Ocular and Periocular Tumors in Xeroderma Pigmentosum: A Study of 120 Asian Indian Patients

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• PURPOSE: We studied the incidence, treatment, and outcome of ocular and periocular tumors in patients with xeroderma pigmentosum (XP).
• DESIGN: Retrospective case series.
• METHODS: This single-institution study included 120 patients with XP who underwent intervention with excisional biopsy, enucleation, or orbital exenteration. The primary outcome measures were the occurrence of eyelid or ocular surface tumor, globe salvage, locoregional and systemic metastasis, and death.
• RESULTS: The mean age at presentation was 19 years. A family history of XP was present in 32 (27%) patients. Over a mean follow-up of 61 months, 34 (28%) patients developed no ocular/adnexal tumor, 86 (72%) developed ocular surface malignancy, 15 (13%) developed eyelid malignancy, and 22 (18%) developed other head and neck malignancies. Of the 86 patients with ocular surface malignancy, 48 (56%) had unilateral tumor and 38 (44%) had bilateral tumors. Invasive squamous cell carcinoma (n = 51, 41%) was the most common ocular surface tumor. Of the 15 patients with eyelid tumors, 14 (93%) had unilateral tumor and 1 (7%) had bilateral involvement. Basal cell carcinoma (n = 8, 50%) was the most common eyelid tumor. There were events of ocular surface tumor recurrence (n = 55 eyes, 44%), eyelid tumor recurrence (n = 5 eyes, 31%), locoregional lymph node metastasis (n = 3, 2%), systemic metastasis (n = 1, 1%), and death (n = 1, 1%). Overall, globe salvage was achieved in 119 (99%) patients (both eyes were salvaged in 92 [76%] patients and at least 1 eye was salvaged in 27 [23%] patients).
• CONCLUSION: XP is frequently associated with ocular surface, eyelid, and other head and neck malignancies. Lifelong follow-up is mandatory in these patients. (Am J Ophthalmol 2019;198:146–153. © 2018 Elsevier Inc. All rights reserved.)

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IN 1874, HEBRA AND KAPOSI FIRST DESCRIBED "XERODERMA or parchment skin" as a skin disorder.[1] Subsequently, it was termed xeroderma pigmentosum (XP) because of the predominant skin pigmentary changes.[2] The association of XP and defective DNA repair was reported in a seminal publication by James Cleaver in 1968.[3] Cleaver demonstrated that after ultraviolet (UV) radiation exposure there was defective DNA repair replication in cultured skin fibroblasts of patients with XP.[3] The combination of increased sun sensitivity, UV light–induced DNA damage, and defective DNA repair in patients with XP results in increased skin pigmentation and an increased risk of UV light–induced malignancies in sun-exposed areas.

The manifestations of XP and age at onset of ocular manifestations depend on the XP complementation groups. There are 8 known XP complementation groups, classical XP (XP-A to XP-G) with a defective nucleotide excision repair pathway and XP variant (XP-V) with a normal nucleotide excision repair pathway but a defective replication system of UV light–damaged DNA.[4–7] Patients with complementation groups A, B, D, F, and G have severe sunburn reactions on minimal sun exposure, an increased frequency of neurologic abnormalities, and develop their first skin cancer at an older age; complementation groups C, E, and V with preserved transcription-coupled DNA repair have normal sunburn reactions to sun exposure and a decreased frequency of neurologic abnormalities but develop their first skin cancer at an earlier age.[8–10]

Compared with the normal population, patients with XP have an increased risk of cancers with a 10,000-fold increased risk of nonmelanoma skin cancer and 2000-fold increased risk of cutaneous melanoma under 20 years of age.[9] The incidence of skin cancers in patients with XP varies from 45% to 65% and ocular surface cancers occur in 2% to 26%.[9–17] Ocular abnormalities are seen in 40% to 100% of cases.[14–17] Herein, we report the incidence of ocular and adnexal tumors in Asian Indian patients with XP and their outcomes.

