*Quest Journals*
*Journal of Medical and Dental Science Research*
*Volume 3~ Issue 4 (2016) pp:17-24*
*ISSN(Online) : 2394-076X ISSN (Print):2394-0751*
www.questjournals.org

**Research Paper**

# The Role of Mitomycin C in Ocular Surface Squamous Neoplasia (OSSN)

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**R**eceived 20 April, 2016; **A**ccepted 03 May, 2016 © The author(s) 2015. Published with open access at **www.questjournals.org**

***ABSTRACT:-***
***Purpose:*** *To report the cure and recurrence rate with excision of primary OSSN with Mitomycin C as an adjunctive treatment over 15 months period.*
***Methods:*** *Twenty eyes of 12 patients with histologically proven primary were included in the study between December 2014 and October 2015. Protocol for the management comprised of surgical excision of the lesion with a 3 mm of healthy rim followed by topical Mitomycin C 0.04% four times a day to all postoperative patients in 3-4 cycles of alternate on and off weekly courses. At each visit, patients were looked for recurrence of tumor and corneal alterations like keratitis or erosions. Efficacy of Mitomycin C as an adjuvant therapy was measured in terms of clinical cure and recurrence of the tumor.*
***Results:*** *Average age in this study was 42.25 years with 33% patients below 40 years with 75% male preponderance. With a follow up period of 6 months, 83.3% success rate was found despite of late stage presentation in our study.*
***Conclusion:*** *Mitomycin C treatment following surgical excision decreases the recurrence rate of primary ocular surface neoplasia and should be considered as an adjunctive therapy in primary treatment.*

***Keywords:-*** *Mitomycin C, ocular surface squamous neoplasia, recurrence of ocular surface squamous neoplasia*

## I. INTRODUCTION

The term ocular surface squamous neoplasia (OSSN) was first described in 1995 by Lee and Hirst to denote a spectrum of neoplasm originate from squamous epithelium ranging from simple dysplasia to invasive squamous cell carcinoma(SCC), involving the conjunctiva, the limbus, and the cornea [1]. This tumor is considered as a low grade malignancy but invasive lesion can spread to the globe or orbit. OSSN is considered an uncommon disease with geographic incidences which vary from 0.2 to 3.5 per 100,000, with greater frequency near the equator. OSSN accounts for only 5% of all ocular malignancies [1]. It is the most common ocular surface tumor in many series. Prior to HIV pandemic, OSSN was noted to occur predominantly in the elderly for whom it was the third most common oculo-orbital tumor after malignant melanoma and lymphoma[1]. Although conjunctival tumors may arise from any type of the conjunctival cells, epithelial and melanocytic are the most frequent origins. Epithelial tumors account for a third to half of all tumors, with a higher prevalence in countries with larger actinic exposure. Aproximately 40% of the tumors have an epithelial origin and 64.5% of them were pre-cancerous lesions[2].

Squamous cell neoplasia may occur as a localized lesion confined to the surface epithelium (conjunctival intraepithelial neoplasia) or as a more invasive squamous cell carcinoma that has broken through the basement membrane and invaded the underlying stroma[3]. Currently, the accepted term for the localized variety is conjunctival intraepithelial neoplasia (CIN). Those cases where the cornea is invaded by the process are usually called conjunctiva-cornea intraepithelial neoplasia (CCIN). Squamous neoplasia constitutes the most frequent primary malignancy of the ocular surface. The term CIN was suggested in 1978, according with the general pathologic classification of intraepithelial tumors developed for cervical intraepithelial neoplasia[4]. CIN includes previous terms referred to this epithelial neoplasia such as: Bowen´s disease, Bowenoid epithelioma,

intraepithelial epithelioma, intraepithelioma, dysplasia and carcinoma in situ (CIS). Subjective symptoms referred by the patients include: foreign body sensation, redness, irritation, and a growth on the ocular surface[5]. Clinically, CIN appears as a fleshy, sessile or minimally elevated lesion usually at limbus (Fig.1) in the interpalpebral fissure and less commonly in the forniceal or tarsal conjunctiva[3]. The limbal lesion may extend for a variable distance into the epithelium of the adjacent cornea (Fig.1). A white plaque (leukoplakia) may occur on the surface of the lesion due to secondary hyperkeratosis (Fig.2).

