Dissertation on

"ANALYTICAL STUDY OF NON INVASIVE TECHNIQUES IN DIAGNOSING OCULAR SURFACE SQUAMOUS NEOPLASIA"

Submitted in partial fulfillment of requirements of

M.S.OPHTHALMOLOGY

BRANCH – III

REGIONAL INSTITUTE OF OPTHALMOLOGY

MADRAS MEDICAL COLLEGE

CHENNAI – 600 003

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY
CHENNAI- 600003
APRIL 2017

CERTIFICATE

This is to certify that the dissertation titled , **"ANALYTICAL STUDY OF NON INVASIVE TECHNIQUES IN DIAGNOSING OCULAR SURFACE SQUAMOUS NEOPLASIA"** is a bonafide research work done by Dr.RADHA PRIYADHARSHINI.R, post graduate in Regional Institute of Ophthalmology and Government Ophthalmic Hospital, Madras Medical Medical College, Chennai - 3, in partial fulfillment of the regulations laid down by The Tamil Nadu Dr.M.G.R. Medical University for the award of M.S. Opthalmology Branch III, under guidance and supervision during the academic years 2014-2017.

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DECLARATION

I, Dr.RADHAPRIYADHARSHNI.R solemnly declare that the dissertation on **"ANALYTICAL STUDY OF NON INVASIVE TECHNIQUES IN DIAGNOSING OCULAR SURFACE SQUAMOUS NEOPLASIA"** was done by me at Madras Medical College during 2014-2017 under the guidance and supervision of **Prof. DR.M.ANANDA BABU M.S., D.O.,** Chief, Department of Ophthalmology (Cornea services), Regional institute of Ophthalmology and Government ophthalmic hospital, Madras Medical College, Chennai – 3.

The dissertation is submitted to the Tamil Nadu Dr.MGR Medical University towards the partial fulfillment of the rules and regulations for the award of **M.S.Degree in Ophthalmology (Branch- III).**

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

Place : CHENNAI **Dr. RADHAPRIYADHARSHNI.R**

Date :

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CERTIFICATE OF APPROVAL

To
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Madras Medical College
Chennai 600 003

Dear Dr.R.Radha Priyadharshini,

The Institutional Ethics Committee has considered your request and approved your study titled " **ANALYTICAL STUDY OF NON INVASIVE TECHNIQUES IN DIAGNOSING OCULAR SURFACE SQUAMOUS NEOPLASIA" NO.-17052016**

The following members of Ethics Committee were present in the meeting hold on **03.05.2016** conducted at Madras Medical College, Chennai 3.