METHODS

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Prasad Eye Institute, Hyderabad, India. Institutional review board approval was obtained for the study. A database search was conducted for the diagnosis of XP from January 1989 to December 2017. All cases with a clinical diagnosis of XP based on cutaneous findings, histopathologic confirmation of ocular/adnexal tumors, and those who had completed a minimum follow-up of 6 months from the time of presentation to the oncology clinic were included in the study. Those with inadequate follow-up or incomplete documentation were excluded from the study.

The following data were extracted from each patient's medical record: age at presentation, gender, history of consanguineous marriage in parents, family history of XP, and details of affected family members. Visual acuity and anterior segment and posterior segment findings were recorded. During follow-up, occurrences of any ocular or adnexal or any other malignancy were noted. The details of ocular surface tumor included laterality, history of previous treatment, presenting complaints, duration of symptoms, tumor location, tumor size, tumor morphologic pattern, associated features (eg, keratin, feeder vessels, intrinsic vascularity), and tumor extent. The details of eyelid tumor included presenting complaints, duration of symptoms, tumor epicenter, tumor morphologic pattern, and tumor extent. Ocular surface and eyelid tumors were retrospectively classified based on the eighth edition of the American Joint Committee on Cancer staging manual.[18,19] The details of primary treatment, adjunctive treatment, histopathologic diagnosis, and tumor recurrence were also recorded for eyelid and/or ocular surface tumors. Details of other head and neck malignancies were also recorded. Tumor recurrence was defined as recurrence of a tumor at the site of a previous tumor after complete disappearance of the previous tumor after surgical or medical treatment. The final outcome (tumor-free, globe salvage, locoregional metastasis, systemic metastasis, or death) at last follow-up was recorded.

RESULTS

TWO HUNDRED PATIENTS WITH XP WERE SEEN DURING THE study period. All patients already had a known diagnosis of XP before referral to the oncology clinic. Of these, 120 were included in this study based on the defined inclusion criteria of 6 months follow-up duration from the date of presentation, while 72 patients did not have a minimum follow-up period of 6 months and 8 patients had inadequate documentation of clinical findings and were excluded. Of the 120 patients included in the study, 51 patients had an ocular surface tumor at presentation. Two patients had an eyelid tumor at presentation. The remaining 67 patients were seen in oncology clinic as a part of routine surveillance for ocular and periocular tumors in patients with XP. The mean age at presentation to the oncology clinic was 19 years (median 18 years; range 1–53 years). History of consanguineous marriage in parents was noted in 57 (48%) patients. There was a known family history of XP in 32 (27%) patients. The affected family members included mother (n = 1, 1%), father (n = 1, 1%), and siblings (n = 30, 25%) (Table 1).

TABLE 1. Patients With Xeroderma Pigmentosum: Demographics and Tumors

Feature	Patients (N = 120)
Mean age at presentation, y (median [range])	19 (18 [1–53])
Gender, n (%)	
Male	76 (63)
Female	44 (37)
Parental consanguinity, n (%)	
No	63 (52)
Yes	57 (48)
Family history of xeroderma pigmentosum, n (%)	
No	88 (73)
Yes	32 (27)
Tumors, n (%)	
No ocular or adnexal tumor	34 (28)
Eyelid tumor	15 (13) patients/16 eyes
Conjunctival tumor	86 (72) patients/124 eyes
Other head and neck malignancies	22 (18)
Other significant features, n (%)	
Symblepharon/ankyloblepharon	20 (8)
Cicatricial ectropion	11 (5)
Vernal keratoconjunctivitis	19 (8)
Conjunctival pigmentation	96 (40)
Corneal opacity	125 (52)
Corneal ulceration	4 (2)
Cataract	9 (4)
Phthisis bulbi	4 (2)