Squamous cell carcinoma is characterized by an extension of abnormal epithelial cells through the basement membrane to gain access to the conjunctival stroma[3]. Clinically, invasive squamous cell carcinoma is similar to CIN; however, it may be larger and more elevated than CIN (Fig.3). Even though the cells of invasive squamous cell carcinoma gain access to the blood vessels and lymphatic channels, regional and distant metastases are both rather uncommon.

There are many known factors which may contribute to the development of these neoplasias. The first one is the age, with an average of 60 years[1]. However, it ranges from 4 to 90 years (Table 1). The second factor attributed is the UV light exposure[6]. This justify a higher prevalence of CIN in the equatorial areas. The exposition to the petroleum products, heavy cigarrete smoking, light hair and ocular pigmentation have also been associated [7] (Table 2).

CIN is characterized by a slowly progressive course with low malignant potential. In general, two forms of CIN have been described: nodular (or well localized) and diffuse. The diffuse type is less common and very difficult to diagnose in early stages. The typical location of this slow-growing lesion is the interpalpebral limbus, but it may also arise in the forniceal and palpebral conjunctiva. Limbal lesions may spread onto the cornea. The abnormal corneal epithelium has a frosted appearance with fringed borders and usually demonstrates diffuse punctate staining. Flat or elevated, the lesion may appear relatively translucent, gelatinous, or pearly white. Secondary hyperkeratosis over the surface of the lesion may give rise to a white plaque-like appearance clinically named leukoplakia. Often, there are surrounding corkscrew-like vascular tufts (Fig.4). Pigmentation may be seen and the lesion may be clinically misdiagnosed as melanoma[8]. In cases of SCC the tumor may reach to eye globe, the orbit and cranial extension, with vision loss due to a enucleation or exenteration [9]. Up to 4% rates of metastasis to cervical lymph nodes have been reported, while metastases to distance are less common[10]. Precancerous lesions are actinic keratosis and conjunctival keratotic plaque. Both lesions, impossible to differentitate clinically, consist in a white plaque on the limbal or bulbar conjunctiva, in the exposed interpalpebral conjunctiva. They have a low grade of proliferation and very few possibilities to convert into CIN or SCC. Definitive diagnosis consisted in the histological study[3]. Leucoplakia (white plaque,Fig.2) consist in a conjuctival lesion, generally at the limbus, which may be round or irregular. A process of keratosis is involved[8]. These lesion may also extend onto the cornea. Likewise, leukoplakic lesions may appear onto a very diffuse CIN[11]. Extensive leukoplakia should raise suspiction of invasive SCC[8]. CIN may developed simulating a sessile papilloma. The lesion consist in a fleshy red appearance owing numerous fine vascular channels that ramify throughtout the stroma beneath the epithelial surface of the lesion[8]. The presence of displasic epithelial cells helps to the differential diagnosis between papilloma and CIN. In rare occasions papillomas may developed into a CIN. Clinically, CIN appears as a fleshy, sessile, or minimally elevated lesion usually at the limbus in the interpalpebral fissure and less commonly in the forniceal or palpebral conjunctiva. The size of extension may be variable in each case. The presence of redness may simulate an inflammation. Extensive cases consist in a red gelatinous mass with vascular dilatations that may invade superior and nasal bulbar conjunctiva, including the caruncula, inferior conjuctiva and fornix invading tarsal conjunctiva and even corneal extension. Plaques of leukoplakia may also be present[3,11].

