

## Clinical profile of Ocular Surface Squamous Neoplasia and its surgical outcomes

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### Abstract

**Purpose:** To study the clinical profile of Ocular Surface Squamous Neoplasia and its surgical outcomes.

**Study design:** Retrospective and prospective, observational study

**Results:** We included 36 eyes of 36 patients who histopathologically diagnosed as Ocular Surface Squamous Neoplasia after excisional biopsy. Most of the patients in our study belongs to age group of 41-60 years (mean age 54.31 year for male and 52.4 year for female). Left eye was involved in 61% of patients (p value >0.05). Nasal quadrant was involved most commonly followed by temporal quadrant. Tumor epicentre was located at limbus in most of the patients (44%). Most common symptomatic presentation was mass growth followed by redness. We performed excision followed by cryotherapy and amniotic membrane grafting in more than half of the patients (53%). We achieved marginal clearance in more than 60% cases. Mean follow-up period in our study was 16.86 months. We did not find any recurrence in our study patients during the follow up period.

**Conclusion:** Males and females are equally prone for OSSN. Most of the patients with OSSN belong to 41-60 years age group. Nasal quadrant is most common involved and tumor epicentre most commonly involves limbus. Most common presentation is mass or growth followed by redness and diminution of vision. Carcinoma in situ is most common histopathological diagnosis followed by Dysplasia and Squamous cell carcinoma. Surgical excision and cryotherapy followed by topical Mitomycin C in weekly on and off cycle is associated with best control of primary OSSN with no tumour recurrence.

**Key words:** OSSN, Squamous cell carcinoma, Carcinoma in situ

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### I. Introduction

The term ocular surface squamous neoplasia (OSSN) denotes a spectrum of neoplasm originate from squamous epithelium ranging from simple dysplasia to precancerous lesions and to invasive squamous cell carcinoma (SCC), involving conjunctiva, limbus and cornea.

It is most common ocular surface tumour and third most common oculo-orbital tumour after malignant melanoma and lymphoma in elderly.<sup>1</sup>

OSSN is an uncommon disease usually seen in old age males and residents of lower latitudes closer to equator.

The major risk factors associated with development of OSSN are exposure to ultraviolet rays, human papilloma virus and human immunodeficiency virus. Other less common risk factors are dust exposure, petroleum products, long term use of contact lens and genetic disorders like xeroderma pigmentosum.

OSSN usually present in interpalpebral fissure area. OSSN lesions are slightly elevated and have pearly grey appearance with tufts of vessels, commonly known as sentinel vessels, with or without well defined borders. OSSN is a slow growing tumour of low-grade malignancy, which rarely metastasizes.

Three morphological types of OSSN are described as-

1. Gelatinous 2. Leukoplakic 3. Papilliform

Gelatinous is commonest type and it is again divided into circumscribed, nodular or diffuse variety.

The clinical symptoms are generally nonspecific; vary from asymptomatic to chronic irritation, redness and varying degrees of visual impairment.

It is not possible to distinguish invasive squamous cell carcinoma from intraepithelial lesion or carcinoma in-situ by using clinical features alone. However, an advanced lesion or mass that is immobile and fix to the globe should be suspected as an invasive lesion.

Mucoepidermoid carcinoma and Spindle cell carcinoma are aggressive variants of OSSN, less commonly seen but have tendency to metastasize.

Gold standard for the diagnosis of OSSN is histopathological evaluation after an incision or excision biopsy. The other diagnostic procedures are exfoliative and impression cytology, immunohistochemical analysis, anterior segment OCT and confocal microscopy. Extension of the lesion can be identified by gonioscopy, B-scan ultrasonography, CT scan or MRI.

The treatment of OSSN varies with extent of lesion. The most accepted method of treatment remains complete surgical excision.

The different treatment modalities are:

- (1) Surgical excision
- (2) Cryotherapy
- (3) Radiotherapy
- (4) Topical chemotherapy
- (5) Topical immunotherapy

Depending on size of defect created by excision, defect can either be left to granulate in or closed surgically with or without a flap or graft. If lesion is strongly adherent to sclera at limbus, superficial lamellar keratosclerectomy can be performed.

Aggressive malignant neoplasm of the conjunctiva and cornea occasionally invade the eye or orbit. These advance forms of the disease typically require enucleation or exenteration.