Over a mean follow-up period of 61 months (median 36 months; range 6–349 months), 32 (27%) patients developed no ocular/adnexal tumor or head and neck malignancy, 57 (48%) developed isolated ocular surface malignancy, 14 (12%) developed ocular surface malignancy along with other head and neck malignancy, 0 (0%) had isolated eyelid malignancy, 9 (8%) developed eyelid and ocular surface malignancy, 6 (5%) developed eyelid, ocular surface, and other head and neck malignancy, and 2 (2%) developed other head and neck malignancies without any ocular/adnexal malignancy. There is a possibility of underdiagnosis of head and neck malignancies in this study because routine head and neck imaging or routine surveillance by head and neck oncologist was not performed in all cases. Head and neck examination was done in the ocular oncology clinic and was referred to head and neck oncologist only if any pathology was detected on inspection or palpation of head

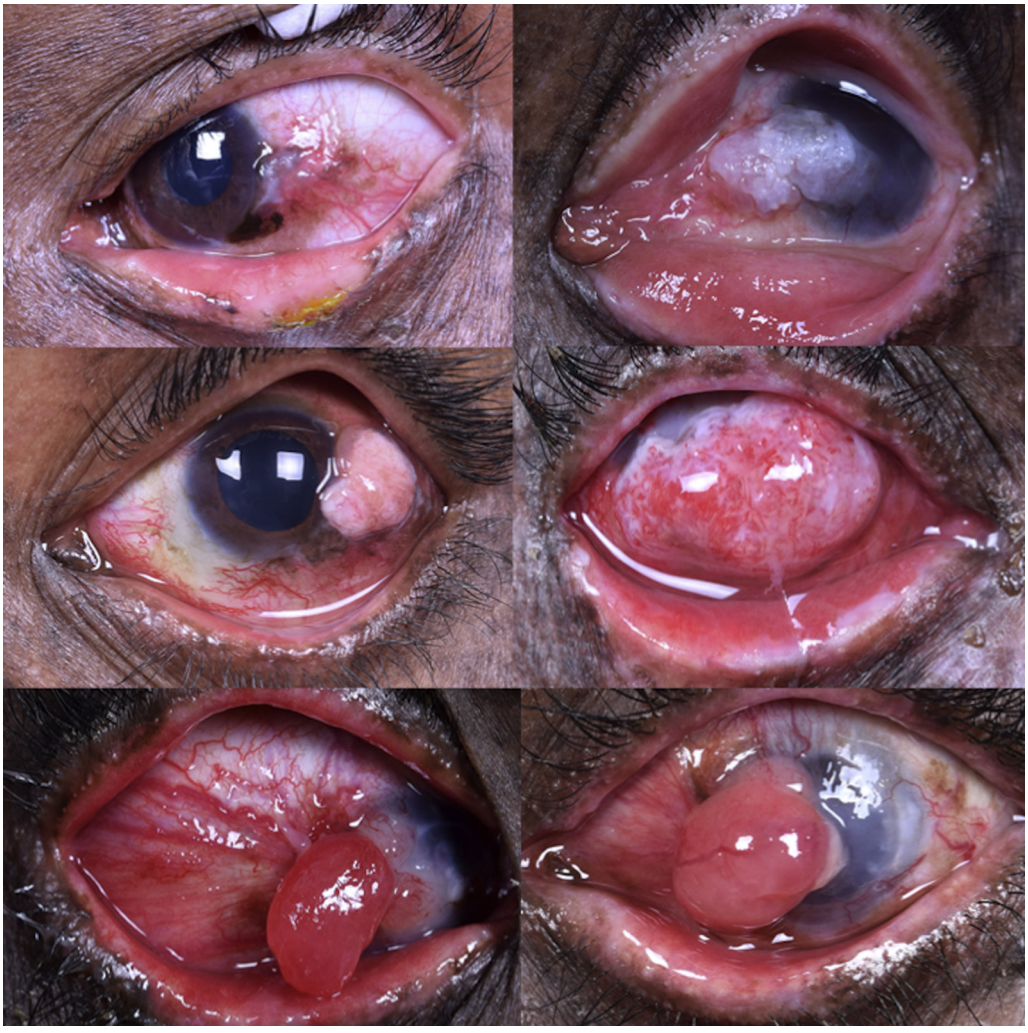

FIGURE 1. Ocular surface malignancies in patients with xeroderma pigmentosum. Top left, A 30-year-old man with ocular surface malignant lesion associated with moderate dysplasia in the left eye. The patient also had lower eyelid basal cell carcinoma. Top right, A 14-year-old male with carcinoma in situ in the medial quadrant. Middle left, A 13-year-old male with invasive ocular surface squamous cell carcinoma. Middle right, A 16-year-old female with massive invasive ocular surface squamous cell carcinoma. Lower left, An 11-year-old male with spindle cell variant of ocular surface squamous neoplasia. Lower right, A 15-year-old female with sarcomatoid carcinoma of the conjunctiva.

and neck region. The details of head and neck malignancies included nonperiocular facial skin cancer (n = 18), squamous cell carcinoma (SCC) of the lip (n = 2), SCC of the tongue (n = 1), SCC of the palate (n = 1), SCC of the scalp (n = 1), and nasopharyngeal SCC (n = 1).

