Dissertation on

STUDY ON THE ROLE OF MITOMYCIN C IN THE MANAGEMENT OF OCULAR SURFACE SQUAMOUS NEOPLASIA

Submitted in partial fulfilment of requirements of

M.S. OPHTHALMOLOGY

BRANCH - III

REGIONAL INSTITUTE OF OPHTHALMOLOGY

MADRAS MEDICAL COLLEGE

CHENNAI- 600 003

THE TAMILNADU

DR.M.G.R. MEDICAL UNIVERSITY

CHENNAI

APRIL 2015

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI-3

EC Reg No.ECR/270/Inst./TN/2013
Telephone No : 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr. C. Menaka,
Post Graduate,
Regional Institute of Ophthalmology & Government Ophthalmic Hospital,
Madras Medical College,
Chennai – 600003.

Dear Dr. C. Menaka,

The Institutional Ethics Committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled **"Role of Mitomycin C in the management of ocular surface squamous neoplasia"** No.12062014

The following members of Ethics Committee were present in the meeting held on 03.06.2014 conducted at Madras Medical College, Chennai-3.

1.	Dr. C. Rajendran, M.D.	-- Chairperson
2.	Dr. R. Vimala, M.D., Dean, MMC, Ch-3.	-- Deputy Chair Person
3.	Prof. Kalaiselvi, MD., Vice-Principal, MMC, Ch-3	-- Member
4.	Prof. Nandhini, M.D. Inst. of Pharmacology, MMC, Ch-3.	-- Member
5.	Dr. G. Muralidharan, Director Incharge , Inst. of Surgery	-- Member
6.	Prof. Md Ali, MD., DM., Prof & HOD of MGE, MMC, Ch-3.	-- Member
7.	Prof. Ramadevi, Director i/c, Biochemistry, MMC,Ch-3.	-- Member
8.	Prof. Saraswathy, MD., Director, Pathology, MMC, Ch-3.	-- Member
9.	Prof. Tito, Director, i/c. Inst. of Internal Medicine, MMC	-- Member
10.	Thiru. Rameshkumar, Administrative Officer	-- Lay Person
11.	Thiru. S. Govindasamy, BABL, High Court, Chennai-1.	-- Lawyer
12.	Tmt. Arnold Saulina, MA MSW	-- Social Scientist

We approve the proposal to be conducted in its presented form.

Sd/Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

Member Secretary, Ethics Committee

CERTIFICATE

This is to certify that this dissertation entitled **"STUDY ON THE ROLE OF MITOMYCIN C IN THE MANAGEMENT OF OCULAR SURFACE SQUAMOUS NEOPLASIA"** is a bonafide record of the research work done by **Dr. C.MENAKA,** post graduate in Regional Institute of Ophthalmology and Government Ophthalmic Hospital, Madras Medical College and Government General Hospital, Chennai-03, in partial fulfilment of the regulations laid down by The Tamil Nadu Dr.M.G.R. Medical University for the award of M.S. Ophthalmology Branch III, under my guidance and supervision during the academic years 2012-2015.

PROF. Dr.M.ANANDABABU M.S.,DO
Chief
Department of Squint & Neuroophthalmology
Regional Institute of ophthalmology&
Government ophthalmic hospital
Madras medical college
Chennai – 03

PROF.Dr.K.NAMITHA BHUVANESWARI,MS.,DO.
Director and Superintendent
Regional Institute of ophthalmology&
Government ophthalmic hospital
Madras medical college
Chennai-03

PROF. Dr. R.VIMALA, M.D
Dean,
Madras Medical College.
and Government General Hospital
Chennai –03

ACKNOWLEDGEMENT

I express my sincere thanks and gratitude to **Prof. Dr.R.VIMALA, M.D,** Dean, Madras Medical College and Government General Hospital for permitting me to conduct this study.

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I express my profound gratitude to **Prof.Dr.M.ANANDA BABU, M.S., DO.,** my unit chief and my guide for his valuable guidance and constant support at every stage throughout the period of this study.

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I wish to express my sincere thanks to all the professors, assistant professors and all my colleagues who had helped me in bringing out this study.

Finally, I am indebted to all the patients for their sincere co-operation for the completion of this study.

DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation entitled "**STUDY ON THE ROLE OF MITOMYCIN C IN THE MANAGEMENT OF OCULAR SURFACE SQUAMOUS NEOPLASIA"** is a bonafide and genuine research work carried out by me under the guidance of **PROF.DR.M.ANANDA BABU.**

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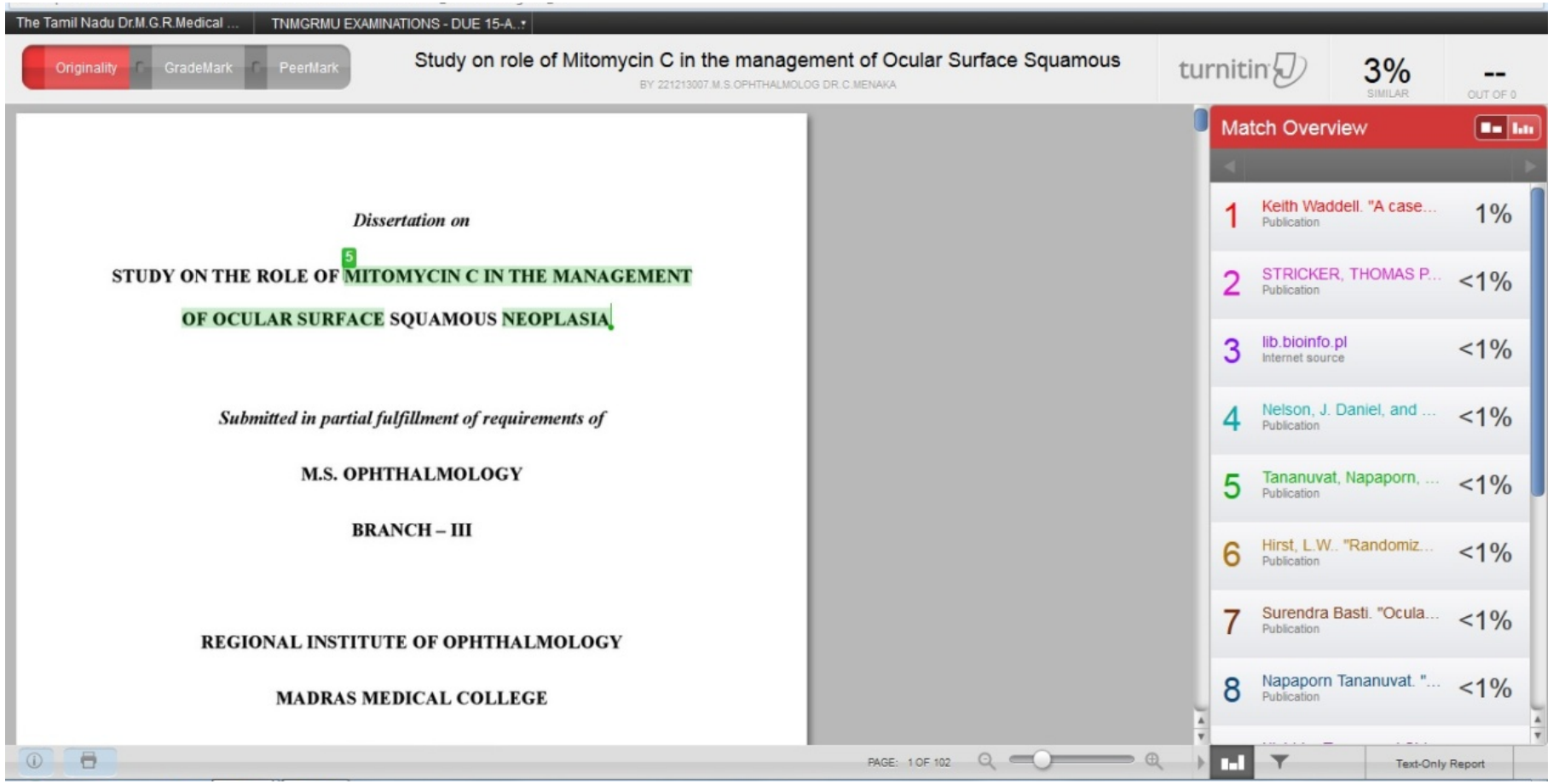
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ABBREVIATIONS

OSSN	-	OCULAR SURFACE SQUAMOUS NEOPLASIA
MMC	-	MITOMYCIN C
5 –FU	-	5 FLUOROURACIL
IFN α2b	-	INTERFERON α 2b
SCC	-	SQUAMOUS CELL CARCINOMA
IC	-	IMPRESSION CYTOLOGY
CCIN	-	CONJUNCTIVAL-CORNEAL INTRAEPITHELIAL NEOPLASIA

PART 1

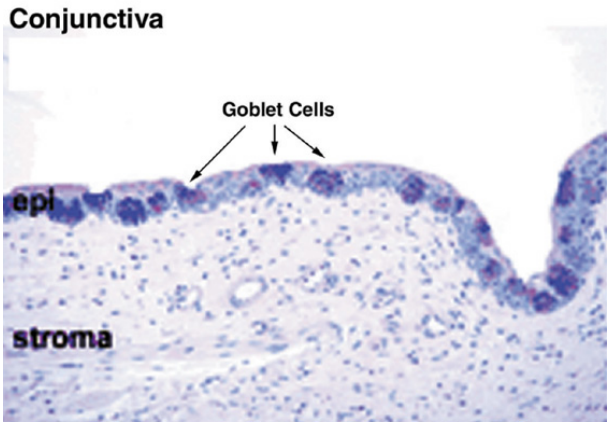
ANATOMY

Ocular surface comprises of cornea, conjunctiva and limbus. The conjunctiva extends from mucocutaneous junction of the lids to the limbus . It can be divided into 3 geographic zones: palpebral, fornical, and bulbar .

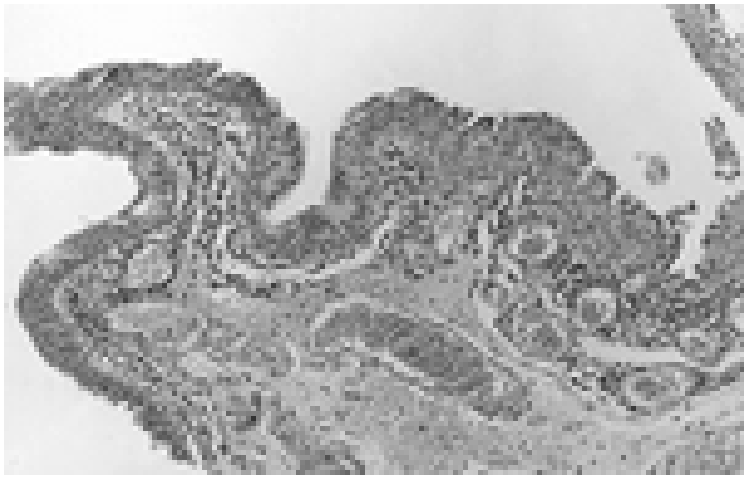
“The *palpebral conjunctiva* starts at the mucocutaneous junction of the eyelid and it covers the inner surface eyelid. This part of conjunctiva attaches firmly to the tarsus”.

“The delicate *bulbar conjunctiva* is freely movable over the globe but fused with the Tenon’s capsule and gets inserted into the limbus”.

“The conjunctival tissue becomes superfluous and freely movable in the fornices *(forniceal conjunctiva)*, where it gets enmeshed with the fibrous elements of levator aponeurosis and Muller’s muscle of the upper eyelid. And in the lower eyelid fibrous extensions of the inferior rectus muscle fuse with the inferior tarsal muscle”.

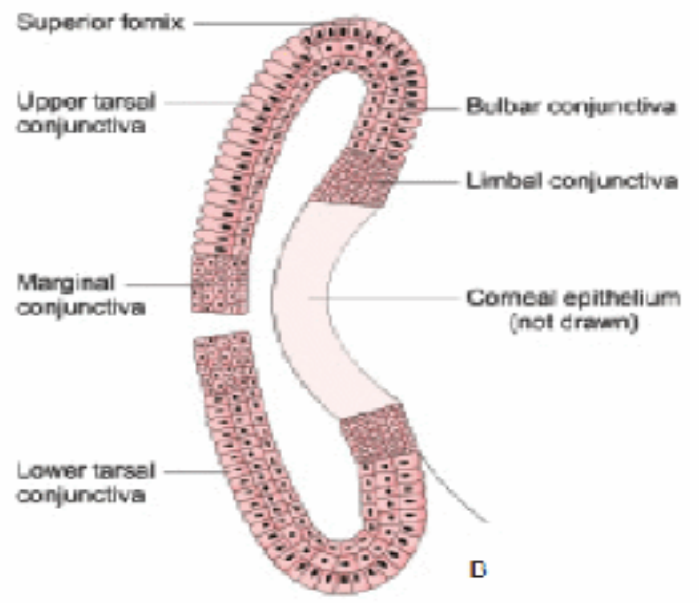


The conjunctiva is a mucous membrane lined with non keratinizing squamous epithelium with numerous goblet cells and a thin highly vascularized substantia propria containing lymphatic vessels, plasma cells, macrophages and mast cells. A lymphoid layer extends from the bulbar portion of conjunctiva to the sub tarsal folds of the eyelids. In places specialized aggregations of *conjunctiva-associated lymphoid tissue (CALT)* corresponding to the *mucosa associated lymphoid tissue (MALT)* elsewhere and contains collections of T and B lymphocytes lying underneath a modified epithelium. These regions are supposed to be concerned with antigen processing.



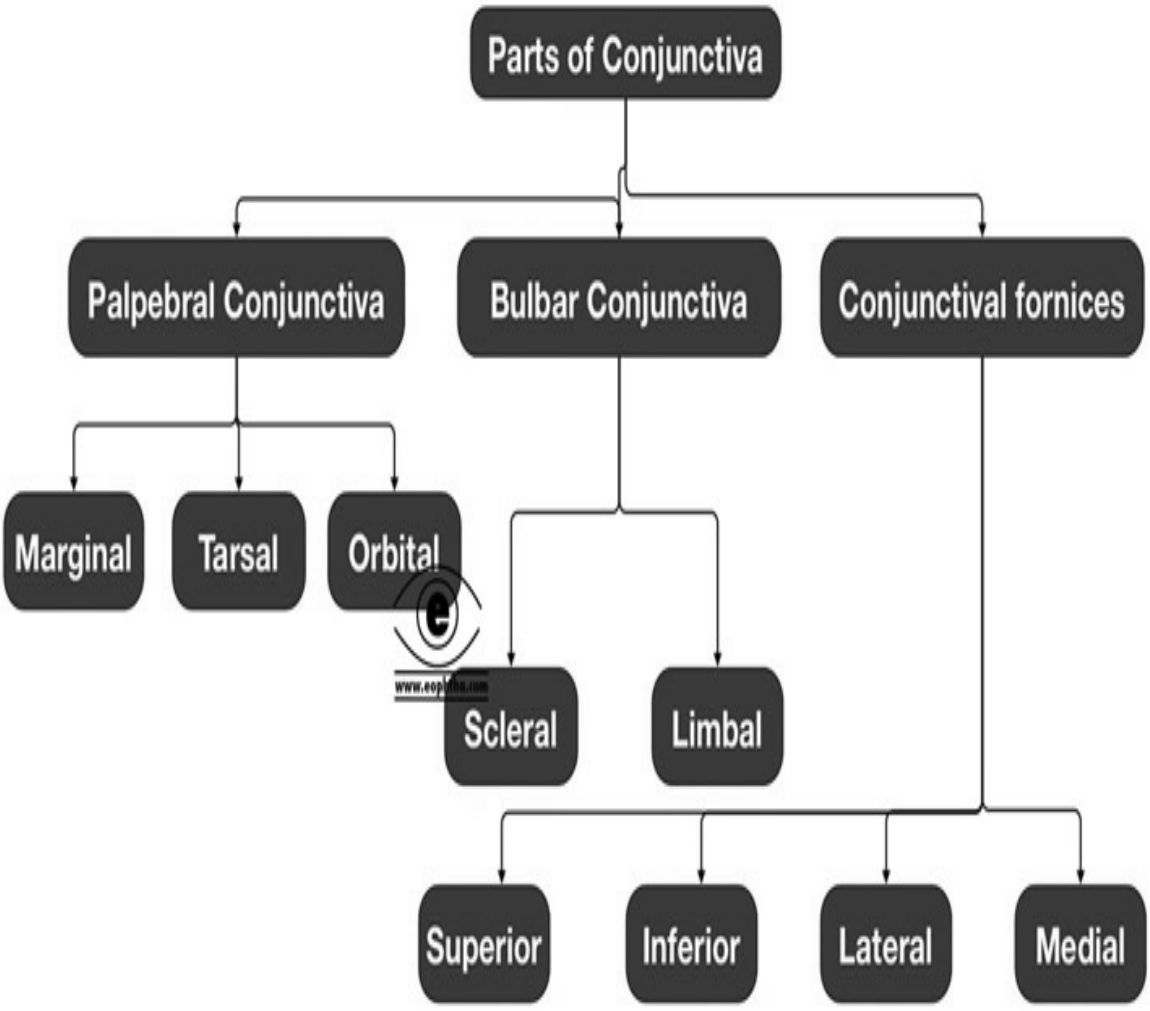
Stratified nonkeratinizing squamous epithelium with goblet cells covers a vascular lamina propria

The thickness of the conjunctival epithelium varies from 2 to 5 cells size. The basal cells of the conjunctival epithelium are cuboidal and progress into flattened polyhedral cells as they reach the conjunctival surface. Goblet cells (unicellular mucous glands) are seen concentrated near the inferior and medial portions of the conjunctiva, especially in the region of the plica semilunaris and caruncle. Goblet cells are sparsely distributed throughout the remaining portion of the conjunctiva and are absent in the limbal region.



The conjunctiva reflects on three sides to form a fornix. Medially plica semilunaris is situated. The loose conjunctiva in this area allows for free movement of the eyelids and the eyeball. Conjunctival folds decrease the surface area of contact, increasing its surface area, and decrease contact between the tarsal and bulbar conjunctiva.

PARTS OF CONJUNCTIVA



Superior fornix being larger and is formed by smooth muscle strips extending from the lower part of levator palpebrae muscle to get inserted into the conjunctiva. Thus during upward gaze it prevents the superior fornix of conjunctiva from moving down and obscuring vision.

"Temporal conjunctiva gets attached to lateral rectus tendon by fine fibrous strips which maintains its position during horizontal gaze. Except in adduction there is no true fornix medially. Fibrous strips from the tendon of medial rectus get inserted into the caruncle and plica semilunaris. When medial rectus contracts during adduction of eye, a cul-de-sac is formed medially when these slips contracts". The surface area of each eye of adult conjunctiva including cornea averages about 16 cm^2.

"Plica semilunaris is a semi lunar- shaped fold of conjunctiva whose outer border lies 3–6 mm lateral to conjunctival caruncle. A cul-de-sac of 3 mm depth is formed on adduction that obliterate when the eye abduct. Goblet cells are found in conjunctival epithelium, it also consists of langerhans cells, dendritic melanocytes".

"The substantia propria is a highly vascular structure and it may contain smooth muscle fibres, sympathetic nerves, fatty tissue, and cartilage".

In the interpalpebral fissure caruncle is located medially measures horizontally 4 mm and 3mm vertically. It is joined to the medial rectus muscle and goes along with plica while moving the eyeball. It is contains accessory lacrimal gland , pilosebaceous units, eccrine glands and few non striated muscle fibres. Sometimes in the deeper portion of the caruncle lots of large sebaceous glands may be noted like meibomian glands.

“In the mucocutaneous junction of the lid margin epithelium changes from keratinized stratified squamous epithelium to the non keratinized stratified squamous epithelium”.

“Meibomian glands appears as yellow round forms that are secluded by blood vessel arches of tarsal plate of the upper and lower eyelids running perpendicular to the lid margin”.

Hydrophobic strip of lipid seperates the nonkeratinized portion of the lid from keratinized part. These lipids are produced by the meibomian glands lying over mucocutaneous junction.

