliary body melanoma

Like iris melanomas, ciliary body melanomas too have two distinct morphological patterns: circumscribed and annular (ring configuration). During the early stages of growth, circumscribed ciliary body melanomas are largely confined to the ciliary body and are asymptomatic. Gradually they push or even infiltrate the root of the iris and invade the anterior chamber. They can cause secondary glaucoma due to anterior chamber seeding, infiltration of the angle and the iris. Eventually they may even grow in a ring configuration, which may be picked up by UBM.[33]

Annular (ring) variant of ciliary body melanoma presents with more than 180° of circumferential ciliary body extension and disproportionately less anteroposterior growth. In certain cases there is circumferential growth in the trabecular meshwork, with relative sparing of the ciliary body and iris. Such a variant is classified as 'ring melanoma of the anterior chamber angle.[36] Sectoral iris neovascularization, sectoral cataract, localized shallowing of the anterior chamber are signs that could indicate the presence of a circumferential (ring) ciliary body melanoma.[37]

Choroidal melanoma

Reduced vision, blurring of vision, flashes, floaters, metamorphopsia, micropsia, scotomata, diplopia and photophobia are the common symptoms. About a tenth of the patients of choroidal melanoma however remain asymptomatic. This possibly indicates a small or a medium sized tumor that is away from the macula, perhaps the equator or beyond. Rarely, large melanomas may develop necrosis and result in sterile inflammation which may masquerade orbital cellulitis.[38]

Diagnosis of Uveal Melanoma

Classical features of a choroidal melanoma on ultrasound examination are the presence of an acoustic quiet zone within the tumor and choroidal excavation seen posteriorly. Low to medium internal reflectivity is seen within the tumor on A-scan. Typically a high initial spike also called 'positive-angle kappa sign' is also seen.

Melanomas that are still under the Bruch's membrane assume a dome shaped configuration with their thickness equal to about half their diameter. As the size gradually increases, the tumor ruptures the Bruch's membrane and as a result the classical mushroom shape or collar stud appearance is noted.

Ultrasonography is also sensitive in detecting extrascleral extension of intraocular melanomas.[39] However, MRI of the brain and orbit can be helpful in identifying intraocular features consistent with melanoma in cases when the diagnosis of melanoma needs to be established.[38] Ultrasound biomicroscopy (UBM) is useful in the diagnosis and assessment of iris and ciliary body lesions.[39] UBM demonstrates a high correlation with histopathologic features of anterior uveal melanomas, including shape, reflectivity, and local extension; especially for anteriorly located melanomas.[40]

Trans-scleral fine needle aspiration cytology may be performed to confirm the diagnosis. One study reported that trans-scleral FNAB at the time of I-125 plaque brachytherapy was not associated with endophthalmitis, orbital dissemination, or local treatment failure. Post-brachytherapy retinal detachment was rare. Their 5-year metastatic rate was not statistically different from the rate of 13% reported by the COMS for tumors of the same size treated by brachytherapy without biopsy. In this study however, the aim of performing the biopsy was to obtain tumor cells for cytogenetic investigations to check for abberations such as monosomy-3 and not to confirm the diagnosis.[41]

Treatment of Melanomas

All cases of uveal melanomas require baseline investigations that include metastatic evaluation. Routinely, liver function tests and computed tomography of the chest with contrast are advised for all patients diagnosed with uveal melanoma. Although some argue that liver ultrasound examination is adequate, others advise CT or MRI to check for hepatic metastasis. Furthermore, an annual metastatic screening is repeated during the follow-up of all cases to monitor the progress of the disease. This is important since almost 50% of patients of uveal melanoma develop metastatic disease, which is almost always fatal.[42]

Once the diagnosis of melanoma is established, the next step is the staging of the disease. The American Joint Committee on Cancer (AJCC) classification, which utilizes the TNM system of staging, is currently the preferred system for staging.