Patients whose tumours are excised completely by histopathological criteria are usually cured. In contrast, patients whose tumours are excised incompletely have a substantial risk of local tumour recurrence.

**Aim of the study** was to find the clinical profile of Ocular Surface Squamous Neoplasia and its surgical outcomes.

## **II. Material & Methods**

It is a study conducted at Sankar Foundation Eye Hospital, Visakhapatnam and Department of Ophthalmology, J L N Medical College, Ajmer India.

All the patients, who report to our centre and diagnosed as ocular surface squamous neoplasia between January 2013 to December 2019, were included in the study. Sample was selected from the target population as per the listed inclusion and exclusion criteria.

This was a retrospective and prospective observational study.

**Sample Size:** In present study all OSSN patients diagnosed histopathologically after surgical excision biopsy done at Sankar Foundation Eye Hospital, Visakhapatnam, India and Department of Ophthalmology, J L N Medical College, Ajmer India during January 2013 to December 2019 were included. After satisfying inclusion criteria, total 36 patients were selected as study participant. Nature and intention of the study was fully explained to the study participants in details before commencement of study and written consent was obtained.

**Study Duration:** Patients satisfying inclusion, exclusion criteria were included in the study which was done from July 2014 to December 2019.

### **Inclusion Criteria:**

- (1) Cases diagnosed clinically and confirmed as ocular surface squamous neoplasia by histopathology.
- (2) Cases that were followed up for  $\geq 1$  year.

### **Exclusion Criteria:**

- (1) Non-consenting patient
- (2) Non-cooperative patient
- (3) Poor general condition
- (4) Single eye patient
- (5) Recurrent case
- (6) Followed up for less than 1 year

## **III. Methodology**

A clearance from the Institutional Research Board of Sankar Foundation Eye Hospital and Institute of Ophthalmology and Department of Ophthalmology, J L N Medical College, Ajmer India was obtained prior to the commencement of the study. A pre designed proforma was used for data recording of all the participants and follow up. Participants were enrolled after prior informed consent. Single eye patients and recurrent OSSN cases were not included.

All patients were thoroughly examined for general and ocular conditions.

Detailed medical history was obtained. The past and present history of Diabetes Mellitus, Hypertension, Collagen Vascular Disease or any other major illness was obtained. Past history of any ocular surgery was obtained. Occupational history especially outdoor activity was obtained. Complete general physical examination was done. Complete 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, 1% rose bengal staining, Gonioscopy under slit-lamp biomicroscopy and funduscopy was done to make a clinical diagnosis.

Complete surgical excision was advised for suspected OSSN cases.

Informed consent was taken from the patient after thoroughly explaining about the patient's eye condition, surgical procedure and its complications and expected prognosis.

General condition of all patients was assessed by qualified physician before surgery. Patients with adverse general conditions were removed from the surgery list.

All the surgeries were done by highly experienced cornea surgeons .

### **Surgical Procedure:**

All patients were given peribulbar anesthesia by the operating surgeon only. Mild digital massage was given followed by scrubbing of lids and lashes with 5% betadine. No pre-operative antibiotics used.

Rose Bengal staining was done to delineate the tumor extent.

Conjunctival incision was made approximately 4mm outside the clinically determined tumor margin. The incision incorporates full thickness conjunctiva and tenon's fascia. Dissection was carried out in the episcleral plane to reach the limbus. In same plane controlled corneal epitheliectomy done.

The entire tumor was removed in one piece without touching the tumor by excising it along the limbus.

Cryotherapy, double freeze-thaw cycle was applied to the edge and underneath the remaining bulbar conjunctival margins. Minimal cryotherapy was applied towards limbal margin.

Depending on size of defect created by excision, defect was left to granulate in or closed surgically with Amniotic membrane graft, conjunctival auto graft or corneal patch graft.

Two sutures were kept at different position of excised tissue and mentioned in histopathology requisition form regarding laterality and location. Excised tissue sent for histopathology in 10% formaline solution.

All histopathology samples were examined by single pathologist. For the purpose of study all slides were again cross checked by another pathologist.

### **Post-Operative Care:**

Medications include Gatifloxacin and Prednisolone combination eye drops 4 times a day for first two weeks followed by 2 times a day for next two weeks.

Tear supplement include Carboxymethyl cellulose 0.5% given for 4 times a day for 3-4 months.

