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Prevalence of Choroidal Melanoma in a Hill Population of Northern India

Deepesh Arora[1, *], Anuj Sharma[1], Devesh Sharma[2], Bhavna Tiwari[3], Abhishek Kumar[4], Kanika Gupta[5], Rohan Mehra[6], Abhinav Arora[7], Dinesh Sharma[4]

[1]Department of Vitreo-Retina, Amritsar Eye Clinic, Dehradun, India

[2]Department of Cornea and Refractive Surgery, Amritsar Eye Clinic, Dehradun, India

[3]Department of Occuloplasty, Amritsar Eye Clinic, Dehradun, India

[4]Department of Cataract and Refractive Surgery, Amritsar Eye Clinic, Dehradun, India

[5]Department of Paediatric Ophthalmology, Amritsar Eye Clinic, Dehradun, India

[6]Department of Cataract and Refractive Surgery, Eye Clinic, Saharanpur, India

[7]Department of Comprehensive Ophthalmology, Nirmal Ashram Hospital, Rishikesh, India

Email address:

drda198591@gmail.com (D. Arora), dr.anuj18@gmail.com (A. Sharma), drdevesh@amritsareye clinic (D. Sharma), drbhavnatiwari75@rediffmail.com (B. Tiwari), drabhi09@gmail.com (A. Kumar), dr.kanika_021987@yahoo.com (K. Gupta), rohan_65@rediffmail.com (R. Mehra), abhinav296@gmail.com (A. Arora), drdineshsharma@rediffmail.com (D. Sharma)

[*]Corresponding author

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Abstract: Aim: To assess prevalence and presentation of choroidal melanoma in a hill population of northern India along with its demographics, features, diagnostics, treatment and outcome with comparison to western population. Method: Choroidal melanoma constitutes most common intraocular malignancy with early appearance in Asian population. This is the 1st case series from a hill state of Uttarakhand, northern India involving medium to large size tumour with extraocular extension. In this retrospective study we assessed the prevalence, clinical presentation, diagnostic modalities, treatment plan, disease outcome, prognosis with survival and mortality. The study was carried out in time duration from February 2019-March 2021. Results: Data shows the presence of five patients, four male and 1 female in age range of 47-77 years, with median age at 62 years. Patient presented with visual equity in range of 6/18 to perception of light in time range of six months to 2 years. Fundus examination revealed presence of medium to large size choroidal mass with surface pigmentation and serous detachment. Neovascular glaucoma was present in three patients. Three patients underwent brachytherapy with I 125 and Ru 106, two cases responded well to therapy, one case presented with recurrence of tumour and neovascular glaucoma, underwent preenucleation radiation with external beam radiation therapy (EBRT) and the eye was lost following enucleation. Among five patients three underwent enucleation and thereafter were referred to surgical oncology for enlarged regional and cervical chain of lymph nodes for suspected metastasis. Histopathology via fine needle aspiration cytology (FNAC) or biopsy from whole specimen showed two cases of spindle cell, one of mixed cell variety and two of epitheloid cell type. Two cases of eitheloid cell type and one of spindle cell type needed EBRT as there was extraocular extension. All cases with enucleation were adviced an ocular implant. A diligent post treatment follow was maintained to look out for local recurrence and distant metastasis. Conclusion: Hill states have poor accessibility to healthcare. Our study shows existence of choroidal melanoma may be much larger than anticipated and cases could have been missed, hence making the need for dilated fundus examination a requirement and necessity. Histopathology, serology and imaging are much needed tools for diagnosis and staging of disease along with treatment of choroidal melanoma eventually indicating prognosis, survival and mortality. Treatment modalities as brachytherapy and EBRT are more frequently being used, indicating a shift in treatment more towards organ salvaging and preservation so as to maintain best visual function.

Keywords: Brachytherapy, Choroidal, EBRT, Enucleation, Melanoma, Mortality, PET-scan, Prognosis

1. Introduction

Posterior uveal melanoma is uncommon disease frequently diagnosed in the sixth decade of life and its incidence rises steeply with age. Its incidence of 5-6 cases/million population per year has remained stationary for last 50 years and it is the most common primary intraocular malignancy [1]. Recent data obtained from surveillance, epidemiology and end results (SEER) program database in the USA (1973-2008), the mean adjusted incidence estimate for ocular melanoma in the USA is 5.1 cases / 1 million population [2]. Its incidence in Europe is 1.3-8.6 cases per million per year. Incidence of uveal melanoma (UM) followed a very typical decreasing gradient from a minimum of 2 per million per year in Spain and southern Italy to a maximum of 8 per million per year in Norway and Denmark, following a north to south decreasing gradient related to the protective effect of ocular pigmentation in the southern population with respect to higher exposure to ultraviolet light at lower latitudes [3]. Its incidence in Asian Indians, black Africans and other pigmented races is estimated to be 0.2-0.4 per million contributing to nearly 1600 cases per year. As reported the mean age of presentation is approximately 45-80 years in nonHispanic Caucasians with occurrence a decade or two earlier in Asians [4-6].

They occur in children in teenage years, tend to be small and frequently pigmented involving choroid or iris showing better systemic prognosis when compared to older adults [7]. Age adjusted analysis of SEER program datatbase showed the incidence of uveal melanoma as 5.8 per million in males compared to 4.4 per million in females [3]. “Shields et al” in a large study of 8033 consequetive patients found the incidence to be 50% in males as well as females [8]. Most common site for uveal melanoma is the choroid. Assessment of ocular melanoma has shown that 83% arise from uvea, 5% from conjunctiva and 10 % from other sites [9]. “Shields et al” have reported in their large study of uveal melanoma that the tumour was located in the iris in (4%), ciliary body (6%) and in choroid (90%) [8]. White population is more afflicted by uveal melanoma in comparison to blacks with a ratio of Black: White at 1:15 to 1:50 [10-12]. “Shield et al” found no statistical difference in metastasis, or death from uveal melanoma based on race [10]. “Margo et al” found the risk of melanoma low in blacks. They were of the opinion that in white Hispanics compared to white non-Hispanics, protective effects related to dark skin pigmentation along with cultural-environmental exposure or socioeconomic factors could be at play here [11, 12].

Choroidal nevus found in nearly 5% of Caucasians in the United States is a fairly common intraocular lesion [13] whos risk of malignant transformation gradually increases with age and is mathematically calculated at 1 in 8845 based on the premise that all melanomas arise from nevus [14]. The annual rate of malignant transformation of choroidal nevus is 1 in 269565 for the youngest age group (15-19 years) and 1 in 3664 for the oldest age group (80-84 years) [14]. High risk factors indicating transformation of nevus to melanoma include tumour thickness >2 mm, subretinal fluid, orange pigment, margin near disc, ultrasonographic hollowness, and absence of halo or drusens [15]. Melanoma of choroid may appear as a dome-shaped elevated mass (75%) or has mushroom configuration as it ruptures Bruchs membrane (19%) and occasionally presents as diffuse variant (6%). It can be pigmented (55%), nonpigmented (15%), or may have mixed colour (30%), associated with retinal detachment (71%), intraocular hemorrhage (10%), or extraocular extension (3%). In a review of 7256 cases involving choroidal melanoma (CM), the mean basal diameter was 11.3 mm and mean tumor thickness was 5.5 mm [8]. These lesions have propensity to metastasize most commonly to liver (89%), lungs (29%), bone (17%), skin, subcutaneous tissue (12%), and lymph node (11%) [16]. Amongthose patients who died of uveal melanoma, 90% died within 15 years and 98% died within 28 years [17].

The purpose of this study was to assess the prevalence of choroidal melanoma in a hill terrain poorly accessible by transport and to assess local disease with systemic presentation in comparison to western population and to draw a plan where disease could be detected and treated early thereby saving vision and life.

2. Patients and Methods

Posterior uveal melanoma is an uncommon tumour and till present no study or case series has been documented from a hill population of Uttarakhand. It is a retrospective case study, carried out at a tertiary eye care hospital, Amritsar Eye clinic, in Uttarakhand, India. The study was in time duration from February 2019-March 2021. The purpose of this study is to document presentation of choroidal melanoma in the hills along with assessing disease severity. Aim is to concurrently study the demographic data, clinical presentation, diagnosis, histopathological assessment, management and outcome of choroidal melanoma. The retrospective study included 5 patients diagnosed and confirmed with choroidal melanoma. All patients had a detailed eye examination which included visual acuity, slitlamp biomicroscopy with 78D biconvex lens and indirect ophthalmoscopy. A detailed physical examination was carried out in all cases. Suspected cases underwent imaging which included clinical photography, fundus fluorescein angiography (FFA), optical coherence tomography (OCT), Ultrasound A-scan, B-scan for suspicious intraocular and subretinal pathology. Positeron emission tomography scan (PET scan), computerized tomography (CT) and magnetic resonance imaging (MRI) were used to diagnose case of ciliary and choroidal melanoma and to detect presence of local and distant metastasis.

3. Results

Among the 5 patients which were assessed and confirmed with choroidal melanoma, 4 (80%) were males and one was female (20%), Male: Female ratio being 1:0.25. Age of these patients ranged from 47 to 77 years. All the patients were from hill area. All our cases had unilateral presentation. Health and wellbeing was good in 3 patients (Case 1, 2, 3) and poor in 2 (case 4, 5). Presentation ranged from diminution of vision to progressive visual decline, distortion of vision, central or peripheral scotoma and radiating eye pain. Anterior segment showed new vessels on iris and angle, hence diagnosed with neovascular glaucoma (Case 1, 4, 5), with intraocular pressure elevated in these 3 cases, intraocular pressure (IOP) was in normal range in (Case 1, 2). IOP range in five cases was 14-34 mm of Hg. Fundus examination showed medium to large mushroom shaped choroidal mass with "peau de orange" appearance, surface pigmentation and atrophic areas (Case 1, 2, 3, 4, 5) with two cases positioned juxtapapillary (Case 1, 2). Nidek-3000A Echoscan depicted medium to high amplitude spikes corresponding to choroidal melenoma. USG- B Scan (Nidek-3000A Echoscan) displayed a distinct picture of dome to mushroom shaped elevated solid mass with scleral thickening with choroidal excavation and shadowing effect seen in orbit. Fundus flourescein angiography (FFA) showed extensive leakage with progressive fluorescence with zone of hypoflourescence and multiple pin point leaks seen at level of retinal pigment epithelium (RPE) designated as "hot spots". OCT showed variable features as intraretinal cystoid spaces with odema, loss of inner-outer retinal layers, loss of photoreceptors, loss of external limiting membrane with loss of IS-OS junction and presence of subretinal fluid (SRF) with thickened and irregular retino-choroidal complex (Case 1 and 2). Fine needle aspiration cytology (FNAC) (Case 1, 2, 3) and full specimen post enucleation biopsy (Case 4, 5) was done to classify choroidal melanoma histopathologically. (Details in Table 1, Table 2, Table 3, Table 4, Table 5) (Figures 1-14 placed in individual cases).