Of the 86 patients with ocular surface tumors (Figure 1), 51 (59%) patients had an ocular surface tumor at presentation to the oncology clinic, while 35 (41%) patients developed an ocular surface tumor during the follow-up period. The mean interval between the initial presentation and development of an ocular surface tumor in these 35 patients was 46 months (median 27 months; range 2–159 months). The mean age at the time of detection of an ocular surface tumor was 21 years (median 20 years; range 2–46 years). Of the 86 patients with ocular surface tumors, 48 (56%) had unilateral tumor and 38 (44%) had bilateral tumors (Table 2). At the time of initial diagnosis of ocular surface tumors, 71 (83%) patients had unilateral ocular surface tumors, of which 23 (17%) subsequently developed bilateral involvement. History of a previous intervention was noted in 30 (24%) eyes, including excisional biopsy in 21 eyes and topical mitomycin-C in 9 eyes. The mean duration of symptoms related to the ocular surface lesion was 10 months (median 4 months; range <1–120 months). The tumor epicenter was more commonly located in the limbus (n = 66, 53%). Medial (n = 46, 37%) and lateral (n = 42, 34%) quadrants were more commonly involved. The mean basal diameter of the tumor was 7 mm (median 6 mm; range <1–60 mm). Multifocal tumors were noted in 14 (11%)

TABLE 2. Conjunctival Tumors in Patients With Xeroderma Pigmentosum.

Feature	Patients (n = 86) and involved eyes (n = 124)
Laterality, n (%)	
Unilateral	48 (56)
Bilateral	38 (44)
Mean tumor basal diameter, mm (median [range])	7 (6 [<1–60])
T category based on AJCC 8th ed, n (%)	
Tx	26 (21)
Tis	29 (23)
T1	21 (17)
T2	19 (15)
T3	22 (18)
T4	7 (6)
Primary treatment, n (%)	
Topical chemotherapy/immunotherapy	16 (13)
Wide excisional biopsy and cryotherapy	90 (73)
Extended enucleation	10 (8)
Orbital exenteration	8 (6)
Tumor recurrence, n (%)	55 (44)

AJCC = American Joint Committee on Cancer.