After confirming histopathological diagnosis of OSSN, Topical Mitomycin C started in all patients usually after two weeks of surgery.

MMC 0.04% was prepared and given to patients for four times daily for seven consecutive days followed by seven days off. All patients were advised to shake the eye drop bottle several times before application, to close the eye 5 minute after using the drop and to close the punctum by applying finger pressure for at least 1 minute. Punctal plugs were not used. Patients were asked to return medication bottle after each week of use. The treatment cycle (7 days on MMC and 7 days off) were repeated three times in tumour margins negative cases and four times in HIV and margins positive cases.

Other medications were used as and when required basis.

All patients were followed up post operatively on day 1, 2, 7, 14, then weekly till completion of MMC treatment, then three monthly till six months followed by six monthly reviews.

In all follow up visits, BCVA, IOP were measured; slit lamp biomicroscopy was done for anterior segment and indirect ophthalmoscopy for posterior segment evaluation. Rose Bengal staining was done on each follow up for any recurrence.

Patients were counselled to come for examination and when necessary in between regular schedule if they feel any problem in the operated eye. If any problem noticed in the follow-up period they were addressed promptly by the operated surgeon.

### **Statistical analysis:**

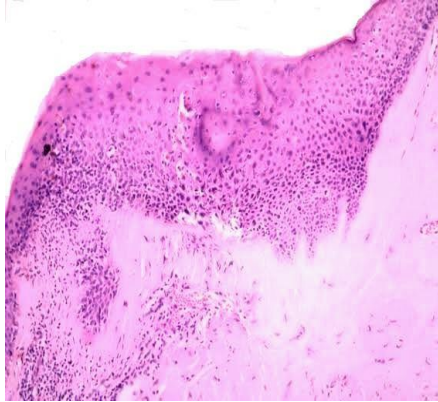
For patients diagnosed in between January 2013 to December 2019, all clinically relevant data was extracted from clinical case records and entered into study performa.

The results were recorded in tabulated form and analysed using spread sheets (Microsoft Excel 2013).

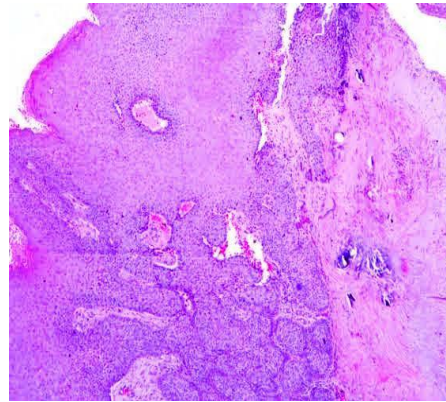
#### **IV. Data Analysis**

Descriptive statistics (mean, standard deviation, and range) are calculated for all important parameters. Mean and standard deviation is calculated for quantitative variables like age. Frequency and percentage is calculated for qualitative variables like gender. Data presentation tools like bar charts, pie charts and cross tabulations are used. Hypothesis are formulated and tested for significance using Z test and Chi-square test. P value of 0.05 or less is considered statistically significant.