3.1. Case 1

Female patient, 57 years presented with oculus sinister (OS) diminution of vision, central scotoma and metamorphopsiae since 2 years, having been lost to follow up 1.5 years ago. Her visual acuity (Va) had reduced from 6/60 to 3/60 on revisit. Fundus revealed mediumsize oval shaped juxtapapillary elevated choroidal mass placed at posterior pole with "peau de orange" appearance with diffuse pigmentationand serous retinal detachment (SRD). Ultrasonogram brightness scan (USG B-scan) confirmed dome shaped elevated solid mass with scleral thickening with altered parameters since last visit. On USG B-scan apical height had increased from 3.93 mm to 4.63 mm and basal diameter had changed from 10.06 mm to 11.85 mm with presence of orbital shadowing. (OCT and FFA: Table 2). Positeron emission tomography magnetic resonance imaging (PET-MRI) of orbit and whole body showed a focal plaque like enhancing area in posterior aspect of left globe abutting the inner coats showing homogenous enhancement and presence ofchoroidal lesion suggestive of melanoma. No involvement of local or systemic nodes were detected. Fine needle aspiration cytology (FNAC) confirmed spindle B cell melanoma, grade 1 (G1) (>90% spindle cells), basal dimension 15.45 mm, maximum thickness 5mm, with sclera, ciliary body, optic nerve head free of tumor. She was referred to oncologist and as per eight edition of American joint cancer committee classification for posterior uveal melanoma (choroidal and ciliary body), regional lymph nodes and distant metastasis her (AJCC) staging was "Stage II A". She was given Ruthemium 106 plaque brachytherapy with dosage of 3100 Gy to tumor base and 130 Gy to tumor apex for 6 months, having observed optic disc and macula constraint since tumour involved both these sites. Follow up showed recurrence of melanoma with presence of neovascular glaucoma (NVG) with total visual loss. She underwent preenulceation external beam radiation therapy (EBRT) at 120 CGE (Cobalt Gy equivalent) by proton beam, delivered in five equal fractions over 10 days followed by surgery. The eye could not be salvaged, was enucleated and she was referred to surgical oncologist for further assessment and management. (Figure 1: Color photo, Figure 2: FFA, Figure 3: OCT 1st visit, Figure 4: OCT 2nd visit, Figure 5: USG B-scan 1st visit, Figure 6: USG B-scan 2nd visit, Figure 7: PET MRI orbit, Figure 8: PET MRI body).

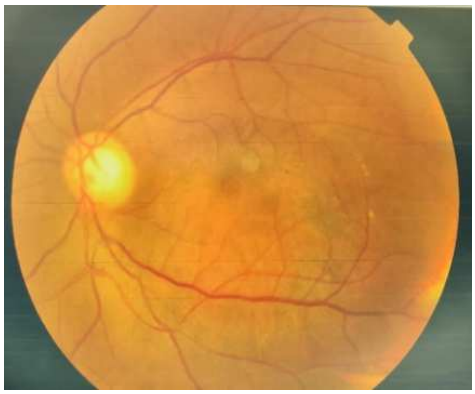

Figure 1. *Oval pigmented, peau de orange appearance choroidal mass (Case1) involving posterior pole placed adjacent to optic nerve head.*

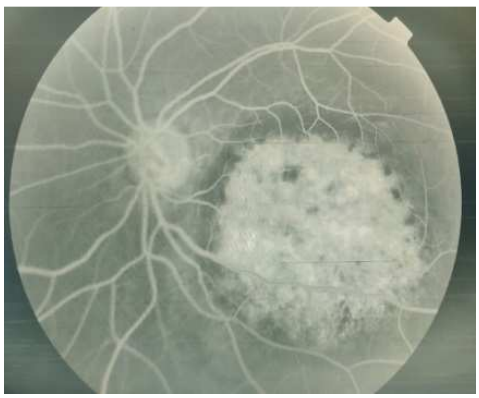

Figure 2. *FFA (Case 1) late phase shows fluorescent lesion with pin point areas of hyperflourescence.*

Figure 3. *OCT (Case 1) image shows elevated retinochoroidal complex, shaggy photorecptor, subretinal fluid and retinal odema seen on 1st visit of patient.*

Figure 4. *Second visit (Case 1) a year later shows change in architecture with thining of retinochoroidal complex, total loss of photoreceptors, subretinal fluid and development of maculaschisis.*

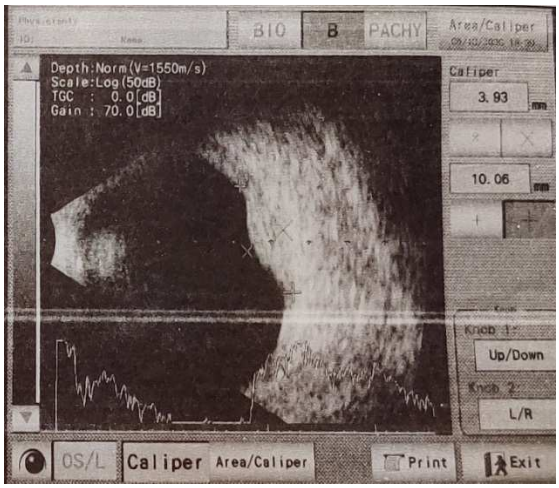

Figure 5. *Oval elevated hollow mass originating from choroid, is seen adjacent to optic nerve head measuring (apical height) 3.93 x 10.06 mm (basal diameter). (Case 1).*

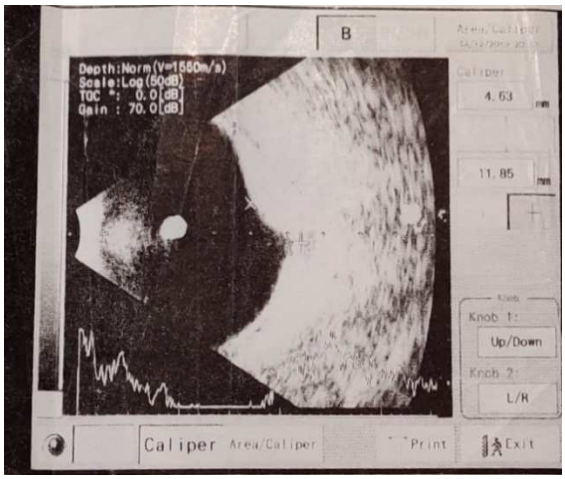

Figure 6. *(Case 1) followed up a year later with change in apical height and basal diameter (4.63 x 11.85 mm).*

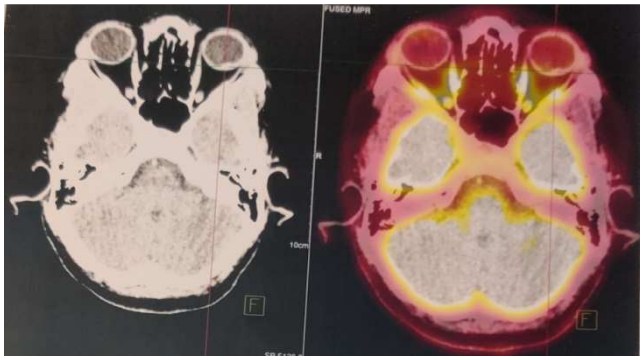

Figure 7. *PET MRI (Case 1) shows radiopaque focal plaque like enhancing area in left globe posteriorly abutting the inner coats showing homogenous enhancement suggesting choroidal melanoma.*

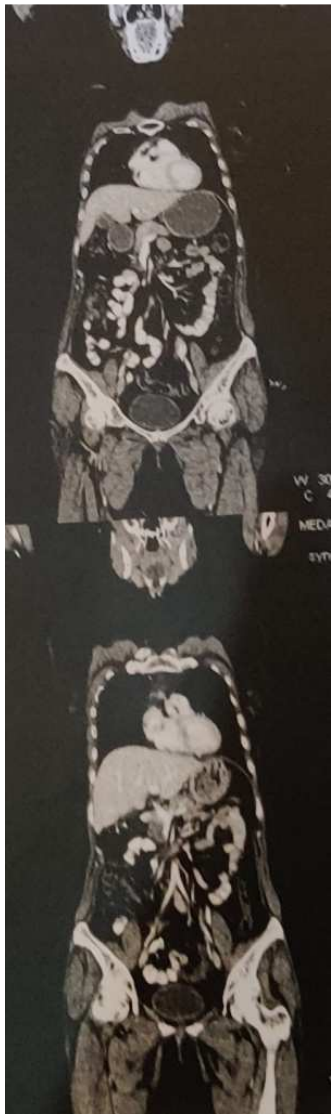

Figure 8. *Liver and systemic lymph nodes (Case 1) are negative for radioactive contrast uptake on PET MRI scan.*

3.2. Case 2

Male 47 years presented with (Va) of 6/24 oculus dexter (OD) with complaints of immobile dark spot in peripheral field of vision increasing in size since last 6 months. Fundus

examination showed medium size oval shaped choroidal mass located in inferotemporal quadrant (ITQ) adjoining optic nerve head (ONH). The mass encroaching fovea also showed diffuse orange surface pigmentation. USG B-Scan detected a dome shaped elevated solid mass with scleral thickening having apical height 2.52 mm and basal diameter 9.14mm. FNAC confirmed spindle B cell melanoma, grade 1 with basal dimension 12mm and thickness 4.5mm. The MRI orbital study showed intraocular mass located in inferomedial aspect of right eye presenting as T1 high and T2 low signal intensity appearing hyperintense on T1W1. Patient had no local or systemic node involvement and was placed in "Stage II A" as per AJCC classification. Oncologist placed him on I 125 episcleral plaque brachytherapy, dosage 85 Gy directed towards tumour apex and 30 Gy directed towards tumour base for 6 months, observing constaint for optic disc. (Figure 9: Colour photo, Figure 10: FFA, Figure 11: Oct-macula, Figure 12: USG B-scan).

Figure 9. *Oval elevated pigmented choroidal mass (Case 2) placed in inferotemporal quadrant is seen adjacent to optic nerve head involving fovea.*

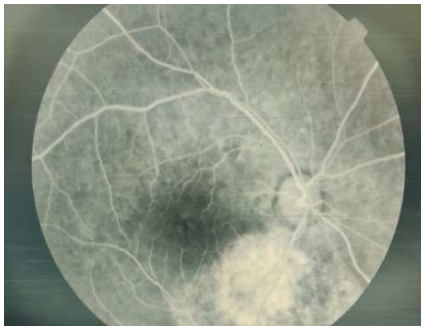

Figure 10. *FFA (Case 2) in late phase shows a hyperflourescent lesion with irregular edges with zones of hypoflourescence with leakage extending to disc and involving fovea.*

Figure 11. *OCT (Case 2) shows loss of inner retinal layers with presence of maculaschisis.*

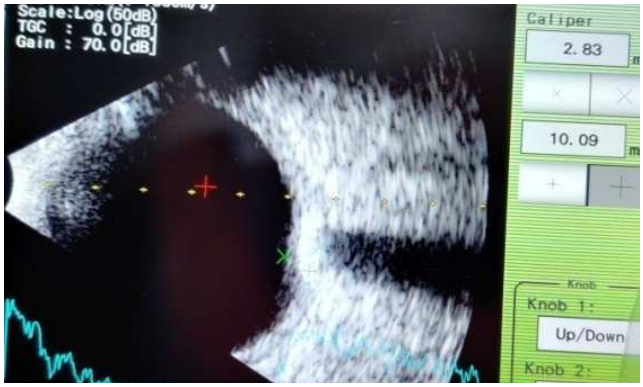

Figure 12. *USG B scan (Case 2) shows oval elevated acoustically hollow mass involving macula and disc measuring (apical height) 2.83 x 10.09 mm (basal diameter).*

3.3. Case 3

Male 64 year with (Va) 6/18 (OD), presented with complaint of superior scotoma since last 9 months. Examination detected medium size mushroom shape elevated choroidal mass with surface pigmentation with serous RD located in inferonasal quadrant (INQ). Surrounding area showed heavy pigmentation with atrophy. USG B-Scan revealed oval shaped elevated solid mass with scleral thickening having apical height of 4 mm with basal diameter 11.12 mm. FNAC confirmed basal dimensions 11.98mm and thickness 6.5mm. The MRI orbital study showed intraocular mass located in inferomedial aspect of right eye presenting as T1 high and T2 low signal intensity appearing hyperintense on T1W1 on MRI. MRI of head, neck and abdomen was normal. He showed regional lymphadenopathy and enlargement of cervical chain. FNAC showed inflammatory change in both regional and cervical chain nodes. Histopathologically mixed cell melanoma (>10% epitheloid cell and 90% spindle cell), grade 2 was confirmed. As per AJCC classification he was placed under "Stage II B". Ruthemium 106 episceral plaque was placed at dosage of 2100 Gy to apex and 400 Gy to tumor base given for duration of 9 months.