eyes. Nodular (n = 20, 16%) and papillary (n = 18, 15%) morphologic patterns were more common. Orbital tumor extension was noted in 6 (5%) patients. The other significant ocular findings are listed in Table 2. Tis (n = 29, 23%) was the most common tumor category based on the eighth edition of the American Joint Committee on Cancer staging manual.[18] The most common primary treatment modality for ocular surface tumor was wide excisional biopsy by no-touch technique including 4-mm tumor-free margins, cryotherapy to surgical margins, and ocular surface reconstruction with amniotic membrane graft (n = 90, 73%). Adjunctive treatment modalities included plaque radiotherapy for tumor residue at the base (n = 13, 10%), topical mitomycin-C for tumor residue at the margins (n = 8, 6%), topical interferon alfa-2b for tumor residue at the margins (n =3, 2%), and additional cryotherapy (n = 8, 6%) for tumor residue at the margins. Tumor recurrence was noted in 55 (44%) eyes. Of these 55 patients, 8 patients had dysplasia involving ≥1 surgical margin and 7 patients had tumor infiltrating the base after the primary tumor resection. All patients with margin involvement had received topical mitomycin-C for 3 months and the patients with base involvement had undergone plaque radiotherapy. The mean number of recurrences during the follow-up period was 2 (median 1; range 1–4). The mean interval between initial treatment and ocular surface tumor recurrence was 32 months (median 13 months; range 2–110 months). The mean follow-up duration in patients with tumor recurrence was 70 months (median 60 months; range 6–179 months) and those with no tumor recurrence was 54 months (median 29 months; range 6–209 months). Recurrent tumors were subsequently treated by topical mitomycin-C (n = 3), topical interferon alfa-2b (n = 2), wide excisional biopsy and cryotherapy (n = 48), extended enucleation (n = 1), or orbital exenteration (n = 1).

Of the 15 patients with eyelid tumor (Figure 2), 14 (93%) had unilateral tumor and 1 (7%) had bilateral involvement (Table 3). At presentation, all (100%) patients had unilateral eyelid tumor, of which 1 (7%) subsequently developed bilateral involvement. Of the 16 tumors, 14 (88%) were located in the lower eyelid. Based on the histopathologic diagnoses (Table 4), basal cell carcinoma was located in lower eyelid (n = 7) or lateral canthus (n = 1), SCC in the lower eyelid (n = 6), and malignant melanoma in the upper (n = 1) or lower eyelid (n = 1). The mean duration between initial presentation and detection of eyelid tumor was 35 months (median 11 months; range 0–149 months). Only 2 patients had eyelid tumor at presentation, while the remaining were detected along the follow-up period. The tumor was multifocal in 1 (6%) patient. The mean basal diameter of the tumor was 11 mm (median 9 mm; range 3–30 mm). Based on the eighth edition of the American Joint Committee on Cancer staging manual,[19] T1 (n = 10, 63%) was the most common tumor category and wide excisional biopsy with 4-mm tumor-free margins under frozen section control (n = 15, 94%) was the most common primary treatment modality. Tumor recurrence was noted in 2 (13%) patients. The mean interval between initial treatment and eyelid tumor recurrence was 32 months (median 32 months; range 23–41 months).

The histopathologic diagnoses of tumors are listed in Table 4. The mean follow-up period of patients with no tumor was 61 months (median 31 months; range 6–349 months), with ocular surface tumor was 60 months (median 38 months; range 6–209 months), and with both eyelid and ocular surface tumor was 68 months (median 38 months; range 11–200 months). Overall, over a mean follow-up period of 61 months, there were events of locoregional lymph node metastasis (n = 3, 2%), systemic metastasis (n = 1, 1%), and death (n = 1, 1%). One patient developed locoregional lymph node metastasis and subsequent systemic metastasis to parotid gland, lungs, and brain. At presentation, he had carcinoma in situ of the conjunctiva in both eyes for which he underwent wide excisional biopsy. He had massive tumor recurrence in right eye 9 years later necessitating orbital exenteration, radical neck dissection, and systemic chemotherapy. He died 4 years later. The second patient who developed locoregional lymph node metastasis had conjunctival mild dysplasia in the right eye, invasive conjunctival squamous cell carcinoma in the left eye, and left lower eyelid SCC. Tumor recurrence was noted in the right eye 44 months after wide excisional biopsy. The patient was advised to undergo wide excisional biopsy of the recurrent tumor and radical neck dissection for