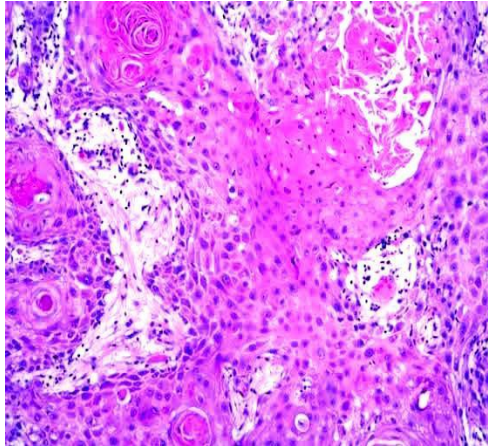
**Figure 1- ossn with dysplasia**



**Figure 2- ossn with carcinoma in situ**



**Figure 3- well differentiated squamous cell carcinoma**



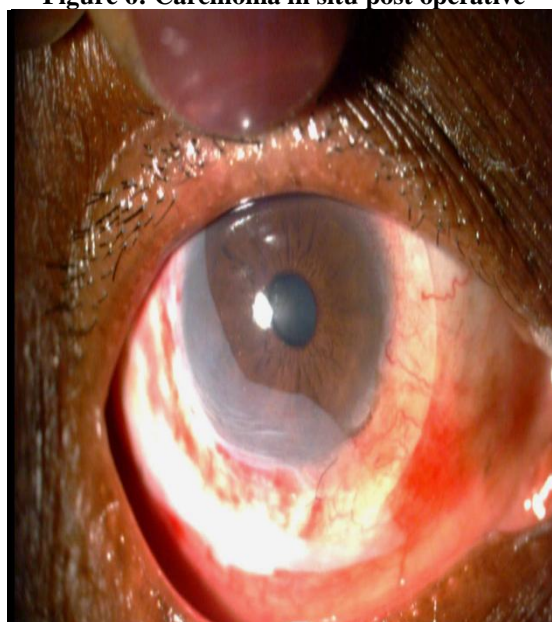
**Figure 4- simple dysplasia**



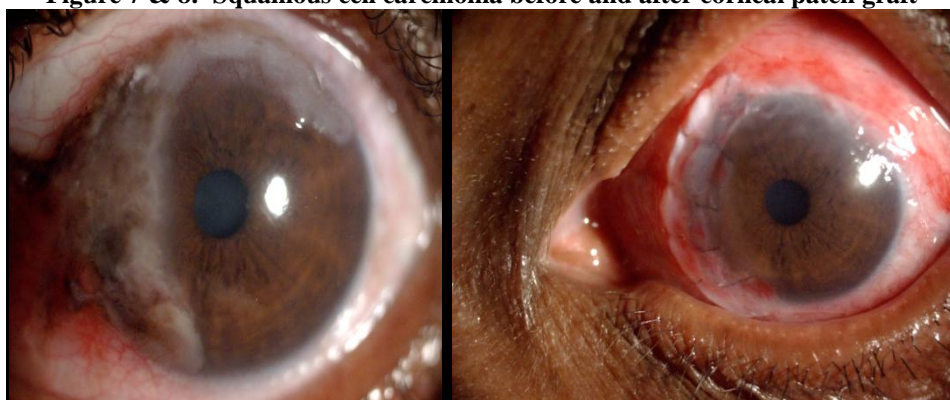
**Figure 5- carcinoma in situ pre op**



**Figure 6: Carcinoma in situ post operative**



**Figure 7 & 8: Squamous cell carcinoma before and after corneal patch graft**



## V. Results

**Table 1: Age distribution and gender**

AGE GROUP (IN YEARS)	MALE	FEMALE
21-40	3	4
41-60	9	12
61-80	4	4
TOTAL	16	20

### Age range

Male - 33-80 Year  
Female - 29-74 Year

### Mean age

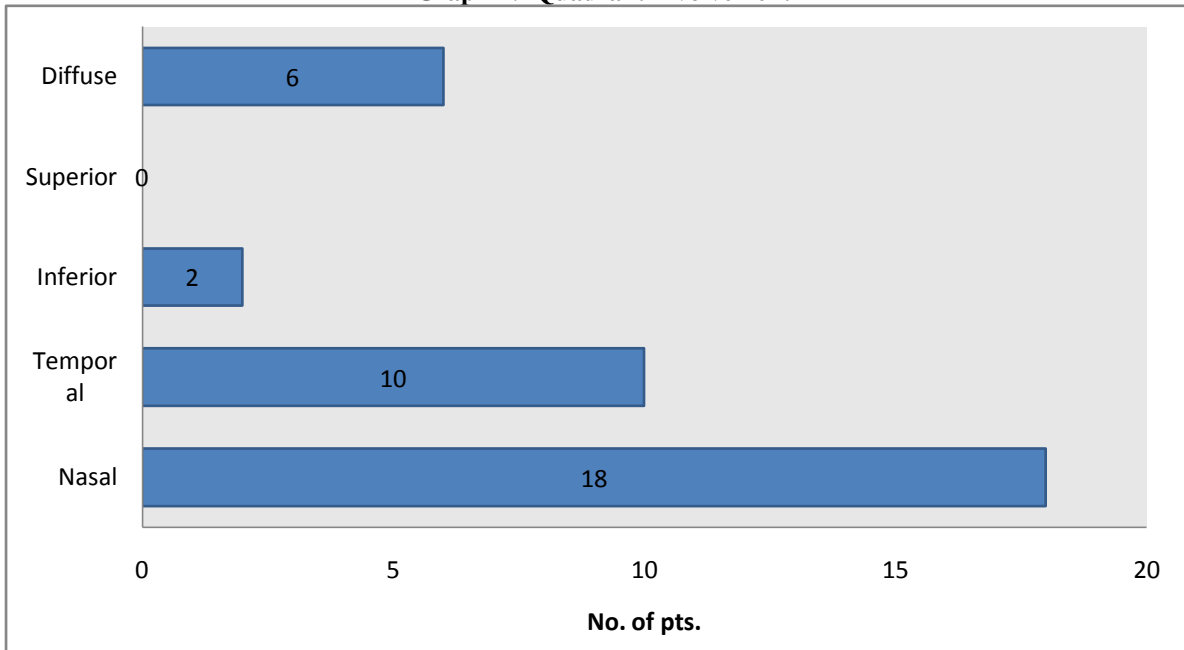
Male- 54.31 Year  
Female - 52.4 Year

**Table 2: Laterality distribution of ossn**

EYE INVOLVED	NO. OF PATIENTS	PERCENTAGE
RIGHT EYE	14	39%
LEFT EYE	22	61%
TOTAL	36	100%

Out of 16 male patients, Right eye was involved in 6 patients and left eye was involved in 10 patients.  
Out of 20 female patients, Right eye was involved in 8 patients and left eye was involved in 12 patients.