Earlier, various factors were used to prognosticate uveal melanoma such as location of the tumor, basal diameter, thickness, presence of necrosis, histopathological factors and genetic factors amongst others. The AJCC is an attempt to introduce a single standardized system that unifies risk features into a single classification system.[43] The AJCC

classification correlates well with the final prognosis: compared with uveal melanoma classified as AJCC stage I, the rate of metastasis/death was 3 times greater for stage II, 9 to 10 times greater for stage III, and further greater for stage IV.[44]

Uveal melanoma is generally classified based on size and prognosis is directly related to size. Before delving into the treatment options for choroidal melanoma, it is important to know the relevance of the background. Currently treatment offered rests largely on the evidence that has been put forth by the Colloborative Ocular Melanoma Study (COMS). COMS was a multicentric study with participating centers across the United States and Canada. The investigators conducted two randomized trials and an observational study; in addition to reports on these studies, several technical papers have been published on the basis of the COMS results. The two randomized clinical trials were designed to compare the effectiveness of brachytherapy to enucleation for treatment of medium-size choroidal melanomas, and the effectiveness of enucleation with and without preoperative external-beam radiotherapy for large choroidal melanomas. The third arm was an observational study of small choroidal melanomas. COMS classified small tumours as those measuring between 1.5–2.4 mm height and 5–16 mm diameter; medium tumours were those measuring between 2.5–10 mm apical height with a basal diameter d"16 mm diameter; large tumours has apical height greater than 10 mm and basal diameter in excess of 16 mm.[44]

The most important outcome of COMS was one of the radomized trials that studied medium-sized choroidal melanomas where patients were randomized to receive either enucleation or Iodine-125 plaque brachytherapy.[45] The final 12-year follow-up data showed no difference in melanoma-related morbidity between the two treatment arms. Visual loss secondary to brachytherapy correlated with tumor thickness, tumor proximity to the foveal avascular zone, and a history of diabetes. Visual loss was significant, with 43% of patients progressing to a visual acuity of 20/200 (legal blindness) within 3 years. COMS also noted that for small choridal melanomas (those tumors less than 3.0 mm in apical height) characteristics associated with greater likelihood of growth included the presence of orange pigment, tumor thickness of at least 2 mm, and largest basal diameter of at least 12 mm.[46,47]

Transpupillary Thermotherapy

During thermotherapy the tumor is heated to a temperature of 60–65°C by means of an infrared diode laser introduced via the pupillary aperture, hence the name of this modality – TTT: transpupillary thermotherapy. TTT is typically indicated for small, posterior tumors that are not involving the optic disc. Media opacities such as cataractous lens and vitreous hemorrhage are contraindications for TTT. The treatment is usually administered with a 3mm diode laser beam. The beams heat the tumor to a temperature of approximately 60–65°C for about 1 minute(. Although not preferred as the sole mode of treatment, TTT is usually administered with adjunctive radiotherapy – as sandwich therapy. TTT is also particularly useful after radiotherapy for tumor recurrence or exudation.[48,49]

Proton beam radiotherapy

Proton beam radiotherapy is a form of external beam radiation treatment that uses protons rather than electron X-rays to treat choroidal melanomas if the tumors are large and/or located near the optic nerve or macula.[50,51] In proton beam radiotherapy, most of the energy is deposited at the end of beam therefore leaving little exit dose radiation. It also allows good control of radiations as it is administered with safety margins, 3mm laterally and up to 4mm longitudinally. At some centers, for iris melanomas, the first choice of treatment is proton beam radiotherapy primarily because it is an outpatient procedure with acceptable morbidity. If the tumor is diffuse, then whole-anterior segment proton beam radiotherapy is delivered.[52,53] At most ocular oncology centers, plaque radiotherapy is the first choice of treatment for uveal melanoma over proton beam radiotherapy since it is more reliable, less expensive that proton beam radiotherapy and far less invasive than local resection.

Surgery

Surgical resection of uveal tumors can be a good treatment option for globe salvage provided the size and location of the tumor permit the surgery to be performed. Small iris and ciliary body tumors (less than 4 clock hours) can be safely resected by iridectomy or iridocyclectomy. Polyopia, glare, coloboma, cataract, lens instability and glaucoma are few of the possible complications arising from ciliary body excision. Trans-scleral resection of choroidal tumors can also be attempted, however this exposes the patient to the potential risk of orbital seeding of the tumor as well as expulsive hemorrhage. Advances in microsurgery and

hypotensive anesthesia have also made it possible to remove large tumors extending as far posteriorly as the fovea.[54]

Endoresection of choroidal melanoma is performed using a vitreous cutter, either through a hole in the retina or a retinal flap. Some surgeons administer adjunctive radiotherapy after the endoresection; others give proton beam or stereotactic radiotherapy prior to the procedure.[55] Endoresection however, is not a commonly performed surgery and requires high degree of skill. This surgery remains controversial due to the possibility of seeding of malignant cells to other parts of the eye, as well as the orbit and systemically. Recent evidence however, suggests it may be a viable option in some cases. Foulds and associates compared patients with uveal melanoma managed with tumor resection versus enucleation and found equivalent survival in both groups.[56] Kivela and colleagues, in their case-control analysis compared patients with large melanoma managed with transscleral resection versus plaque radiotherapy and found equivalent survival.[57]