Histologic features of OSSN can be classified according to the presence of dysplastic cells originating in the basal cell layers which extend toward the surface. There are various patterns of dysplastic changes, ranging from the small squamous cells with increased nuclear-tocytoplasmic (N/C) ratio, large squamous cells with hyperchromatic nuclei, and spindle cells bearing oval-shaped nuclei. The dysplastic cells contain abnormal nuclei either with nuclear pleomorphism or anisonucleosis. In addition, mitotic figures are increased and gradually pushed upward to the surface along with the degree of dysplasia. Many mitotic figures are abnormal. The cytologic features of OSSN have been reviewed by several authors[1] . Dysplasia: Squamous cells with enlarged nuclei bearing fine to coarse granulation of the nuclear chromatins, irregular nuclear borders, scanty cytoplasm. The background is clean. Carcinoma in situ: Variable numbers of dysplastic cells with an admixture of intact and well preserved malignant cells. They are variable in size with scanty cytoplasm, usually < 1 nuclear diameter in width. The enlarged nuclei displays neoplastic features of hyperchromatism, irregular nuclear membrane thickening, or crusting of nuclear membranes. The other nuclear features include abnormal clearing or condensation of nuclear chromatins and large acidophilic nucleoli. However, background of the smear is clean. Invasive squamous cell carcinoma: Cytologic features of the SCC have been graded into two groups.

- Grade 1-2: Marked cytologic aberration with bizarre malignant cell features including tadpole cells with cytolplasmic tails, fiber or spindle cells, hyperkeratinized cells with opaque refractile red or orange cytoplasm, and malignant nuclei.
- Grade 3-4: Large or small cancer cells with scanty cytoplasm. Nonkeratinized cells maybe partially destructed cells, or complete loss of cytoplasm bearing large to huge pleomorphic nuclei. With deeper invasion and ulceration, tumor "diathesis" background- necrotic tumor cells, debris, blood, and leukocyte exudates are more prominent.

The definitive term of CIN or SCC corresponds to the histologic study (Fig.5). Mild CIN (dysplasia) is characterized by a partial thickness replacement of the surface epithelium by abnormal epithelial cells which lack of normal maturation. Severe CIN (severe dysplasia) is characterized by a nearly full-thickness replacement of the epithelium by similar cells. Carcinoma-in-situ represents full thickness replacement by abnormal epithelial cells [12]. Squamous cell carcinoma is an extension of abnormal epithelial cells through the basement membrane to gain access to the conjunctival stroma and have grown in sheets or cords into the stromal tissue.
The management of CIN or SCC of the conjunctiva varies with the extent or recurrence of the lesion. While the extent of the lesion determines the management of lesions in the limbal area involves alcohol epitheliectomy for the corneal component and partial lamellar scleroconjunctivectomy, with wide margins (4-5 mm) for the conjunctival component followed by freeze-thaw cryotherapy to the remaining adjacent bulbar conjunctiva (The no touch technique) [3]. In some cases, microscopically controlled excision (Mohs surgery) may be performed at the time of surgery to ensure tumor free margins [12]. Those tumors in the forniceal region can be managed by wide local resection and cryotherapy. Following surgical excision, large conjunctival defects may be successfully reconstructed with transpositional conjunctival flaps, free conjunctival grafts, oral mucosal grafts, and amniotic membrane grafts [13]. In all cases, the full conjunctival component along with the underlying Tenon's fascia should be excised using the "no touch technique". A thin lamella of underlying sclera should be removed, in the limbal region, when the tumor is adherent to the globe. Intraoperative mitomycine-C (MMC) application has also been combined with excision of ocular surface neoplasia to prevent postoperative recurrences [14]. However, studies show a 53% recurrence rate in pathologic studies which revealed involved margins and a 5% recurrence rate when clear margins are confirmed [15]. In extensive lesions, surgical excision is difficult, and additional procedures have been employed. Extensive resections in very extensive CIN may produce a limbal stem deficiency [11]. Adjuvant radiation has the potential complications of cataracts, scleral necrosis, corneal rupture, scarring of the cornea and conjunctiva, moderate to severe conjunctivitis, and loss of eyelashes [5]. For those patients with extensive tumors or those tumors that are recurrent, treatment with topical mitomycin C, 5-fluorouracil, or interferon alfa 2b have been employed.

