Uveal Melanoma in Asians: A Review

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Keywords

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Abstract

Despite limited data, some differences in the clinical profile can be observed in Asian population when compared with presentation of uveal melanoma (UM) in white population. The incidence of UM is higher in Whites than in Asians. For the purpose of comparison with Asian population, data from North America, Europe, and Australia were considered as that of “white” population. The annual incidence of UM has been reported to be 5–6 cases/million in whites. The incidence in different parts of Asia is estimated at 0.2–0.6 per million. The age of presentation is around 40–55 years in Asians, which is younger when compared to that of whites (mean age of 58 years). At presentation, mean basal diameter of tumors in Asians is greater compared to whites but overall, medium-size tumors are most common. Clinical presentation is straightforward in majority of cases with retinal detachment, acute glaucoma, uveitis, cataract, or vitreous hemorrhage as common symptoms. Epithelioid cell-type

variant carries the worst prognosis. Management options for choroidal melanoma include transpupillary thermotherapy, plaque radiotherapy, charged particle irradiation, local resection, enucleation, or orbital exenteration. Most commonly used modalities are enucleation and plaque radiotherapy.

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Introduction

Being uncommon in Asian population, uveal melanoma (UM) may be overlooked as a diagnostic consideration leading to delayed diagnosis causing visual loss and potential metastasis. Asia being the largest as well as the most populous continent in the world is diverse in its ethnicity and geography. The implications of this diversity make drawing uniform conclusions across populations impractical. However, there exist obvious differences in the presentation and outcomes of UM in Asians from that reported from Europe, North America, and Australia. For the purpose of comparison with Asian population, data from North America, Europe, and Aus-

Table 1. Demographic profile of patients with UM in studies from Asian countries

No.	Authors	Study type	Year	Country	N	Population	Gender (male%)	Age in years (range)	Incidence (per million/year)
1	Park et al. [4]	Review of registry	1999–2011	S. Korea	326	Korean	48.9	54	0.42
2	Liu et al. [11]	Retrospective hospital based	2005–2015	China	582	Chinese	49.3	44.6 (5–77)	na
3	Tomizuka et al. [7]	Review of registry	2011–2013	Japan	163	Japanese	50.3	63.5	0.64
4	Zewar et al. [9]	Retrospective hospital based	2006–2014	Jordan	46	Middle East/ Arabic	45	46 (1.5–75)	na
5	Alsuhaibani [10]	Retrospective hospital based	1983–2005	Saudi Arabia	40	Arabic	60	50 (24–77)	na
6	Frenkel et al. [8]	Retrospective hospital based	1988–2007	Israel	558	West Asian	44.6	60.8 (5–95)	6.71
7	Liu et al. [6]	Retrospective hospital based	1990–2005	Taiwan	26	Chinese	42	50	0.6
8	Yue et al. [12]	Retrospective hospital based	2003–2012	China	171	Chinese	49	48.6 (14–83)	na
9	Wong et al. [13]	Retrospective hospital based	2002–2017	Singapore	11	Chinese-63.6, Malay 9.1, Indian 9.1, Caucasian 9.1, Iranian 9.1	54.5	42.9 (27–67)	na
10	Biswas et al. [14]	Retrospective hospital based	1987–2001	India	103	Asian Indian	61.16	45.7 (14–82)	na
11	Kashyap et al. [15]	Retrospective hospital based	2001–2011	India	76	Asian Indian	51.3	46	na
12	Hamal et al. [16]	Prospective hospital based	2017–2018	Nepal	8	Nepali	62.5	47 (18–73)	na

No., number; S. Korea, South Korea; na, not available; UM, uveal melanoma.

tralia were considered as that of “white” population. This review article intends to compare the incidence, presentation, management, and outcomes of UM in Asians with that of whites.

Method of Literature Search

A literature search was carried out in PubMed database for all publications from 1980 to 2019 using the keywords “Uveal melanoma,” “choroidal melanoma,” “ciliary body melanoma,” “iris melanoma,” and “Asia.” Countries were included from Asian geographical subregions, that is, north Asia, central Asia, western Asia, south Asia, east Asia, and southeast Asia. Non-English manuscripts were not included. It revealed 54 reports, of which 12 relevant studies that included demographic, clinical, histopathological profile of patients and being representative of individual countries were shortlisted. Further, literature search was carried by entering individual Asian country name as an additional keyword to avoid missing any study(ies). Data from the studies were tabulated.