In cases where no vision is salvageable and the morbidity associated with other treatment modalities is not acceptable, enucleation is performed. In large tumors, enucleation remains the preferred mode of treatment. The procedure is standard and requires no additional steps. The operating surgeon's implant of choice can be used. However as is the case in all cases of enucleation for intraocular tumors, the tumor must be visualized again by binocular indirect ophthalmoscopy, after draping the patient and covering the other eye to ensure that the eye with tumor is enucleated. Histopathological examination of the tumor is extremely important. Once enucleated, a thorough external examination of the enucleated eye must be done to look for areas of scleral thinning, extraocular extension, dilated vortex veins and any other abnormal finding. The basal diameter of the tumor must be documented after visualizing the tumor with transillumination.

Plaque Brachytherapy

Brachytherapy is the implantation of radioactive material either within or close to the tumor. The preferred choice of treatement modality where globe salvage is possible is plaque brachytherapy. In the United states, Iodine 125 is the preferred source for radiation . The half-life of Iodine 125 is 59.4 days. In centers across Europe and in the authors' centres in India, Ruthenium 106 is used. The half-life of ruthenium 106 is 373.6 days, therefore the re-use of Ru-106 plaques is feasible. Ru-106 plaques are considerably thinner than the I-125 plaques used in COMS, hence placement for the surgeon and comfort and tolerance for the patient are better with the ruthenium plaques. It must be noted that Iodine plaques emit ã radiation and therefore can be successfully treat tumors as thick as 10 mm as opposed to Ruthenium plaques, which are suitable for uveal melanomas up to 5 mm thick as they emit beta radiation. Collateral damage to surrounding healthy ocular structures is more with I-125 plaques.[58]

Indirect ophthalmoscopy, ultrasound examination and CT or MRI are used to determine the exact location of the tumor. Following this, the optimal plaque size is chosen to give a 2–3 mm margin around the tumor base.[59] The total dose provided from the source and the radioactive dose per time unit of exposure (dose rate) are estimated at various distances from the radioactive source. Usually the typical tumoricidal dose is between 80-100Gy. A higher dose increases ocular morbidity due to the effects of radiation to the healthy tissue whereas lower doses may result in incomplete tumor control. Dosimetry for episcleral plaques is calculated by different methods but the results are reasonably consistent.[58,59,60]

Placement and removal of the plaque are done in the operating room maintaining complete radiation precaution. Dummy plaques are used to mark out the intended location of placing the plaque and sutures are placed. The tumor location is reconfirmed and then the plaque is placed and sutures are tied. Common complications include dry eye, radiation retinopathy, glaucoma, maculopathy and rarely, scleral necrosis.

The COMS trials reported that patient survival following episcleral brachytherapy of uveal melanoma is not significantly different from that after enucleation.[61] Patients with uveal melanoma randomized to either enucleation or iodine brachytherapy had 5-year survival rates of 81% and 82%, respectively. The rates of histopathologically proven hepatic metastasis at 5 years were nearly the same in both groups. Furthermore, the patients treated with ruthenium brachytherapy had similar survival rates.[62] To summarize, although the true viability and metastatic potential of irradiated uveal melanoma cells has not been established, most clinical studies have reported local control of choroidal melanoma.[63]

Hepatic Intra-arterial chemotherapy, intra-arterial chemo-embolization, isolated hepatic perfusion, immuno-embolization and conventional chemotherapy are the modalities empoloyed to treat hepatic metastasis from ocular melanoma, with varying degrees of success.[64] There is not enough clinical evidence regarding the efficacy of photodynamic therapy with verteporfin as a primary or adjuvant treatment.

Conclusion

Choroidal melanoma is a disease with a grim prognosis, where large proportions of the patients develop metastasis and eventually die of the disease. Evidence suggests that there is no difference in survival between surgical and conservative treatments of the intraocular tumor. Treatment of melanoma requires a multimodal approach that involves a team effort. Newer techniques in local disease control have not changed the rates of metastasis and death. Therefore, the ability to detect subclinical metastasis at the time of diagnosis, targeted therapy with minimal collateral damage and improving visual and functional outcomes are areas that require more research.