Topical chemotherapy has a number of advantages over surgical approach. It enables to treat the entire ocular surface and is not dependent upon surgical margins. Primary treatment with a chemotherapeutic agent avoids potential complications of surgery, which can include scarring of the conjunctiva and cornea, limbal stem cell failure and incomplete excision of the lesion. Topical chemotherapics may be preferred over surgery by some patients, and when the patient refuse surgery, topical chemotherapics have been successfully used as primary treatment. For tumors with extensive involvement, where surgical removal bears significant risks for postoperative problems, topical MMC should have been considered for a long time. Topical MMC 0.02% or 0.04% 4 times daily in 7 to 14-day for two cycles [3] have been successfully employed for preoperative chemo reduction and to manage recurrent and residual tumors following surgical resection [16] . MMC had been effectively used to treat primary CIN, with reported success rates between 85% [17] and 100% [18]. Tumor regrowth occurred in approximately 17% of cases [19]. To avoid possible complications, the lacrimal punctal occlusion is mandatory during topical treatment. Chemoreduction with MMC cycles reduced the tumor size, especially in the surrounding thinner portions, and allowed for a subsequent limited surgical excision in all cases [20]. Possible complications with topical MMC include superficial punctate epitheliopathy [3], conjunctival hyperemia, pain, allergy, corneal-scleral, melting disturbance of tear film stability, goblet cell loss, squamous metaplasia and limbal stem cells depletion [17,21]. MMC toxicity seems to be dose dependent, occurring with the repetition of treatment cycles.

## II. MATERIALS AND METHODS

Twelve eyes of 12 patients with primary OSSN who presented between December 2014 and October 2015 were included in this study. A detailed history on demographic details, symptoms and its durations, exposure to risk factors were taken. The institutional ethical committee approval was obtained and written consent taken from all patients.

Clinical examination included visual acuity, refraction, anterior segment, evaluation for shape, size, extent, mobility of the lesion, anterior chamber reaction, involvement of cornea, sclera, fluorescein, and 1% rose bengal staining under slit-lamp biomicroscopy, lymphadenopathy to make a clinical diagnosis. Routine

laboratory work up including human immunodeficiency virus (HIV) serology tests was done. Fitness for surgery local anesthesia was obtained in all patients. Inclusion criteria were clinically diagnosed cases of OSSN by slit-lamp bio microscope and OSSN with < 5 clock hour involvement/15 mm in diameter. While exclusion criteria were those which would interfere with the outcome like HIV/acquired immune deficiency syndrome diseases, immune compromised status, xeroderma pigmentosa, and ocular conditions like severe dry eye, limbal stem cell deficiency.

Protocol for the management comprised of surgical excision of the lesion with a 3 mm of healthy rim, using no irrigation and single touch technique, instruments were changed once the tumor was removed, followed by cryotherapy to the cut end of conjunctival under surface for 20 seconds and the cornea and limbus for 10 seconds using double freeze thaw technique.

The ocular surface was left to heal or amniotic membrane grafting was done if the ocular surface defect was bigger than 25 × 25 mm. Specimen sent for histopathological examination. On confirming epithelial healing, topical Mitomycin C 0.04% four times a day to all postoperative patients in 3-4 cycles of alternate on and off weekly courses was advised. Preoperative topical Mitomycin C was instilled in cases of large mass or when surgery had to be postponed on nonmedical grounds. Patients were followed up weekly after the start of treatment protocol and monthly after treatment ended. At each visit, slit-lamp examination with rose bengal 1% and sodium fluorescein 1% drops was performed along with routine examination for recurrence of tumor and corneal alterations like keratitis or erosions. Efficacy of Mitomycin C as an adjuvant therapy was measured in terms of clinical cure and recurrence of the tumor.

## III. RESULTS

Mean age of patients was 42.25 years (range: 24-76 years). A total of 4 of 12 (33%) patients were below 40 years and with male preponderance (75%) (Table 1). A total of 9 of 12 (75%) patients had temporal limbal lesions and 8 patients (67%) had lesion in their left eye. Symptoms at presentation mainly were foreign body sensation followed by mass per eye, redness, injury, burning sensation etc.(Table 2). Duration of symptoms showed 33% presented beyond 6 months. Sunlight exposure was present in nine (75%) patients and four (33%) were smokers (Table 4).