3.4. Case 4

Male 73 years, presented with radiating eye pain and painful progressive visual deterioration over 1.5 years with (Va) perception of light (PL+) with scleral pigmentation and corneal odema with new vessels on iris involving (OS). His IOP was 32 and he was diagnosed on presentation with neo vascular glaucoma (NVG). USG B-Scan detected large mushroom shaped choroidal mass, acoustically hollow with apical height 9mm, width 8.75 x 10.29 mm and basal diameter 2.45 cm also confirming extraocular extension < 5mm. CT scan of orbit showed a large mushroom shaped mass lesion projecting into vitreous cavity occupying 80% of intraocular space. The lesion appeared hyperdense. FNAC confirmed basal diameter at 2.55mm and epitheloid cell melanoma, grade 3 (G3) (> 90 % epitheloid cells) with involvement of ciliary body. Oncologist staging placed it

under "Stage IV" as per AJCC classification with enlarged cervical chain. Preenulceation EBRT was given at 100 CGE (Cobalt Gy equivalent) by proton beam, delivered in five equal fractions over 10 days followed by surgery. She was there after referred to surgical oncology and chemotherapy was adviced initially.

3.5. Case 5

Patient aged 66 years, male, presented with progressive visual decline with pain of 2 years duration involving (OD) with IOP 34 and poor general health. Examination showed extrascleral spread of melanoma with new vessels over iris and angle on gonioscopy. USG B-scan depicted large mushroom shaped choroidal lesion with RD. On USG B-scan apical height was 9.75 mm, width 9.15 x 10.34 and basal diameter was 2.5 cm with extraocular extension > 5mm. USG B scan showed large mushroom shaped choroidal mass with presence of RD with choroidal excavation and shadowing in orbit. CT scan of orbit presented a large mushroom shaped mass with features suggestive of RD and presence of subretinal fluid. CT neck, chest and abdomen confirmed enlarged cervical chain and intraocular mass occupying 85-90% of intraocular volume appearing hyperdense. FNAC confirmed metastatic spread to lymph nodes along with histopathologically confirming epitheloid cell melanoma, grade 3 (G3) (> 90% epitheloid cell). He was placed under "Stage IV" as per AJCC classification. EBRT 90 CGE proton beam was delivered by five equal fractions for 10 days period followed by enucleation. He was referred to surgical oncology for further management, where chemotherapy was adviced. (Figure 13: Globe image, Figure 14: USG B-scan).

Postoperative diligent follow up was maintained on all patients keeping a check on blood profile, imaging and oncologist review. Three cases (Case 1, 4 and 5) had been referred to surgical oncology of which two cases (Case 4 and 5) were thereafter referred for chemotherapy along with palliative care. Till last follow up in August 2021 two cases (Case 2, 3) were in remission and all 5 cases were systemically stable with no evidence of recurrence or metastasis.

Figure 13. *Colour photo (Case 5) shows extrascleral spread of choroidal melanoma, > 5mm with presence of sentinel vessel.*

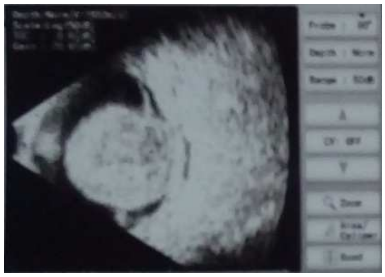

Figure 14. *Mushroom shaped elevated choroidal mass (Case 5) acoustically hollow with retinal detachment and choroidal excavation.*

Table 1. *Anthropology data of patients Detected with Choroidal Melanoma from a hill terrain in Northern India.*

Patient no.	Age	sex	Eye	IOP	Chief eye complaints	Systemic complaints	General Health of patient
1.	57	F	OS	18	Diminution and distortion of vision / central scotoma/metamorphopsiae since 2 years	Nil	Good
2.	47	M	OD	20	Floaters / Diminution of vision since 6 months	Nil	Good
3.	64	M	OD	14	Scotoma SNQ since 9 months	Nil	Good
4.	77	M	OS	32	Radiating & Progressive Eye Pain/ Rapid visual deterioration 1.5 years (NVI)	Poor general health	Poor
5.	66	M	OD	34	Progressive visual decline (extrascleral spread) 2 years	Poor general health	Poor

IOP=Intraocular pressure, NVI= New vessel, OD=Oculus dexter, OS= oculus sinister.

Table 2. *Clinical Examination and Local Imaging Data.*

No	Vision	Anterior segment	Posterior Segment	OCT	USG Bscan
1	OS: 6/60	Normal	OS: Large Oval shape elevated posterior pole placed choroidal mass with "peau de orange" appearance and diffusely pigmented with presence of serous RD OS: Follow up (1.5 year later) of lesion shows similar elevated mass with increase in pigmentation and appearance of serous RD	1. Intrareinal cystoid spaces and oedema 2. Loss of photoreceptors 3. Loss of ELM 4. Loss of IS-OS junction 5. Presence of SRF LE: Follow up (1.5 year) shows 1. Large cystic spaces with intraretinal oedema 2. Loss of inner and outer retinal layers 3. Thickened and irregular retino-choroidal complex with minimal subretinal fluid	1. Dome shaped elevated solid mass with scleral thickening 2. Apical height 3.93mm 3. Basal diameter was 10.06mm. 3. Shadowing in orbit seen Follow up (1.5 year later) 1. Large dome shape elevated solid mass with scleral thickening 2. Apical height 4.63mm with basal diameter 11.85 mm 3. Shadowing in orbit seen

No	Vision	Anterior segment	Posterior Segment	OCT	USG Bscan
2	OD: 6/24	Normal	OD: ITQ peripappilary located medium size oval shape choroidal mass wiith diifuse orange pigmentation with edges darkly pigmented along with presence of serous RD encroaching fovea	1. Intraretinal oedema 2. Intraretinal large cystic spaces 3. Loss of IS-OS junction and RPE 4. Loss of ELM 5. Maculaschisis	1. Dome shaped elevated solid mass with scleral thickening 2. Apical height 2.52 mm 3. Basal diameter 9.14mm 3. Shadowing effect seen
3	OD: 6/18	Normal	OD: INQ located medium size round to oval elevated choroidal mass with surface pigmentation with serous RD. Surrounding area shows heavy pigmentation with atrophy.	----	1. Medium size mushroom shaped elevated solid mass with scleral thickening 2. Apical height 4 mm with basal diameter 11.12 mm 3. Shadowing effect seen
4.	OS: PL + positive PR faulty	1. Diffuse scleral pigmentation 2. Corneal oedema 3. NV present on iris and angle (vessels in 4 Q) 4. Extraocular extension present	------	--------	1. Large mushroom shaped elevated choroidal lesion seen. 2. Acoustically hollow lesion 3. Choroidal excavation and shadowing in the orbit. 4. Apical height 9 mm with basal diameter 2.45 mm and width 8.75 x 10.29 mm
5.	OD: Perception of Light?	1. Extraocular extension of ciliochoroidal melanoma seen 2. NV present on iris and angle (4Q)	----------	---------	1. Large mushroom shaped choroidal lesion seen 2. Presence of RD 3. Choroidal excavation and shadowing in the orbit seen 4. A pical height 9.75 mm with basal diameter 2.50 mm and width 9.15 x 10.34 mm

ITQ= Inferior temporal quadrant, INQ= Inferior nasal quadrant, NVE= New vessel OCT=Optical coharance tomography, OD= Oculus dexter, OS= Oculus sinister, PR= Projection of light.

Table 3. *Radiological Imaging in Diagnosis of Choroidal Melenoma.*

No.	FFA	MRI / CT	PET-MRI
1.	OS: 1. Extensive leakage with progressive flouresence with zone of hypoflouresence seen 2. Delayed staining of primary lesion 3. Multiple pin point leaks seen at level of RPE designated as “hot spots”	-------	. MRI: Focal plaque like enhancing area in left globe posteriorly abutting the inner coats showing homogenous enhancementsuggesting choroidalmelenoma Liver and systemic lymph nodes are negative for radioactive contrast uptake.
2.	OD: 1. Extensive leakage with progressive flouresence extending to involve disc seen 2. Delayed staining of primary lesion	The study shows a well defined T1 hyperintense and T2 hypointense lesion along inferomedial aspect of right eye. No systemic metastasis detected	--------
3.	OD: 1. Early phase shows staining of primary lesion 2. Late phase shows active leakage from primary site with involvement of optic disc and staining of atrophic edges of primary lesion	The study shows Intraocular mass located in inferomedial aspect of right eye presenting as T1 high and T2 low signal intensity appearing hyperintense on T1W1 on MRI. Enlarged and inflamed regional with cervical chain of lymph nodes.	-------
4.	OS: Opaque media	CT scan of orbit shows a large mushroom shaped mass lesion projecting into vitreous cavity occupying 80% of intraocular space. The lesion appears hyperdense.	Inflammed enlarged regional and cervical chains. Metastasis possibility.
5.	OD: Opaque media	CAT scan of orbit presents a large mushroom shaped mass with features suggestive of RD and presence of srf. Mass occupies 85-90% of intraocular volume appearing hyperdense.	Imaging free for neck, chest and abdomen. Metastasis in regional and cervical chain of lymph nodes.

CAT= Computerized axial tomography, FFA=Fundus Flourescein Angiography, MRI= Magnetic resonance Imaging, PET= Positeron emission tomography, RD= Retinal detachment.