References

1. Eagle RC Jr. The pathology of ocular cancer. Eye (Lond). 2013;27(2):128-36.
2. Strickland D, Lee JA. Melanomas of eye: stability of rates. Am J Epidemiol 1981; 113: 700–702.
3. Kivela T. The epidemiological challenge of the most frequent eye cancer: retinoblastoma, an issue of birth and death. Brit J Ophthalmol 2009; 93: 1129–1131. (
4. Shields CL, Kaliki S, Furuta M et al. Clinical spectrum and prognosis of uveal melanoma based on age at presentation in 8033 cases. Retina 2012; 32:1363 – 1372.
5. Shields CL, Manalac J, Das C, Ferguson K, Shields JA. Choroidal melanoma: clinical features, classification, and top 10 pseudomelanomas. Curr Opin Ophthalmol. 2014;25(3):177-85.
6. Singh AD, De Potter P, Fijal BA, Shields CL, Shields JA, Elston RC. Lifetime prevalence of uveal melanoma in white patients with oculo (dermal) melanocytosis. Ophthalmology 1998; 105: 195-8.
7. Pane AR, Hirst LW. Ultraviolet light exposure as a risk factor for ocular melanoma in Queensland, Australia. Ophthalmic Epidemiol 2000;7(3):159 – 67.
8. Guenel P, Laforest L, Cyr D, Fevotte J, Sabroe S, Dufour C, et al. Occupational risk factors, ultraviolet radiation, and ocular melanoma: a case-control study in (France. Cancer Causes Control 2001;12(5):451 – 9.
9. Gallagher RP, Elwood JM, Rootman J, Spinelli JJ, Hill GB, Threlfall WJ, et al. Risk factors for ocular melanoma. Western Canada Melanoma Study. J Natl Cancer Inst 1985;74(4):775 – 8.
10. Rootman J, Gallagher RP. Color as a risk factor in iris melanoma. Am J Ophthalmol 1984;98(5):558 – 61. (
11. Tucker MA, Shields JA, Hartge P, Augsburger J, Hoover RN, Fraumeni Jr JF. Sunlight exposure as risk factor for intraocular malignant melanoma. N Engl J (Med 1985;313(13):789 – 92.
12. Kliman GH, Augsburger JJ, Shields JA. Association between iris color and iris melanocytic lesions. Am J Ophthalmol 1985;100(4):547 – 8.
13. Singh AD, Kalyani P, Topham A. Estimating the risk of malignant transformation of a choroidal nevus. Ophthalmology 2005; 112: 1784-9.(
14. Greenstein MB, Myers CE, Meuer SM, et al. Prevalence and characteristics of choroidal nevi: the multiethnic study of atherosclerosis. Ophthalmology 2011; 118:2468 – 2473
15. Li HK, Shields CL, Mashayekhi A, Randolph JD, Bailey T, Burnbaum J, Shields JA. Giant choroi- dal nevus clinical features and natural course in 322 cases. Ophthalmology 2010; 117: 324- 33.
16. Singh AD, Bergman L, Seregard S. Uveal Melanoma: Epidemiologic Aspects. Ophthalmol Clin North Am. 2005;18(1):75-84, viii.
17. Weis E, Shah CP, Lajous M, Shields JA, Shields CL. The association of cutaneous and iris nevi with uveal melanoma: a meta-analysis. Oph- thalmology 2009; 116: 536-543, e2.
18. Landreville S, Agapova OA, Harbour JW. Emerging insights into the molecular pathogenesis of uveal melanoma. Future Oncol. 2008; 4(5): 629–636.
19. van der Velden PA, Metzelaar-Blok JA, Bergman W, et al. Promoter hypermethylation: a common cause of reduced p16(INK4a) expression in uveal melanoma. Cancer Res 2001;61(13):5303–5306.