Position of mucocutaneous junction is determined by tear film meniscus air–fluid border . “The mucocutaneous junction will move anteriorly in case of entropion and the mucocutaneous junction will move posteriorly in case of ectropion” .

The anterior corneal surface have a smooth surface due to tarsal conjunctiva being strongly attached to tarsal plate. Subconjunctival tissue plane is not available for dissection in the tarsal conjunctiva. A shallow subtarsal groove is present posterior to the lid margin along the tarsal surface which is less than 1-mm in depth.

“In this region the nonkeratinized squamous epithelium of lid margin get transformed into cuboidal epithelium of the tarsal part of conjunctiva”

In between tarsal groove and eyelid margin there are many grooves and ridges which communicates to the invagination surfaced with goblet cells of the conjunctiva. Few of these crypts are seen since childhood and many of them develops at the time of puberty. “Above the age of 50 years these crypts are identified in about one-third of conjunctival specimens. Crypts are usually more in number closer to the medial portion of the conjunctiva and in the region of plica semilunaris”.

“Glands of wolfring is seen in the palpebral conjunctiva and Glands of Krause is found in forniceal conjunctiva ”.

Bulbar conjunctiva receives blood supply from the Anterior ciliary arteries. The tarsal conjunctiva receives blood supply from the branches of the marginal arcades of the eyelids. The proximal arterial arcade running along the upper border of the eyelid as the posterior conjunctival arteries, send branches proximally to supply the fornical and then the bulbar conjunctiva.

The Limbus receives blood supply from the ciliary arteries through the anterior conjunctival arteries. Vascular watershed between the anterior and posterior vascular territories lies approximately 3 or 4 mm from the limbus.

The innervation of the conjunctiva is derived from the ophthalmic division of Trigeminal nerve.

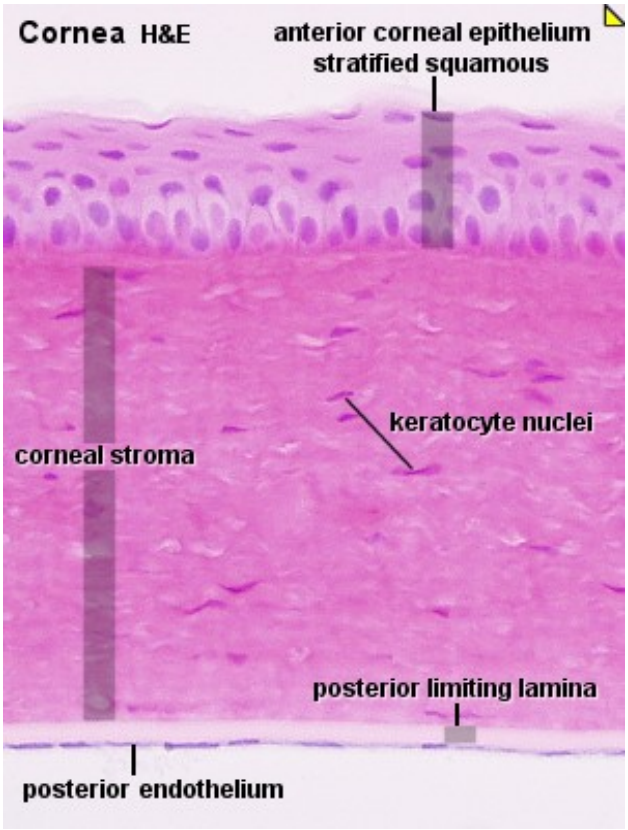
CORNEA

Cornea is a transparent avascular watch glass like structure which is lined by stratified squamous epithelial cells which is about 50-90µm in thickness and contains 5-6 layers of cells.

Limbal basal layer contains corneal epithelial stem cells. The corneal epithelial stem cells proliferate continuously to form the superficial layer and it changes to form superficial cells.

The air- tear interface at the surface of cornea forms a positive lens of approximately 43 diopters (D) and constitutes the main refractive factor of the eye. The central third of the cornea measures about 4 mm in diameter in the normal eye and is nearly spherical. As the posterior surface of the cornea is more curved than the anterior surface, the central cornea is much thinner (0.5 mm) than the peripheral cornea (1.0 mm).

The cornea gets flatter near the periphery but the rate of flattening is not symmetrical. Corneal flattening is more widespread nasally and superiorly than temporally and inferiorly. This topography is more important when fitting a contact lens.



The anterior surface of cornea is derived from surface ectoderm and is lined by nonkeratinising stratified squamous epithelium whose basal columnar layer by hemidesmosomes gets attached to a basal lamina. The basal cells of cornea have a width of about 12 µm and a density of approximately 6000 cells/mm2.

Improper formation of hemidesmosomes after an epithelial abrasion may contribute to the occasional recurrence of corneal erosion following a traumatic corneal abrasion. 2 or 3 layers of polygonal "wing" cells overlie the basal cell layer.

The superficial corneal epithelial cells are extremely thin (30 µm) and get binds to one another by zonules. These zonules give the properties of a semipermeable membrane to the corneal epithelium. Microvilli and Microplicae makes the superficial surfaces of the wing cells highly irregular, but the precorneal tear film makes the corneal surface optically smooth.

Although the deeper epithelial cells are strongly attached to one another by desmosomes, they migrate constantly from the basal region towards the tear film, where they are shed. They also migrate from their stem cell source at the limbus centripetally.

Diffuse damage to the limbal stem cells (chemical burns, trachoma) leads to chronic epithelial surface defects. Division of the slow-cycling stem cells at the limbus gives rise to a progeny of daughter cells (transient amplifying cells), whose division helps to maintain the integrity corneal epithelium.

LIMBUS

Limbus is the transition zone between the peripheral cornea and the anterior sclera. Though it is not a distinct anatomical structure, the limbus is important for two reasons:

1) Its relationship to the chamber angle and

2) It acts as a surgical landmark.

The following structures are included in the limbus:

- Conjunctiva and limbal palisades
- Corneoscleral stroma
- Tenon capsule
- Episclera
- Aqueous outflow apparatus

The transition from opaque sclera to clear cornea is difficult to define histologically and it occurs gradually over 1.0-1.5 mm area. The

sclerocorneal junction begins centrally in a plane linking the end of Bowman's layer and the Schwalbe’s line. Internally posterior limit of sclerocorneal junction is the anterior tip of the scleral spur. The surgical limbus can be divided conceptually into 2 equal zones:

I) Anterior bluish gray zone lying over clear cornea extending from Bowman's layer to the Schwalbe’s line

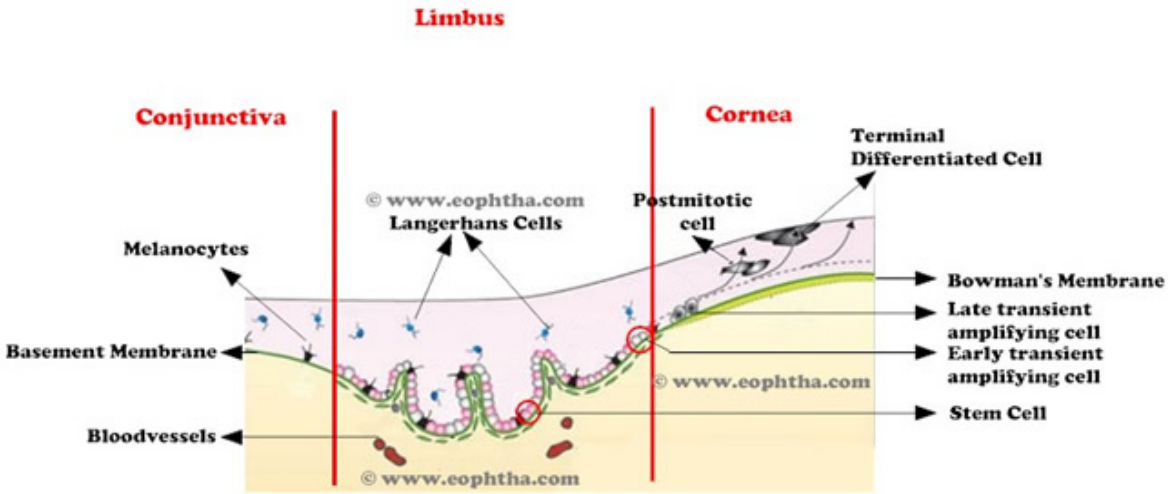
2) A posterior white zone lying over the trabecular meshwork, extending from the Schwalbe’s line to the scleral spur or iris root.

Familiarity with these landmarks is important to the surgeon performing cataract surgery or a glaucoma- filtering operation.

INTRODUCTION

"In 1995 LEE and HIRST first coined the word Ocular Surface Squamous Neoplasia (OSSN)".

It consists of a spectrum of neoplasm that originates from the conjunctival limbal stem cells and extends beyond the limbus to involve the adjacent cornea and conjunctiva, varies from "simple dysplasia to more invasive squamous cell carcinoma". Ocular Surface Squamous Neoplasia is a localised slow growing neoplasm which has a low metastatic potential but invasive type of lesion can locally invades into the eyeball and the orbital cavity. Death results if the invasive tumour goes untreated. Ocular Surface Squamous Neoplasia has a high recurrence rate even following management.



OSSN is a rare ocular tumour, first most common being melanoma and second common being lymphoma and OSSN comes after these two tumours. Prevalence of OSSN is more near the equator and possibly related to sunlight exposure. Prevalence is more common in males and Caucasian race. It occurs most commonly in the age group of 50-60 years, but also more common in patients lesser than 50 years of age living close to equator.

ETIOLOGIC FACTORS

1. Ultraviolet irradiation
2. HPV infection.

The above two being the most common cause

OTHER RISK FACTORS

1. HIV positivity,
2. Immunosuppression,
3. Old age,
4. Male sex,
5. Fair skin,
6. Smoking,
7. Exposure to petroleum products,
8. Vitamin A deficiency,
9. Exposure to chemicals such as trifluridine and arsenicals,
10. Xeroderma pigmentosum,
11. European ancestry,
12. Long standing use of ocular prosthesis and contact lens wear.
13. Exposure to dust,
14. Ocular trauma
15. Pinguecula

16. Pterygium
17. Solar keratosis.

UV-B RADIATION

Evidence from epidemiological studies have showed that the incidence of OSSN was found to be increased in population living in proximity to the equator due to increased exposure to solar UV radiation.

For each 10 degree rise in latitude the occurrence of carcinoma decreases by 40-50%. Limbus being the most common area for development of tumour as the inter palpebral area is highly exposed to sunlight. Dysplasias are more common in limbus as the squamous and columnar epithelium meets at the limbus.

Risk for developing OSSN depends on the intensity of exposure, type of UV rays, total cumulative exposure and the magnitude of the light-absorbing ‘‘protective mantle’’ of melanin. “The UV portion of the solar spectrum can be subdivided into three wavelength ranges: UVA (320–400 nm), UVB (280–320 nm), and UVC (200– 280 nm)”. Of these three forms UVB is believed to be responsible for inducing various cutaneous and ocular surface malignancies.

Exposure to UVB light causes

1) Formation of pyrimidine dimers in DNA.

2) Damage to the nucleotide excision repair pathway (which plays an important role in repairing the DNA damage caused by UV-B exposure).
3) Unrepaired alterations in the DNA are the essential step in the process of initiation of malignant transformation.
4) UV radiation is known to cause mutations in tumour suppressor genes like p53

These alterations become heritable once these altered and injured DNA undergoes a cycle of proliferation, this stimulus to the proliferation could be provided by the UV rays themselves or by virus such as HPV or some chemical stimulus. An altered pattern of expression of MMP-1 and MMP-3, following ultraviolet B radiation is responsible for the development of OSSN in a study published in 2008 regarding the role of matrix metalloproteinases (MMP) and tissue inhibitors of matrix metalloproteinases in the development of OSSN (Ng et al. 2008)

HUMAN PAPILLOMA VIRUS:

The reason for the development of OSSN in those affected with HPV is not clear. About 50% of the squamous cell carcinoma of the cornea, conjunctiva, limbus and lacrimal sac were linked to the infection with Human papilloma virus (Nakamura et al. 1997).

"HPV 16 & 18 DNA were demonstrated in high grade OSSN and invasive type of OSSN (Verma et al. 2008, Sjo et al. 2007)". HPV 6 & 11 were found to be associated with the causation of conjunctival papilloma (Nakamura et al. 1997). It is stated that additional risk factor like exposure to ultra violet irradiation is needed for the causation of tumour.

"One study found out the DNA of Human Papilloma Virus 16, 18 and mRNA of Human Papilloma Virus noted in *E6* region, and it denotes the transcribed form of viruses from the samples of patients with CCIN by using the Polymerase Chain Reaction method (Scott et al. 2002)".

HUMAN IMMUNODEFICIENCY VIRUS:

At present OSSN is considered as an HIV associated malignancy. In Africa following a huge pandemic of HIV infection there is an increase in the number of cases of OSSN. A case control study to demonstrate the relationship of conjunctival squamous cell carcinoma and HIV infection demonstrated a 10 fold increased risk in HIV infected individuals in Uganda (Waddell et al. 1996). The risk was found to be highest in patients with age $\geq$ 50 years and in those who are exposed to high ultraviolet irradiation.

In those infected with HIV infection the disease is more aggressive and also seen in younger age group requiring enucleation or even

exenteration (Newton et al. 2002). “OSSN specimens from HIV infected individuals showed multiple oncogenic viruses like HPV, KSHV, EBV suggesting these viruses may also responsible for the occurance OSSN (Simbiri et al. 2010)”. Several studies reported that OSSN considered is as the first clinical presentation of HIV in younger patients.

IMMONOSUPPRESSION

Those who undergo corneal grafting the development Ocular Surface Squamous Neoplasia is related to local immunosuppression. “Human Papilloma Virus or neoplastic cells from the donor’s corneal epithelial cells may leads to the development of OSSN if they are present in the graft (Ramasubramanian et al. 2010)”.

XERODERMA PIGMENTOSUM

Xeroderma pigmentosum (XP) is an autosomal recessive disorder, with defective mechanism of DNA repair. It can predispose to Ocular Surface Squamous Neoplasia and other cutaneous and mucosal cancers with an aggressive presentation even at a younger age. A patient of Xeroderma Pigmentosum was reported to have OSSN as early as 3 years of age. In a study conducted at National Eye Institute with 87 participants having Xeroderma Pigmentosum ,10% of the patients in age range 5–28 years with Xeroderma Pigmentosum had ocular surface cancers.

OTHER RISK FACTORS

Ocular injury and exposure to dust particals were also implicated as a possible risk factors in the development Ocular Surface Squamous Neoplasia, but there are only few reports supporting this fact based on few case studies. There is an increased risk associated with a report of prior trauma to the affected eye; which was first established in an observational study. As the precise nature of the previous eye injury was not available it was relevant only in about 8% of cases.

"In 1979 Clear et al. analysed 234 conjunctival biopsies and identified that pinguecula, solar keratosis and pterygium represents a continuous spectrum of the same pathological event finally leading to carcinomatous change".

Evidence relating to the nature of the association between exposure to solar UV and development of pinguecula and to a lesser extent pterygium is relatively sparse.

"In around 98% of cases having clinically identified pinguecula in the contra-lateral eye developed OSSN thus stating the association between the presence of pinguecula and risk of OSSN". But in those with pterygium development of OSSN was relatively rare in both cases and controls and thus revealing that there is no association between pterygium and OSSN.

CLINICAL MANIFESTATIONS

Primary tumours of the cornea and conjunctiva can be classified into two groups: congenital tumours and acquired tumours. Tumours arising from squamous epithelial cells, melanocytes & lymphocytes are included under the group of acquired lesions.

Ocular Surface Squamous Neoplasia are classified into

"Benign type contains lesions like conjunctival Papilloma, Pseudoepitheliomatous hyperplasia and hereditary intraepithelial dyskeratosis".

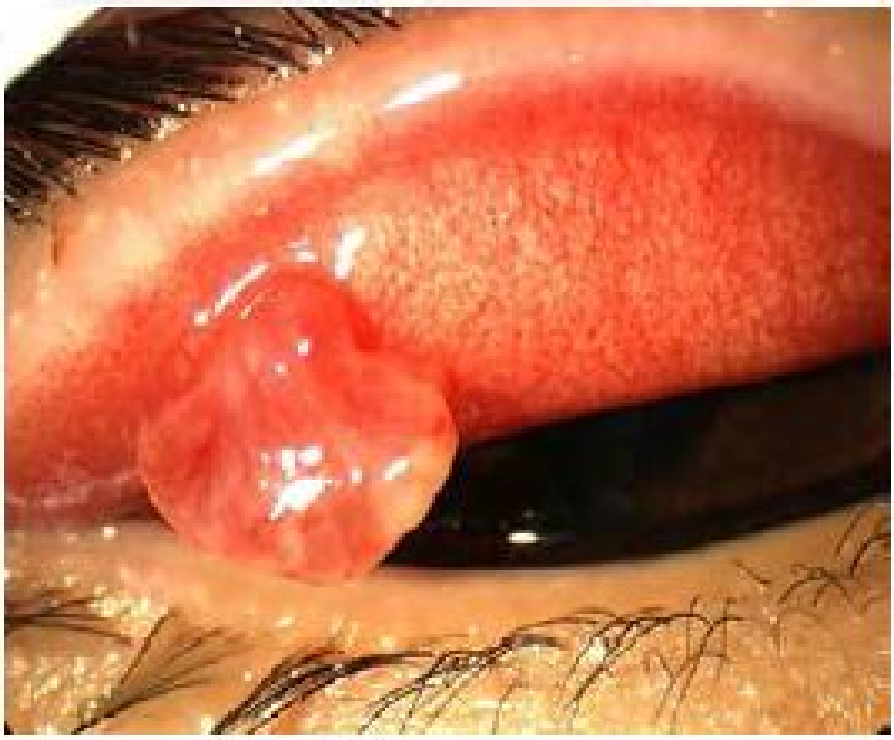
Preinvasive- in this the lesions are limited to the epithelium which can be classified as mild CCIN, Moderate CCIN, Severe CCIN

Squamous cell carcinoma comes under invasive type of Ocular Surface Squamous Neoplasia in which the epithelial basement membrane is breached by tumour cells.

Another aggressive variant of OSSN is Mucoepidermoid carcinoma.

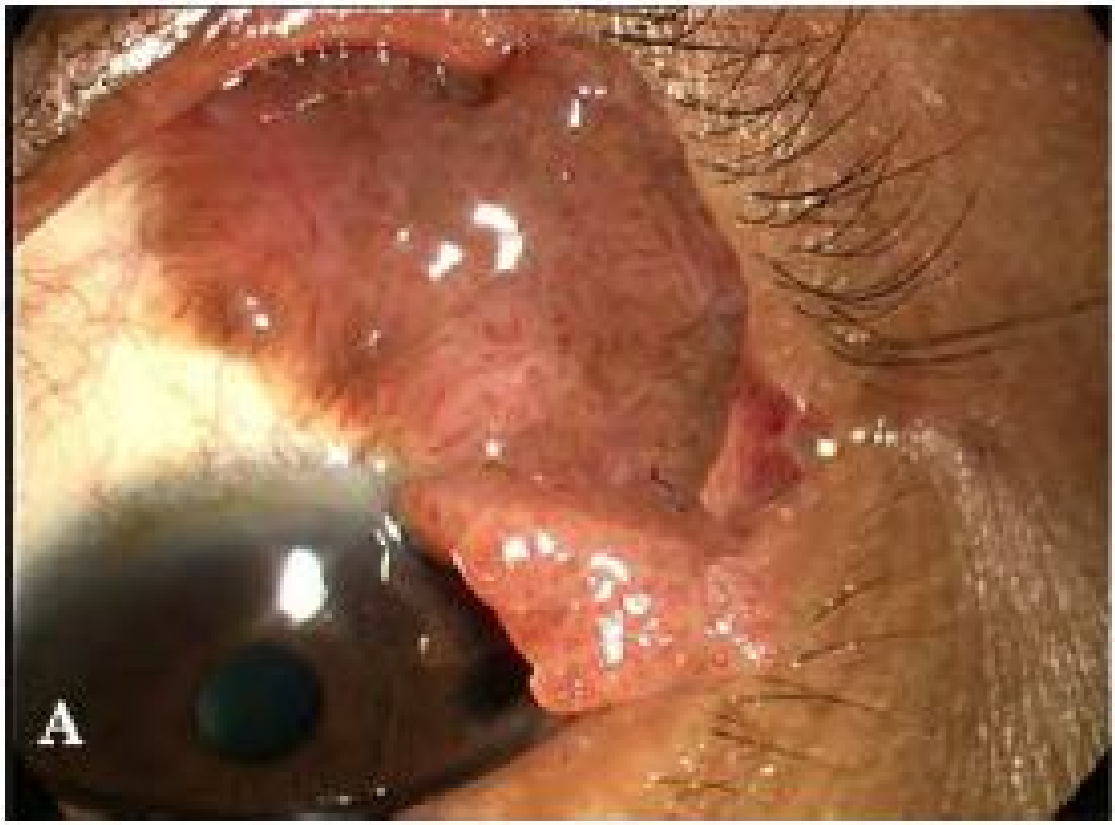
CONJUNCTIVAL PAPILLOMA

Conjunctival papilloma can be divided into sessile, pedunculated type . Pedunculated form contains a stalk which is formed by a fibro vascular core. It is associated with HPV 6 & 11infection and is most commonly seen in children and most common site of origin is inferior fornix. It may regress spontaneously.