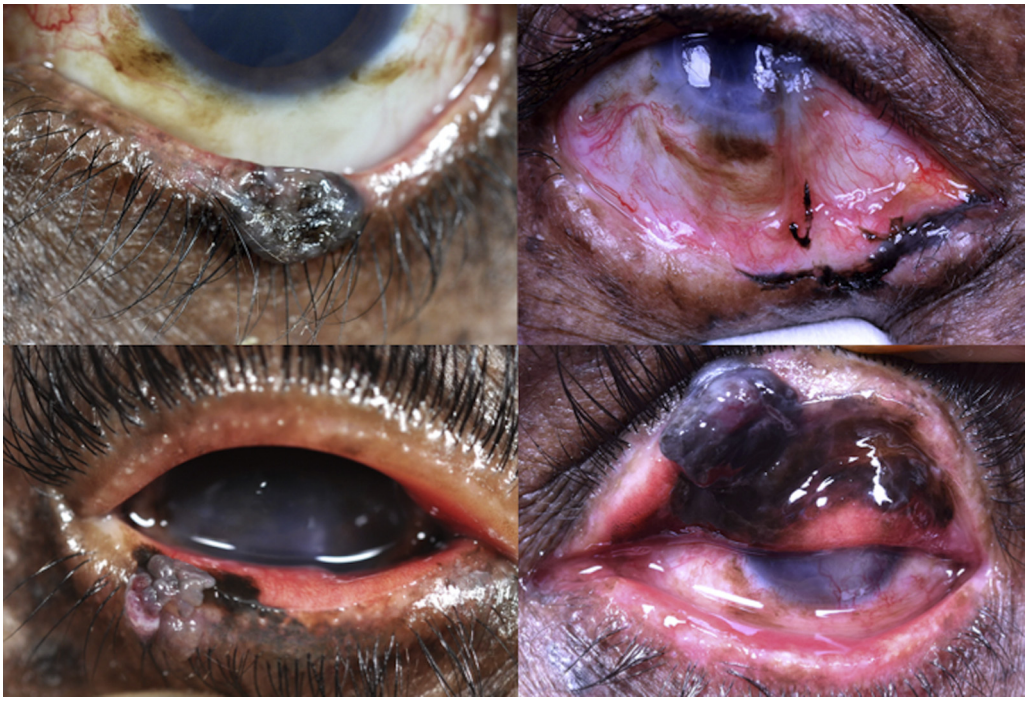

FIGURE 2. Eyelid malignancies in patients with xeroderma pigmentosum. Top left, A 29-year-old woman with placoid basal cell carcinoma involving the lower eyelid margin. Top right, A 19-year-old man with noduloulcerative basal cell carcinoma involving the lower eyelid margin. Lower left, A 9-year-old male with lower eyelid squamous cell carcinoma. Lower right, A 31-year-old man with malignant melanoma of the upper eyelid margin and upper tarsal conjunctiva.

TABLE 3. Eyelid Tumors in Patients With Xeroderma Pigmentosum

Feature	Patients (n = 15) and tumors (n = 16)
Laterality, n (%)	
Unilateral	14 (93)
Bilateral	1 (7)
Mean tumor basal diameter, mm (median [range])	11 (9 [3–30])
T category based on AJCC 8th ed, n (%)	
T1	10 (63)
T2	5 (31)
T3	0 (0)
T4	1 (6)
Primary treatment, n (%)	
Wide excisional biopsy	15 (94)
Systemic chemotherapy	1 (6)
Tumor recurrence, n (%)	2 (13)

AJCC = American Joint Committee on Cancer.

lymph node metastasis. The patient was subsequently lost to follow-up. The third patient who developed locoregional lymph node metastasis had invasive conjunctival SCC in the right eye, conjunctival carcinoma in situ in the left eye, and left lower eyelid malignant melanoma. He underwent orbital exenteration of the right eye, wide excisional biopsy of the eyelid and conjunctival tumors in the left eye, and radical neck dissection for lymph node metastasis. He is alive and well at 18 months' follow-up.