20. Weber A, Hengge UR, Urbanik D, et al. Absence of mutations of the BRAF gene and constitutive activation of extracellular-regulated kinase in malignant melanomas of the uvea. Lab Invest 2003;83(12):1771–1776.
21. Hanahan D, Weinberg RA. The hallmarks of cancer. Cell 2000;100(1):57–70
22. Prives C, Hall PA. The p53 pathway. J Pathol 1999;187(1):112–126.
23. McGill GG, Horstmann M, Widlund HR, et al. Bcl2 regulation by the melanocyte master regulator Mitf modulates lineage survival and melanoma cell viability. Cell 2002;109(6):707–718.
24. Brantley MA Jr, Harbour JW. Deregulation of the Rb and p53 pathways in uveal melanoma. Am J Pathol 2000;157(6):1795–1801.
25. Sun Y, Tran BN, Worley LA, Delston RB, Harbour JW. Functional analysis of the p53 pathway in response to ionizing radiation in uveal melanoma. Invest Ophthalmol Vis Sci 2005;46(5):1561–1564.
26. Grimberg A. Mechanisms by which IGF-I may promote cancer. Cancer Biol Ther 2003;2(6):630–635.
27. Ehlers JP, Worley L, Onken MD, Harbour JW. Integrative genomic analysis of aneuploidy in uveal melanoma. Clin Cancer Res 2008;14(1):115–122.
28. Jager MJ, Hurks HM, Levitskaya J, Kiessling R. HLA expression in uveal melanoma: there is no rule without some exception. Hum Immunol 2002;63(6):444 – 51.
29. Mooy CM, Luyten GP, de Jong PT, Luider TM, Stijnen T, van de Ham F, et al. Immunohistochemical and prognostic analysis of apoptosis and proliferation in uveal melanoma. Am J Pathol 1995;147(4):1097 – 104.
30. Coupland SE, Anastassiou G, Stang A, Schilling H, Anagnostopoulos I, Bornfeld N, et al. The prognostic value of cyclin D1, p53 and MDM2 protein expression in uveal melanoma. J Pathol 2000;191(2):120 – 6.
31. Onken MD, Worley LA, Person E, et al. Loss of heterozygosity of chromosome 3 detected with single nucleotide polymorphisms is superior to monosomy 3 for predicting metastasis in uveal melanoma. Clin Cancer Res 2007;13(10):2923–7. (
32. Shields CL, Kaliki S, Hutchinson A, Nickerson S, Patel J, Kancherla S, Peshtani A, Nakhoda S, Kocher K, Kolbus E, Jacobs E, Garoon R, Walker B, Rogers B, Shields JA. Iris nevus growth into melanoma: analysis of 1611 consecutive eyes: the ABCDEF guide. Ophthalmology. 2013;120(4):766-72.
33. Char DH. Uveal malignant melanoma: differential diagnosis. In: Singh AD, Damato BE, Pe'er J, et al. (eds): Clinical Ophthalmic Oncology. Philadelphia, Saunders-Elsevier, 2007: 212-218.
34. Ferry AP. Lesions mistaken for malignant melanoma of the posterior uvea. A clinicopathologic analysis of 100 cases with ophthalmoscopically visible lesions. Arch Ophthalmol 1964; 72: 463–469. (
35. Long JC, Black WC, Danielson RW. Aspiration biopsy in intraocular tumors. Arch (Ophthalmol 1953; 50: 303–310. (
36. Demirci H, Shields CL, Shields JA, Eagle RC Jr, Honavar S. Ring melanoma of the anterior chamber angle: a report of fourteen cases. Am J Ophthalmol 2001; 132: 336–342.
37. Demirci H, Shields CL, Shields JA, Honavar SG, Eagle RC Jr. Ring melanoma of the ciliary body: report on twenty-three patients. Retina 2002; 22: 698–706. (
38. Nair AG, Kaliki S, Ali MJ, Naik MN, Vemuganti GK. Intraocular malignant melanoma of the choroid presenting as orbital cellulitis. Int Ophthalmol. 2014;34(3):647-50.
39. Katz NR, Finger PT, McCormick SA et al. Ultrasound biomicroscopy in the management of malignant melanoma of the iris. Arch Ophthalmol 1995; 113: 1462–1463.
40. Bakri JS, Sculley L, Singh AD. Diagnostic Techniques. In: Singh AD, Damato BE, Pe'er J, et al. (eds): Clinical Ophthalmic Oncology. Philadelphia, Saunders-Elsevier, 2007: 175-180.
41. McCannel TA, Chang MY, Burgess BL. Multi-year follow-up of fine-needle aspiration biopsy in choroidal melanoma. Ophthalmology. 2012;119(3):606-10
42. Mellen PL, Morton SJ, Shields CL. American joint committee on cancer staging of uveal melanoma. Oman J Ophthalmol. 2013; 6(2): 116–118.

43. Shields CL, Kaliki S, Furuta M, Fulco E, Alarcon C, Shields JA. American Joint Committee on Cancer Classification of Uveal Melanoma (Anatomic Stage) Predicts Prognosis in 7731 Patients: The 2013 Zimmerman Lecture. Ophthalmology. [Epub ahead of print]

44. Margo CE. The Collaborative Ocular Melanoma Study: An overview. Cancer Control 2004;11(5):304-9.

45. Jampol LM, Moy CS, Murray TG, et al. The COMS randomized trial of iodine 125 brachytherapy for choroidal melanoma: IV. Local treatment failure and enucleation in the first (5 years after brachytherapy. COMS report no. 19. Ophthalmology 1. 2002;109(12):2197–206.