**Graph 1: Quadrant involvement**



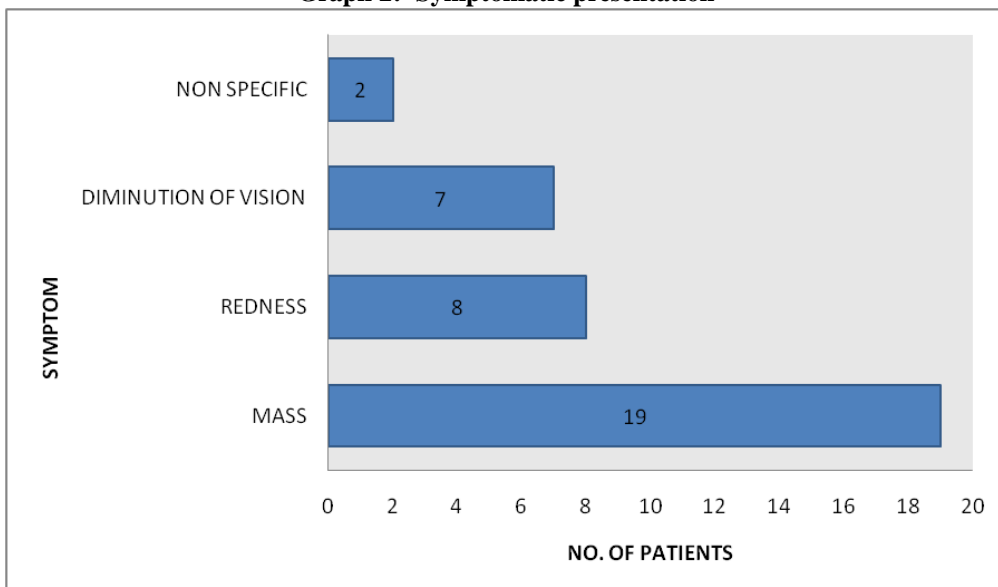
Nasal quadrant was involved in 18 (50%) patients.  
 Temporal and inferior quadrant was involved in 10(28%) and 2 (5%) patients respectively.  
 We did not find any patient with superior quadrant involvement.  
 Among 36 patients 6 (17%) patients had diffuse involvement.

**Table 3: Tumor epicenter location**

EPICENTRE	NO. (%)
LIMBUS	16 (44%)
BULBAR CONJUNCTIVA	8 (22%)
CORNEA	6 (17%)
DIFFUSE	6 (17%)

Tumor epicentre was located at limbus in 16(44%) patients followed by bulbar conjunctiva in 8 (22%) patients we studied.  
 Tumor epicentre was located at cornea in 6(17%) patients, while it was diffuse in 6 (17%) patients.

**Graph 2: Symptomatic presentation**



Most common reported complaint by patients was mass growth. Almost half of the patients (19 out of 36) complained of growing mass.

Second most common complaint was redness (22%) closely followed by diminution of vision (19.5%) of patients we studied.

Two patients had non specific complaints like irritation, watering.