Table 4. *Histopathology and staging of choroidal melanoma.*

No.	Ocular histopathology	AJJO staging	Systemic Histopathology
1.	Spindle B cell melanoma, grade1 (G1) (>90% spindle cells), basal dimension 18mm, maximum thickness 5mm, sclera, ciliary body, optic nerve head free of tumour.	AJCCpTNM stage-p T2aN0M0 Stage IIA	None
2.	Spindle B cell melanoma, grade 1 (G1), basal dimension 12mm, maximum thickness 4.5mm, sclera, ciliary body, optic nerve head free of tumour.	AJCCpTNM stage-p T2N0M0 Stage IIA	None
3	Mixed cell melanoma (>10% epitheloid cell and 90% spindle cell), grade2 (G2), basal dimension 11.98mm, maximum thickness 6.5mm, ciliary body involved but sclera and optic nerve head free of tumour.	AJCCpTNM stage-p T2bNXM0 Stage IIB	Cervical and regional lymph node chain inflamed.
4	Epitheloid cell melanoma, grade3 (G3) (>90%epitheloid cells), basal diameter2.55cm, apical height 9mm, ciliary body involved by tumour.	AJCCpTNM stage-p T4bNIaMI Stage IV	Cervical and regional lymph node chains enlarged due to inflammation and metastasis
5	Epitheloid cell melanoma, grade3 (G3)(> 90% epitheloid cell), basal diameter 2.5cm, apical height 9.75mm, ciliary body, optic nerve head and sclera involved with tumour.	AJCCpTNM stage-p T4eNIaMI Stage IV	Regional and cervical lymph node chain involved due to metastasis

AJCC=American joint cancer committee, G= Grade, TNM= Tumour Node Metastasis.

Table 5. *Treatment of 5 cases involving choroidalmelenoma.*

No.	Metastasis present/absent	Enucleation with coral Implant	EBRT	Plaque Brachytherapy	Whole body Irradiation	Chemotherapy
1.	Absent	Recurrence of tumour with NVG: Enucleation with coral implant	Recurrence 120 CGE x proton x 5 fractions over 10 days	OS: Ruthemium106 plaque brachytherapy Dosage: 3100 Gy to tumor base and 130Gy to tumor apex for 6 months	Not required	Nil
2.	Absent	Not done	Nil	OD. Iodine 125: Episcleral plaque brachytherapy Dosage: 85 Gy directed towards tumour apex and 30 Gyritowards base for 6 months.	Nil	Nil
3.	Absent	Not done	Nil	OD: Ruthemium 106 Dosage: 2100 to apex and 400 to tumour base for 9 months	Nil	Nil
4.	Present	OS: EBRT followed by Enucleation and orbital implant	EBRT: 100 CGE proton beam (Cobalt Gy equivalent each delivered in 5 fractions in 10day period)	Nil	Nil	Added
5.	Absent	OD: EBRT followed by Enucleation and orbital implant	EBRT 90 CGE proton beam (Cobalt Gy equivalent each delivered in 5 fractions in 10 day period)	Nil	Nil	Added

CGE= Cobalt grey equivalent, EBRT= External beam charge particle radiation therapy, Gy= Gyri, NVG= Neovascular Glaucoma.

4. Discussion

Four of our patients came from hill terrain of Uttarakhand where transportation and accessibility to healthcare is poorly available. The other patient was from plains. Source of livelihood in hills is difficult, making healthcare affordability a secondary need which could have been reason for advance stage of disease presentation.

Among 5 patients who were assessed and confirmed for choroidal melanoma, 4 (80%) were male (median age 62) and 1 (20%) was female, there ratio being 1:0.25. Data from majority of studies place the median age at detection around 55 years [18, 19]. Among various studies and review articles from Indian subcontinent, “Kashyap et al” reported the mean age of patients as 46 ± 13.1 years [20], “Dhupper et al” placed the mean age at 45.9 ± 14.84 years [6] and “Machegowda et al” placed the age of presentation in Asians at 40-55 years [21].” Shields et al” and collaborative ocular melanoma study (coms) report no.9 documented the mean age as 60 years [22, 23]. “Jensen et al”reported decline in males after 69 years in contrast to Finnish cancery registry reporting decline in females in mid 60s [18, 19, 24]. In New England the overall rate was found to be similar in males and females [25]. Similar results have been shown by “Shields et al” [8]. It has been documented that 90% of eye cancers detected in white population are ocular melanoma with majority involving uveal tract [26]. “Zloto et al”and “Riechtel et al” documented higher risk of melanoma related metastasis with worst prognostic outcome and death in males [27, 28] related to hormonal factors [27, 29] namely estrogen which could be responsible in inhibiting growth of micro-metastasis within the liver [27]. In our study, age of these 5 patients ranged from 47-77 years. The youngest and eldest

patients were both males aged 47 and 77 years with median age 62 years.

Most prevalent presenting symptom in patients with uveal melanoma (UM) appears to be blurring of vision (37.8%), followed by photopsiae (8.6%), floaters (7%), visual field loss (6.1%), visible tumor growth (3.1%), pain (2.4%) and metamorphopsia (2.2%). All our patients presented with blurring along with diminution of vision (Case 1, 2, 3, 4, 5), other features of photopsiae and metamorphopsiae (Case1), floaters (Case 2), scotoma (Case 3) and radiating eye pain (Case 4) were also seen. A large number of patients are symptom free at the time of diagnosis (30.2%) [30]. It is imperative to remember that clinical presentation of UM eventually depends on its size and location. Visual acuity assessment using snellens chart and torch light placed the best to worst vision at 6/18 to perception of light (PL+ve). Loss of vision may be caused by tumour involvement of macula or by exudative retinal detachment [32]. Choroidal melanoma presents as dome or mushroom shaped subretinal mass whereas ciliary body melanoma may cause wide dilated pupil, presenting as dome shaped or sessile lesion, causing lens displacement with accommodative disturbances, localized cataract or increased intraocular pressure. Metastatic lesions are multifocal and bilateral consistent with choroidal metastasis. All our cases had unilateral presentation. Haemorrhage, inflammation and pain may form part of presentation involving large tumors [32, 33].

Benign pigmented naevi pose a challenge in diagnosis of UM. “Shields et al” adviced to look for factors which may be associated with increased risk of malignant transformation. These were presence of symptoms, tumor thickness greater than 2mm, subretinal fluid, orange pigment, tumour margin less than 3mm to disc, ultrasonographic hollowness and lack of surrounding hollow [15, 33]. “Shields et al” showed that tumor growth was detected in approximately 36%, 45%, 50%, 51% and 56% of patients with presence of 1, 2, 3, 4 or all risk factors [15]. Choroid being highly vascular tissue, most frequent mode of spread is haemmatogenous [34, 35]. “Shields et al” suggested 10 pseudomelenommas that need to be differentiated by their unique clinical features from UM consisted of choroidal nevus, peripheral exudative haemorrhagic chorioretinopathy, congenital hypertrophy of retinal pigment epithelium (RPE), haemorrhagic RPE detachment, choroidal haemangioma, age related macula degeneration, RPE hyperplasia [36].

Various investigative and diagnostic modalities are available at hand for confirmation of UM. Clinically relevant are fundus photography, OCT and OCT-Angio, FFA, USG B-Scan, PET-CT and MRI. “Shields et al” in a study of 37 eyes with small choroidal melanoma found statistically significant enhanced depth imaging optical coherence tomography (EDI-OCT) changes which included intraretinal edema, shaggy photoreceptors or loss of photoreceptors, loss of external limiting membrane, loss of inner segment-outer segment junction, irregularity of inner plexiform layer, irregularity of ganglion cell layer were found in overlying small choroidal melanoma but were not observed in overlying choroidal nevus. Small choroidal melanoma tumor thickness was overestimated by 55% on ultrasonography compared with enhanced depth imaging optical coherence tomography (EDI-OCT) [37]. Our three cases (Case 1, 2, 3) presented with similar findings, the other two cases (Case 4 and 5) had opaque media. In another study of 23 eyes with choroidal tumours “Torres et al” reported success using enhanced depth imaging spectral domain-optical coherence tomography (EDI SD-OCT) to get a cross-sectional view of choroidal tumors and in diagnosing small choroidal tumors undetectable by ultrasonogram (USG) [38].

Fundus fluorescein angiography (FFA) was available for 3 of our cases with no distinct pattern in each of them. Both (Case 1 and 2) showed obscured fluorescence with scattered hyperfluorescent spots in the early phase increasing towards late phase, appearing as confluent bright hyperfluorescent spots and a zone of ring like hypoflouresence. Case 3 showed early minimal staining of surrounding atrophic pigmented retinal pigment epithelium (RPE). FFA has limited role in establishing clinical diagnosis of UM [39]. Features of double circulation, extensive leakage with progressive flourescence from primary lesion, typical late staining of lesion with multiple pin point leaks (hot spots) seen at level of RPE are some of the features that form part of FFA picture of CM [40, 41].

USG B-scan shows three distinct features of CM, presence of acoustically silent zone within the melanoma, excavation of choroid and orbital shadowing. It has been shown that tumour which are greater than 3 mm in thickness, a combination of USG-A and B-scan can diagnose CM with greater than 95% accuracy [39]. Smaller tumors are best diagnosed on USG B scan having propensity to be missed on MRI and CT scan. On USG B scan CM appear spherical or mushroom shaped arising from the choroid giving the indication of having breached bruchs membrane. It may also show presence of vitreous haemmorhage, subretinal fluid (SRF) and retinal detachment (RD). In our study, 3 cases (Case 1, 2, 3) presented as spherical lesion and two other as (Case 4, 5) mushroom / collar stud like growth with case 5 also showing retinal detachment (RD). In our study A-scan showed initial high spike followed by low to medium intensity spike followed by high spike. In a study of 36 eyes with small to medium size CM, 91.7% were found to be flat or dome shaped, 86.1% showed lower echo than adjacent orbital tissue and 16.7% showed choroidal excavation not seen with other tumours, 80.6% showed secondary retinal detachment and low internal echo and large height, these were risk factors of choroidal melanoma while low echo and large base height ratio were risk factors of choroidal metastasis [42]. “Sobottka et el” too confirmed the height to base ratio finding, with polygonal surface in metastasis and greater reflectivity in choroidal metastasis thus enabling a highly significant discrimination and difference between metastasis and melanoma [43]. “Romanowska-Dixon et al” in a retrospective study of 171 enucleated eyes with CM and deep intrascleral tumor invasion with extrascleral extension showed that extrascleral extension was detectable before

enucleation in 31 eyes (18.24%) and ultrabiomicroscopy is crucial in detecting the routes of extrascleral extension of UM [44].“Papayiannis et al” in a comparative study between MRI and USG B-scan found USG to be more sensitive than MRI in detection of RD [45]. MRI of malignant malenoma which contain melanin and has intrinsic T1 and T2 shortening effects, classically manifests with hyperintense signal on T1-weighted magnetic resonance (MR) images and with hypointense signal on T2-weighted images. Amelanotic or mildly pigmented lesions of melanoma do not demonstrate these characteristic on MR imaging, features appearing slightly hyperintense or isointense on T1WI [46]. We found radiological evidence to suggest extraocular involvement by CM in 3 of our cases as the tumour had become extrascleral and cervical chains of lymph nodes were enlarged (Case1, 4, 5). Metastasis when it occurs tend to extend in choroidal plane with minimal increase in thickness in contrast to protuberant melanoma shows bilaterality, presence of retinal detachment and hemorrhagic mass [47]. When present, choroidal metastases usually have a higher reflectivity on A-scan and appear echo-dense on B-scan, with a significantly lower height to base ratio compared to melanomas [48, 49]. It has been seen, < 0.5% of metastases present with a “mushroom” or “collar-button” configuration [50, 51]. Thickness of metastasis tends to correlate to origin, with a mean thickness of metastases secondary to melanoma measuring 1 mm, breast 2 mm, lung and prostate 3 mm, and gastrointestinal and kidney measuring 4 mm [50].