PEDUNCULATED CONJUNCTIVAL PAPILLOMA

Sessile papillomas are usually found near the coneoscleral junction there is no stalk in this type. It is related to HPV 16 & 18 infection. This type is more common adults and there are more chances for dysplastic change to take place.



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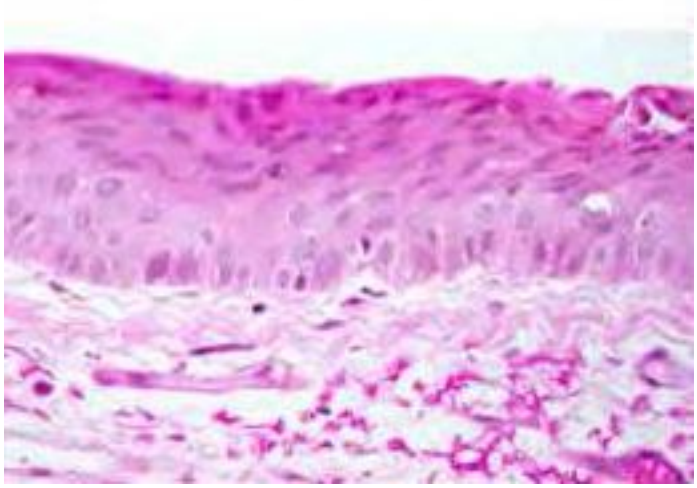
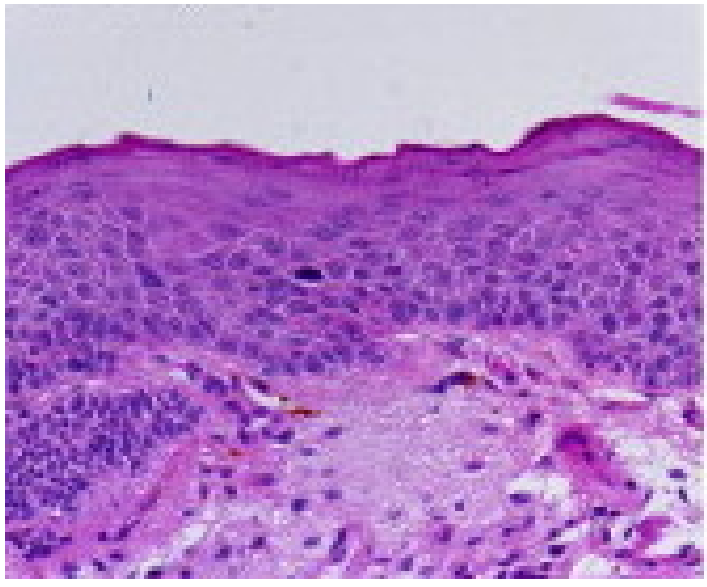
SESSILE CONJUNCTIVAL PAPILLOMA

CONJUNCTIVAL - CORNEAL INTRAEPITHELIAL NEOPLASIA:

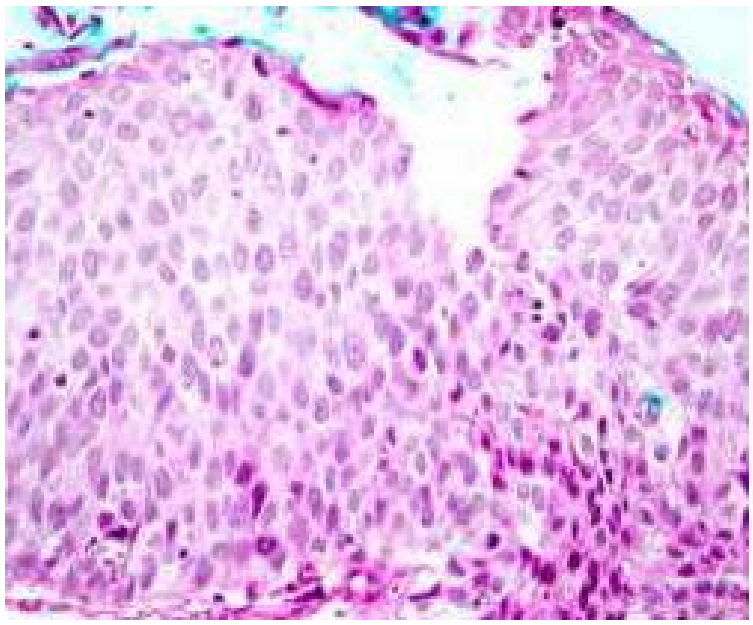
There are three grades of CCIN based on the level of epithelial involvement CCIN grade 1- In this type the tumour cells are limited to lower 1/3 of epithelium.



CCIN grade 2 – in this type the tumour cells are involving upto 2/3 of the epithelium.



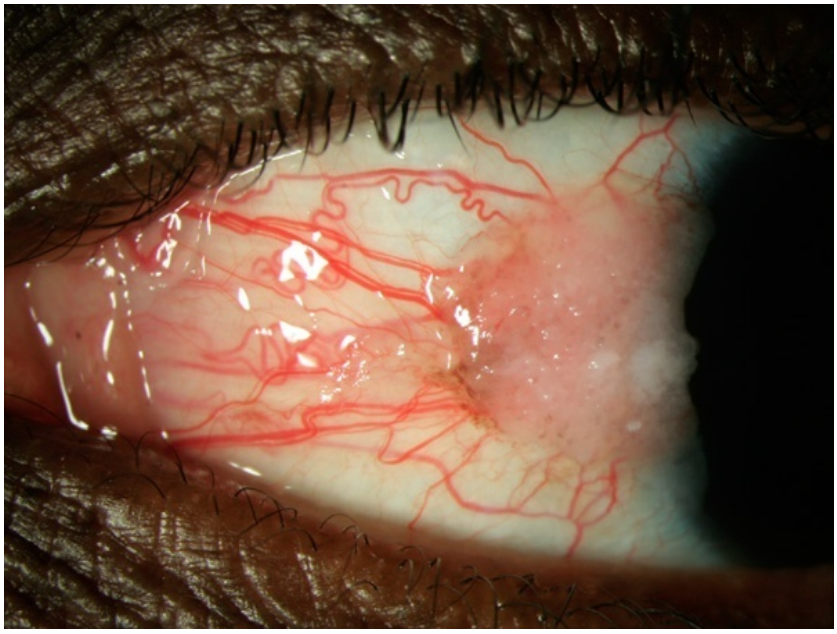
CCIN grade 3- in this type the full thickness of the epithelium in involved by tumour cells. Here the basement membrane is not breached by tumour cells.



Conjunctival - corneal intraepithelial neoplasia may be classified into three types

- papilliform,
- gelatinous,
- leukoplakic.

GELATINOUS TYPE



Gelatinous is the most common type and it appears as an ill defined translucent thickening. There are three varients

- Circumscribed
- Nodular and
- Diffuse type.

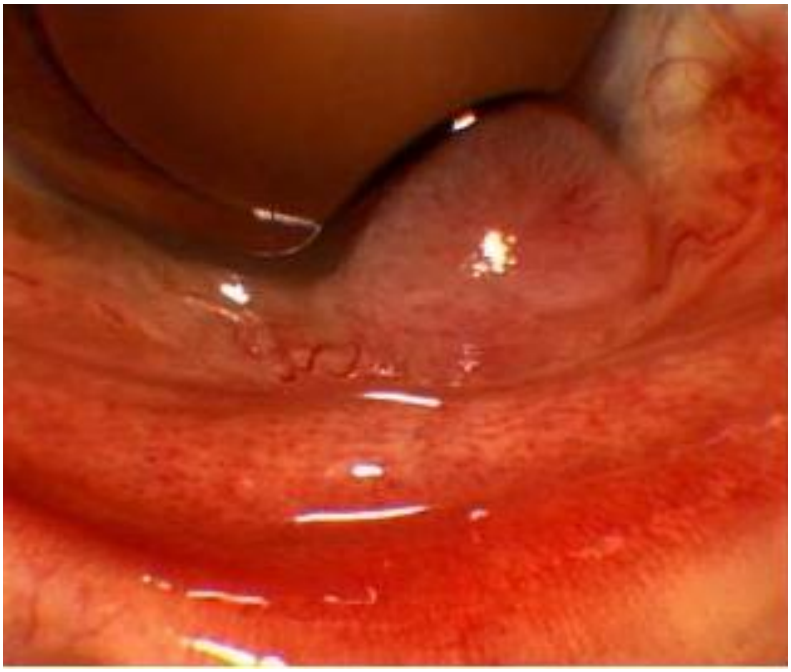
  Nodular variant is rapidly growing with a high incidence of metastasis.

  Diffuse type is slow growing and it mimics conjunctivitis

Both benign and malignant lesions resembles each other thus making it difficult to differentiate.

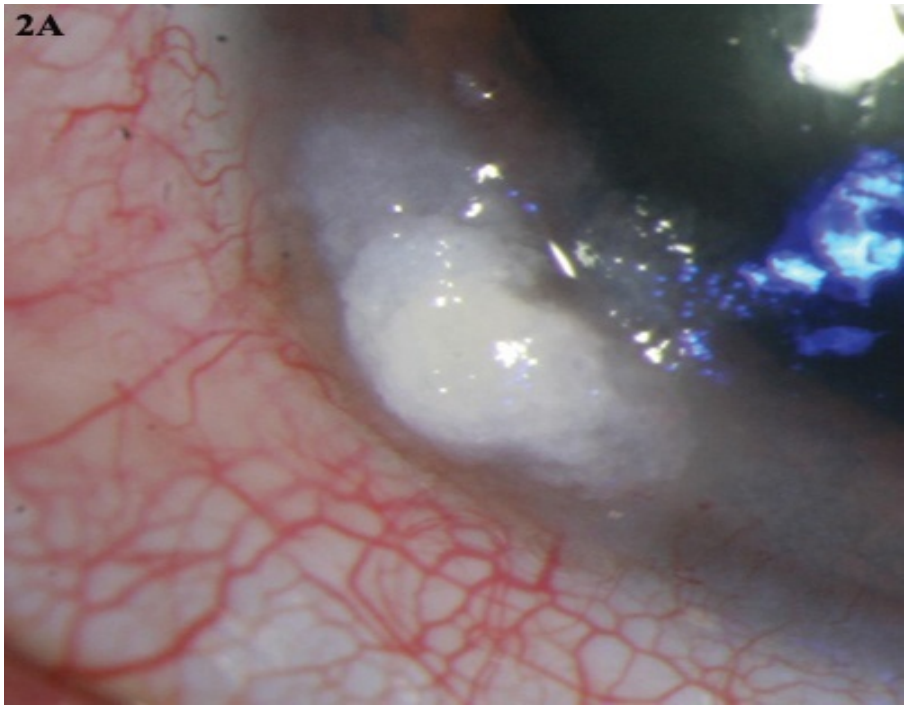
PAPILLIFORM TYPE

Papilliform type is a fleshy mass with numerous hyperaemic spots over its surface which may match up to the location of fibrovascular core. They are clinically benign and they look like a highly vascularised soft tissue mass.



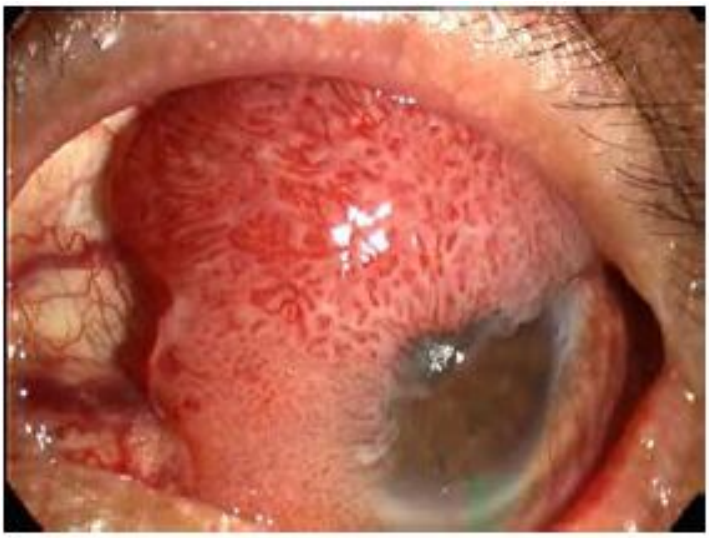
LEUKOPLAKIC TYPE

"Leukoplakic type appears as a focal thickening of stratified squamous epithelium.The most common site of origin of this type is conjunctiva near the limbus. The lesions may have pigmentations and pretend to be as malignant melanoma (Shields et al. 2008)".



Corneal OSSN is most commonly an expansion from conjunctival lesions. This type have a greyish white appearance with a well demarcated borders and have finger like projections. These lesions are usually avascular. They are typically idle, develops very slowly and are liable for reappearance. "Isolated corneal involvement has found to be very aggressive in rare cases, as the bowman's layer is resistant to invasive lesions (Cha et al. 1993)".

INVASIVE OCULAR SURFACE SQUAMOUS NEOPLASIA



It is characterised by groups of tumour cells that invades stroma by breaching the basement membrane of the conjunctival epithelium. The most common route of tumour spread is by local invasion.

Uveitis, increased intra ocular pressure, detachment of retina and globe rupture can occur if it invades intraocularly. Metastasis is uncommon. Regional lymphnodes are involved initially among the extraocular structures. “There are two forms of cells noticed associated with tumour cells Spindle type cells and mucoepidermoid cells”. Mucoepidermoid cells are known to spread intra orbitally and prone for recurrence.

Lesions are usually asymptomatic or may present with irritation, redness or visual impairment. Patient may present without any symptoms or with unbearable pain, defective vision.

Mucoepidermoid carcinoma is a uncommon variety of OSSN. It is usually noticed in elderly individuals. As it is more aggressive wide excision and close follow up is usually necessary. Local recurrence rate reported to be about 5% and regional lymph node metastasis at about <2%. Aggressive variants like muco-epidermoid carcinoma, spindle cell carcinoma and immunocompromised patients have a worst prognosis.

DIAGNOSIS AND INVESTIGATIONS

First the lesion should be assessed clinically to look for

- Type of lesion,
- Dimension,
- Location,
- External appearance,
- Blood vessels

Intraocular involvement should be assessed by slit lamp examination, dilatated fundus examination and gonioscopy.

Lymphatic spread to cervical lymph node group 1 and group 2, group 3, 4 and 5 should be examined to look for metastasis .

B scan should be done in patients with opaque media to assess the scleral involvement and intraocular spread. Non-invasive techniques like UHR OCT and ultrasound biomicroscopy has made it possible to evaluate the extent of corneo-scleral invasion in OSSN.

ULTRASOUND BIOMICROSCOPY

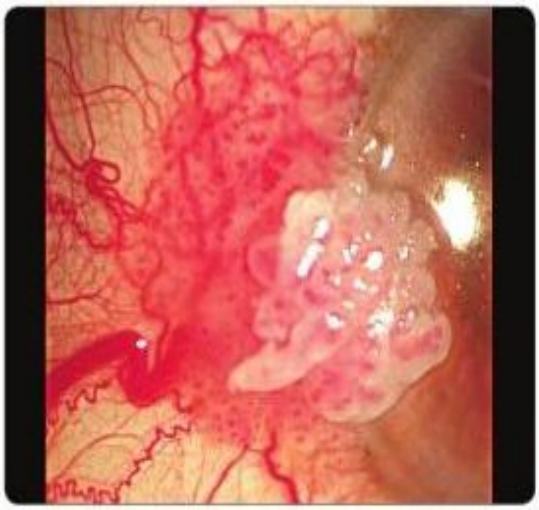
Ultrasound biomicroscopes helps in complete imaging of deep ocular structures by reflecting high energy sonic waves from inside of the eye. An ultrasonic biomicroscope is perfect for glaucoma screening, determining lens and cornea pathologies,intra ocular tumours, ocular surface lesions or sizing phakic intraocular lenses. Ultrasonic biomicroscopes typically operate with frequencies up to 50MHz, with detection depths of 8mm or more.

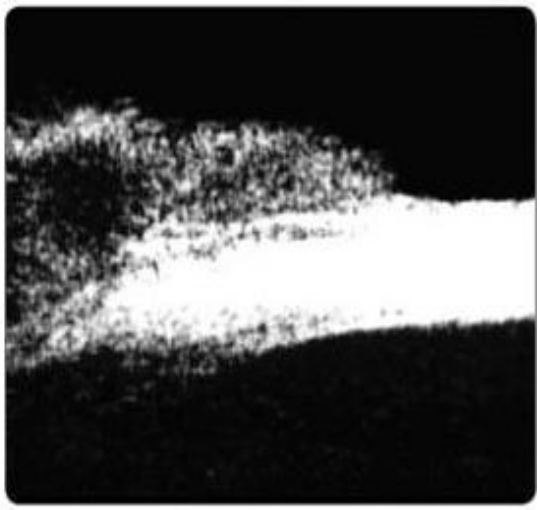
ADVANTAGES

- High scan penetrance, especially useful for large lesions

DISADVANTAGES

- Low resolution,
- Cannot evaluate epithelial versus subepithelial nature of lesion



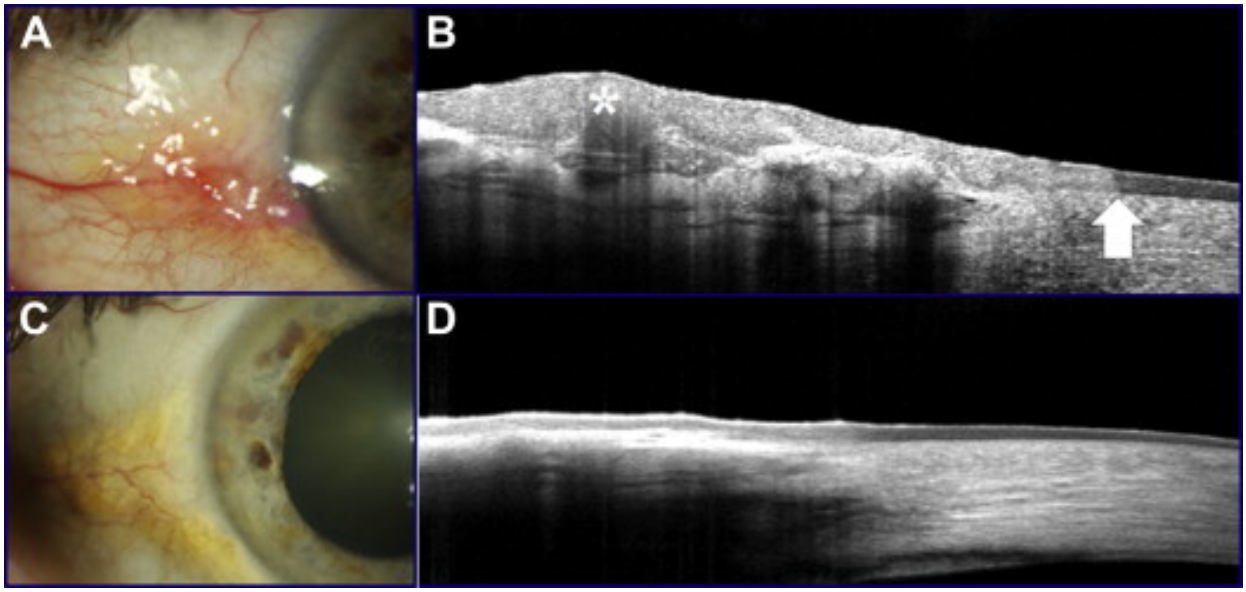


ANTERIOR SEGMENT OCT

"Anterior segment optical coherence tomography (OCT) allows in vivo examination of morphologic and even histological characteristics of the tissues". UHR OCT provides a non-invasive , noncontact and high axial resolution imaging for in vivo detection of various anterior segment pathologies.