Smallest mass measured 2.2 × 3.1 mm, while the largest was 14.8 × 14.1 mm. Size of the mass was more than 8 mm in diameter or more than 3 clock hours in eight patients (67%). Corneal infiltration was evident in seven (58%) cases. Visual acuity remained stationary/improved in cases where lesion covered the visual axis postsurgery; clinically, OSSN may be leukoplakic lesion (Fig.2) to large cauliflower-surfaced gelatinous lesion. Histopathologically, eight (67%) cases had SCC either with well or moderate differentiation as shown in (Fig.3), with four (33%) having carcinoma in situ (Table 5). Only five (42%) cases showed marginal clearance, while four (33%) had at least one margin showing dysplasia and three (25%) cases had at least two margins showing dysplasia (Table 6). Mean follow-up of 6 months revealed recurrence in two eyes with success rate being 83.3%. A repeat protocol for the recurrent lesion resulted in 100% success.

## IV. FIGURES AND TABLES

**Figure 1: Conjunctival intraepithelial neoplasia (CIN) of left eye presenting as nodular mass over conjunctiva, limbus & cornea (1a) & post surgery image of same patient (1b).**

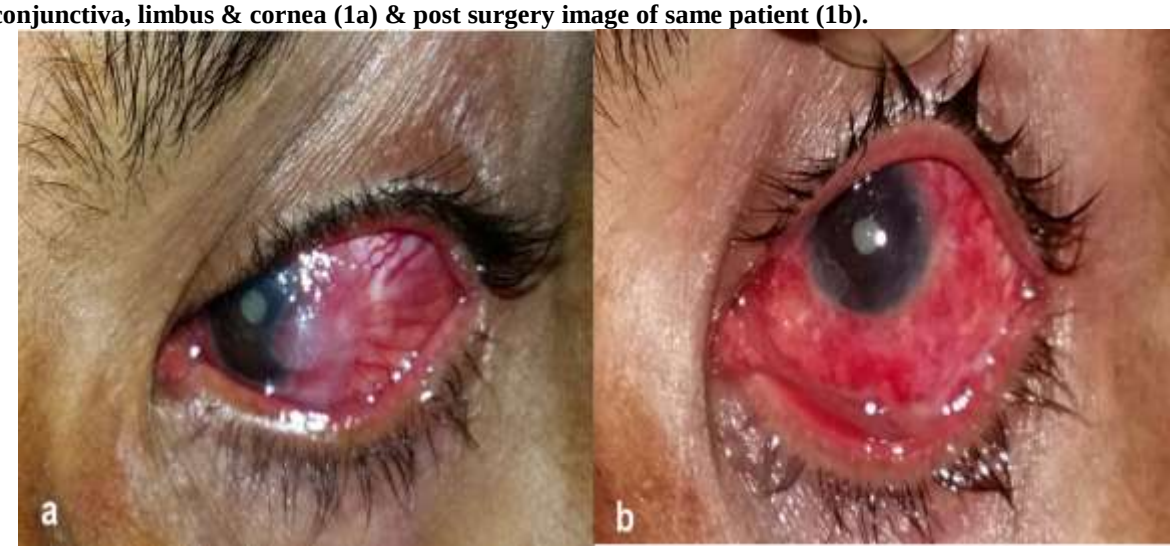

**Figure 2: Leukoplakia occupying conjunctiva & limbus at interpalpebral fissure of left eye of two patients (2a, 2b).**


**Figure 3: Squamous cell carcinoma (SCC) of left eye of patient involving two quadrants of conjunctiva & cornea (3a) & post surgery image of same patient (3b).**