**Table 4: Surgical procedure**

SURGERY	NO. OF PATIENTS	%
EXCISION + CRYOTHERAPY	9	25%
EXCISION + CRYOTHERAPY + AMNIOTIC MEMBRANE GRAFT	19	53%
EXCISION + CRYOTHERAPY + CLAG	5	14%
EXCISION + CRYOTHERAPY + CORNEAL PATCH GRAFT	3	8%

Excision and Cryotherapy was done in all patients.

The defect created by excision was closed by Amniotic membrane graft in 19 (53%) patients, while it was closed with Conjunctivo limbal autograft in 5(14%) patients.

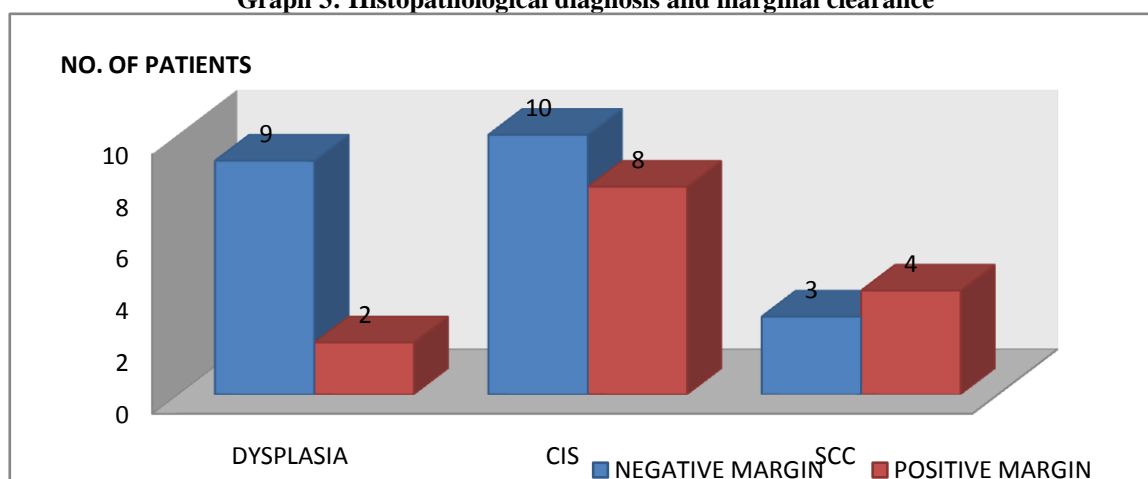
Excision and Cryotherapy alone with no placement of graft, was done in 9 (25%) patients.

Excision, Cryotherapy and Corneal patch placement was done in 3 (8%) patients.

**Table 5: Histopathological diagnosis**

HISTOLOGY	NO. OF PATIENTS	PERCENTAGE %
DYSPLASIA	11	31%
CIS	18	50%
SCC	7	19%
<b>TOTAL</b>	<b>36</b>	<b>100%</b>

**Graph 3: Histopathological diagnosis and marginal clearance**



Out of 11 patients who had dysplasia, 9 patients had surgical margin clearance while 2 patients had positive surgical margins.

Out of 18 patients who had CIS, 10 patients had surgical margin clearance while 8 patients had positive surgical margins.

Out of 7 patients who had SCC, 3 patients had surgical margin clearance while 4 patients had positive surgical margins

**Table 6: Treatment with topical mitomycin-c**

	3 CYCLES OF MMC TREATMENT	4 CYCLES OF MMC TREATMENT
NO. OF PATIENTS	20	16
PERCENTAGE	56%	44%

**Table 7: Follow up and surgical outcome**

PARAMETER	FOLLOW UP (IN MONTHS)
RANGE	12-26
MEAN	16.86
MEDIAN	16
MODE	14
STANDARD DEVIATION	3.65

The follow up period ranged from 12 to 26 months with the mean and standard deviation of 16.86 and 3.65 months, respectively.

The main outcome measures were tumour recurrence and medication related toxicity.

None of the patients in our study reported with any serious side effect due to MMC.

Few patients complained mild to moderate eye redness and irritation that was controlled with lubricants and corticosteroid eye drops.

On each follow up visit Rose Bengal staining was done to look for any recurrence.

We did not find any recurrence in our study patients during the follow up period.

## **VI. Discussion**

The aim of this study was to evaluate demographic patterns, clinical presentations and surgical outcome of OSSN.