PET-CT imaging can also be used as a screening tool for the detection and localisation of metastatic choroidal melanoma. In a study involving 52 patients with choroidal melanoma were screened for metastasis, two (3.8%) were confirmed for metastatic melanoma with other sites being liver (100%), bone (50%) and lymph nodes (50%) [52]. In another study patients underwent whole-body 18-fluoro-2-deoxy-D-glucose (FDG) PET/computed tomography imaging for suspected metastatic choroidal melanoma, common sites for metastases were the liver (100%), bone (50%), lung (25%), lymph nodes (25%), and subcutaneous tissue (25%). The study also showed cardiac, brain, thyroid, and posterior abdominal wall lesions (12.5%) with six patients (75%) having multiple organ involvement [53]. PET-CT is capable of physiologically identifying medium (T2) and most large sized (T3) CM, though it has been suggested by authors that functionally fused PET-CT localised the tumors within the eye and assessed their physiological activity [54]. PET-CT hence may have an advantage over other imaging modalies for local tumour detection and screening for distant metastasis.

Fine needle aspiration cytology (FNAC) or post enucleation histopathology confirms the diagnosis and helps in planning treatment along with determining the outcome [55]. COMS report no.6 presented histopathologic characteristics of uveal melanomas in 1,527 (99.7%) of 1,532 cases examined. It showed spindle cell (9.0%), mixed cell (86.0%), and epithelioid cell (5.0%) histopathological types of CM [55]. In our study two patients were of spindle cell (40%) melanoma (Case1 and 2), two of epitheloid cell (40%) (Case 4, 5) and one of mixed cell type (20%) (Case 3). Scleral involvement was seen in (Case 4 and 5) with eitheloid cell melanoma. In a study of 113 patients of CM in Indian population, “Dhupper et al” reported that mixed cell type was seen in (63%), spindle cell type (28%), epitheloid cell type in (10%) and necrotic type in (2%) of patients. The mean basal diameter was 12.41 ± 1.4mm [6]. “Kashyap et al” reported spindle cell morphology as the most common subtype in 10 year analysis of CM in north Indian population [20]. “Manchegowda et al” in a review article on UM in Asians, reported mean basal diameter greater compared to whites, medium size tumours being more common and epitheloid cell variant carried the worst prognosis [21].

Various modalities of treatment options are available for CM including observation. Most commonly applied treatment methods are enucleation along with plaque brachytherapy and external beam radiation therapy (EBRT). Among our five patients of CM, three cases underwent brachytherapy (Case 1, 2, 3) alone or in combination with EBRT and three needed enucleation (Case 1, 4, 5). Among the 3 cases (Case 1, 2, 3) that underwent plaque brachytherapy, (Case 1, 2, 3) were of medium size tumour. First case (Case 1) showed tumor recurrence, developed NVG leading to total visual loss and received preenucleation EBRT. The other two cases (Case 2, 3) responded well to brachytherapy. Two other patient with large tumour (Case 4 and 5) presented with findings suggestive of new vessel on iris or fully established neovascular glaucoma (NVG) with ciliary body and extrasceleral spread of tumor also involving cervical chains. They underwent pre enucleation external beam radiotherapy (EBRT) (Case 1, 4, 5). It has been seen that ideal treatment for CM depends on location of tumour, tumour size, shape, tumour activity, central visual acuity of the affected eye, intraocular complications, contralateral eyestatus, age and general health of the patient, along with presence of metastasis [56]. Aim of intraocular therapy is to control tumour growth locally, so as to reduce risk of metastasis and preserving the eyeball to salvage visual function. Most frequently used treatment is radiotherapy, ruthemium (Ru-106) is commonly used in Europe and iodide (I-125) applicators in USA [57]. COMS report no.16 showed 43% to 49% of treated eyes had substantial impairment in visual acuity by 3 years after I 125 brachytherapy, defined as a loss of six or more lines of visual acuity from the pretreatment level (49% of eyes) or visual acuity of 20/200 or worse (43% of eyes) that was confirmed at the next 6-month examination [58]. In our case series pretreatment visual acuity ranged from 6/18 to perception of light on snellens chart. Definitive visual decline is seen in cases with posterior pole and juxtapappilary placed lesions as seen in our 4 cases (Case 1, 2, 4, 5).

Other studies involving 125I and 106Ru episcleral plaques usage has shown outcome with both agents to be equally effective in preservation of vision over 2.5 years with none being superior [59]. Radiation induced side effects reported by “Gunduz et al” documented maculopathy at 5 years in

40% of the patients, cataract in 32%, papillopathy in 13% and tumor recurrence in 9% [60]. COMS report no. 30, detected retinopathy after I-125 brachytherapy appearing as macular microaneurysm (75.6%), macular angiographic leakage (75.1%), and optic neuropathy (62.8%) [61]. None of our patients showed features suggestive of radiation retinopathy. Coms report no. 19 documented enucleation of 69 eyes and treatment failure for 57 eyes during the first five years after iodine 125 brachytherapy. Kaplan-meir placed patients who underwent enucleation by 5 years at 12.5% and risk of treatment failure at 10.3%. Hence treatment failure was the most common reason for enucleation with in 3 years of treatment [62]. Three of our patients under went EBRT (Case 1, 4, 5). EBRTs presence in India may be restricted due to its availability and the issue of cost factor may be at play here. "Damato et al" reported high rates of local tumour control with proton beam radiotherapy. Incidence was 3.5% for local tumor recurrence, 9.4% for enucleation, 79.1% for conservation of vision of counting fingers or better, 61.1% for conservation of vision of 20/200 or better, 44.8% for conservation of vision of 20/40 or better [63]. "Abrams et al" compared brachytherapy (BT) and EBRT, found no difference in 5 year overall survival (83.3% EBRT vs. 82.5% BT) [64]. "Margo et al" reported from COMS study having seen similar rates of mortality with both brachytherapy and enucleation, have shifted focus to outcomes such as preservation of vision and to understand biologic dissemination to achieve an appreciable impact on CM survival [65].

The prognosis in UM is dependent on clinical, histopathological and cytological factors [66]. The clinical features associated with poor prognosis in patients with UM include older age at presentation, male gender, larger tumor basal diameter and thickness, ciliary body location, diffuse tumor configuration, association with ocular/oculodermal melanocytosis, extraocular tumor extension, and advanced tumor staging by American joint committee on cancer classification (AJCC) [67]. "Diener-West et al" reported 5-year mortality rates associated with uveal melanoma were 16% for small tumors (<2 or 3 mm tumor thickness and <10 or 11 mm basal diameter), 32% for medium tumors (3-8 mm tumor thickness and <15 or 16 mm basal diameter), and 53% for large tumors (>8 mm tumor thickness and >15 mm basal diameter) [68]. The medium sized tumor trial (2.5-10 mm tumor thickness and <16 mm basal diameter) by COMS group report no. 28 revealed 5, 10, and 12 years melanoma-related mortality at 10%, 18%, and 21%, respectively, for patients in the I-125 brachytherapy treatment arm and 11%, 17%, and 17%, respectively, for those in the enucleation treatment arm [69]. In the large tumor trial (>10 mm tumor thickness or >2 mm tumor thickness and >16 mm basal diameter) by COMS group report no. 10, melanoma-related mortality at 5 and 10 years was 28% and 40% respectively for patients in the enucleation treatment arm and 26% and 45% in the external beam radiotherapy preceding enucleation treatment arm [70, 71].

Histopathological classification for CM given by "Callender" is now used as "Modified calendar classification". Depending on cell types, tumor is classified into spindle A, spindle B, epithelioid, and mixed cell tumours [72]. "Maclean et al"noticed that the "Modified Callender classification" showed an improved correlation between the cell type and mortality [72]. "Paul et al" in their study of 2652 enucleated eyes with UM reported the 15-year mortality for spindle A tumor at 19%, spindle B 26%, mixed spindle B and epithelioid 59%, and epithelioid tumor at 72% [73]. The 15-year mortality of patients with melanomas of mixed cell type is three times that of patients with tumors of pure spindle cell type [74]. We had one case (Case 3) with mixed cell type (20%), two cases (Case 1 and 2) of spindle cell type (40%) and two of epitheloid (Case 4 and 5) type (40%) which were placed under different staging as per "AJCC classification" (Table 4). Various studies have established that the spindle cell uveal melanoma has the best prognosis, mixed cell melanoma an intermediate, and epithelioid cell melanoma has the worst prognosis [73-79].

The prognosis worsens with increasing number of epithelioid cells per high power field (HPF) [78]. In a study involving 232 enucleated eyes from patients with UM, the 10-year survival was 82% in patients with < 0.5 epithelioid cells/HPF, 55% for 0.5 to 4.9 epithelioid cells/HPF, and 33% in patients with > 5 epithelioid cells/HPF [78]. Histopathologically presence of epitheliod cell type is highly suggestive of poor prognostic outcome [67]. Epithelioid cell melanomas association with monosomy 3 and class 2 molecular profile, which are indicative of high metastatic and mortality rate indicates a poor prognosis, worsening with increasing number of epithelioid cells per high power field (HPF) [78]. COMS report no. 6 documented high accuracy in histopathological confirmation of the diagnosis at 99.7%. It showed preenucleation irradiation significantly reduced the number of mitotic figures [55]. Other features indicative of poor prognosis include high mitotic activity, higher values of mean diameter of ten largest nucleoli, higher microvascular density, extravascular matrix patterns, tumor-infiltrating lymphocytes, tumor-infiltrating macrophages, higher expression of insulin-like growth factor-1 receptor, and higher expression of human leukocyte antigen Class I and II [67]. Monosomy 3, 1p loss, 6q loss, and 8q and those classified as Class II by gene expression are also predictive of poor prognosis of uveal melanoma [80-82].

Extraocular tumour extension, is seen as a poor prognostic sign, is visible in 8-15% cases [55, 76, 83-87]. In a study involving 610 patients with UM the 5 year mortality rate for patients with microscopic extension and small extraocular extension (EOE) were 37% and 24% respectively. Markedly higher 5 year mortality rate at 78% was seen in those with large EOE [84]. We had two cases (Cases 4 and 5) where EOE was confirmed on USG-B scan, both cases having large CM with NVG. In a study of 7731 patients with posterior uveal melanoma based on T category of AJCC classification, the 10-year metastatic rate was 15% for T1 tumors, 25% for T2, and 49% for T3, and 63% for T4. The risk for metastasis and death increased two-fold with each increasing tumor

category [87]. Based on AJCC staging for posterior uveal melanoma, 10-year metastatic rate was 12% for "Stage I tumors", 29% for "Stage II", and 61% for "Stage III". The risk for metastasis and death increased three-fold with each increasing melanoma staging [87]. Among our patients as per AJCC classification, two patients were in "Stage II A" (Case 1 and 2), one in "Stage II B" (case 3) and the other were in "Stage IV" (Case 4 and 5).