Epidemiology

Incidence

The ancestral population of modern-day Asians has its origins in the 2 primary prehistoric settlement centers – greater southwest Asia and the Mongolian plateau. Prominent ethnolinguistic groups include Mongols, Turkic, Indo-Aryans, Arabians in central Asia, Han, Tibetans, Joseon, Yamato in east Asia, Tartars, Paleo-Siberian in north, and Dravidians in south. Hence, studies must be analyzed by the ethnolinguistic population represented therein. The annual incidence of UM has been reported to be 5–6 cases/million in the USA, Europe, and Australia [1, 2]. The incidence in different parts of Asia has been estimated to range between 0.25 and 0.64 per million [3–8]. A study by Kaneko [3] in Japanese population showed an incidence of 0.25 per million, although recent epidemiological studies in the Asian continent showed incidence of UM to be ranging from 0.42 to 0.64 per million [4–7]. On the other hand, a study in Israel showed a significantly higher incidence of 6.71 per million [8]. This is attributed to the predominant white Jewish population in the region and cannot be treated as reflection of Asian

Fig. 1. External photograph reveals ocular melanocytosis (a), slit-lamp examination with diffuse illumination (b) reveals ectropion uveae, and ultrasound B-scan (c) reveals a large mushroom-shaped choroidal mass with acoustic hollowing. Vitreous echoes denote hemorrhage.

population, in general. The incidence rate of UM in Asian population is far below the reported incidence from the Europe, North America, and Australia.

Age

The mean age of presentation is around 42.9–63.5 years in Asians according to different studies [4–16]. Only 2 studies conducted in Japan and Israel have shown mean presenting age above 60 years [7, 8]. In other studies, mean presenting age ranges between 42.9 and 54 years, which is a decade or 2 earlier compared to that of whites (mean age 58 years) [17]. It could be assumed that the age at presentation might likely get lower with implementation of improved screening strategies in Asian countries. Demographic data are summarized in Table 1.

Sex

UM is more common in males. Although a high incidence of 61% males was noted in the study by Biswas et al. [14], it was based on data collected from a tertiary-care referral hospital that does not reflect a true population-based incidence. UM in males tends to be larger in size compared to that in females [18]. Some studies in white population showed a higher incidence of metastasis in males [19, 20]. However, a large study in Chinese population did not show such an association with males [11].

Race

In comparison with whites, a lower incidence of UM in Asians is well documented, lying between that of Whites and Africans. The order of incidence as follows: Non-Hispanic whites > Hispanics > Asians > Africans [1].

Geographic Factors

Blond hair with light eyes and skin along with higher latitudes [21] are some of the recognized risk factors. A lower incidence in pigmented Asian races and a higher incidence in predominantly white Israeli population points to possible risk factors beyond geographical limits [8].

Genetics

BAP-1 mutations linked to UM have been described as inheritable cases of melanoma in many studies. These cases tend to present at an early age and have predisposition for mesothelioma, cutaneous melanoma, renal cell carcinoma, breast, and ovarian malignancies [22]. Incidence of UM has remained stable in most White and Asian populations over several decades. However, a South Korean study showed statistically significant rise in the incidence during last decade of the study period [4]. A case series from China highlighted FAM111B and DSC2 gene mutations in patients with nevus of Ota having concomitant UM [23]. Yet, there is a lack of Asian studies reporting on the incidence of UM risk factors like familial cases or dysplastic nevus syndrome.

Classification

Based on Tumor Size

COMS (collaborative ocular melanoma study) classification was based on tumor size measured in terms of largest basal diameter, and height (thickness) of tumor [24]. As per size, medium-sized tumors are most common, followed by large-sized tumors, and small-sized tumors being the least common. Liu et al. [11] found 78% of tumors to be of medium size. Many Asian studies have