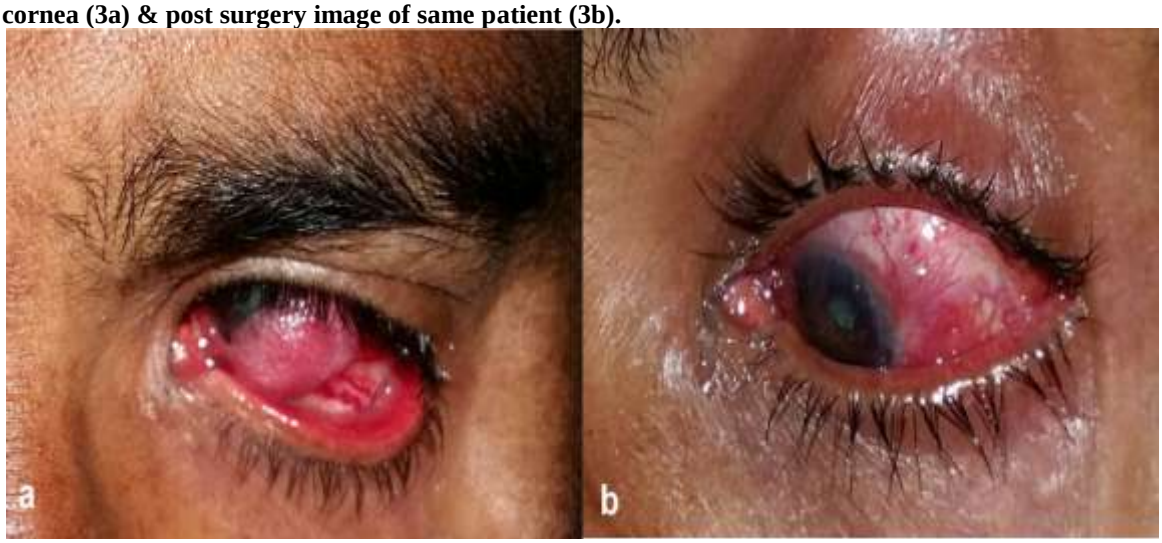


**Figure 4: Invasive Squamous cell carcinoma (SCC) in left eye having cork screw vascular tufts pattern present on mass with feeder vessel.**

**Figure 5: Histopathology slide of Conjunctival intraepithelial neoplasia (CIN) showing hyperplastic squamous epithelium replaced by pleomorphic cell having round over hyper traumatic nuclei & eosinophilic cytoplasm (Circle).**

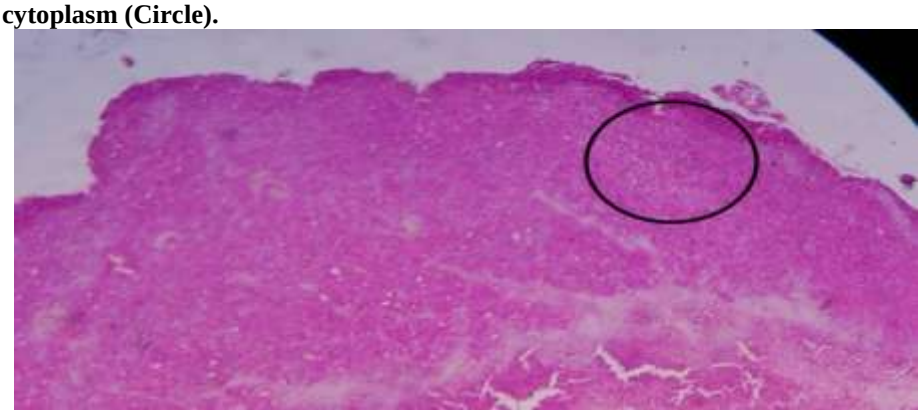

**Table 1: Demographic profile**

| Age in years | No.of patients (%) |
|---|---|
| **20-40** | 4 (33) |
| **41-60** | 5 (42) |
| **61-80** | 3 (25) |
| **Gender** | |
| **Male** | 9 (75) |
| **Female** | 3 (25) |