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

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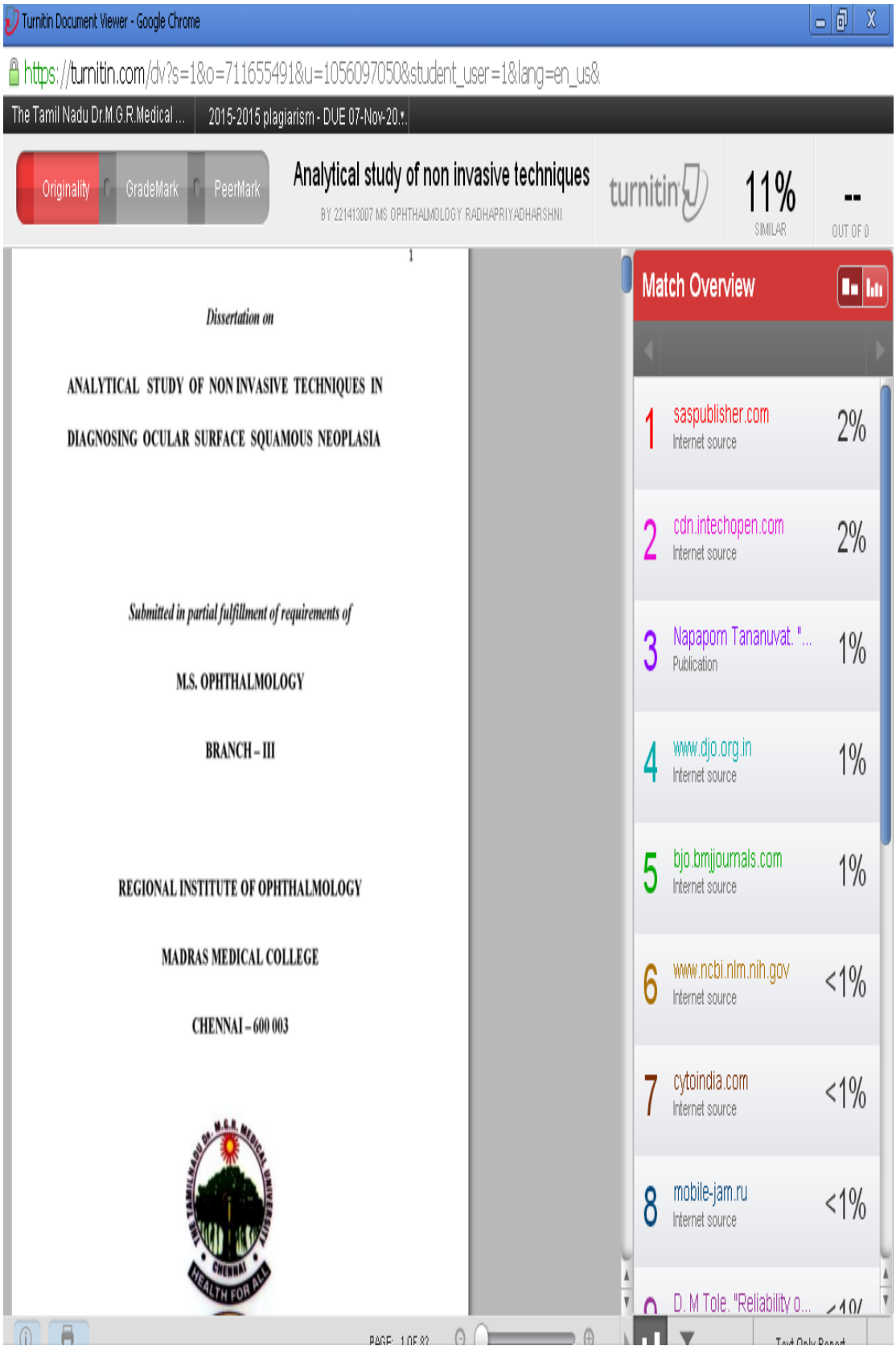
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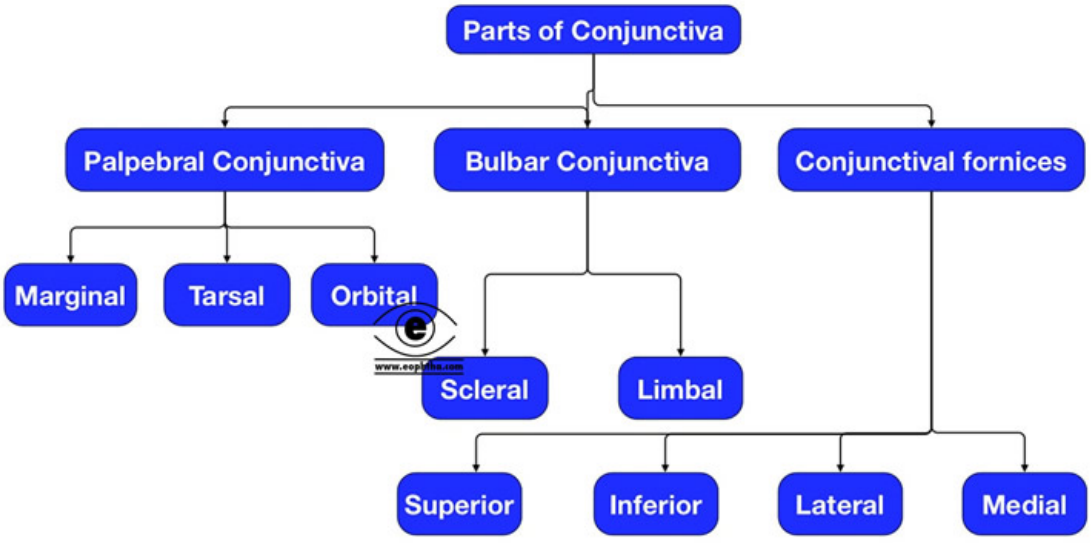
INTRODUCTION:

Anatomy of Ocular surface:

Ocular surface includes conjunctiva, cornea and limbus.

Conjunctiva: It is a transparent mucous membarane covering the anterior surface of eyeball and posterior surface of eyelids. It extends from mucocutaneous junction of the lids to the limbus. It is composed of 3 geographic zones: palpebral, fornical, and bulbar .



"The *palpebral conjunctiva* begins at the mucocutaneous junction of the eyelid and it covers the inner surface eyelid. This part firmly attached to the tarsus".