"Anterior segment Ultra High Resolution Optical Coherence Tomography (UHR OCT) in ocular surface squamous neoplasia reveals epithelial thickening, increased reflectivity of the epithelium, and an abrupt demarcation from normal to abnormal tissue".

Typically there is sharp demarcation betweeen the reflectivity of normal and diseased epithelium,thus allowing for exact localization of the tumour margins. It is also helpful in the delineation of the tumour and to detect early subclinical recurrences.



CONFOCAL MICROSCOPY

Confocal microscopy aids in initial clinical evaluation of OSSN, treatment , estimation of recurrence and in patients with OSSN it helps to assess the effectiveness of chemotherapeutic drugs. It is able to differentiate between various presentations of OSSN.

ADVANTAGES

- It can be done as an outpatient procedure, less invasive and there is no pain during the procedure.

- It is helpful while managing incapacitated elderly individuals or patients who doesn't want to undergo surgery.

- It can improve the potency of diagnosis as the cytological picture obtained can be analysed without delay by pathologist.

- Confocal microscopy is helpful in differentiating invasive tumour & carcinoma insitu.

- Assessment of subtypes ,
- Detect recurrent tumours and
- Follow-up.

DISADVANTAGES

- Confocal microscopy when compared to UHR OCT provides a transverse view without referring to the neighbouring corneal layer.

- Only upto 500µm of depth can be assessed by this method.

CT scans or MRI are used to assess the orbital or anterior eye involvement.

HISTOPATHOLOGIC EXAMINATION

The investigation of choice for diagnosing OSSN being tissue biopsy from the lesion. Based on the report mode of treatment can be planned.

"Small tumours with minimal limbal involvement or ≤ 15 mm size excision and biopsy is ideal. Wedge biopsy is considered for lesions with large diameter".

Microscopic examination of the excised tissue with negative margin shows an abrupt transition of the epithelium from the adjacent uninvolved normal conjunctival epithelium. Lesion should be studied microscopically for architectural and cytological atypia. Both margin and base of the lesion should be studied.

Types of dysplastic cells are

1) Small cell with high nucleus- cytoplasmic ratio,
2) Spindle cell bearing oval-shaped nucleus,
3) Large cell with hyperchromatic nucleus .

Tumour cells also contains pleomorphic nucleus and high mitotic figures..

The histopathologic terms used to describe the Ocular Surface Squamous Neoplasia includes (Font et al. 2006)

1) Dysplasia

There are three grades of dysplasia based on the intraepithelial involvement. PAS staining is used to assess the depth of epithelial involvement by detecting glycogen in normal cells.

"The proliferating cell nuclear antigen (PCNA), Ki-67 and p53 immunostaining and argyrophillic nucleolar organizer region (AgNOR) staining may also be useful for grading the dysplastic lesions and to correlate it with clinical and morphological findings (Aoki et al. 1998)".

It can classified into

a) Mild – < 1/3 of epithelium is involved by dysplastic cells
b) Moderate – Atypical cells extends upto the middle third of epithelium
c) Severe - Entire width of epithelium is involved by dysplastic cells.

2) Carcinoma in situ

Involvement of entire width of epithelium, with retained

Integrity of epithelial basement membrane is known as carcinoma in situ.

3) Invasive carcinoma:

The basement membrane has been breached by dysplastic cells upto the level of substantia propria. Even one cancer cell with abnormal nuclei and formation of cancer cell nest is a definitive indicator of invasive carcinoma.

CYTOLOGY

Cytology is done by two methods

1) Exfoliative cytology – In this the cells are taken up for study by spatula or cytobrush.
2) Impression cytology- In this the cells are taken by special devices.

EXFOLIATIVE TECHNIQUE

In this a cytobrush is used to collect the tumour cells, because there is less adhesions between the tumour cells.

ADVANTAGES

- Simple technique in diagnosing and patients can be reviewed after management for OSSN.
- Helpful in detection of recurrences.

DISADVANTAGES

- Discomfort for the patient,
- Problems with drying artifacts,
- Problems with cellular overlap.

IMPRESSION CYTOLOGY

"Impression cytology is easy and cheap and the association between the cells is maintained.but these specimens should be processed without any delay. Impression cytology has been widely used as a non-invasive method for conjunctival biopsy in cases of suspected Ocular Surface Squamous Neoplasia".

"Using CAP for specimen collection, about 80% correlation was found between diagnosis from impression cytology and results of histopathology specimens obtained from incisional biopsy. IC using biopore membrane is highly accurate. In IC cellulose acetate paper with a pore size ranging from 0.025 – 0.45 micron or other materials like nitrocellulose filters, Biopore membranes, or polyether sulfone filters are used and the cells that get adhered to exterior surface of device and was taken up for examination".

ADVANTAGES

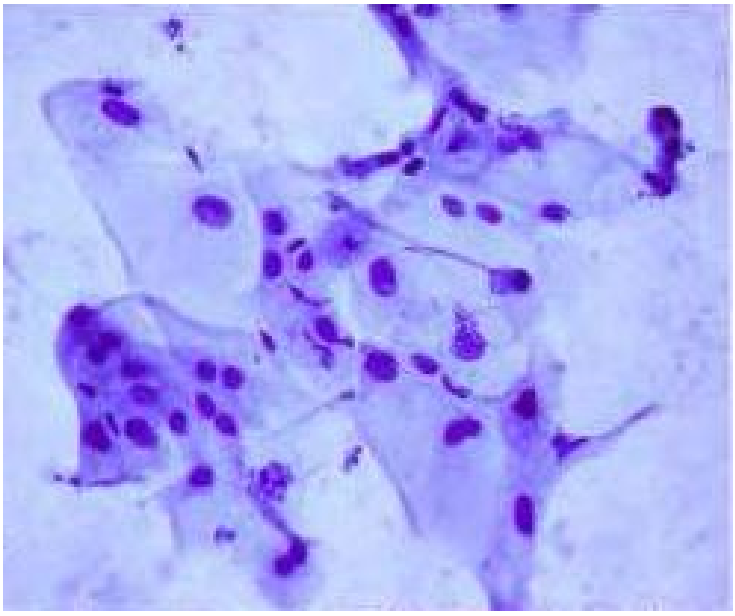
- Simple and non-invasive procedure for both diagnosing and review of patients.
- Relatively easy to collect samples from epithelium,
- Less discomfort for patient,
- Suitable to do as a day care procedure,
- Exact localisation of the key area,
- Association between the cells can be studied.

DISADVANTAGES

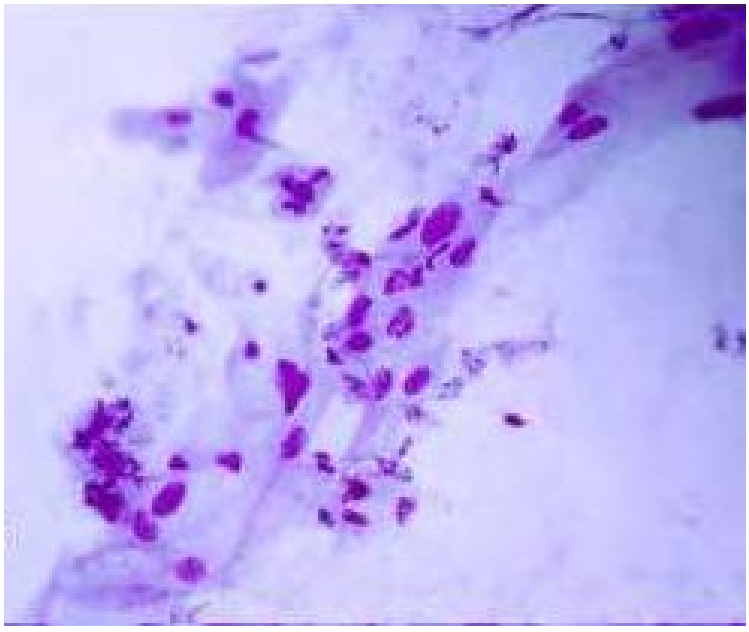
- It is not suitable for patients having keratotic lesions, as the keratotic lesions are more common in OSSN (68%)
- As IC can study superficial cells alone it very difficult to differentiate between CCIN and invasive carcinoma.
- If the report came as negative excision biopsy is needed

"At present, no cytologic criteria have been identified that reliably differentiate invasive carcinoma from in situ in Impression Cytology samples. Squamous cell abnormalities may be classified into 4 groups, using a modification of the Bethesda system in cervical cytology(Solomon et al.2002)"

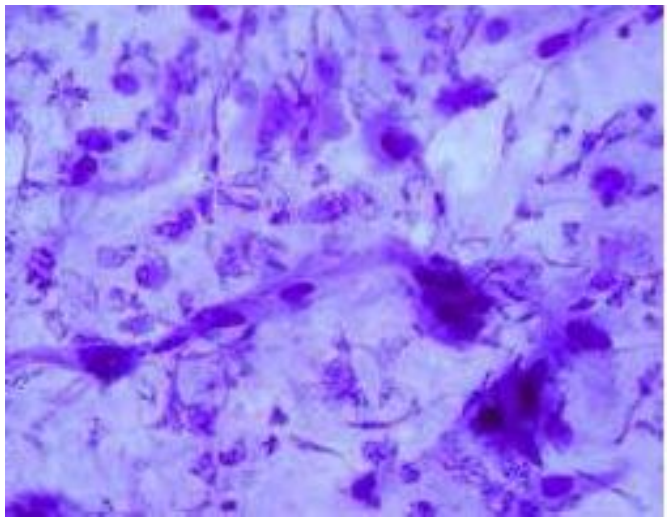
- Atypical squamous cells (ASC)
- Low grade squamous intraepithelial lesions (LSIL), includes squamous papilloma & mild dysplasia



- High grade squamous intraepithelial lesions (HSIL), including moderate to severe dysplasia & carcinoma in situ (CIS).



- Squamous cell carcinoma.



“One series of OSSN found that SCC from cytology had a highest rate of correlation(91.7%) with histology followed by HSILs (45.5%), ASCs(42.9%), normal epithelia (33%), and LSILs (21.4%), respectively.(Tananuvat et al. 2008)”

“Barros and co workers used a scoring index modified from the Bethesda system which revealed a predictive index score of ≥4.5 represented the best cut-off point for diagnosis of SCC by using IC with a sensitivity of 95%, specificity of 93%, positive predictive value of 95%, and a negative predictive value of 93%.(Barros et al. 2009)” However, the skill and the experience of cytologist are necessary for interpretation of the IC specimens.

IMMUNOHISTOCHEMICAL ANALYSIS

Number of Ki-67 positive cells in conjunctival SCC and CCIN increases from normal to low grade Squamous Intraepithelial lesions to high grade Squamous Intraepithelial Lesions. Hence Ki-67 may be used as a useful diagnostic indicator for Ocular Surface Neoplasia.

TREATMENT

The available treatment options are

- Surgery
- Topical chemotherapy
- Cryotherapy
- Topical immunotherapy
- Radiotherapy

"The main strategy in the treatment of OSSN is complete excision of the tumor with wide tumour free margin followed by double freeze-thaw cryotherapy for the conjunctival margin" and "alcohol epitheliectomy for the corneal component of the lesion". When the tumor is attached to the globe, a thin strip of sclera should be excised. In every patients no touch surgical method is followed to avoid tumour handling which may result in tumour seeding.

SURGICAL EXCISION

Excision allows an immediate histopathological evaluation, debulking of the lesion and excludes invasive carcinoma. Special stains like Rose Bengal or Lissamine Green can be used to demarcate the tumour outline.

'No-touch' Surgical method :

It can be performed under local peribulbar or retrobular anesthesia by using a 1:1 mixture of 0.75% bupivacaine and 2% lidocaine. 2.5% Phenylephrine drops are used to cause vasoconstriction, thus reducing bleeding perioperatively and allows better visualization of the corneal involvement of the tumor.

The borders of the tumor outlined and 4-mm margins of the tumour are marked with the help of calipers at the edge of sclera. Conjunctiva is lifted with the help of forceps and with a pair of Westcott scissors first incision is made.

Initial dissection is limited to the marked margins of the tumour and any contact of the tumor with the instruments is better avoided to prevent tumor seeding. Once the dissection of the peripheral marked

margins is completed, the dissection is focussed towards the center of the lesion. If the tumor gets adhered to the sclera, with the help of blade and forceps a partial thickness sclerectomy is done. The tumour is removed in toto and the specimen is sent for histopathological evaluation in formalin.

Absolute alcohol epitheliectomy is indicated in cases of corneal involvement. For better visualization of the corneal involvement. Slit lamp is used to make a careful picture of the lesion. The pupil must be dilated to better visualize the corneal involvement during surgery. The epithelium that are devitalized is scraped with a blade removing about 3–4 mm of safety margins similar to that of conjunctiva. The scraped cells are then placed in a cellulose sponge and sent for histopathological examination.

The scleral bed and limbus are also to be scraped, and then the conjunctival margins of the lesion and the limbus were frozen, and the scleral bed is cauterized. By doing so complete hemostasis is achieved and the residual tumor cells are made nonviable.

Tumour should be removed along with 3mm of normal conjunctiva is essential. If the raw area resulting from excision is small then it should be corrected by primary suturing and larger gap needs either a

transpositoned flap from conjunctiva, autograft from opposite eye, or buccal mucosal graft or amniotic membrane graft.

Frozen section is accurate in delineating the horizontal tumor spread can be helpful in evaluate the sufficiency of tumour removal. If excised margin is positive for tumour cells then the free conjunctival edges are excised by 2 mm.

Negative margins will have a recurrence rate which range from 5% to 33% to as high as 56% in those where margins were found to be positive. Higher recurrence rates were found in more severe grades of OSSN. In patients with intraocular spread enucleation is preferred. For patients with orbital invasion treatment modality may range from local resection of the tumour and or irradiation to orbital exenteration sparing the eyelid .

COMPLICATIONS

Complications of surgical treatment are those resulting from healing process particularly in patients with advanced lesions such as tissue granulation, pseudopterygium formation, symblepharon, diplopia from shortening of tissues, blepharoptosis and limbal stem cell deficiency.

CRYOTHERAPY

Along with surgical removal cryotherapy is essential and is usually done in all cases with OSSN.

MECHANISM OF ACTION

It causes ischemic necrosis of the tumour tissue by occluding the microcirculation and the tumour tissues are freezed.

ADVANTAGES

Radical surgeries like enucleation and exentration can be avoided by this procedure as it can destroy groups of tumour cells and tumour cells that are locally invasive.

PROCEDURE

NO cryoprobe with a diameter of 2.5mm or 5mm is used to form an ice ball. The cryoprobe is used under the edges of excised conjunctiva. Cryotherapy is usually done by deep freezing the tumous tissues then allowing them to thaw slowly. This cycle can be done upto 3 times. Site of the tumour determines the time required for cryotherapy. The cryoprobe should not be applied for more than three seconds. In all the patients with OSSN Corneoscleral junction should be covered by cryotherapy.

COMPLICATIONS

The complications of this technique are sclera and corneal thinning, cataract, uveitis, phthisis bulbi and limbal stem cell deficiency. The size of the iceball is 0.5 mm for the cornea, 2 mm for conjunctiva and 1mm for episclera.

TOPICAL CHEMOTHERAPY

Topical chemotherapy offers a noninvasive mode of managing the ocular surface neoplasia with less importance given to the tumor margin, and it potentially eliminates subclinical lesions.

INDICATIONS

1) Conjunctival lesion of more than two quadrants,
2) Tumour with corneal involvement covering the pupillary area,
3) Limbal involvementof > 180 degrees,
4) Inadequate tumour margin clearance,
5) Patients with severe comorbid condition.

Drugs that can be used are,

1) Mitomycin C (MMC) - most commonly used

2) 5-fluorouracil

3) IFN α2B.

These agents can be used alone or as an adjuvant with surgery (preoperatively, intraoperatively, and postoperatively) for treatment of Ocular Surface Squamous Neoplasia .

ADVANTAGES

1) Highest drug concentration can be achieved locally,

2) No systemic side effects,

3) Stress, trauma, pain & increased cost associated with surgical procedure are avoided.

DISADAVANTAGES

1) In case of large tumours drug penetration is limited.

2) Prolonged use can cause deleterious effect on the ocular surface and nasopharyngeal mucosa.

MITOMYCIN C

"The role of Mitomycin C in the treatment of Ocular Surface Squamous Neoplasia was first described in 1994 by Frucht-Pery & Rozenman". Topical application of MMC in the management of OSSN has gained popularity over the past 16 years, as the "whole eye treatment" with MMC offers potential benefits over cryotherapy & excision for the treatment of extensive and subclinical cases.

MMC is used preoperatively for chemoreduction, intraoperatively and postoperatively to prevent recurrence of tumour.

Mitomycin C is an alkylating agent isolated from actinobacterium Streptomyces Caespitosus. It is an anti-tumour antibiotic with a molecular weight of around 334 daltons.

MECHANISM OF ACTION

1) It interferes with the cell cycle at G1 and S phase and causes cell death by inducing apoptosis and cell necrosis, by inhibiting the production of DNA.
2) Main target for action are fastly replicating cells.

It decrease extracellular matrix production, inhibits immigration of fibroblast cell.

3) It suppresses Cellular RNA and protein synthesis.
4) Through peroxidation of lipids it causes damage to the DNA and it mainly acts under aerobic conditions producing free radicals and causing cytotoxicity.

ABSORPTION

Systemic absorption following ocular administration of mitomycin c is unknown, but is sought to be of varying magnitudes lower than those achieved by administrating intravenously.

METABOLISM

It gets cleared from ocular tissue after intraoperative topical application and irrigation and the metabolism of MMC occurs in other affected tissues. Systemic clearance of Mitomycin C is affected primarily by metabolism in liver.

ELIMINATION

10% of the applied drug is excreted unchanged in urine.

ADVANTAGES

1) Effects of local application of MMC can lasts for 8 months to years even after termination of the treatment thereby mimicing ionizing radiation (cytolmegaly, nucleomegaly, and vacuolation).
2) Lesion located anywhere in the ocular surface even those on the conjunctival fornices can be managed.

3) Prevents new tumour cells originating from other areas of ocular surface by destroying subclinical disease.

DOSE

"0.02% - 0.04% given four times per day for 7 days in alternate weeks (1 week on and 1 week off), similar to those used in fractionation of radiation in treatment of systemic cancers".

" Ando *et al*21 concluded that 0.04% mitomycin C was relatively non-toxic to intact corneal epithelium".

MITOMYCIN C EYE DROPS DOSE PREPARATION

0.02-0.04% Mitomycin eye drops is prepared by reconstituting it with distilled water.

0.02% MMC EYE DROPS PREPARATION

- 0.5 mg/ml can be achieved by mixing 5 mg vial with 10 ml distilled water.

- To a sterile eye dropper bottle 6ml of the diluted solution is transferred.

- Then 9ml of distilled water is mixed with the above.

- The final solution contains 0.02% of Mitomycin C

0.04% MMC EYE DROPS PREPARATION

- 0.5 mg/ml can be achieved by mixing two 5 mg vials with 10 ml of distilled water.

- To a sterile eye dropper bottle 12ml of the diluted solution is transferred.

- Then 3ml of distilled water is mixed with the above.

The final solution contains 0.04% of Mitomycin C The reconstituted solution can maintain its stability only for 2 days if the solution is kept under room temperature and it can maintain its stability for two weeks if kept under refrigeration.