Table 2. Clinical characteristics of UM in studies from Asian countries

No.	Authors	Year	Country	N	Site of melanoma, %			Size, mm		Size classification (COMS)		
					Ch	CB	Iris	LBD	Ht	S	M	L
1	Park et al. [4]	1999–2011	S. Korea	326	81.6	18.4		na	na	na	na	na
2	Liu et al. [11]	2005–2015	China	582	94.2	5.7	0.2	na	na	1.1	77.9	21
3	Tomizuka et al. [7]	2011–2013	Japan	163	85.9	14.1		na	na	na	na	na
4	Zewar et al. [9]	2006–2014	Jordan	46	87	13	0	na	na	2	52	46
5	Alsuhaibani [10]	1983–2005	Saudi Arabia	40	70	30	0	5–26	3.2–16	50	50	0
6	Frenkel et al. ^a [8]	1988–2007	Israel	558	86.9	16.8	6.6	na	na	9	64.5	17.9
7	Liu et al. [6]	1990–2005	Taiwan	26	88	12	0	12	7.7	na	na	na
8	Yue et al. [12]	2003–2012	China	171	98	2	0	11.8	8.6	na	na	na
9	Wong et al. [13]	2002–2017	Singapore	11	100	0	0	15	8	9.1	54.5	36.4
10	Biswas et al. [14]	1987–2001	India	103	87.4	12.6		13.43	9.63	na	na	na
11	Kashyap et al. ^b [15]	2001–2011	India	76	92.1	2.6	0	14.8	10.09	0	9.2	90.7

No., number; na, not available; S. Korea, South Korea; COMS, collaborative ocular melanoma study; Ch, choroid; CB, ciliary body; mm, millimeter; LBD, largest basal diameter; Ht, height; S, small; M, medium; L, large; UM, uveal melanoma. ^a % distribution in site of melanoma adds to >100 because of contiguous tumors. ^b 5.2% had ciliochoroidal melanoma.

shown a larger mean basal diameter in Asians compared to whites (Fig. 1) [14]. The mean largest basal diameter varied from 12 to 14.8 mm in various Asian studies (Table 2). Tumor size has been considered as the most significant factor for survival in a study involving 582 patients [25].

Based on Histopathology

Modified Callendar Classification is widely used histopathological classification of UM worldwide [26]. Studies from India [15, 27] and China [11] showed a higher incidence of spindle type tumor as compared to mixed cell-type tumor. Table 3 summarizes the histopathological features and treatment modalities in various Asian studies.

Based on Molecular Testing

- Class 1
- Class 2

Or

- Disomy 3 and 8
- Monosomy 3 and 8q gain

Molecular studies using gene expression and chromosomal aberration analysis have helped to stratify UM into 2 prognostic classes. Class 1 tumors or disomy 3 (D3) pos-

sess low risk of liver metastasis whereas Class 2 tumors or with monosomy 3 (M3) have a high risk of liver metastasis. In addition to chromosome 3, aberrations in chromosomes 1 and 8 also have been studied in UM [28–30]. Abnormalities in the HLA class I, β 2-m, and HLA class II antigens have been reported in UM by an Indian study group [31]. Another study from India [32] highlights the significance of antigen processing molecules in MHC class I expression in UM.

Clinical Presentation

Symptoms

Persistent photopsia (flashes), floaters, visual field loss, and diminution of vision are the frequent symptoms reported in Asian studies. Patients may develop pain secondary to glaucoma, orbital involvement, tumor-related inflammation, or necrosis [33]. About 20–25% of patients remain asymptomatic or tumor is detected as an accidental finding during routine fundus examination. Hence, indirect ophthalmoscopic evaluation of the dilated fundus is essential for identification and for follow-up of progressive benign lesions. In majority of Asian nations, UMs are detected late due to inadequate screening [34].

Table 3. Histopathological features and treatment modalities of UM in studies from Asian countries

No.	Authors	Year	Country	Patients, <i>n</i>	Modalities, %					Histopathology, %		
					plaque RT (element)	primary enuc	resection	secondary enuc	others	spindle	epitheloid	mixed
1	Liu et al. [6]	2005–2015	China	582	71.3 (na)	20.4	8.2	10	0	71.7	10.7	17.6
2	Zewar et al. [9]	2006–2014	Jordan	46	28 (I)	39	0	4.3	0	10	20	70
3	AlSuhaibani [10]	1983–2005	Saudi Arabia	40	15 (I)	82.5	2.5	0	0	70.6	0	29.4
4	Frenkel et al. [8]	1988–2007	Israel	558	74 (Ru)	17.9	2.5	6.1	5.5	na	na	na
5	Liu et al. [6]	1990–2005	Taiwan	26	0	100	0	0	0	23	77	0
6	Wong et al. [13]	2002–2017	Singapore	11	18.2 (na)	18.2	0	0	63.6	20	20	40
7	Biswas et al. [14]	1987–2001	India	103	0	100	0	0	0	35	10.7	54.3
8	Kashyap et al. [15]	2001–2011	India	76	0	100	0	0	0	53.9	18.4	18.4
9	Meeralakshmi et al. [27]	2008–2015	India	44	50 (I)	50	0	6.8	0	41	9	41
10	Hamal et al. [16]	2017–2018	Nepal	8	25	75	0	12.5	0	42.9	57.1	0