Over all human mortality rates in studies involving treatment of UM stood at 50% within 10-15 years after enucleation [88]. COMS reports no. 5 documented that small choroidal melanomas which were managed by observation, 21% demonstrated growth by 2 years and 31% by 5 years [89]. Large tumours were more often necrotic, composed of epitheloid cells (Case 4 and 5), or featured extrascleral extension (Case 4 and 5). Tumours with significant scleral invasion or extrascleral extension were more common in elderly patients as seen in our two patients (Case 4 and 5). Melanoma-related deaths appeared from 24 to 6848 days (18 years 8 months) after enucleation [77]. COMS report no. 11 commenting on complications, showed incidence rates and prevalence at the 5-year examination were similar in the two treatment arms [90]. Tumor related 5 year mortality rate were 26–28% in large, 9–11% in medium and 1% in small size tumour [70, 89, 90]. No survival advantage was found in pre-enucleation radiation group by COMS report no. 24 [71]. Mortality rates for patients in both treatment groups, at 5- and 10-year were 19% and 35%, 12 years mortality was 43% among patients in the (125I) brachytherapy group and 41% in the enucleation group [69].

"Bensoussan et al" commented on role of EBRT in treatment of T 3-4 choroidal melanoma showed enucleation at 19.5% with 5 year local control at 94%. At 5 years, 25% of T3 patients presented with metastasis with overall and specific survival rates were 65% and 75%, hence EBRT may be considered efficient and safe alternative to enucleation for large choroidal melenomas [91]. "Lin et al" in a retrospective analysis of brachytherapy versus proton beam external therapy of 1224 patients revealed that the 2-year overall survival was 97% vs. 93%, and 5-year overall survival was 77% vs. 51% for brachytherapy and protons beam respectively [92]. "Abrams et al" compared efficacy of EBRT vs BT in 1004 cases of CM who were Tumour 1-4, Node 0, Metastasis 0 (T-tumour, N-node, M-metastasis), found no difference in the 5-year overall survival (83.3% EBRT vs. 82.5% BT) and 5-year cause-specific survival (88.3% EBRT vs. 88.3% BT) [64].

All patients with CM were screened to rule out recurrence of disease or appearance of metastasis. Assay of serum levels of alkaline phosphatase, aspartate aminotransferase (AST), alanine transaminase (ALT) and bilirubin were done in all our patients at initial work up and post therapy/enucleation follow up. Those with elevated serum levels needed further intervention such as imaging which included USG of liver, CT, MRI or PET scan to detect secondaries. Metastasis from CM may have onset when its dimensions are 3.0 mm in basal diameter and 1.5 mm in thickness. Various studies have shown that at 5 years, metastasis occurs in 16% of patients with small choroidal melanomas (less than 4 mm thick), 32% of those with medium-sized (4-8 mm thick) and 53% of those with large (more than 8 mm thick) tumors [93]. In a study by "Bedikian et al", time interval from resection of primary tumor to detection of systemic metastases ranged from one to 201 months [88]. COMS report no.15 confirmed that 269 patients (62%) had histopathologically confirmed melanoma metastasis at the time of death, with secondaries present in liver (93%), lung (24%), and bone (16%) [94]. The survival duration ranged between one to 31 months from time of development of systemic metastasis with a one-year survival rate of 29%. The median survival of patients from diagnosis of ocular melanoma was 52 months, with a five-year survival rate of 43% [88]. "Diener west et al" in their COMS 26 report involving 739 patients found five and 10-year cumulative metastasis rates at 25% and 34%, the death rate from melanoma metastasis was 80% at 1 year and 92% at 2 years [16]. COMS 10 reported from 269 patients who had histologically confirmed melanoma metastases at the time of death, 5-year survival rates for this secondary outcome were 72% for enucleation and 74% for pre-enucleation radiation with no difference in survival attributed to pre-enucleation radiation of large choroidal melanoma [70].

5. Conclusion

Choroidal melanoma being the most common intraocular malignancy is mainly diagnosed on routine examination and not commonly when symptom appears. The lesion is rare in Asian subcontinent compared to western world, awareness and a regular dilated eye examination would help in detection. Accessibility and cost of healthcare may be a deterrent, however early detection and treatment is able to prolong life and help in maintaining quality of vision. Serology involving liver function test with imaging studies of PET-MRI, PET-CT, MRI and USG of liver are needed to keep a watch for metastasis. Histopathology helps in estimating response to treatment and mortality index. Enucleation has seen a decline in recent times as requirements shift more to organ preservation so as to maintain visual function. Brachytherapy and proton beam radiotherapy have paved the way for less destructive therapies.

6. Recommendation

Recommendations are given keeping in view behavior pattern and evolving trends in treatment of choroidal melanoma. Choroidal melanoma appears in Asians early needing stringent screening protocol to cover a yonger and much larger population with the aim of reducing chances of dropout of suspicious cases. Population being large, supportive para medical staff should be simultaneously trained for detailed dilated fundus examination as accessibility to healthcare is difficult in economically poor zones. A comprehensive eye examination is essential to evaluate and stage the patients. Genetic studies for germ line

BAP1 mutation associated with worse survival than EIFAX1 associated with virtual no risk need to be assessed along with histopathology and other risk factors to predict prognostic outcome. Biopsy performed through molecular testing too can be done for prognostic purpose. We must remember the cost factor associated with genetic and molecular testing being on the higher side is not economically feasible for all patients, hence low cost testing must be looked into. As treatment shifts more towards preservation the role of radiation therapy has expanded with promising outcome. Surveillance in patients to assess recurrence needs whole body imaging with special liver imaging as high risk UM metastasizes to liver. Treatment of UM requires multidisciplinary approach needing surgical and medical oncology services to work closely for best results to improve quality of life and patient survival.

Competing Interest

The authors declare that they have no competing interests.

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References

[1] Scotto J, Fraumeni JF Jr, Lee JA. Melanomas of the eye and other noncutaneous sites: epidemiologic aspects. J Natl Cancer Inst. 1976 Mar; 56 (3): 489-91. doi: 10.1093/jnci/56.3.489.

[2] Singh AD, Turell ME, Topham AK. Uveal melanoma: trends in incidence, treatment, and survival. Ophthalmology. 2011 Sep; 118 (9): 1881-5. doi: 10.1016/j.ophtha.2011.01.040. Epub 2011 Jun 24. PMID: 21704381.

[3] Virgili G, Gatta G, Ciccolallo L, Capocaccia R, Biggeri A et al, EUROCARE Working Group. Incidence of uveal melanoma in Europe. *Ophthalmology* 2007; 114: 2309–2315. [PubMed] [Google Scholar].

[4] Biswas J, Krishnakumar S, Shanmugam MP. Uveal melanoma in Asian Indians: A clinicopathological study. *Arch Ophthalmol.* 2002; 120: 522–3. [PubMed] [Google Scholar].

[5] Kashyap S, Venkatesh P, Sen S, Khanduja S, Shrey D, Tinwala S, et al. Clinicopathologic characteristics of choroidal melanoma in a North Indian population: Analysis of 10-year data. *Int Ophthalmol.* 2014; 34: 235–9. [PubMed] [Google Scholar].

[6] Dhupper M, Biswas J, Gopal L, Kumar SK, Khetan V. Clinicopathological correlation of choroidal melanoma in Indian population: A study of 113 cases. *Oman J Ophthalmol.* 2012; 5: 42–5. [PMC free article] [PubMed] [Google Scholar].

[7] Shields CL, Kaliki S, Arepalli S, Atalay HT, Manjandavida FP, Pieretti G, Shields JA. Uveal melanoma in children and teenagers. Saudi J Ophthalmol. 2013 Jul; 27 (3): 197-201. doi: 10.1016/j.sjopt.2013.06.013. Epub 2013 Jul 5. PMID: 24227986; PMCID: PMC3770213.

[8] Shields CL, Furuta M, Thangappan A, Nagori S, Mashayekhi A, Lally DR et al. Metastasis of uveal melanoma millimeter-by-millimeter in 8033 consecutive eyes. *Arch Ophthalmol* 2009; 127 (8): 989–998. [PubMed] [Google Scholar].

[9] Chang AE, Karnell LH, Menck HR. The National Cancer Data Base report on cutaneous and noncutaneous melanoma: a summary of 84,836 cases from the past decade. The American College of Surgeons Commission on Cancer and the American Cancer Society. *Cancer* 1998; 83 (8): 1664–1678. [PubMed] [Google Scholar].

[10] Shields CL, Kaliki S, Cohen MN, Shields PW, Furuta M, Shields JA. Prognosis of uveal melanoma based on race in 8100 patients: The 2015 Doyne Lecture. *Eye (Lond)* 2015; 29 (8): 1027–1035. [PMC free article] [PubMed] [Google Scholar].

[11] Margo CE, Mulla Z, Billiris K. Incidence of surgically treated uveal melanoma by race and ethnicity. *Ophthalmology* 1998; 105 (6): 1087–1090. [PubMed] [Google Scholar].

[12] Hu DN, Yu GP, McCormick SA, Schneider S, Finger PT. Population-based incidence of uveal melanoma in various races and ethnic groups. *Am J Ophthalmol* 2005; 140 (4): 612–617. [PubMed] [Google Scholar].

[13] Qiu M, Shields CL. Choroidal nevus in the United States adult population: racial disparities and associated factors in the National Health and Nutrition Examination Survey. Ophthalmology 2015; 122 (10): 2071–2083.

[14] Singh AD, Kalyani P, Topham A. Estimating the risk of malignant transformation of a choroidal nevus. Ophthalmology 2005; 112 (10): 1784–1789.

[15] Shields CL, Cater J, Shields JA, Singh AD, Santos MC, Carvalho C. Combination of clinical factors predictive of growth of small choroidal melanocytic tumors. Arch Ophthalmol 2000; 118 (3): 360–364.

[16] Diener-West M, Reynolds SM, Agugliaro DJ, Caldwell R, Cumming K, Earlees JD et al. Development of metastatic disease after enrollment in the COMS trials for treatment of choroidal melanoma: Collaborative Ocular Melanoma Study Group Report No. 26. Arch Ophthalmol 2005; 123: 1639–1643.

[17] Kujala E, Mäkitie T, KiveläT. Very long-term prognosis of patients with malignant uveal melanoma. Invest Ophthalmol Vis Sci 2003; 44 (11): 4651–4659.

[18] Raivio I. Uveal melanoma in Finland: an epidemiological, clinical, histological, and prognostic study. Acta Ophthalmol Suppl (Copenh) 1977; 133: 1–64

[19] Jensen OA. Malignant melanomas of the uvea in Denmark 1943–1952: a clinical, histopathologic, and prognostic study. Acta Ophthalmol Suppl (Copenh) 1963; 75: 17–78.

[20] Kashyap S, Venkatesh P, Sen S, Khanduja S, Shrey D, Tinwala S, Garg S. Clinicopathologic characteristics of choroidal melanoma in a North Indian population: analysis of 10-year data. Int Ophthalmol. 2014 Apr; 34 (2): 235-9. doi: 10.1007/s10792-013-9821-8. Epub 2013 Jul 4. PMID: 23824661.

[21] Manchegowda P, Singh AD, Shields C, Kaliki S, Shah P, Gopal L, Rishi P. Uveal Melanoma in Asians: A Review. Ocul Oncol Pathol. 2021 Jun; 7 (3): 159-167. doi: 10.1159/000512738. Epub 2021 Feb 9. PMID: 34307326; PMCID: PMC8280446.