Overall, globe salvage was achieved in 119 (99%) patients. Both eyes were salvaged in 92 (76%) and ≥1 eye was salvaged in 27 (23%) patients. Globe salvage of either eye could not be achieved in 1 (1%) patient. He had invasive conjunctival SCC in the right eye and had to undergo orbital exenteration after 4 tumor recurrences; and had conjunctival angiosarcoma in the left eye and had to undergo orbital exenteration after 2 tumor recurrences. The mean follow-up duration in patients with salvaged globes was 62 months (median 38 months; range 6–349 months) and in those with loss of ≥1 globe was 60 months (median 27 months; range 6–179 months).

DISCUSSION

XP IS AN AUTOSOMAL RECESSIVE DISORDER, AND THEREfore parental consanguinity plays an important role. In a review of 830 published cases of XP, parental consanguinity

TABLE 4. Tumors in Patients With Xeroderma Pigmentosum

Feature	Patients (n = 86)
Mean age at detection of first ocular/adnexal tumor, y (median [range])	21 (20 [2–46])
Tumor, n (%)	
No eyelid or conjunctival tumor	34 (28)
Eyelid tumor, n (%)	15 (13) patients/16 eyes
BCC	8 (50)
SCC	6 (38)
Malignant melanoma	2 (12)
Conjunctival tumor, n (%)	86 (71) patients/124 eyes
Ocular surface squamous neoplasia	119 (96)
Mild dysplasia	9 (7)
Moderate dysplasia	17 (14)
Severe dysplasia	5 (4)
Carcinoma-in-situ	38 (31)
Invasive squamous cell carcinoma	51 (41)
Spindle cell variant of squamous cell carcinoma	1 (1)
Angiosarcoma	1 (1)
Malignant mesenchymal tumor	1 (1)
Sarcomatoid carcinoma	1 (1)
Other head and neck malignancies, n (%)	22[a] (18)
Non-periocular facial cutaneous BCC or SCC	18 (82)
Scalp SCC	1 (5)
Lips SCC	2 (9)
Palate SCC	1 (5)
Tongue SCC	1 (5)
Nasopharyngeal SCC	1 (5)

BCC = basal cell carcinoma, SCC = squamous cell carcinoma.

[a]One patient had facial cutaneous SCCs and BCCs and SCC of the tongue. One other patient had facial cutaneous BCC and nasopharyngeal carcinoma.

was noted in 21% of cases, and 67% had relatives with XP.[14] In our study, parental consanguinity was much higher (48%), which could be related to cultural differences between the Asian Indian and the Western population, and 27% patients had relatives with XP, which was much lower than the published literature.

Ocular and adnexal neoplasms and skin cancers are more common in patients with XP and occur much earlier compared with the normal population. This is primarily related to extreme sun sensitivity of patients with XP because of genetic defects in the nucleotide excision repair pathway resulting in defective repair of UV light–induced DNA damage in the cells. This results in the accumulation of unrepaired DNA damage within the cells and cancerous changes in the UV light–exposed areas of the eye and periocular area, such as eyelids and periocular skin, conjunctiva, and cornea.[10,12–14] The median age at first ocular neoplasm in patients with XP is 11 to 21 years,[14,20] and the mean age of skin cancer is 8 years.[14] In our study, the median age at detection of first ocular neoplasm was 20 years. Eyelid and ocular surface tumors are more common in XP while posterior segment tumors are rare[21] owing to protection of the posterior structures from UV damage by the cornea and lens. It is estimated that there is a 2000-fold higher risk for neoplasms of the anterior eye in patients with XP compared with the general population <20 years of age.[22] The incidence of ocular surface tumors in patients with XP is reported at 2% to 26%.[9–17] In our study, the incidence of eyelid tumors was 13% and ocular surface tumors was 72%. The incidence of ocular surface tumors was much higher compared with that reported in the literature, and this could be related to referral bias to our center.