Palpebral conjunctiva inturn divided into mucocutaneous junction, tarsal conjunctiva, orbital conjuctiva.

"The *bulbar conjunctiva* is fused with the Tenon's capsule and gets inserted into the limbus". It is further divided into scleral part and limbal part.

"The *forniceal conjunctiva is* freely movable in the fornices and 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". Plica semilunaris and caruncle is located medially.

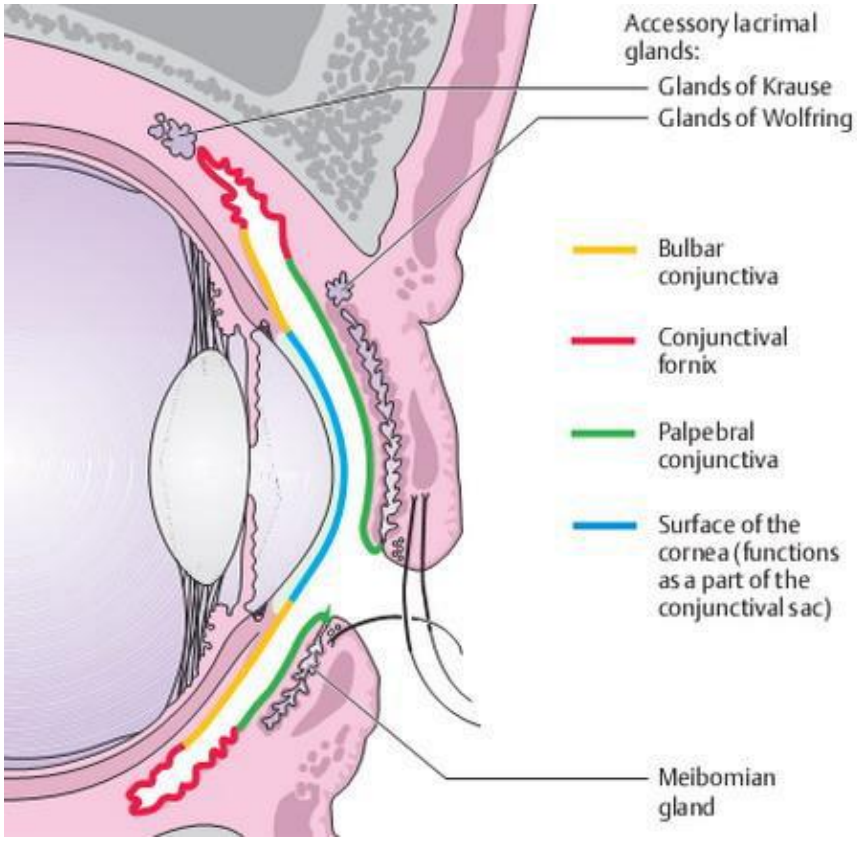


Fig 1 : Parts of Conjunctiva

Glands:

There are two types of glands present in conjunctiva, they are serous glands and mucous glands.

Serous glands includes glands of Krause and glands of wolf ring. Mucous glands consists of glands of henle which are present in the upper edge of superior tarsus and are composed of goblet cells. They secrete mucus.