REASONS FOR INTERMITTENT THERAPY

1) Slower growing cell are protected from injury as intermittent therapy provides time for those cells to recover from damage caused to their DNA by the drug.
2) Decrease in the number of stem cells can be prohibited .

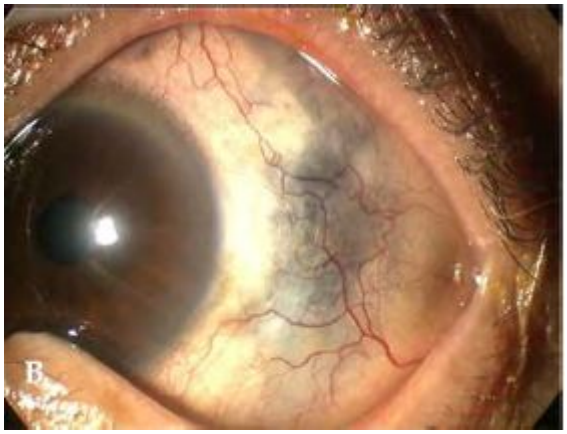
SIDE EFFECTS

Transient side effects are

1) local irritation
2) watering,
3) photophobia,
4) conjunctival hyperemia,
5) allergy,
6) punctate epithelial erosion,
7) corneal edema,
8) pyogenic granuloma,
9) keratoconjunctivitis and
10) Nose bleeds.

Long term complications are

1) punctal stenosis,
2) limbal stem cell deficiency,
3) cataract,
4) persisting keratoconjunctivitis,
5) scleral thinning,
6) glaucoma and
7) uveitis.



SCLERAL THINNING

PRECAUTION

1) Instruct the Patients and their families to carefully handle the medication.
2) Pregnant women and young children should avoid direct contact with the medication.
3) Superior and inferior punctum are pluged to reduce absorption of MMC systemically.
4) Patients are educated to close the eyes after the application of MMC.
5) Used bottles should be handed over to biomedical department for discarding it safely.
6) If accidently administered intraocularly, cell death can occur that may lead to corneal infarction, ciliary body atrophy and retinal infarction.

OTHER USES OF MMC

Current applications include

1) Pterygium surgery :

   Topical concentrations of 0.02% and 0.04% of Mitomycin C has been administered with duration of therapy varying from 5 days to 2 weeks post operatively, as it can prevent the recurrence of pterygium.

2) corneal refractive surgery,

3) glaucoma surgery:

   Mitomycin C is used in trabeculectomy to reduce scarring, thus it helps to prevent closure of the filtration site. It should be reserved for the eyes with a high chance of failure or with a failed previous conventional filtering surgery. 0.01-0.05% of Mitomycin C is administered intraoperatively as a single topical application for 1-5 minutes. The outcome of trabeculectomy is improved with the application of MMC, which was clearly reported in many studies.

   Complications :

   a) persistent hypotony

   b) Endophthalmitis

4) Dacryocystorhinostomy surgeries

5) Allergic eye disease

6) Squint surgeries

7) Cicatricial eye disease.

5 -FLUOROURACIL

When applied as a topical solution it gets metabolised into 5-F DUMP and it prevents DNA and RNA formation by acting on thymydilate kinase enzyme. It is a cell cycle inhibitor acting on S phase. 5 flourouracil can be used alone or as an adjuvant to excision or debulking therapy.

DOSE:

"1% topical solution of 5-FU in cycles of 4 days on followed by 30 days off till the lesion subsides".

ADVANTAGES

1) It a stable solution and there is no need for refrigeration.
2) Fewer side effects,
3) Not expensive
4) Easy to handle by medical practitioners and the patients.

SIDE EFFECTS

Topical 5 flourouracil can cause lid toxicity, epiphora and superficial keratitis.

IMMUNOTHERAPY

"Maskin was the first to report the application of topical interferon (IFN-α2b) in 1994, for the management of multi-focal limbal OSSN".

Interferon alpha 2b (INF-α2b) occurs naturally as a glycoprotein. It has antiviral and antitumor actions.This drug has a negligible action on stem cells.

DOSE

"Recombinant topical IFN-α2b 1 million IU/ml 4 times per day until there is resolution of lesion and continued for a month thereafter".

INDICATIONS

1) Reserved for lesions that are not responsive to topical MMC.
2) For wider and extensive OSSN involving >4 clock hours of the limbus.
3) Recalcitrant, Residual or Multifocal and recurrent lesions,
4) Leisons involving the visual axis where surgery has a limited role.

SIDE EFFECTS

1) Topical - Follicular conjunctivitis, conjunctival injections and corneal epithelial microcyst.

2) Subconjunctival - Transient fever and myalgia.

When compared to Mitomycin C it takes a longer duration for complete resolution of the tumour and it is more toxic.

PEGYLATED INTERFERON ALPHA 2B

It is a derivative of recombinant interferon alpha 2b which was developed to decrease the renal clearance of traditional recombinant INFα 2b. By attaching a single straight-chain polyethylene glycol moiety to interferon alpha 2b there is a significant reduction in renal clearance thus

increasing plasma half-life of the drug to tenfold, but there is no change in volume of distribution or spectrum of activity.

Thus the pegylated interferon can be given once weekly for treating systemic diseases.

DISADVANTAGE

PEGIFNa2b is much costlier than non-pegylated interferon.

The surgical resection of OSSN is usually supported by topical application of drugs based on size of the lesion. Larger the diameter lesion treated by combined modality of treatment proves to be successful.

"Comparing these three drugs in the treatment of noninvasive Ocular Surface Squamous Neoplasia reveals that MMC is the most effective (88%) in clearing the lesion, 5-FU (87%) and IFNα-2b (80%)". MMC has the highest rate of side effects, as it is the most frequently used topical agent. IFNα-2b though is least toxic it is the costliest of the three agents.

OTHER MODALITIES OF TREATMENT

1) Plaque brachytherapy with Iodine-125

2) Immunotherapy with dinitrochlorobenzene (DNCB),

3) Gamma radiation and Beta-radiation therapy (strontium 90 radiation)

4) Urea

5) Anti-VEGF

6) Phototherapeutic keratectomy with the excimer laser

7) Retinoic acid

8) Photodynamic therapy.

All of these treatment modalities have been used occasionally and does not constitute a main treatment options.

Enucleation to be done for intra ocular spread and Exenteration to be done for for orbital invasion.

PHOTODYNAMIC THERAPY

- OSSN can be treated with Photodynamic therapy (PDT) .
- PDT based on the use of verteporfin,
- It is a light-sensitive dye applied intravenously,
- It has a high affinity for abnormal blood vessels.
- When it is exposed to light in the range of 689 or 692 nm, direct cell death and immune-mediated destruction of the nearby cells occur.
- Barbazetto *et al.* have used 6 mg/m^2 body surface of verteporfin injection followed by a light dose of 50 J/cm^2 1 min after giving the injection.
- Localized tumor regression has been noted following PDT.
- It can be combined with other treatment modalities for localised conjunctival OSSN.

RECENT ADVANCES

A potential but as of not tested therapeutic option for the treatment of OSSN is “Cetuximab is an anti-epidermal growth factor receptor monoclonal antibody. Anti-EGFR agents were originally developed as a solid tumour anti-neoplastic therapy just like anti-VEGF antibodies, and are currently used in colorectal, non-small cell lung cancer and ovarian cancers”. They have also been shown to be effective against Squamous

Cell Carcinomas of the head and neck. It is not clear whether epidermal growth factor plays a role in the growth or development of OSSN. There are several ocular side effects that have been reported resulting from systemic administration of anti-EGFR treatment including blepharitis,dysfunctional tear syndrome and trichiasis.

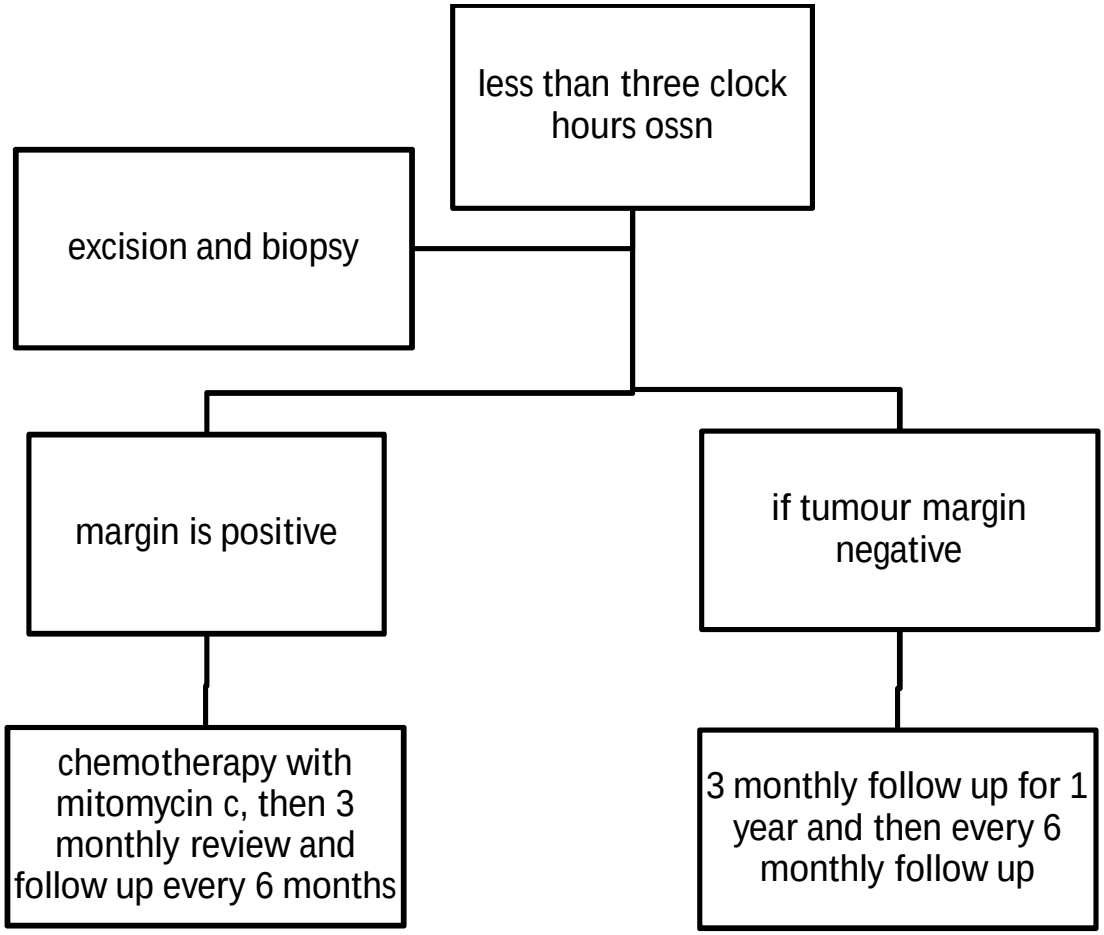
RECURRENCE

Recurrence rates of Ocular Surface Squamous Neoplasia varies from 12-50%. It occurs usually within the first two years of surgery and are most common in patients with positive tumour margins.

Factors predisposing to recurrence of the lesion includes

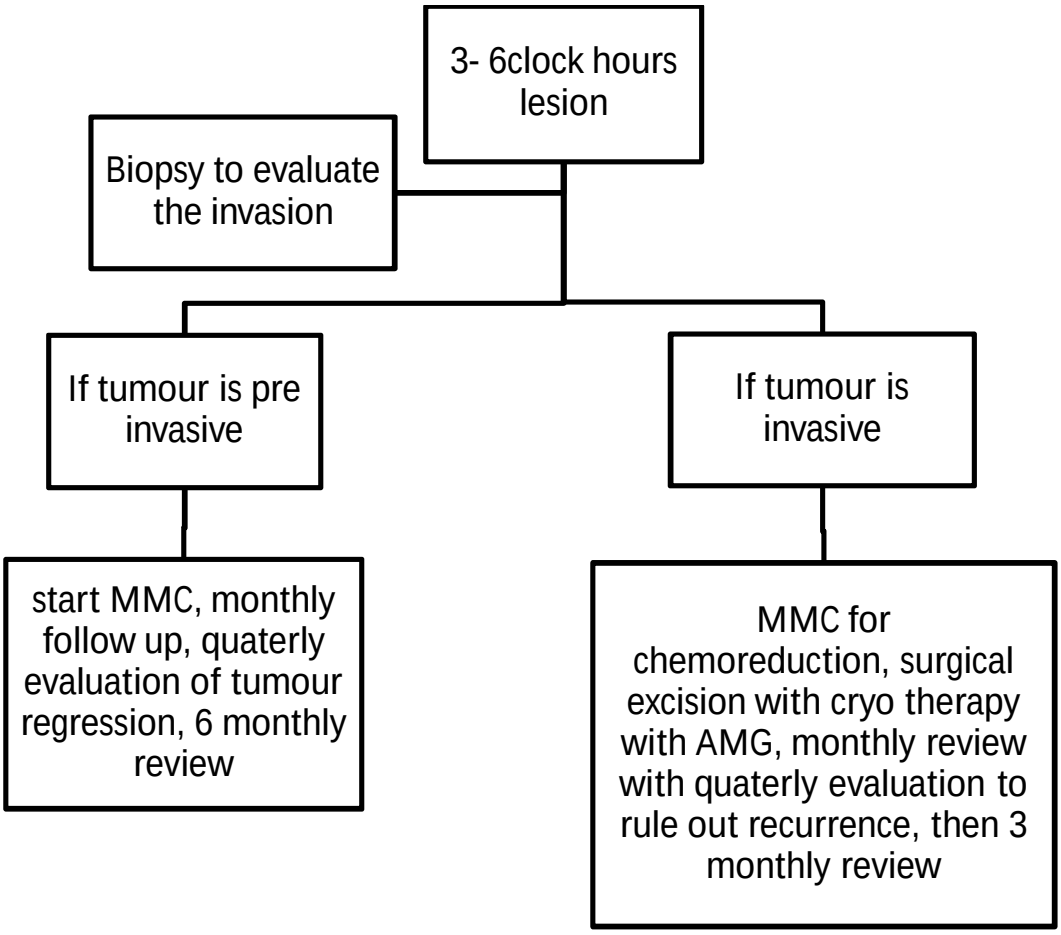
1. positive surgical margin,
2. old age,
3. large diameter lesions,
4. high proliferation index (Ki-67 score) and
5. corneal location.

TREATMENT PLAN FOR OSSN < 3 CLOCK HOUR

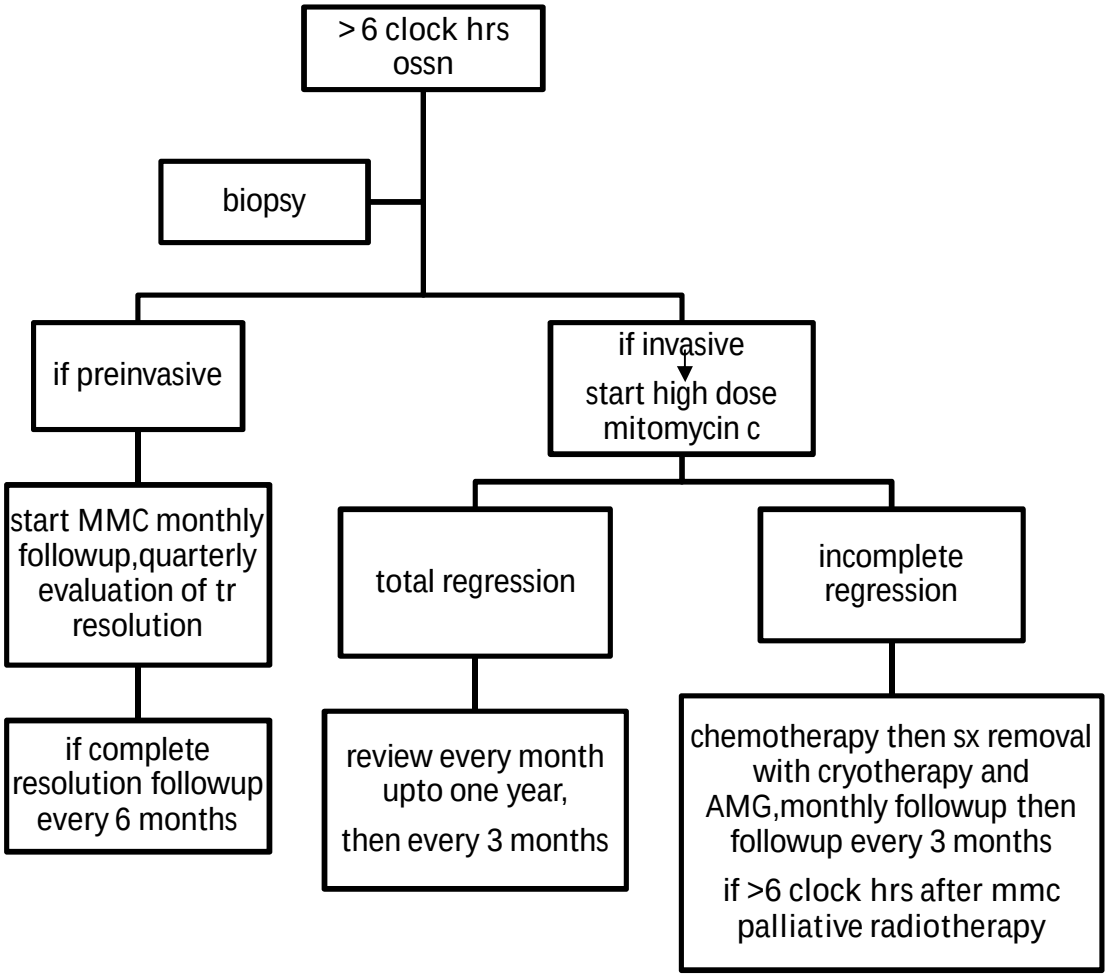


ALGORITHM FOR THREE-SIX CLOCK HRS OSSN

TREATMENT



ALGORITHM FOR MANAGEMENT OF OSSN >6 CLOCK HOURS



DIFFERENTIAL DIAGNOSIS OF OSSN

- Pterygium
- Pannus
- Pseudoepitheliomatous hyperplasia
- Vitamin A deficiency
- Actinic disease
- Benign intraepithelial dyskeratosis
- Pinguecula
- Keratoacanthoma
- Malignant melanoma and nevi
- Pyogenic granuloma
- Dyskeratosis
- Conjunctival lymphoma (salmon patch)

PART 2

AIM

To study the role of Mitomycin c in the management of Ocular Surface Squamous Neoplasia.

PRIMARY OBJECTIVE

To evaluate the role of Mitomycin C as an adjuvant therapy intraoperatively and post operatively in the management of Ocular Surface Squamous Neoplasia.

SECONDARY OBJECTIVE

To determine the role of Mitomycin C in the prevention of recurrence of Ocular Surface Squamous Neoplasia.

MATERIALS AND METHODS

The study was conducted at Regional Institute of Ophthalmology, Government Ophthalmic Hospital, Chennai.

20 Patients with histopathologically proven Ocular Surface Squamous Neoplasia were registered for this study.

INCLUSION CRITERIA

1. Patients in age group of 40 and above.
2. Histopathologically proven limbal OSSN with or without corneal Involvement.
3. Primary and recurrent OSSN.

EXCLUSION CRITERIA

1. Patients aged less than 40 yrs.
2. Patients with scleral involvement.
3. Patients with intraocular and orbital involvement.
4. Patients with other ocular diseases like limbal stem cell deficiency, ocular surface disorders, intraocular tumours.
5. Patients with any other systemic illness.
6. Patients with HIV and other immunocompromised diseases.
7. Pregnant women.

PREOPERATIVE ASSESMENT

Preoperatively detailed history was taken from all the patients, general examination was done, uncorrected and corrected visual acuity were recorded in all the cases. Slit lamp examination was performed and careful assessment of the morphology, site, size shape and colour of the lesion, extent of the lesion, corneal involvement was made along with routine examination of the ocular adnexa and anterior segment. Fundus examination and gonioscopy was done.

A baseline IOP measurement was done in all the cases using applanation tonometry. Investigations like complete blood count, random blood sugar, urine routine, bleeding time, clotting time, HIV serology was done. ultrasound biomicroscopy(UBM) and B scan was done in all the cases.