Studies by Park et al. [4] and Tomizuka et al. [7] were epidemiological studies and did not have treatment components. No., number; na, not available; RT, radiation therapy; Enuc, enucleation; I, iodine-125; Ru, ruthenium-106.

Fig. 2. Color fundus photograph (montage) reveals a large choroidal melanoma with optic disc overhang (a) and retinal invasion (a, b). Photomicrograph of the enucleated eye (Hematoxylin and eosin, ×10) reveals choroid (star) and pigmented tumor cells in the retina (arrow; c).

Signs

UM presents as a typical lesion in majority of cases. Some patients present with retinal detachment, acute glaucoma, uveitis, cataract, or vitreous hemorrhage (Fig. 1) [35, 36]. On the other hand, some other conditions may masquerade as UM, for example, choroidal detachment, choroidal hematoma, or hemorrhagic intraretinal macrocyst [37, 38]. Asian studies show similar characteristics of tumor morphology in comparison to that of whites [4, 11].

Local invasion of choroidal melanoma is frequent with larger tumors. Choroidal tumor close to optic disc and

ora serrata commonly erode and involves the overlying retina (Fig. 2). Iris involvement was seen in 4% of UM cases in a large case series from the USA. This study highlights increases incidence of iris melanoma in children [39]. There is paucity of studies from Asia concentrating entirely on iris melanoma. A large study from China showed iris involvement in 0.2% of UM cases [11], while another study from Israel showed iris involvement in 6.6% of cases [8]. This difference can be attributed to the disparate ethnicity of the 2 countries. None of the other studies reported in iris involvement. Hence, variation in

Fig. 3. Forrest plot showing the mean and range of age at presentation among the 12 Asian studies described, with a weighted mean (red box) at the bottom.

incidence of iris melanoma is not documented from Asian countries. Patients with Nevus of Ota are known to be at higher risk for UM (Fig. 1). This has been reported in a Chinese study as well [23]. This case series described UM in 3 patients with nevus of Ota and also novel genetic mutations like FAM111B and DSC2 which might contribute to etiology of disease. Figure 3 shows a Forrest plot depicting the mean and range of age at presentation amongst the 12 Asian studies described.

Diagnosis

Diagnosis of UMs is clinical, and investigations are usually needed for confirmation, documentation, follow-up, and prognosis estimation. In some circumstances, investigations are quite necessary, especially to differentiate diffuse melanoma from benign choroidal nevus. Ancillary testing commonly used are fundus photography, B-Scan ultrasound, fundus fluorescein angiography, indocyanine green angiography, enhanced depth imaging optical coherence tomography, swept-source OCT, autofluorescence, and fine-needle aspiration biopsy [40]. Since diagnosis of UM is clinical, its relative rarity in

Asians and unfamiliarity of clinical features among ophthalmologists increases the chances of initial misdiagnosis [13].

Treatment

Choices for choroidal melanoma are determined by tumor size and include transpupillary thermotherapy, plaque radiotherapy, charged particle irradiation, local resection, enucleation, or orbital exenteration. Most commonly used modalities are enucleation and focal radiotherapy (plaque therapy). In Asian context, primary enucleation is the most commonly used modality of treatment as listed in (Table 3) except in China and Israel [8, 11] where brachytherapy is more commonly used. Limiting factors in seeking treatment are lack of financial support and limited access to treatment in these regions. Commonly used radioisotopes for plaque radiation therapy are iodine-125 (^{125}I) and ruthenium-106 (^{106}Ru). Advantages of ^{106}Ru are its relative ease of availability, long shelf-life, ease of reuse, and its sparing effect on surrounding healthy tissues. A study conducted among Asian Indians comparing enucleation versus