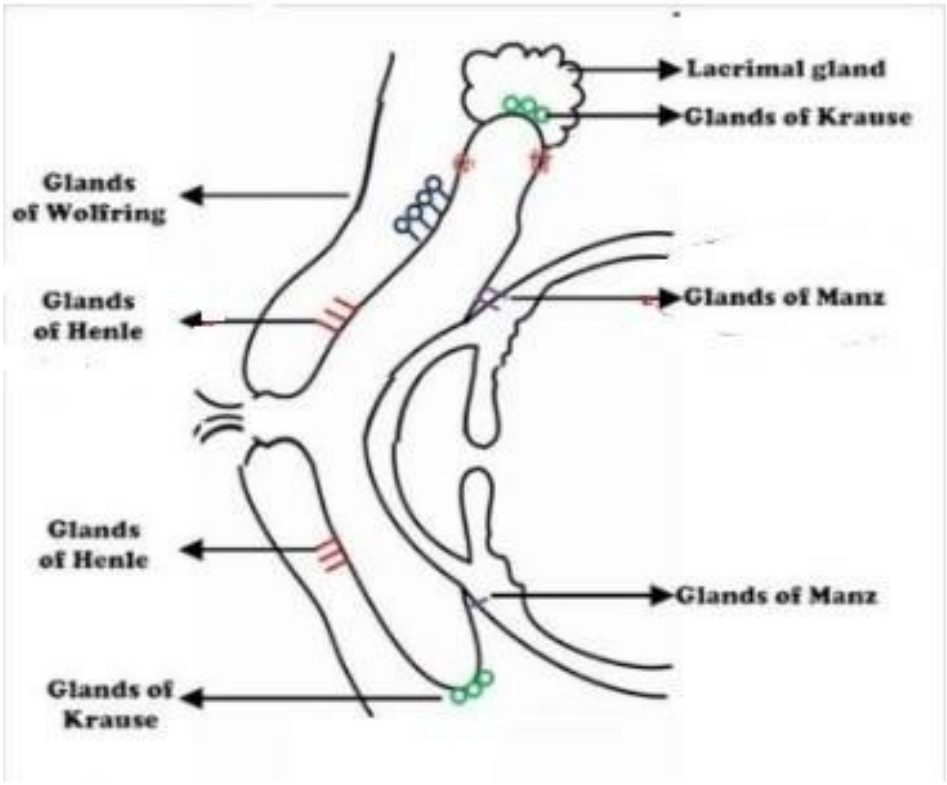


Fig 2 : Glands of Conjunctiva

Histology of Conjunctiva:

Conjunctival epithelium is made up of basal cells, intermediate cells, superficial cells. Other cells include melanocytes which are present in basal layer and langerhan cells which are immuno competent cells. Lymphocytes and neutrophils are present both in epithelium, substantia propria.

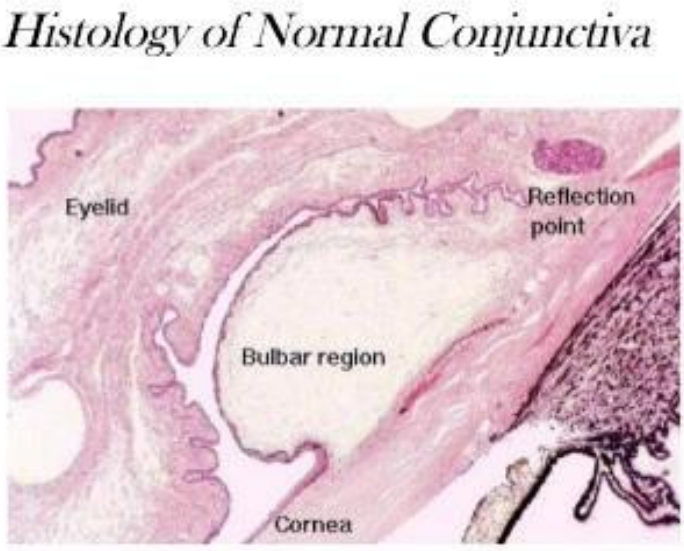


Fig 3 :

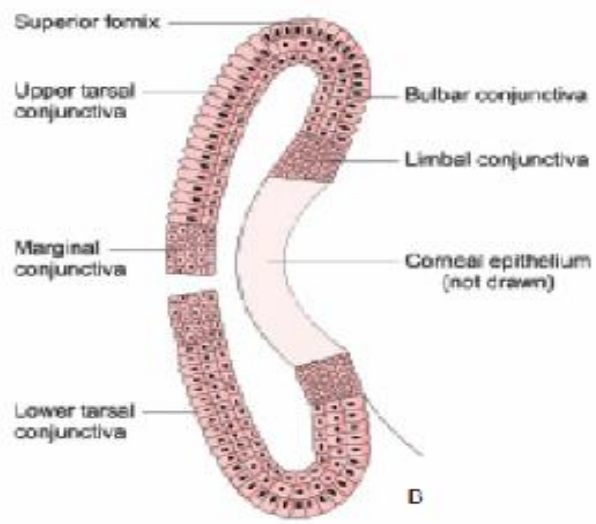


Fig 4 : Different Epithelium of Conjunctiva

The forniceal conjunctiva consists of superficial epithelial cells which are cylindrical in shape. The limbal conjuctival epithelium is the transition zone between corneal and conjunctival epithelia. It consists of stratified epithelium with flattened superficial epithelial cells.

Limbal Epithelial Stem cells:

They are found in basal layer of limbus. It consists of langerhans cells, melanocytes, early transient amplifying cells (eTAC). These early transient amplifying cells can get transformed into late transient amplifying cells and are located in the basal layer of cornea. The conjunctiva is a mucous membrane with rich blood supply and lymphatic vessels.It also contains numerous goblet cells ,plasma cells, macrophages and mast cells. Lymphoid layer extends from the bulbar portion of conjunctiva to the sub tarsal folds of the eyelids. There are some areas of specialized aggregations of *conjunctiva-associated lymphoid tissue (CALT)* corresponding to the *mucosa associated lymphoid tissue (MALT)* are present. They contain collections of T and B lymphocytes lying underneath a modified epithelium and these regions are supposed to be concerned with antigen processing.