SURGICAL PROCEDURE

Under strict aseptic precautions, under peribulbar block, the tumour was surgically removed in toto along with 3-4mm of uninvolved conjunctiva. 0.4mg/ml of Mitomycin C applied over the excised site for 3-4 minutes and then washed with saline. According to the size of the defect in the conjunctiva the surgical site is closed by primary suturing of the conjunctiva or by grafting.

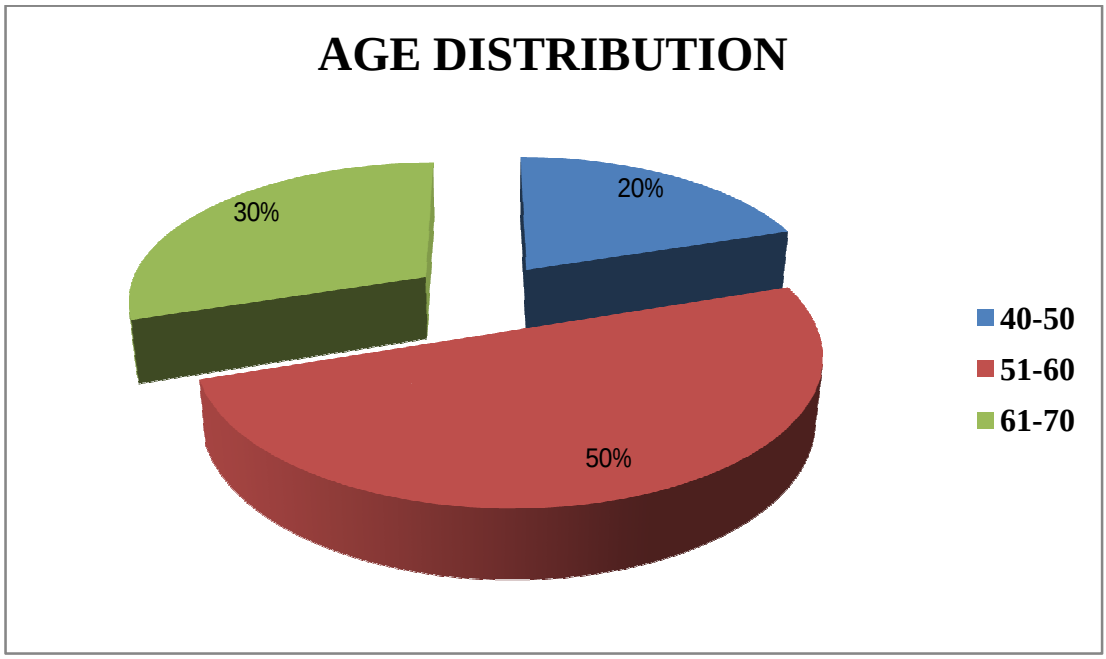
POSTOPERATIVE CARE AND FOLLOW UP

Postoperatively 2 cycles of 0.04% Mitomycin C eye drops 4 times per day was given approximately for 2 weeks after surgical excision, each cycle lasting for 1 week with off period of 1 week in between. All the patients were given topical steroids and lubricants throughout the post op period. Patients were instructed to come for follow up one month following surgery then on third month, sixth month and one year.

ANALYSIS AND RESULTS

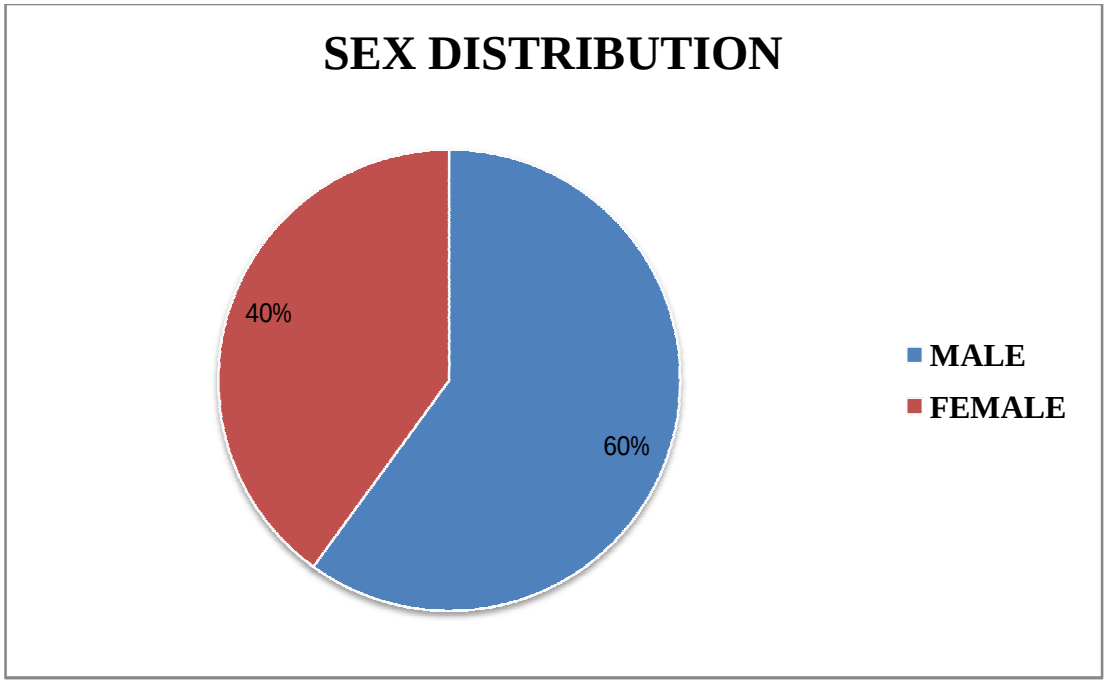
AGE DISTRIBUTION

AGE GROUP	NO. OF PATIENTS	PERCENTAGE
40-50	4	20%
51-60	10	50%
61-70	6	30%
Total	**20**	**100%**



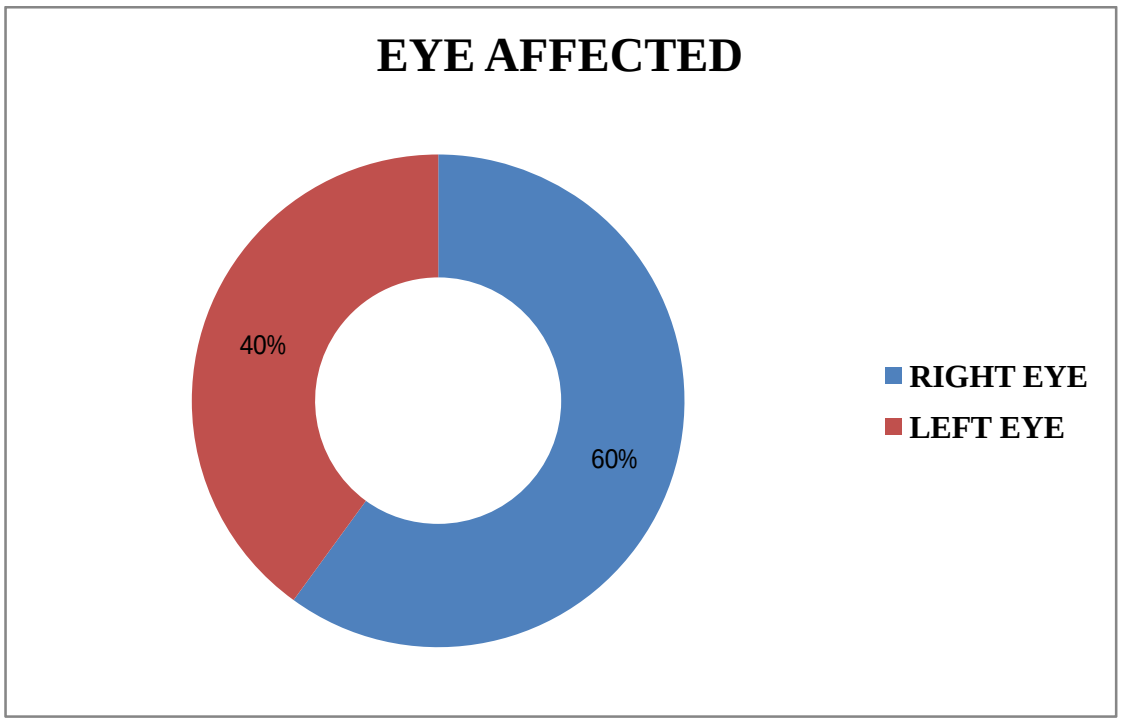
SEX DISTRIBUTION

SEX	NO. OF PATIENTS	PERCENTAGE
MALE	12	60%
FEMALE	8	40%
TOTAL	**20**	**100%**



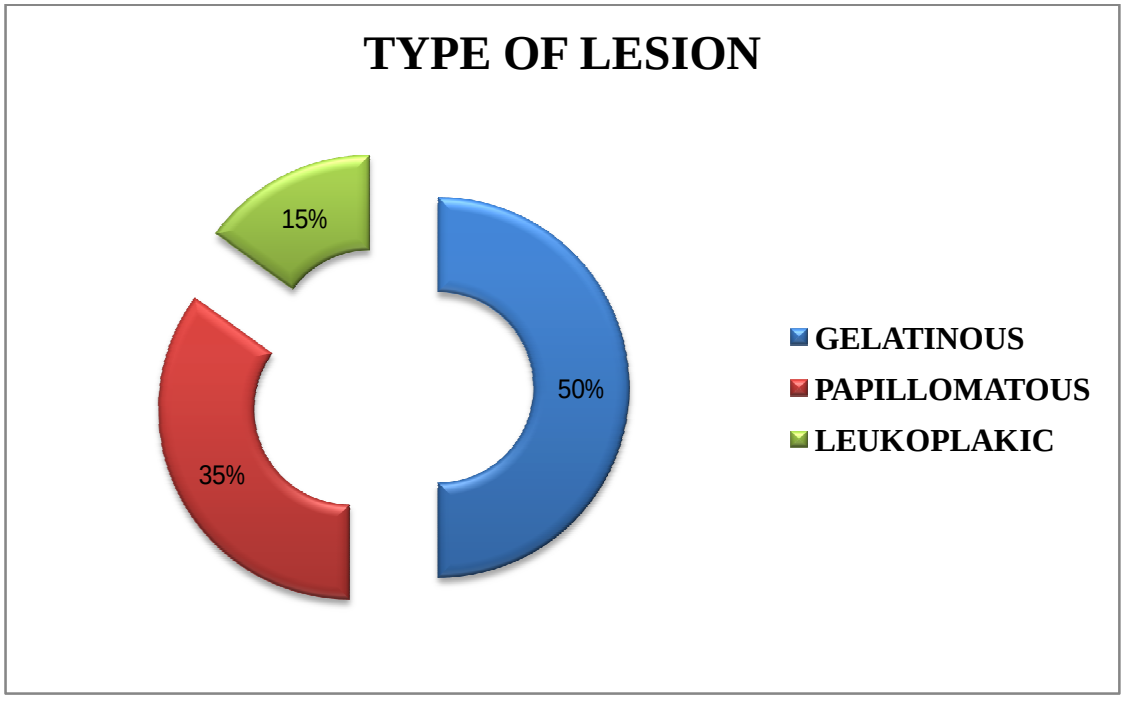
LATERALITY

EYE AFFECTED	NO. OF PATIENTS	PERCENTAGE
RIGHT EYE	12	60%
LEFT EYE	8	40%
TOTAL	**20**	**100%**



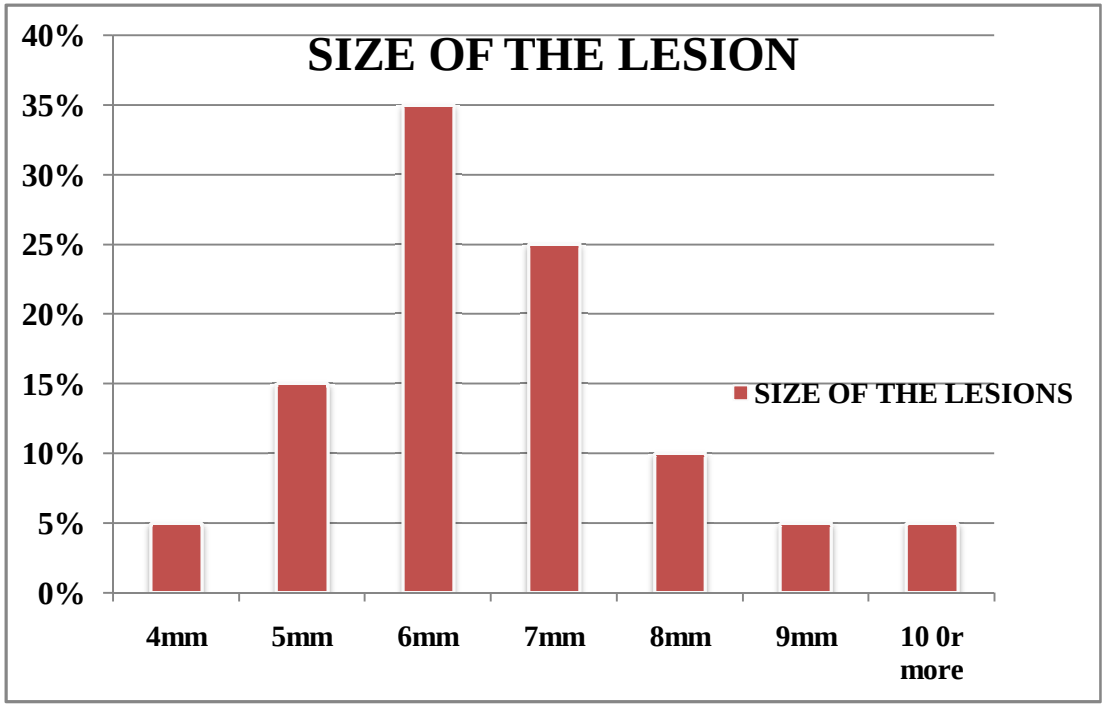
TYPE OF THE LESION

TYPE OF LESION	NO OF PATIENTS	PERCENTAGE
GELATINOUS	10	50%
PAPILLOMATOUS	7	35%
LEUKOPLAKIC	3	15%
TOTAL	**20**	**100%**



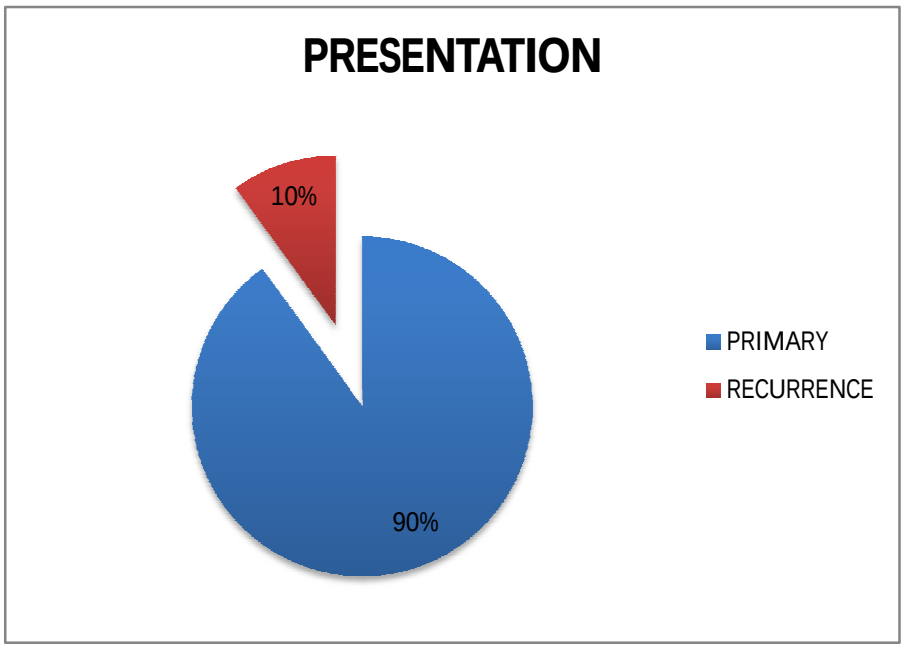
SIZE OF THE LESION

SIZE OF THE LESION	NO OF PATIENTS	PERCENTAGE
4mm	1	5%
5mm	3	15%
6mm	7	35%
7mm	5	25%
8mm	2	10%
9mm	1	5%
>10mm	1	5%
TOTAL	**20**	**100%**


SIZE OF THE LESION
40%
35%
30%
25%
20%
15%
10%
5%
0%
4mm
5mm
6mm
7mm
8mm
9mm
10 0r more
SIZE OF THE LESIONS

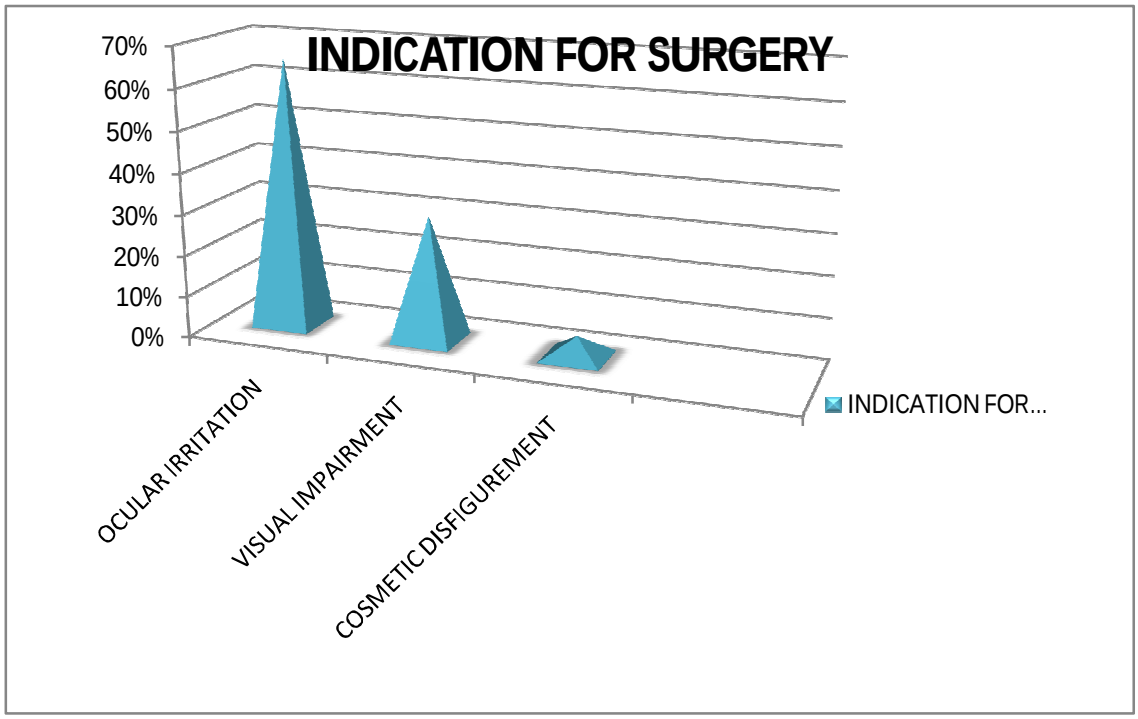
PRESENTATION OF THE PATIENT

PRESENTATION	NO OF PATIENTS	PERCENTAGE
PRIMARY	18	90%
RECURRENCE	2	10%
TOTAL	**20**	**100%**



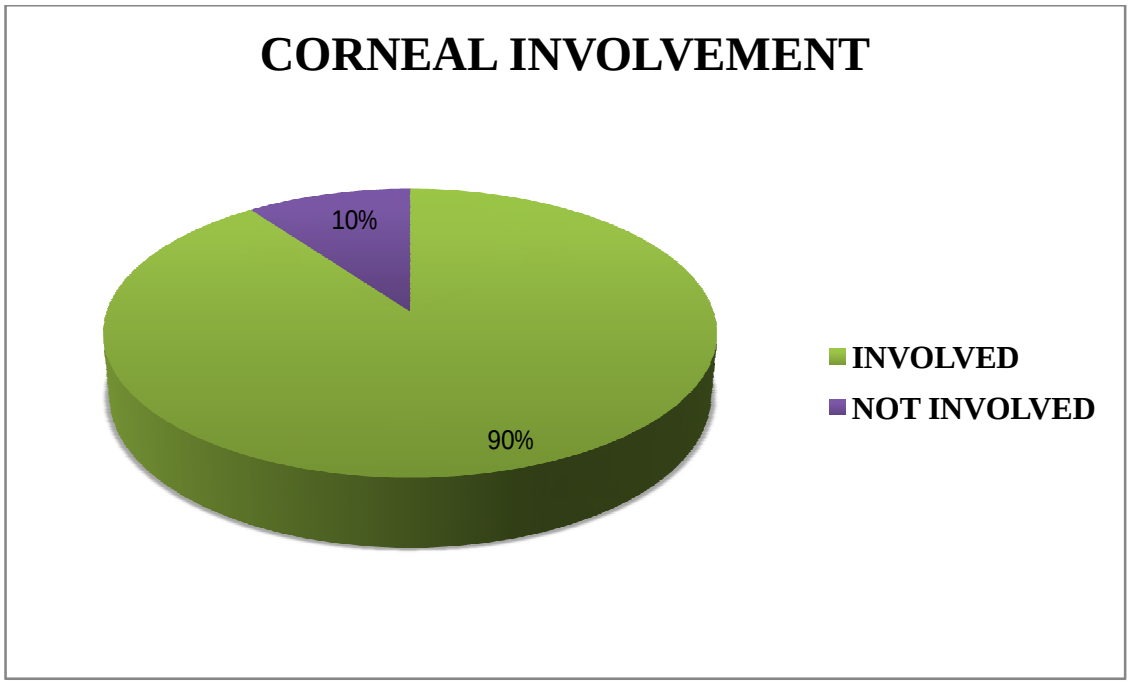
INDICATION FOR SURGERY

INDICATION	NO OF PATIENTS	PERCENTAGE
OCULAR IRRITATION	13	65%
VISUAL IMPAIRMENT	6	30%
COSMETIC DISFIGUREMENT	1	5%
TOTAL	**20**	**100%**