**Table 2: Symptoms of OSSN**

| Symptoms | No.of patients(%) |
|---|---|
| **Foreign body sensation** | 3 (25) |
| **Foreign body sensation+mass in eye** | 3 (25) |
| **Mass in eye** | 4 (33) |
| **Redness** | 2 (17) |

**Table 3: Duration of presentation in OSSN**

| Duration of symptoms | No.of patients(%) |
|---|---|
| **<2 weeks** | 3 (25) |
| **2 weeks- <2 months** | 2 (17) |
| **2 months - <4 months** | 1 (8) |
| **4months- <6 months** | 2 (17) |
| **>6 months** | 4 (33) |

**Table 4: Risk factors in OSSN**

| Risk factors | No.of patients(%) |
|---|---|
| **Sunlight** | 7 (58) |
| **Sunlight+Smoking** | 2 (17) |
| **Smoking** | 2 (17) |
| **Petroleum products** | 1 (8) |

**Table 5: Histological findings in OSSN**

| Histological types | No.of patients (%) |
|---|---|
| **Carcinoma in situ** | 4 (33) |
| **Well differentiated Squamous cell carcinoma(SCC)** | 2 (17) |
| **Moderately differentiated SCC** | 6 (50) |

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**Table 6: Marginal clearance after surgical excision**

| Margin showing dysplasia | No.of patients(%) |
|---|---|
| **Free margin** | 5 (42) |
| **At least one margin** | 4 (33) |
| **With two margin** | 3 (25) |

## V. DISCUSSION

OSSN is no more a rare entity; we had 12 patients with primary OSSN between December 2014 and October 2015. Mean age at presentation was 42.25 years which is much lesser than that observed in other studies; 64 years (range: 47-87), [22] 69 years (range: 32-94). [23] Most common risk factors were exposure to sunlight and smoking similar to other studies. [24] A total of 50% of eyes had FB sensation as the presenting symptom and 33% presented beyond 6 months, dissimilar to that reported by Prabhasawat *et al*. [25] A total of 67% of patients had larger than 8 mm sized tumors and 58% of them had corneal infiltration (7 of 12 eyes) at presentation. A total of 67% had SCC slightly lesser results to Babar et al's study; [26] these presentations in our study suggested that our patients presented at an advanced stage.

Primary excision has been the mainstay of treatment for OSSN, as it is impossible to exclude invasive disease on clinical grounds or with impression cytology. Excision allows an immediate histopathological diagnosis, surgical debulking, and excludes life-threatening invasive carcinoma. [76] As per Kaines *et al*'s study [28], the disadvantage of primary excision alone is the high recurrence rate which ranges from 15% to 52%.Therefore, numerous adjunctive treatments have been described in an attempt to decrease the rate of recurrence and the efficacy of various adjunctive therapies has been debated.

Despite the effort to excise the tumor with a wide healthy rim, only three cases (25%) had marginal clearance and the rest had residual dysplastic edges, suggestive of multifocal origin of OSSN or macroscopically invisible tumor edges. In such a situation, a repeat surgery to clear residual edges with safety margins would leave not only a large defect in ocular surface but also would lead to limbal stem cell deficiency. [27] Hence, Mitomycin C, an alkylating agent which acts by inhibiting DNA synthesis and produces cell death by apoptosis and necrosis was used. [29] As the drug has a preferential action for rapidly dividing cells, acts as a significant antitumor agent and since 1994, several groups have reported the use of MMC in the treatment of both primary and recurrent OSSN.[30,31]

## VI. CONCLUSION

Surgical excision alone does not suffice in the management of OSSN, so a combined therapy with post operative topical Mitomycin C has synergistic effect and certainly prevent recurrence; more so, when patients presents late and less likely to come for follow-up. Post operative MMC in such cases not only avoids repeat surgery but also can treat the entire ocular surface, destroy subclinical disease, and prevent new tumors arising elsewhere on the ocular surface and, thereby would contribute for a better outcome.However a large scale long term follow up study is needed to be commenced to know the recurrence prevention after MMC use in patients of OSSN. Based on this study, we conclude that Mitomycin C could be an effective adjuvant in the management of OSSN.

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