Table 4. Treatment outcomes of UM in studies from Asian countries

No.	Authors	Year	Country	No.	Metastasis, %	Deaths, %	5 year survival rate	Mean follow-up, months	Remarks
1	Liu et al. [11]	2005–2015	China	582	8.4	5.5	92.7	30 (1–124)	Tumor size significant for survival
2	Zewar et al. [9]	2006–2014	Jordan	46	11	8.7	na	27 (6–72)	–
3	AlSuhaibani [10]	1983–2005	Saudi Arabia	40	5	0	na	33.7 (0.5–120)	–
4	Frenkel et al. [8]	1988–2007	Israel	558	13.3	17.4	88.6	66.6	Time from diagnosis to metastasis: 35 months
5	Liu et al. [6]	1990–2005	Taiwan	26	12	12	53	39.5 (2–176)	CB involvement, nonspindle cell type had poor prognosis
6	Yue et al. [12]	2003–2012	China	171	21	17.5	80	63.4 (6.4–140)	BAP1 negative staining had worse prognosis
7	Wong et al. [13]	2002–2017	Singapore	11	45.5	36.4	na	29 (5–475)	Time from diagnosis to metastasis: 79.6 (0–267) months
8	Biswas et al. [14]	1987–2001	India	103	na	0.96	na	na	–
9	MeeraLakshmi [27]	2008–2015	India	44	na	6.8	89	39 (6–86)	–

Studies by Park et al. [4] and Tomizuka et al. [7] were epidemiological studies and did not have treatment components.

brachytherapy yielded similar survival rates in both groups and intergroup observations were not statistically significant [27]. Local resection of tumor has been described in the literature. Although endoresection has been controversial due to chances of dissemination, a case series has shown good results with few recurrences [41]. There are only 3 studies from Asia which included endoresection procedure among which 1 is a large case series from China by Liu et al. [11] with 8% of UM patients.

Other treatment modalities described are proton beam therapy (PBT), carbon ion therapy, and gamma knife surgery. A study from Korea evaluated outcomes of PBT in 24 treatment naïve patients [42]. This study concluded that local control rate and acceptable toxicity in Korean patients were comparable with those in the previously reported PBT series. Charged particle irradiation has also been tried in treatment of UM. A study from Japan involving 116 patients utilized carbon ion radiation therapy in locally advanced and unfavorable tumors, and the results were satisfactory in terms of local tumor control (92.8%), globe survival (92.8%), and toxicity [43]. Gamma knife surgery has been tried in a series of patients with choroidal melanoma [44]. Although the outcomes with these 3 treatment modalities are similar to those of plaque brachytherapy, they

remain way less popular when compared to plaque brachytherapy in this part of the world-likely because of the high capital cost involved.

Prognosis

It is well known that Asian patients have a higher mean basal diameter compared to whites, and hence, they are at more risk for metastases as well [17]. Liu et al. [11] found tumor size as significant factor for patient survival. However, the genetic makeup of tumors may be an important determinant for metastatic risk and prognostication. This needs further study in Asian population. Treatment outcomes are summarized in (Table 4).

To summarize, even though the incidence of UM in Asians is lower than that reported from white population in the USA, Europe, and Australia, it can vary in the context of the ethnolinguistic group the data are collected from. The age at presentation is younger than that of whites. At presentation, the mean basal diameter of tumor in Asians is greater compared to whites, but overall, medium-sized tumors are most common. Clinical presentation is straightforward, but some patients present with retinal detachment, acute glaucoma, uveitis, cataract, or vitreous hemorrhage. Most commonly used mo-

dalities for treatment are enucleation and plaque radiotherapy limited by access. Future efforts must be directed toward early diagnosis of UM improve access to eye conserving therapies.

Statement of Ethics

The authors declare that they have no ethical conflicts to disclose.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest to disclose. Prof. Singh (as one co-author) is the Editor-in-Chief of the journal Ocular Oncology and Pathology.

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Authors Contribution

P.T.M.: literature searches, analysis of the data, wrote the first draft, and manuscript revision. A.D.S.: substantial revision of the manuscript. C.L.S.: contribution to the manuscript revision. S.K.: manuscript revision. P.K.S.: manuscript revision. L.G.: substantial revisions of the manuscript. P.R.: substantial contributions to the conception or design of the work, literature searches, analysis of the data, interpretation of the data, and revising the manuscript critically for important intellectual content. All authors approved the final version as submitted.

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