[22] Shields CL, Shields JA, Milite J, De Potter P, Sabbagh R, Menduke H. Uveal melanoma in teenagers and children. A report of 40 cases. Ophthalmology. 1991 Nov; 98 (11): 1662-6. doi: 10.1016/s0161-6420(91)32071-2. PMID: 1800926.

[23] COMS report No.9 (1998). Randomized trial of pre-enucleation radiation of large choroidal melanoma. I: Characteristics of patients enrolled and not enrolled. Am J Ophthalmol; 125: 767–778.

[24] Mork T. Malignant neoplasms of the eye in Norway: incidence, treatment and prognosis. Acta Ophthalmol 1961; 39: 824–31.

[25] Seddon JS, Egan KM. Application of epidemiologic methods to ophthalmology: uveal melanoma. In: Albert DJ, editor. The principles and practice of ophthalmology. Philadelphia: WB Saunders; 1993; 106: p. 1245–66.

[26] Hakulinen T, Teppop L, Saxen E. Cancer of the eye, a review of trends and differentials. World Health Stat Q 1978; 31: 143–58.

[27] Zloto O, Pe'er J, Frenkel S. Gender differences in clinical presentation and prognosis of uveal melanoma. Invest Ophthalmol Vis Sci. 2013; 54: 652–6. [PubMed] [Google Scholar].

[28] Rietschel P, Panageas KS, Hanlon C, Patel A, Abramson DH, Chapman PB. Variates of survival in metastatic uveal melanoma. J Clin Oncol. 2005; 23: 8076–80. [PubMed] [Google Scholar].

[29] Holly EA, Aston DA, Ahn DK, Kristiansen JJ, Char DH. Uveal melanoma, hormonal and reproductive factors in women. Cancer Res. 1991; 51: 1370–2. [PubMed] [Google Scholar].

[30] Damato EM, Damato BE. Detection and time to treatment of uveal melanoma in the United Kingdom: an evaluation of 2,384 patients. Ophthalmology. 2012 Aug; 119 (8): 1582-9. doi: 10.1016/j.ophtha.2012.01.048. Epub 2012 Apr 11. PMID: 22503229.

[31] Eskelin S, Kivelä T. Mode of presentation and time to treatment of uveal melanoma in Finland. Br J Ophthalmol. 2002 Mar; 86 (3): 333-8. doi: 10.1136/bjo.86.3.333. PMID: 11864894; PMCID: PMC1771030.

[32] 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. PMID: 23826405; PMCID: PMC3693189.

[33] Shields CL, Furuta M, Berman EL, Zahler JD, Hoberman DM, Dinh DH, Mashayekhi A, Shields JA. Choroidal nevus transformation into melanoma: analysis of 2514 consecutive cases. Arch Ophthalmol. 2009 Aug; 127 (8): 981-7. doi: 10.1001/archophthalmol.2009.151. PMID: 19667334.

[34] Albert DM. Principles and Practice of Ophthalmology. In: Albert, Jakobiec, editors. Philadelphia, PA: W. B. Saunders Co; 1994. pp. 3197–8. Ch. 258. [Google Scholar].

[35] Kath R, Hayungs J, Bornfeld N, Sauerwein W, Höffken K, Seeber S. Prognosis and treatment of disseminated uveal melanoma. Cancer. 1993 Oct 1; 72 (7): 2219-23. doi: 10.1002/1097-0142(19931001)72:7<2219: aid-cncr2820720725>3.0.co; 2-j. PMID: 7848381.

[36] Shields CL, Manalac J, Das C, Ferguson K, Shields JA. Choroidal melanoma: clinical features, classification, and top 10 pseudomelanomas. Curr Opin Ophthalmol. 2014 May; 25 (3): 177-85. doi: 10.1097/ICU.0000000000000041. PMID: 24614143.

[37] Shields CL, Kaliki S, Rojanaporn D, Ferenczy SR, Shields JA. Enhanced depth imaging optical coherence tomography of small choroidal melanoma: comparison with choroidal nevus. Arch Ophthalmol. 2012 Jul; 130 (7): 850-6. doi: 10.1001/archophthalmol.2012.1135. PMID: 22776921.

[38] Torres VL, Brugnoni N, Kaiser PK, Singh AD. Optical coherence tomography enhanced depth imaging of choroidal tumors. Am J Ophthalmol. 2011 Apr; 151 (4): 586-593.e2. doi: 10.1016/j.ajo.2010.09.028. Epub 2011 Jan 22. PMID: 21257150.

[39] Char DH, Stone RD, Irvine AR, Crawford JB, Hilton GF, Lonn LI, Schwartz A. Diagnostic modalities in choroidal melanoma. Am J Ophthalmol. 1980 Feb; 89 (2): 223-30. doi: 10.1016/0002-9394(80)90115-4. PMID: 7355976.

[40] Gass JD. Problems in the differential diagnosis of choroidal nevi and malignant melanoma. XXXIII Edward Jackson Memorial lecture. Trans Sect Ophthalmol Am Acad Ophthalmol Otolaryngol. 1977 Jan-Feb; 83 (1): 19-48. PMID: 898474.

[41] Gass JD. Observation of suspected choroidal and ciliary body melanomas for evidence of growth prior to enucleation. Ophthalmology. 1980 Jun; 87 (6): 523-8. doi: 10.1016/s0161-6420(80)35200-7. PMID: 7413141.

[42] Wang ZY, Yang WL, Li DJ, Chen W, Zhao Q, Li YF, Cui R, Shen L, Wei WB. [Ultrasound diagnosis and differential diagnosis of medium and small choroidal melanomas]. Zhonghua Yan Ke Za Zhi. 2018 Nov 11; 54 (11): 843-848. Chinese. doi: 10.3760/cma.j.issn.0412-4081.2018.11.009. PMID: 30440156.

[43] Sobottka B, Schlote T, Krumpaszky HG, Kreissig I. Choroidal metastases and choroidal melanomas: comparison of ultrasonographic findings. Br J Ophthalmol. 1998 Feb; 82 (2): 159-61. doi: 10.1136/bjo.82.2.159. PMID: 9613382; PMCID: PMC1722472.

[44] Romanowska-Dixon B, Jakubowska B, Markiewicz A, Pawlikowski R. Zastosowanie ultrasonografii w diagnostyce zewnatrzgałkowych nacieków czerniaka błony naczyniowej [Ultrasound techniques in diagnosis of extrabulbar extension of uveal melanoma]. Klin Oczna. 2013; 115 (3): 204-7. Polish. PMID: 24741924.

[45] Papayiannis V, Tsaousis KT, Kouskouras CA, Haritanti A, Diakonis VF, Tsinopoulos IT. Investigation into the quantitative and qualitative characteristics of choroidal melanoma through magnetic resonance imaging and B-scan ultrasound. Clin Ophthalmol. 2017 Aug 22; 11: 1557-1564. doi: 10.2147/OPTH.S130009. PMID: 28860706; PMCID: PMC5573043.

[46] Tailor TD, Gupta D, Dalley RW, Keene CD, Anzai Y. Orbital neoplasms in adults: clinical, radiologic, and pathologic review. Radiographics. 2013 Oct; 33 (6): 1739-58. doi: 10.1148/rg.336135502. PMID: 24108560.

[47] Fielding J A. (2001). The eye and orbit. In: Meire H, Cosgrove D, Dewbury K, Farrant P. Clinical ultrasound, a comprehensive text, abdominal and general ultrasound. Vol 2, 2nd ed. Churchill Livingstone: London; p. 676-680.

[48] Sobottka B, Kreissig I. Ultrasonography of metastases and melanomas of the choroid. *Curr Opin Ophthalmol.* 1999; 10: 164–7.

[49] Verbeek AM. Differential diagnosis of intraocular neoplasms with ultrasonography. *Ultrasound Med Biol.* 1985; 11: 163–70. [PubMed] [Google Scholar].

[50] Shields CL, Shields JA, Gross NE, Schwartz GP, Lally SE. Survey of 520 eyes with uveal metastases. Ophthalmology. 1997 Aug; 104 (8): 1265-76. doi: 10.1016/s0161-6420(97)30148-1. PMID: 9261313.

[51] Ward SD, Byrne BJ, Kincaid MC, Mann ES. Ultrasonographic evidence of a mushroom-shaped choroidal metastasis. Am J Ophthalmol. 2000 Nov; 130 (5): 681-2. doi: 10.1016/s0002-9394(00)00604-8. PMID: 11078856.

[52] Finger PT, Kurli M, Reddy S, Tena LB, Pavlick AC. Whole body PET/CT for initial staging of choroidal melanoma. Br J Ophthalmol. 2005 Oct; 89 (10): 1270-4. doi: 10.1136/bjo.2005.069823. PMID: 16170114; PMCID: PMC1772897.

[53] Kurli M, Reddy S, Tena LB, Pavlick AC, Finger PT. Whole body positron emission tomography/computed tomography staging of metastatic choroidal melanoma. Am J Ophthalmol. 2005 Aug; 140 (2): 193-9. doi: 10.1016/j.ajo.2005.02.051. PMID: 15992753.

[54] Reddy S, Kurli M, Tena LB, Finger PT. PET/CT imaging: detection of choroidal melanoma. Br J Ophthalmol. 2005 Oct; 89 (10): 1265-9. doi: 10.1136/bjo.2005.066399. PMID: 16170113; PMCID: PMC1772884.

[55] Histopathologic characteristics of uveal melanomas in eyes enucleated from the Collaborative Ocular Melanoma Study. COMS report no. 6. Am J Ophthalmol. 1998 Jun; 125 (6): 745-66. doi: 10.1016/s0002-9394(98)00040-3. PMID: 9645714.

[56] Shields CL, Shields JA. Recent developments in the management of choroidal melanoma. Curr Opin Ophthalmol. 2004 Jun; 15 (3): 244-51. doi: 10.1097/01.icu.0000120713.35941.e4. PMID: 15118513.

[57] Rusňák Š, Hecová L, Kasl Z, Sobotová M, Hauer L. Therapy of uveal melanoma A Review. Cesk Slov Oftalmol. 2020 Fall; 77 (1): 1-13. English. doi: 10.31348/2020/10. PMID: 33086849.

[58] Melia BM, Abramson DH, Albert DM, Boldt HC, Earle JD, Hanson WF, Montague P, Moy CS, Schachat AP, Simpson ER, Straatsma BR, Vine AK, Weingeist TA; Collaborative Ocular Melanoma Study Group. Collaborative ocular melanoma study (COMS) randomized trial of I-125 brachytherapy for medium choroidal melanoma. I. Visual acuity after 3 years COMS report no. 16. Ophthalmology. 2001 Feb; 108 (2): 348-66. doi: 10.1016/s0161-6420(00)00526-1. PMID: 11158813.

[59] Ghassemi F, Sheibani S, Arjmand M, Poorbaygi H, Kouhestani E, Sabour S, Samiei F, Beiki-Ardakani A, Jabarvand M, Sadeghi Tari A. Comparison of Iodide-125 and Ruthenium-106 Brachytherapy in the Treatment of Choroidal Melanomas. Clin Ophthalmol. 2020 Feb 4; 14: 339-346. doi: 10.2147/OPTH.S235265. PMID: 32099319; PMCID: PMC7007774.