46. The Collaborative Ocular Melanoma Study Group. Factors predictive of growth and treatment (of small choroidal melanoma. COMS report no. 5. Arch Ophthalmol 1997;115(12):1537–44. (

47. The Collaborative Ocular Melanoma Study Group. Mortality in patients with small choroidal (melanoma. COMS report no. 4. Arch Ophthalmol 1997;115(7):886–93. (

48. Journeìe-de Korver HG, Schalij-Delfos NE, Imhof SM. Uveal malignant melanoma: management options – thermotherapy In: Singh AD, Damato BE, Pe'er J, et al. (eds): Clinical Ophthalmic Oncology. Philadelphia, Saunders-Elsevier, 2007: 232-240.

49. Journeìe-de Korver HG, Midena E, Singh AD. Infrared thermotherapy: from laboratory to clinic. Ophthalmol Clin North Am. 2005;18(1):99-110, viii-ix.

50. Damato B. Management of patients with uveal melanoma. In: Singh AD, Damato BE, Pe'er J, et al. (eds): Clinical Ophthalmic Oncology. Philadelphia, Saunders-Elsevier, 2007: 226-231.

51. Lane AM, Gragoudas ES. Uveal malignant melanoma:üÿmanagement options – proton beam radiotherapy. In: Singh AD, Damato BE, Pe'er J, et al. (eds): Clinical Ophthalmic Oncology. Philadelphia, Saunders-Elsevier, 2007: 248-253.

52. Damato B, Kacperek A, Chopra M, Sheen MA, Campbell IR, Errington RD. Proton beam radiotherapy of iris melanoma. Int J Radiat Oncol Biol Phys 2005; 63(1): 109–115.

53. Damato B, Heimann H. Personalized treatment of uveal melanoma. Eye (Lond). 2013;27(2):172-9.

54. Damato BE, Foulds WS. Surgical resection of choroidal melanomas. Chapter 40. In: Schachat AP, Ryan SJ, eds. Retina, 4th edn. St Louis: Mosby, 2006; 769–778.(

55. Bechrakis NE, Hocht S, Martus P et al. Endoresection following proton beam irradiation of large uveal melanomas. Ophthalmologe 2004; 101: 370–376.(

56. Foulds WS, Damato BE, Burton RL. Local resection versus enucleation in the management of choroidal melanoma. Eye (Lond) 1987;1(6):676–679.

57. Kivela T, Puusaari I, Damato B. Transcleral resection versus Iodine brachytherapy for choroidal malignant melanomas 6 millimeters or more in thickness: a matched case control study. Ophthalmology 2003;110(11):2235–2244.

58. Ludwig M, Garden AS, Williams MD, Gombos DS. Management of uveal melanoma. In: Esmaeli B (ed). Ophthalmic Oncology. New York, Springer, 2011: 201-213.

59. Puusaari I, Heikkonen J, Kivela T. Effect of radiation dose on ocular complications after iodine brachytherapy for large uveal melanoma: empirical data and simulation of collimated plaques. Invest Ophthalmol Vis Sci 2004; 45: 3425–3434.

60. Fluhs D, Anastassiou G, Wening J et al. The design and the dosimetry of binuclide radioactive ophthalmic applicators. Med Phys 2004; 31: 1481–1488.

61. The Collaborative Ocular Melanoma Study Group. The COMS Randomized trial of iodine 125 brachytherapy for choroidal melanoma, III: Initial mortality findings. COMS Report no. 18. Arch Ophthalmol 2001; 119: 969–982. (

62. Bergman L, Nilsson B, Lundell G et al. Ruthenium brachytherapy for uveal melanoma, 1979–2003. Survival and functional outcomes in the Swedish population. Ophthalmology 2005; 112: 834–840. (

63. Finger PT. Radiation therapy for choroidal melanoma. Surv Ophthalmol. 1997;42(3):215-32.

64. Jovanovic P, Mihajlovic M, Djordjevic-Jocic J, Vlajkovic S, Cekic S, Stefanovic V. Ocular melanoma: an overview of the current status. Int J Clin Exp Pathol. 2013 Jun 15;6(7):1230-44.