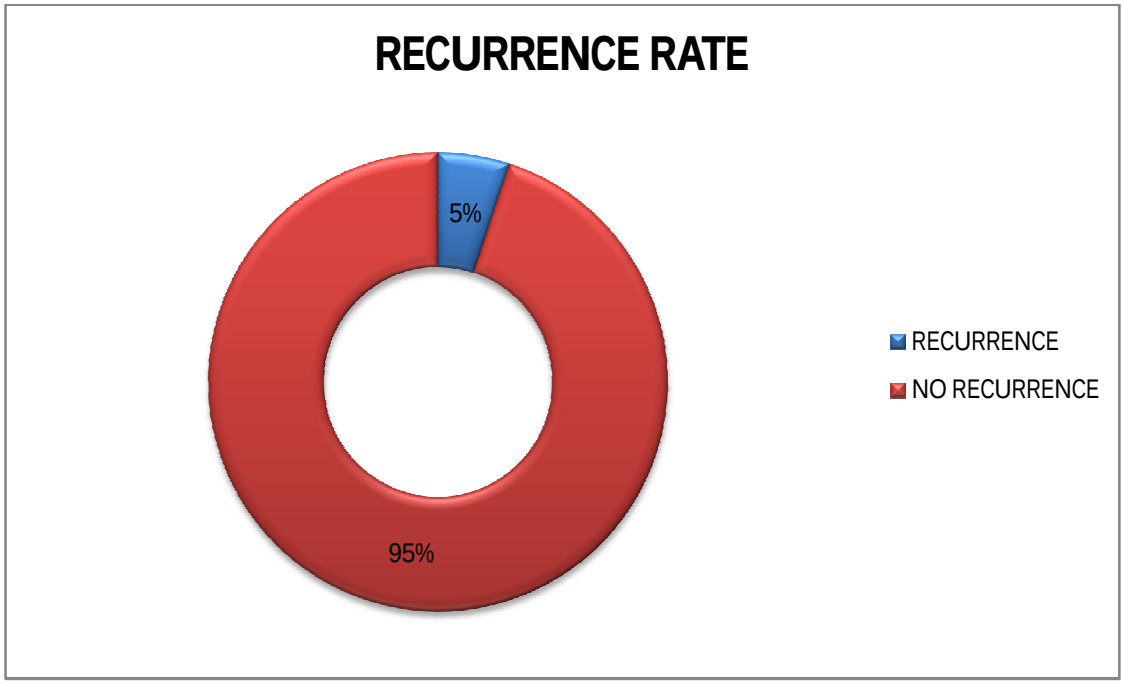
CORNEAL INVOLVEMENT

CORNEAL INVOLVEMENT	NO OF PATIENTS	PERCENTAGE
INVOLVED	18	90%
NOT INVOLVED	2	10%
TOTAL	**20**	**100%**



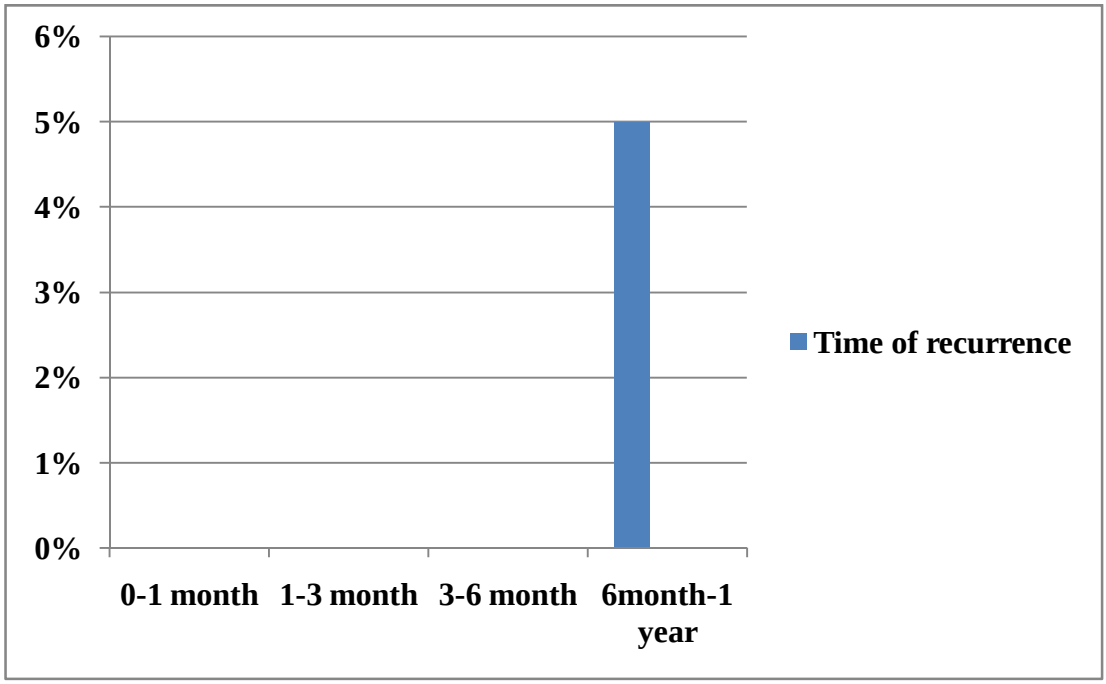
RECURRENCE RATE

RECURRENCE RATE	NO OF PATIENTS	PERCENTAGE
RECURRENCE	1	5%
NO RECURRENCE	19	95%
TOTAL	**20**	**100%**



TIME OF RECURRENCE

TIME OF RECURRENCE	NO OF PATIENTS	PERCENTAGE
0-1 MONTH	NIL	0%
1-3 MONTHS	NIL	0%
3-6 MONTHS	NIL	0%
6 MONTHS- 1 YEAR	**1**	**5%**



POST OPERATIVE FOLLOW UP 6- 12 MONTH

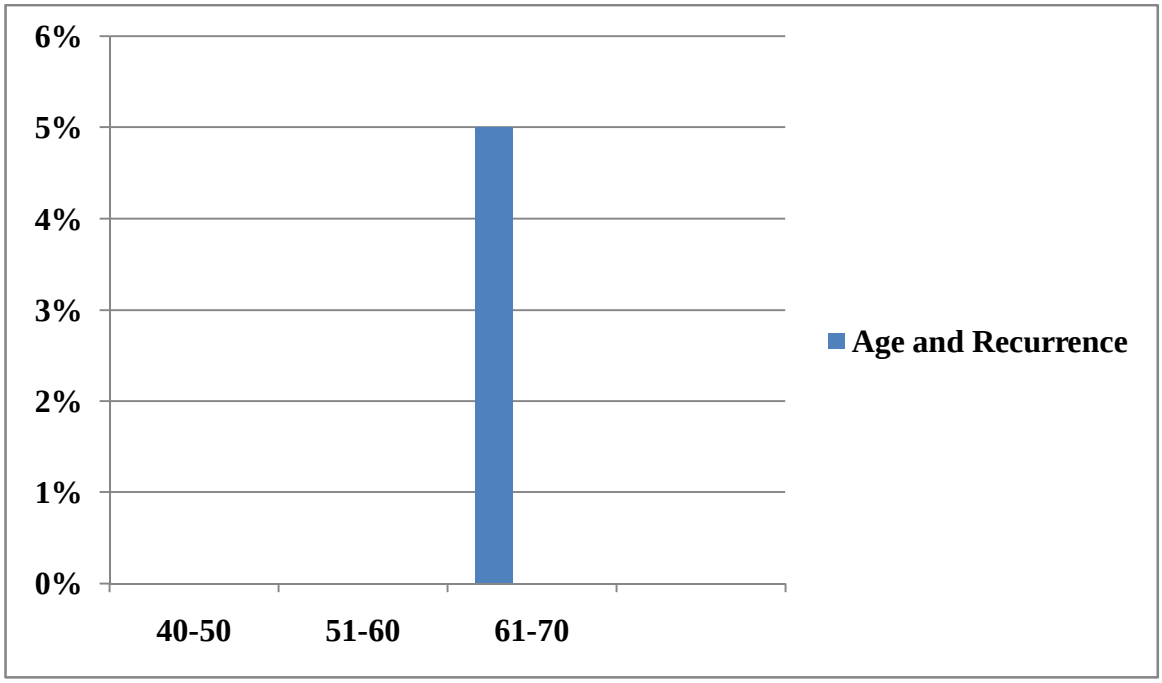
	OBSERVED N	PERCENTAGE	P VALUE
RECURRENCE	1	5	<0.001**
NOT RECURRENCE	19	95	
TOTAL	**20**	**100**	

In the study group with Ocular Surface Squamous Neoplasia who received intraoperative and post operative Mitomycin C on one year follow up recurrence developed only in 5% of patients and the remaining 95% does not had any recurrence. By chi square test it is statistically significant. P value < 0.001**

AGE AND RECURRENCE

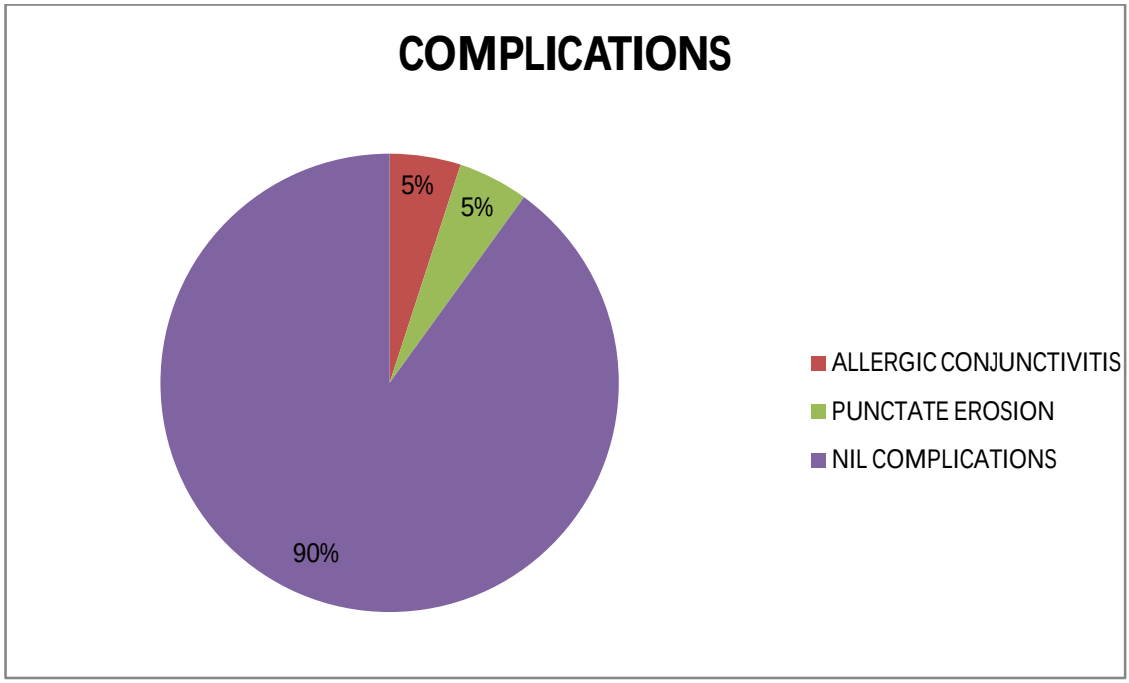
AGE GROUP	NO OF PATIENTS	PERCENTAGE
40-50	NIL	0%
51-60	NIL	0%
61-70	1	5%

AGE AND RECURRENCE



COMPLICATIONS FOLLOWING MMC

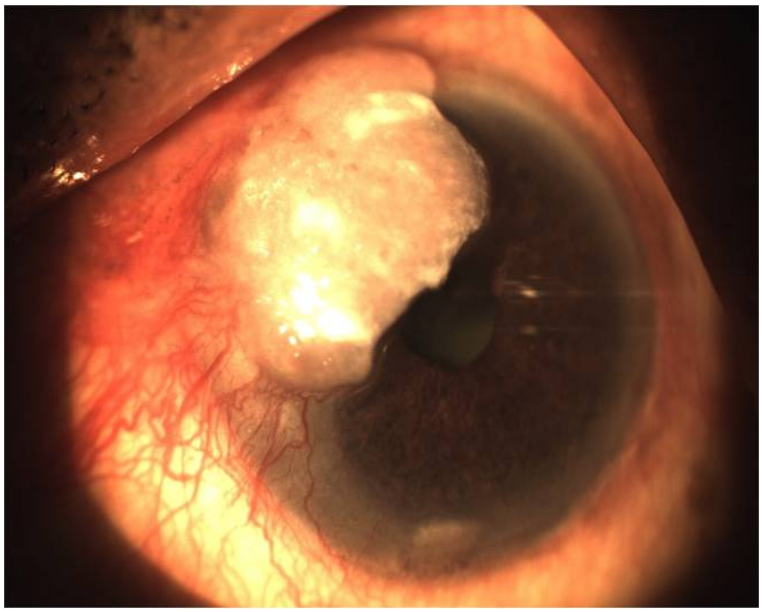
COMPLICATIONS	NO OF PATIENTS	PERCENTAGE
ALLERGIC CONJUNCTIVITIS	1	5%
PUNCTATE EROSION	1	5%
NIL COMPLICATIONS	18	90%
TOTAL	**20**	**100%**



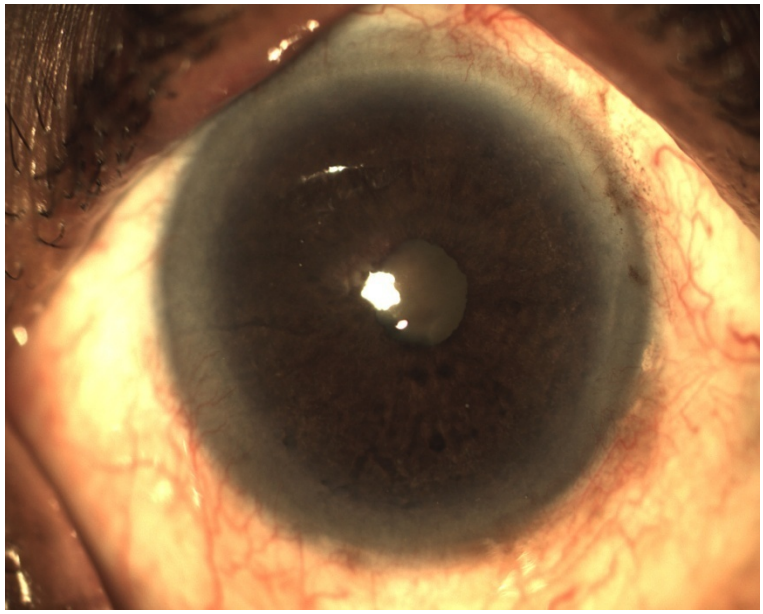
SIZE AND RECURRENCE

SIZE OF LESION	NO. PATIENTS	RECURRENCE	PERCENTAGE
4mm	1	Nil	0%
5mm	3	Nil	0%
6mm	7	Nil	0%
7mm	5	Nil	0%
8mm	2	Nil	0%
9mm	1	Nil	0%
>10mm	1	1	5%
Total	**20**	**1**	**5%**

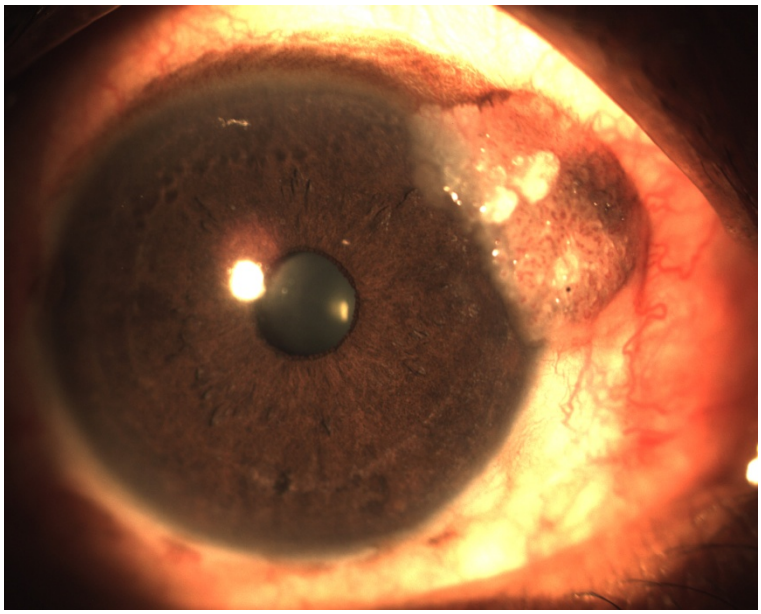
PRE-OPERATIVE PICTURE



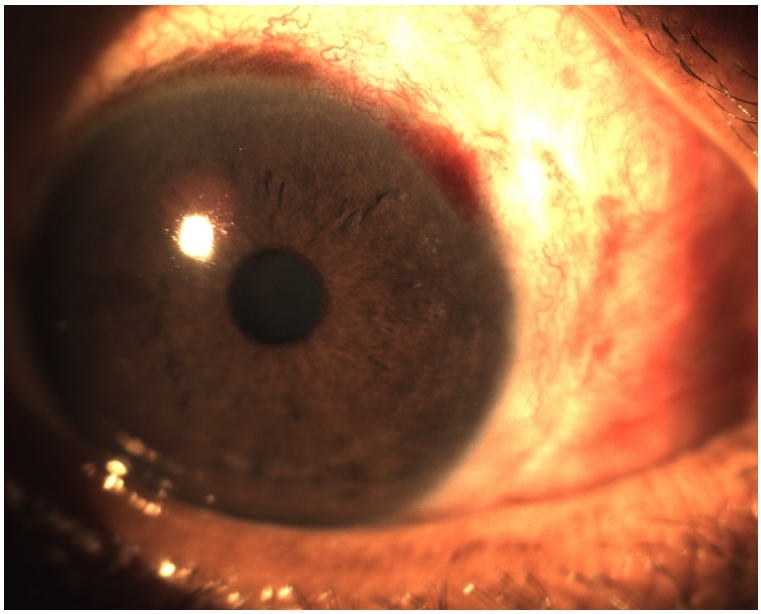
POST-OPERATIVE PICTURE
AFTER MITOMYCIN C APPLICATION