According to previous studies, prevalence of OSSN is higher among men than women. In our study we did not find any statistically significant sex preponderance though female patients were slightly outnumbered male patients (56% vs 44%).

Like other studies, in our study also most of the patients belong to 41-60 year age group. Lee and Hirst, in their study found average age of OSSN patients is 56 year<sup>1</sup>. In our study, mean age of patients was 53.25 year and median age of patients was 53.50 year.

Like other studies, in our study also mean age of Dysplasia and CIS patients was less than SCC patients.

OSSN occurred at an earlier age in HIV infected patients and was often more aggressive than immunocompetent patients, as stated by previous studies, we also found early age of onset in HIV patients with mean age of 32 year with less than six month of symptomatic duration.

There are very less literature available regarding laterality and location of OSSN. One case control study done by Saurabh kamal et al. shows no statistically significant laterality involvement.<sup>2</sup> In our study also we did not find any statistically significant relation though left eye was involved slightly more than right eye. In study done by Sheetal Chauhan et al., left eye was involved in 64% of patients.<sup>3</sup>

In same study, Nasal quadrant was most common involved. In our study also 50% of the patients had nasal quadrant involvement.

According to most of the studies, tumour epicentre most commonly involves limbus. In our study also, in 44% patients tumour epicentre was located at limbus.

Most common presenting complaint in our study was mass growth followed by redness and diminution of vision. Duration of symptoms showed in nearly 70% patients presented beyond six month. Various studies done in past supports the same.

Sunlight exposure is an established major risk factor for development of OSSN. In our study also 78% patients had daily exposure of sunlight more than four hours.

Excision biopsy and cryotherapy was performed in all the patients we studied. Histopathologically, CIS was most common followed by Dysplasia and SCC. In our study 50% patients had CIS. Both CIS and Dysplasia patients were included in single group of Conjunctival corneal intraepithelial neoplasia (CCIN). In our study CCIN accounts for almost 80% of the patients.

Study done by Shields et al. found that CCIN accounts for 39% of all premalignant and malignant lesion of conjunctiva.<sup>4</sup> Saurabh Kamal et al also found that CCIN was more common than SCC in controls while SCC was more common in HIV patients.<sup>2</sup> In some other studies, they found SCC was more common than CCIN.

All the patients in our study, after histopathological confirmation of OSSN were given topical MMC (0.04%) eye drops. Surgical margins negative cases were given three cycles of MMC while margins positive and HIV positive cases given one extra cycle of MMC treatment.

The minimum follow up period in our study was 12 months while maximum was 26 month. The mean follow up period was 16.86 month. In this period we did not find any patient with recurrence of OSSN.

Shields et al. also did not find any recurrence in their study in 6-50 months of follow up.<sup>5</sup> Study done by A. Gupta et al. found no recurrence in primary and localised group of OSSN in 5.8- 119.8 months of follow up.<sup>6</sup>

Chen et al. also found no tumour recurrence in 27 cases with a mean follow-up of 27 months.<sup>7</sup>

Study done by Shashikala Puttaswamy et al. found recurrence in one patient with success rate of almost 92% in 40-49 months of follow up period.<sup>8</sup>

Despite all efforts, our study has some inherent limitations as follows:

- Small sample size so may not be truly representative of all OSSN patients.
- Involvement of only primary OSSN patients as study participants, so clinical profile of recurrent OSSN not studied.



- Relatively less follow-up time, so delayed complications and outcome related changes not observed.

## **VII. Conclusion**

Our study is a retrospective and prospective, observational study. It included 36 eyes of 36 patients who histopathologically diagnosed as Ocular Surface Squamous Neoplasia after excisional biopsy. Demographics and clinical presentations of OSSN were studied along with frequency of different histological presentations and their surgical outcome.

### **The following conclusions are drawn from the present study:**

- Males and females are equally prone for OSSN.
- Most of the patients with OSSN belong to 41-60 years age group.
- Nasal quadrant is most common involved and tumor epicentre most commonly involves limbus.
- Most common presentation is mass or growth followed by redness and diminution of vision.
- Carcinoma in situ is most common histopathological diagnosis followed by Dysplasia and Squamous cell carcinoma.
- Surgical excision and cryotherapy followed by topical Mitomycin C in weekly on and off cycle is associated with best control of primary OSSN with no tumour recurrence.

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