The most common ocular surface malignancy in our series of patients with XP was ocular surface squamous neoplasia (OSSN). OSSN includes a spectrum of epithelial malignancies ranging from mild dysplasia to invasive SCC.[23] OSSN most commonly occurs in the sixth and seventh decades of life.[23] However, it can occur at younger ages in immunocompromised individuals and in those with XP. In immunocompromised individuals, OSSN occurs in the fourth decade of life,[24,25] while in XP it is much earlier with most cases occurring before 20 years of age.[20,26] In our study, the mean age at presentation of OSSN was 21 years, and 54% (n = 45) presented before 20 years of age. Bilateral affliction and multifocality of tumors are common in XP.[26–28] In our study, 44% had bilateral affliction and 11% eyes had multifocal tumors. Tumor excision without wide margins or adjunctive cryotherapy is associated with a tumor recurrence rate of 24% to 56%,[23,29,30] which can be reduced to 7% to 12% with the use of adjunctive cryotherapy and wide margin excisional biopsy.[31] Status of tumor margin is the most important predictor of tumor recurrence.[30] However, in XP, the rate of tumor recurrence is common in spite of meticulous wide excisional biopsy and adjunctive cryotherapy. In a study of 7 cases of OSSN in patients with XP, the tumor recurrence was as high as 64%.[26] In our study, the tumor recurrence rate was 44%, and the mean interval between primary treatment and tumor recurrence was 32 months. Five patients developed tumor recurrence after an interval of 5 years from primary treatment, which emphasizes the importance of long-term follow-up in these cases with XP. Also, it should be noted that the mean follow-up duration in patients with ocular surface tumor recurrence was longer at 70 months compared with 54 months in patients with no ocular surface tumor recurrence. The difference in the follow-up duration between these 2 groups could have led to underrepresentation of ocular surface tumor recurrence in patients with XP in our study.

Skin cancers in sun-exposed areas are commonly seen in patients with XP. The most common skin malignancies include basal cell carcinoma (9–29%), SCC (3–17%), and malignant melanoma (2–5%).[11,12,14] Periocular malignancy is noted in 11% to 26% cases.[10,13,31] Basal

cell carcinoma is the most common eyelid malignancy, accounting for 57% to 70% of eyelid malignant lesions.[13,31,32] Similarly, in our study, basal cell carcinoma was the most common eyelid malignancy, accounting for 50% cases. The mean interval of initial presentation and detection of eyelid tumor was 35 months in our study compared with 10 months for ocular surface tumor. This suggests that most patients develop an eyelid tumor much later than an ocular surface tumor, therefore warranting a careful examination of eyelids in patients with XP during the follow-up period. This indicates that conjunctiva is more sensitive to UV light–related changes in the eye in these patients compared with eyelids. Tumor recurrence is rare for completely removed eyelid basal cell carcinoma with margin control. However, in our study, tumor recurrence rate was noted in 2 (25%) of 8 cases of basal cell carcinoma despite margin control by frozen section diagnosis. However, the sample size (n = 8) was too small to reach a definite conclusion.

The drawbacks of our study include its retrospective nature, the lack of molecular genetic analysis and categorization by complementation groups, and the lack of correlation of eyelid and ocular surface malignancies by complementation groups. Referral bias could have contributed to high rate of periocular and ocular surface malignancies in our study. The level of sunlight exposure and the level of UV light protection could not be determined accurately in our patients. The sunlight exposure factor could have certainly influenced the incidence rate of ocular and periocular tumors.

In conclusion, patients with XP have a high incidence of eyelid and ocular surface malignancies. The main source of harmful short wavelength UV light is sunlight. Emphasis regarding minimizing sunlight exposure and ensuring adequate protection against UV light by appropriate clothing and shoes, sunscreen, UV protective glasses, or full-face visors is of paramount importance in these patients. Lifelong monitoring for malignancies in sun-exposed areas is mandatory.

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