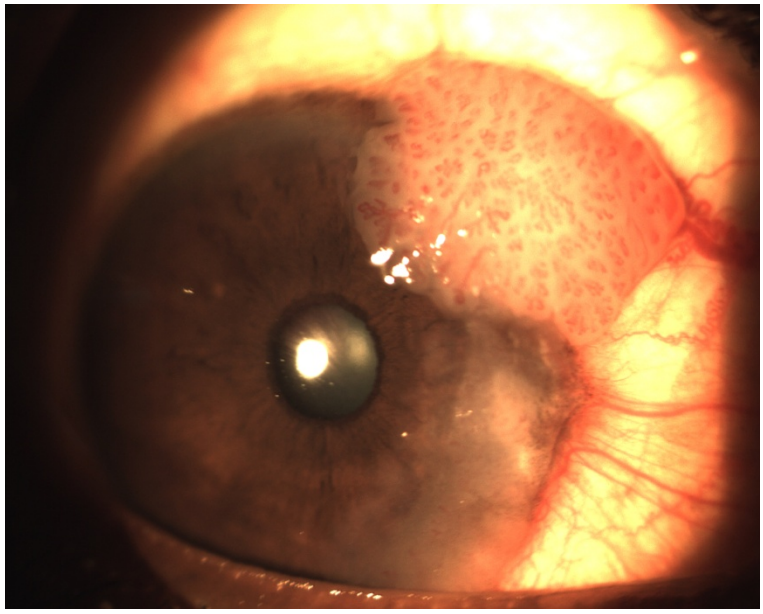
PRE-OPERATIVE PICTURE



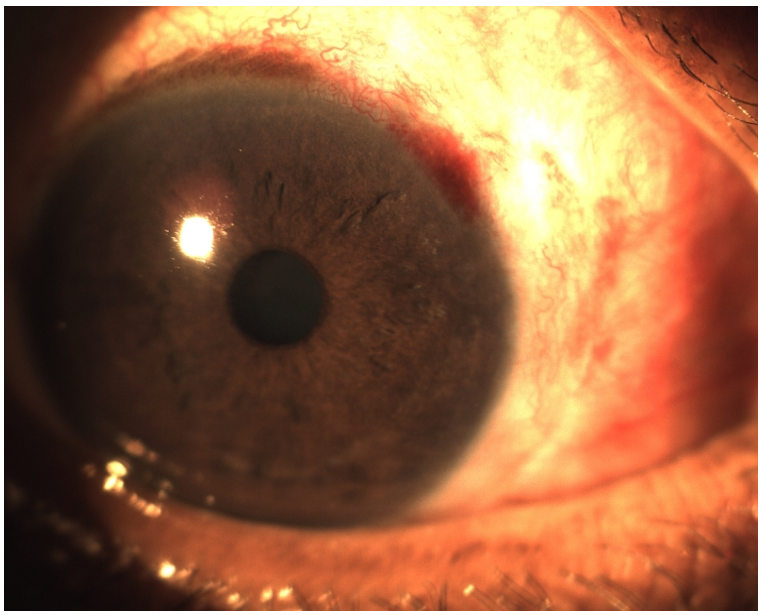
POST-OPERATIVE PICTURE
AFTER MITOMYCIN C APPLICATION



PRE-OPERATIVE PICTURE



POST-OPERATIVE PICTURE
AFTER MITOMYCIN C APPLICATION



DISCUSSION

Surgical excision is the main modality of treatment for OSSN. Clinical examination and impression cytology are not effective in diagnosing invasive lesions, hence surgical excision becomes the first step in the management of OSSN. Advantages of surgical excision are a bulk of tumour can be removed, immediate microscopic examination of the tissue is possible, presence of invasive disease can be ruled out. The main drawback of surgical excision is high recurrence rate. So several other treatment modalities are used intraoperatively and postoperatively to reduce the rate of recurrence.

Intraoperative adjunctive treatments include cryotherapy, mitomycin c application, alcohol keratectomy and lamellar sclerokeratectomy. postoperative adjunctive treatments include – chemotherapy by using anti metabolites (MMC, 5-fluorocil), β irradiation, topical urea and immunotherapy (IFN α-2B, dinitrochlorobenzene).

The residual tumour cells along the margins of surgical excision were destroyed by using intraoperative cryotherapy. Thereby it can decreases the recurrence and hence it is most commonly used along with primary surgical excision. “The overall recurrence does not change significantly between those patients treated with intraoperative cryotherapy and those did not received cryotherapy (Br J Ophthalmol 2004; 88:17–18)”.

Intraoperative and post operative topical Mitomycin C as an adjunctive to surgical excision have many advantages in those patients with diffuse type of lesion and in those with recurrence. This drug has a significant anti-tumour activity and has a selective action on fastly replicating tumour cells.

Lesion located anywhere in the ocular surface even those on the conjunctival fornices can be managed effectively with MMC. It can prevent new tumour cells originating from other areas of ocular surface by destroying subclinical disease.

Mitomycin C has a long lasting effect even after completion of treatment thus reducing the potential for local metastatic spread .The bare surface created by surgery can be closed with the adjacent conjunctival tissues after Mitomycin c application, and it may be effective in eliminating residual tumour cells in the conjunctiva following surgical excision.

“Since 1994 several studies have reported the role of MMC in the treatment of both primary and recurrent OSSN”.

Mitomycin C should not be used alone and it should be combined with surgical excision as the invasive tumours may go unnoticed and this drug may have a limited penetrance into the deeper tumour tissues.

“Complications of Mitomycin C are common but are largely confined to the ocular surface. Self-limiting short-term complications were common however, deficiency of limbal stem cell appears to be a significant long-term complication (Br J Ophthalmol 2010; 94:1316-1321)”.

One of the patient in this study developed punctuate corneal erosion and another patient in this study developed allergic conjunctivitis. Those patients in our study does not show severe side effects like scleral thinning, cataract and iritis. This is due to intermittent therapy as the slower growing cell are protected from injury and it provides time for those cells to recover from damage caused to their DNA by the drug and decrease in the number of stem cells can also be prohibited .

Thus when contemplating use of topical Mitomycin C these serious complications should be taken into consideration. Serious side effects due to this drug can be acceptable when compared to beneficial effects if this drug.

“Our study demonstrates the use of intra operative and post operative Mitomycin C reduces the recurrence rate of OSSN and should be considered as an adjuvant treatment modality along with surgical excision”.

There is a significant reduction in the recurrence rate of Ocular Surface Squamous Neoplasia following two courses of Mitomycin C.

“These properties of mitomycin C support its potential chemotherapeutic effectiveness, as an adjunct to surgical excision”.

“We also noted that there are no systemic complications following the use of Mitomycin C”.

About 95% patients in this study does not developed any recurrence on one year follow up period. 5% of patients developed recurrence that may be attributed to old age and large diameter lesion. It is not possible to strongly believe that the tumour will not recur even after following up of the patients for a prolonged period of time.

“But close ongoing follow-up is recommended in view of the significant risk of persistent or recurrent disease”.

REVIEW OF LITERATURE

"A study was perfomed by C Chen, D Louis, T Dodd, J Muecke between 1998-2003(Br J Ophthalmol 2004; 88:17–18). In this study intraoperative mitomycin c was not given. Topical mitomycin c was given only postoperatively. 26 patients with hitologically proved non invasive limbal primary ossn in 27 eyes, with corneal involvement of < 4 clock hours extent was taken for this study. All the lesions were surgically excised completely. All cases received two 1 week courses of Mitomycin C 0.04% drops four times per day. All the patients were reviewed at 6 monthly intervals for 2 years. None of the patients showed recurrence. They concluded that topical Mitomycin C after surgical excision reduces the recurrence of OSSN and hence it can be considered as an adjuvant therapy in the management of OSSN".

"A similar study was conducted by E G Kemp, A N Harnett, S Chatterjee between May 1998 and April 2000(Br J Ophthalmol 2002;86:31–34) comprising of 11 patients. In this study pre operative and intra operative mitomycin c was given. All the 11 patients received topical Mitomycin C adjuvant therapy as 0.04% eye drops in two weekly courses four times a day either preoperatively alone or also intra operatively. All patients showed a positive response in the form of

decreased growth or regression in size of the lesion and no serious complication. Postoperative follow up of these patients for 6 months to 3 years after surgery showed no evidence of recurrence in all the patients. Thus they concluded that adjunctive therapy with mitomycin C for recurrent or diffuse OSSN was well acceptable and showed a good outcome".

"A retrospective study conducted in 2010 (Br J Ophthalmol 2010; 94:1316e1321) a 10-year review of the treatment outcomes and complications of topical mitomycin C in the treatment of OSSN. Of all the cases treated short-term complications occurred in 52% of the patients, of which only 7% of cases required cessation of treatment. Long-term complications like persistent keratoconjunctivitis, corneal problems and epiphora occurred in 31% of cases. Most important long-term complication is deficiency of limbal stem cells occurring in 12% cases. Self-limiting short-term complications were common. The results thus substantiate the success of Mitomycin C therapy in the treatment of OSSN".

"In this study 90 patients with primary/recurrent lesions are taken up for the study (Br.j.ophthalmology 2010; 94:555-558). All the cases were treated by surgical excision ± cryotherapy, followed by 2 or 3 courses of topical Mitomycin C post operatively. 73 cases of localised non-invasive conjunctival corneal intraepithelial neoplasia and 8 cases of recurrent conjunctival corneal intraepithelial neoplasia were managed by surgical excision with or without cryotherapy along with post operative Mitomycin C. 10 cases in the study group with diffuse conjunctival corneal intraepithelial neoplasia managed by Mitomycin C alone. Follow-up of these patients showed no recurrences (0%) in the localised primary group and two recurrences (30%) and one persistent case in the diffuse primary group. One case of recurrence (12.5%) in the recurrent group, but that was in the eye with a diffuse lesion. They concluded that topical Mitomycin C application after surgery reduce the recurrence of localized lesions and can be used as an adjunctive therapy in the management of OSSN. Mitomycin C can be used alone in the management of large lesions but periodic review is necessary as there is a significant risk of persistent or recurrent disease.

"*C.S. SIGANOS ET AL* in this study eight cases of OSSN were included. All of them received 0.02% of intraoperative MMC. Two of these patients received conjunctival limbal autograft during surgery. Seven patients does not showed any recurrence during follow up and only one patient with histologically proved squamous cell carcinoma showed recurrence and this patient was treated by topical Mitomycin C and on subsequent follow up he did not show any recurrence. Hence it was proved that surgical excision combined with Mitomycin c application reduces recurrence. It was also concluded that limbal autografting along with Mitomycin C does not alter the outcome."

SUMMARY

In this study of 20 patients with Ocular Surface Squamous Neoplasia, 50% of patients were in the age group of 51-60 years. 60% of patients in this study group are Men and 5% of patients had gelatinous type of lesion. Right eye is affected in 60% of patients. Primary OSSN occurs in 90% of patients. The commonest indication for surgery is ocular irritation (65%). Only 5% of the patients developed recurrence after intraoperative and post operative Mitomycin C application. Recurrence developed in the age group of about 70 years, and patients with lesion of more than 10mm size. 2 patients developed self limiting complications like allergic conjunctivitis and punctuate corneal erosion. None of them developed serious and long term side effects.

CONCLUSION

The results confirms that introperative and post operative Mitomycin C application is the most effective adjuvant therapy in the management of ocular surface squamous neoplasia

The advantages of Mitomycin C over other adjuvant therapies are

1) The recurrence rate following intraoperative and postoperative Mitomycin C is significantly lower than other modalities of adjuvant therapy
2) It mimics ionizing radiation because its effects can persists for many years even after cessation of treatment
3) By destroying the subclinical disease it prevents the formation of recurrence in the ocular surface including the conjuctival fornices

Short term complications following the treatment are common but self limiting, serious complications are avoided by intermittent therapy .

There are no systemic side effects.

PART 3

BIBLIOGRAPHY

1. Duke-Elder S, Leigh AG. Diseases of the outer eye.In: Duke-Elder S, ed. Systems of Ophthalmology, Vol 7, Part 2. St Louis: CV Mosby, 1985:1154–1159.
2. Nichols JV. Epithelial plaques of the conjunctiva and cornea. Arch Ophthalmol 1939; 22:370–6.
3. McGavic JS. Intraepithelial epithelioma of the cornea and conjunctiva (Bowen's disease). Am J Ophthalmol 1942; 25:167–76.
4. Ash JE, Wilder HC. Epithelial tumors of the limbus.Am J Opthalmol 1942; 25:926–32.
5. Janert H. Zur peracancerose der cornea und con- junctiva. Von Graefes Arch Ophthalmol 1956; 157:380–96.
6. Lugossy G. Precancerous conditions of the bulbar conjunctiva. Am J Ophthalmol 1956; 42:112–25.
7. Winter FC, Kleh TR. Precancerous epithelioma of the limbus. Arch Ophthalmol 1960; 64:208–15.
8. Irvine AR Jr. Dyskeratotic epibulbar tumors. TransAm Ophthalmol Soc 1963; 61:243–73.
9. Pizzarello LD, Jakobiec FA. Bowen's disease of the conjunctiva: a misomer. In: Jakobiec FA, ed. Ocu- lar Adnexal Tumors, Birmingham, AL: Aescula- pius, 1978:553–571.

10. Lee GA, Hirst LW. Ocular surface squamous neoplasia.SurvOphthalmol 1995; 39:429-450.

11. Basti S, Mascai MS. Ocular surface squamous neoplasia. Cornea 2003;22(7):687-704

12. Kiire CA, Srinivasan S, Karp CL. Ocular surface squamous neoplasia.IntOphthalmolClin. 2010;50(3): 35-46 cryotherapy, and mitomycin-C for recurrent ocular surface squamous neoplasia. Cornea 2002; 21:189–91

13. Wilson MW, Hungerford JL, George SM, et al. Topical mitomycin C for the treatment of conjunctival and corneal epithelial neoplasia with topical mitomycin C. Am J Ophthalmol 1997;124:397–9.

14. Vann RR, Karp CL. Perilesional and topical interferon alfa-2b for conjunctival and corneal neoplasia. Ophthalmology 1999;106:91–7.

15. Kaines A, Malhotra R, Selva D, et al. Conjunctival squamous cell carcinoma with perineural invasion. Arch Ophthalmol

16. Sudesh S, Rapuano CJ, Cohen EJ, et al. Surgical management of ocular surface squamous neoplasms : the experience from a cornea center. Cornea 2000;19:278–83.

17. McKelvie Daniell M. Impression cytology following mitomycin C therapy for ocular surface squamous neoplasia. Br J Ophthalmol 2001;85:1115–19.

18. Rozenman Y, Frucht-Pery J. Treatment of conjunctival intraepithelial neoplasia with topical drops of mitomycin C. Cornea 2000;19:1–6.
19. Frucht-Pery J, Sugar J, Baum J, et al. Mitomycin C treatment for conjunctival-corneal intraepithelial neoplasia: a multicentre experience. Ophthalmology 1997;104:2085–93.
20. Finger PT, Czechonska G, Liarikos S. Topical mitomycin C chemotherapy for conjunctival melanoma and PAM with atypia. Br J Ophthalmol 1998;82:476–9.

PROFORMA

NAME :

AGE :

SEX :

OCCUPATION :

ADDRESS :

DATE :

IP NUMBER :

DOA :

DOS :

DOD :

COMPLAINTS :

PRESENT HISTORY:

PAST HISTORY :

PERSONAL H/O :

GENERAL EXAMINATION

EXAMINATION OF THE EYES	RE	LE
VISUAL ACUITY :		
SLITLAMP EXAMINATION	RE	LE
LIDS :		
OCULAR MOVEMENTS :		
CONJUNCTIVA :		
CORNEA :		

EXAMINATION OF THE LESION

MORPHOLOGY OF THE LESION :

SITE :

SIZE :

SHAPE :

COLOUR :

SURFACE :

EXTENT :

IRIS :

ANTERIOR CHAMBER :

PUPILS :

LENS :

FUNDUS

INVESTIGATIONS

RE LE

SYRINGING OF NASOLACRIMAL DUCT

SCHIRMER'S TEST

INTRAOCULAR PRESSURE

GONIOSCOPY

B SCAN

UBM

COMPLETE BLOOD COUNT :

BLEEDING TIME :

CLOTTING TIME :

RANDOM BLOOD SUGAR :

URINE albumin &sugar :

HIV SEROLOGY :

BLOOD PRESSURE :

SURGERY PERFORMED :

DONE ON :

POST OPERATIVE TREATMENT :

DATE OF MITOMYCIN EYE DROPS STARTED POST OPERATIVELY

HISTOPATHOLOGICAL REPORT :

FOLLOW UP

AT EACH VISIT –

VISUAL ACUITY

SLIT LAMP EXAMINATION OF THE EXCISED SITE

1 MONTH :

3 MONTHS :

6 MONTHS :

1 YEAR :

MASTER CHART

1	2	3	4	5	6	7	8	9	10	11	12				13
											a	b	c	d	
1.	Sherifabee	65/f	41951	RE	G	8mm	P	VI	RE	a	NR	NR	NR	NR	
2.	Subramani	45/m	58888	RE	P	6mm	P	OI	RE	a	NR	NR	NR	NR	
3.	Mani	55/m	68875	RE	P	7mm	P	VI	RE	a	NR	NR	NR	NR	
4.	Nagammal	45/f	57667	RE	P	6mm	P	OI	RE	a	NR	NR	NR	NR	
5.	Kalyani	70/f	70202	RE	L	7mm	P	OI	RE	a	NR	NR	NR	NR	
6.	Rathinavelu	70/m	26130	RE	G	11mm	P	VI	RE	a	NR	NR	NR	R	
7.	Arunachalam	45/m	65536	RE	G	5mm	P	OI	RE	a	NR	NR	NR	NR	
8.	Sumathy	50/f	74754	RE	G	9mm	P	VI	RE	a	NR	NR	NR	NR	
9.	Umaiyal	60/f	75126	LE	L	5mm	P	OI	LE	b	NR	NR	NR	NR	
10.	Vellatchi	55/f	73216	LE	G	7mm	P	OI	LE	a	NR	NR	NR	NR	

11.	Saroja	57/F	62835	RE	G	6mm	P	OI	RE	a	NR	NR	NR	NR	Allergic conjuctivitis
12.	Palani	63/m	68653	LE	P	6mm	P	OI	LE	a	NR	NR	NR	NR	
13.	Veeran	54/m	25321	LE	P	6mm	P	CD	LE	a	NR	NR	NR	NR	
14.	Ravi	55/m	42168	LE	P	7mm	P	OI	LE	a	NR	NR	NR	NR	
15.	Muniammal	57/f	28321	RE	G	5mm	P	OI	RE	a	NR	NR	NR	NR	
16.	Ramadoss	58/m	56234	LE	G	8mm	P	VI	LE	a	NR	NR	NR	NR	
17.	Manickavelu	62/m	74638	LE	G	4mm	R	OI	LE	b	NR	NR	NR	NR	
18.	Indiran	63/m	57271	RE	L	6mm	P	OI	RE	a	NR	NR	NR	NR	Punctate erosion
19.	Ramamoorthy	59/m	42675	LE	G	7mm	R	VI	LE	a	NR	NR	NR	NR	
20.	Prakasam	57/m	26832	RE	P	6mm	P	OI	RE	a	NR	NR	NR	NR	

KEY TO MASTER CHART

1)Serial number

2)Name of the patient

3)Age & Sex

4)Op/Ip number

5)Eye affected

6)Type of the lesion

G-Gelatinous type, P-Papillomatous,L-Leukoplakic

7)Size of the lesion

8)Presentation of the patient

P-Primary,R-Recurrent

9)Indication for surgery

OI-Ocular irritation,VI-Visual impairment,CD-Cosmetic disfigurement

10)Eye operated

11)Corneal involvement

a-corneal involved,b-not involved

12)Post operative follow up

a-monthly,b-3 months,c-6 months,d-1 year

NR-No recurrence,R-Recurrence

13)Complications of Mitomycin c