[60] Gündüz K, Shields CL, Shields JA, Cater J, Freire JE, Brady LW. Radiation complications and tumor control after plaque radiotherapy of choroidal melanoma with macular involvement. Am J Ophthalmol. 1999 May; 127 (5): 579-89. doi: 10.1016/s0002-9394(98)00445-0. PMID: 10334352.

[61] Boldt HC, Melia BM, Liu JC, Reynolds SM; Collaborative Ocular Melanoma Study Group. I-125 brachytherapy for choroidal melanoma photographic and angiographic abnormalities: the Collaborative Ocular Melanoma Study: COMS Report No. 30. Ophthalmology. 2009 Jan; 116 (1): 106-115.e1. doi: 10.1016/j.ophtha.2008.10.013. PMID: 19118701; PMCID: PMC3202984.

[62] Jampol LM, Moy CS, Murray TG, Reynolds SM, Albert DM, Schachat AP, Diddie KR, Engstrom RE Jr, Finger PT, Hovland KR, Joffe L, Olsen KR, Wells CG; COMS Follow-up of Plaqued Eyes Working Group. 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. 2020 Apr; 127 (4S): S148-S157. doi: 10.1016/j.ophtha.2020.01.032. PMID: 32200815.

[63] Damato B, Kacperek A, Chopra M, Campbell IR, Errington RD. Proton beam radiotherapy of choroidal melanoma: the Liverpool-Clatterbridge experience. Int J Radiat Oncol Biol Phys. 2005 Aug 1; 62 (5): 1405-11. doi: 10.1016/j.ijrobp.2005.01.016. PMID: 16029800.

[64] Abrams MJ, Gagne NL, Melhus CS, Mignano JE. Brachytherapy vs. external beam radiotherapy for choroidal melanoma: Survival and patterns-of-care analyses. Brachytherapy. 2016 Mar-Apr; 15 (2): 216-23. doi: 10.1016/j.brachy.2015.12.001. Epub 2016 Feb 1. PMID: 26846381.

[65] Margo CE. The Collaborative Ocular Melanoma Study: an overview. Cancer Control. 2004 Sep-Oct; 11 (5): 304-9. doi: 10.1177/107327480401100504. PMID: 15377989.

[66] Singh AD, Shields CL, Shields JA. Prognostic factors in uveal melanoma. Melanoma Res. 2001 Jun; 11 (3): 255-63. doi: 10.1097/00008390-200106000-00007. PMID: 11468514.

[67] Kaliki S, Shields CL, Shields JA. Uveal melanoma: estimating prognosis. Indian J Ophthalmol. 2015 Feb; 63 (2): 93-102. doi: 10.4103/0301-4738.154367. PMID: 25827538; PMCID: PMC4399142.

[68] Diener-West M, Hawkins BS, Markowitz JA, Schachat AP. A review of mortality from choroidal melanoma. II. A meta-analysis of 5-year mortality rates following enucleation, 1966 through 1988. Arch Ophthalmol. 1992 Feb; 110 (2): 245-50. doi: 10.1001/archopht.1992.01080140101036. PMID: 1531290.

[69] Collaborative Ocular Melanoma Study Group. The COMS randomized trial of iodine 125 brachytherapy for choroidal melanoma: V. Twelve-year mortality rates and prognostic factors: COMS report No. 28. Arch Ophthalmol. 2006 Dec; 124 (12): 1684-93. doi: 10.1001/archopht.124.12.1684. PMID: 17159027.

[70] The Collaborative Ocular Melanoma Study (COMS) randomized trial of pre-enucleation radiation of large choroidal melanoma II: initial mortality findings. COMS report no. 10. Am J Ophthalmol. 1998 Jun; 125 (6): 779-96. doi: 10.1016/s0002-9394(98)00039-7. PMID: 9645716.

[71] Hawkins BS; Collaborative Ocular Melanoma Study Group. The Collaborative Ocular Melanoma Study (COMS) randomized trial of pre-enucleation radiation of large choroidal melanoma: IV. Ten-year mortality findings and prognostic factors. COMS report number 24. Am J Ophthalmol. 2004 Dec; 138 (6): 936-51. doi: 10.1016/j.ajo.2004.07.006. PMID: 15629284.

[72] McLean IW, Foster WD, Zimmerman LE, Gamel JW. Modifications of Callender's classification of uveal melanoma at the Armed Forces Institute of Pathology. Am J Ophthalmol. 1983 Oct; 96 (4): 502-9. doi: 10.1016/s0002-9394(14)77914-0. PMID: 6624832.

[73] Paul EV, Parnell BI, Fraker M. Prognosis of malignant melanomas of the choroid and ciliary body. *Int Ophthalmol Clin.* 1962; 2: 387–402. [Google Scholar].

[74] McLean IW, Foster WD, Zimmerman LE. Uveal melanoma: location, size, cell type, and enucleation as risk factors in metastasis. Hum Pathol. 1982 Feb; 13 (2): 123-32. doi: 10.1016/s0046-8177(82)80116-0. PMID: 7076200.

[75] Seddon JM, Albert DM, Lavin PT, Robinson N. A prognostic factor study of disease-free interval and survival following enucleation for uveal melanoma. Arch Ophthalmol. 1983 Dec; 101 (12): 1894-9. doi: 10.1001/archopht.1983.01040020896012. PMID: 6651594.

[76] Coupland SE, Campbell I, Damato B. Routes of extraocular extension of uveal melanoma: risk factors and influence on survival probability. Ophthalmology. 2008 Oct; 115 (10): 1778-85. doi: 10.1016/j.ophtha.2008.04.025. Epub 2008 Jun 13. PMID: 18554722.

[77] Seregard S, Kock E. Prognostic indicators following enucleation for posterior uveal melanoma. A multivariate analysis of long-term survival with minimized loss to follow-up. Acta Ophthalmol Scand. 1995 Aug; 73 (4): 340-4. doi: 10.1111/j.1600-0420.1995.tb00039.x. PMID: 8646581.

[78] Seddon JM, Polivogianis L, Hsieh CC, Albert DM, Gamel JW, Gragoudas ES. Death from uveal melanoma. Number of epithelioid cells and inverse SD of nucleolar area as prognostic factors. Arch Ophthalmol. 1987 Jun; 105 (6): 801-6. doi: 10.1001/archopht.1987.01060060087039. PMID: 3579712.

[79] Gamel JW, McLean IW, Foster WD, Zimmerman LE. Uveal melanomas: correlation of cytologic features with prognosis. Cancer. 1978 May; 41 (5): 1897-901. doi: 10.1002/1097-0142(197805)41:5<1897: aid-cncr2820410534>3.0.co; 2-2. PMID: 647633.

[80] Scholes AG, Damato BE, Nunn J, Hiscott P, Grierson I, Field JK. Monosomy 3 in uveal melanoma: Correlation with clinical and histologic predictors of survival. *Invest Ophthalmol Vis Sci.* 2003; 44: 1008–11. [PubMed] [Google Scholar].

[81] Tschentscher F, Hüsing J, Hölter T, Kruse E, Dresen IG, Jöckel KH, et al. Tumor classification based on gene expression profiling shows that uveal melanomas with and without monosomy 3 represent two distinct entities. *Cancer Res.* 2003; 63: 2578–84. [PubMed] [Google Scholar].

[82] Onken MD, Worley LA, Ehlers JP, Harbour JW. Gene expression profiling in uveal melanoma reveals two molecular classes and predicts metastatic death. *Cancer Res.* 2004; 64: 7205–9. [PMC free article] [PubMed] [Google Scholar].

[83] Affeldt JC, Minckler DS, Azen SP, Yeh L. Prognosis in uveal melanoma with extrascleral extension. Arch Ophthalmol. 1980 Nov; 98 (11): 1975-9. doi: 10.1001/archopht.1980.01020040827006. PMID: 7436829.

[84] Pach JM, Robertson DM, Taney BS, Martin JA, Campbell RJ, O'Brien PC. Prognostic factors in choroidal and ciliary body melanomas with extrascleral extension. Am J Ophthalmol. 1986 Mar 15; 101 (3): 325-31. doi: 10.1016/0002-9394(86)90828-7. PMID: 3953727.

[85] Gündüz K, Shields CL, Shields JA, Cater J, Brady L. Plaque radiotherapy for management of ciliary body and choroidal melanoma with extraocular extension. Am J Ophthalmol. 2000 Jul; 130 (1): 97-102. doi: 10.1016/s0002-9394(00)00385-8. PMID: 11004266.

[86] Edge SB, Fritz AG, Byrd DR, Greene FL, Trotti A III, Compton CC, editors. 7th ed. New York: Springer; 2010. AJCC Cancer Staging Manual; pp. 547–59. [Google Scholar].

[87] Shields CL, Kaliki S, Furuta M, Fulco E, Alarcon C, Shields JA. American Joint Committee on Cancer classification of posterior uveal melanoma (tumor size category) predicts prognosis in 7731 patients. Ophthalmology. 2013 Oct; 120 (10): 2066-71. doi: 10.1016/j.ophtha.2013.03.012. Ep88.

[88] Bedikian AY, Kantarjian H, Young SE, Bodey GP. Prognosis in metastatic choroidal melanoma. South Med J. 1981 May; 74 (5): 574-7. doi: 10.1097/00007611-198105000-00017. PMID: 7244714.

[89] Factors predictive of growth and treatment of small choroidal melanoma: COMS Report No. 5. The Collaborative Ocular Melanoma Study Group. Arch Ophthalmol. 1997 Dec; 115 (12): 1537-44. doi: 10.1001/archopht.1997.01100160707007. PMID: 9400787.

[90] The Collaborative Ocular Melanoma Study (COMS) randomized trial of pre-enucleation radiation of large choroidal melanoma III: local complications and observations following enucleation COMS report no. 11. Am J Ophthalmol. 1998 Sep; 126 (3): 362-72. doi: 10.1016/s0002-9394(98)00091. PMID: 9744369.

[91] Bensoussan E, Thariat J, Maschi C, Delas J, Schouver ED, Hérault J, Baillif S, Caujolle JP. Outcomes After Proton Beam Therapy for Large Choroidal Melanomas in 492 Patients. Am J Ophthalmol. 2016 May; 165: 78-87. doi: 10.1016/j.ajo.2016.02.027. Epub 2016 Mar 3. PMID: 26940166.

[92] Lin AJ, Rao YJ, Acharya S, Schwarz J, Rao PK, Grigsby P. Patterns of care and outcomes of proton and eye plaque brachytherapy for uveal melanoma: Review of the National Cancer Database. Brachytherapy. 2017 Nov-Dec; 16 (6): 1225-1231. doi: 10.1016/j.brachy.2017.07.014. Epub 2017 Sep 28. PMID: 28966081.

[93] Shields CL, Demirci H, Materin MA, Marr BP, Mashayekhi A, Shields JA. Clinical factors in the identification of small choroidal melanoma. Can J Ophthalmol. 2004 Jun; 39 (4): 351-7. doi: 10.1016/s0008-4182(04)80005-x. PMID: 15327099.

[94] Collaborative Ocular Melanoma Study Group.. Assessment of metastatic disease status at death in 435 patients with large choroidal melanoma in the Collaborative Ocular Melanoma Study (COMS): COMS report no. 15. Arch Ophthalmol. 2001 May; 119 (5): 670-6. doi: 10.1001/archopht.119.5.670. PMID: 11346394.