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.

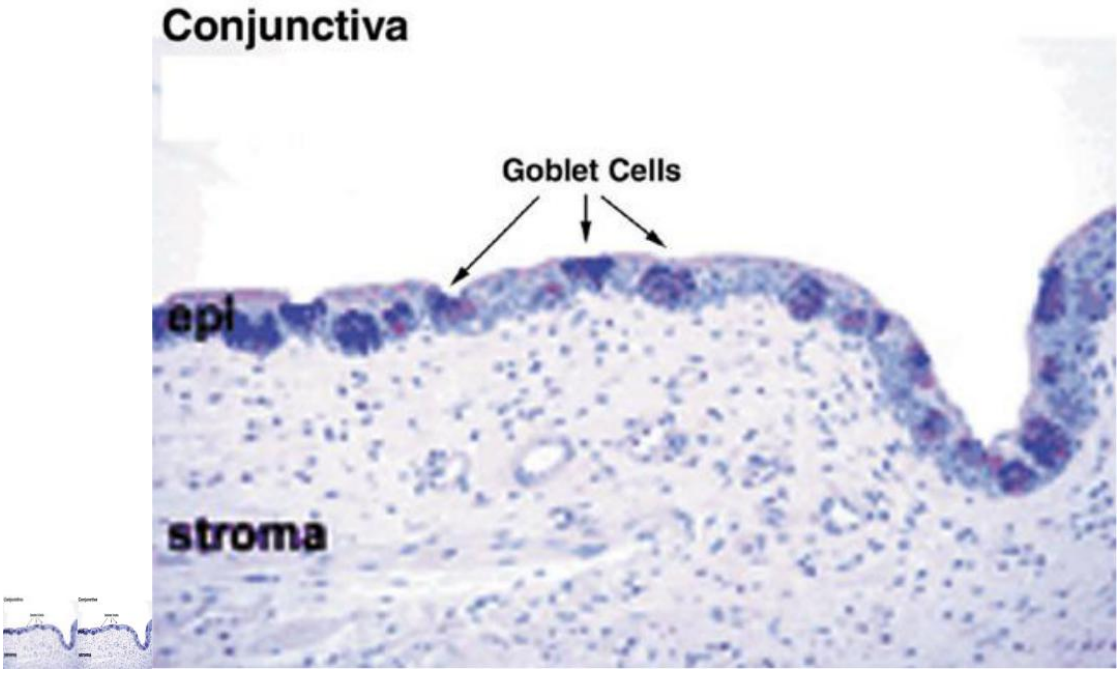


Fig 5 : Goblets Cells of Conjunctiva

The conjunctiva reflects on all the three sides to form a fornix except medially where plica semilunaris is located. The conjunctiva is loose in this area which allows free movement of the eyelids and the eyeball . The folds of Conjunctiva increase the surface area and decrease the contact between tarsal and bulbar conjunctiva.

The superior fornix is large and it is formed by smooth muscle strips which extend and from the lower part of levator palpebrae muscle to the conjunctiva. Hence during upward gaze it prevents the superior fornix of conjunctiva from moving down and obscuring vision.

The temporal conjunctiva gets attached to lateral rectus tendon by means of fine fibrous strips which maintains its position during horizontal gaze. Fibrous strips from the tendon of medial rectus get inserted into the caruncle and plica semilunaris .During medial rectus contraction adduction of eye occurs and a cul-de-sac. The surface area of each eye of adult conjunctiva including cornea is about 16 cm^2 .

Plica semilunaris is a semi lunar- shaped fold of conjunctiva .Its outer border lies 3–6 mm lateral to the conjunctival caruncle and a cul-de-sac of 3 mm depth is formed on adduction that obliterate when the eye abduct.

The substantia propria has high blood supply. It contains smooth muscle fibres, sympathetic nerves, fatty tissue and cartilage.

In the interpalpebral fissure caruncle is situated medially. It is about 4mm horizontally and 3mm vertically and it joins the medial rectus muscle and travels along with plica while moving the eyeball. It also contains accessory lacrimal gland , pilosebaceous units, eccrine glands and few non striated muscle fibres. The caruncle may have lots of large sebaceous glands and noted like meibomian glands sometimes.

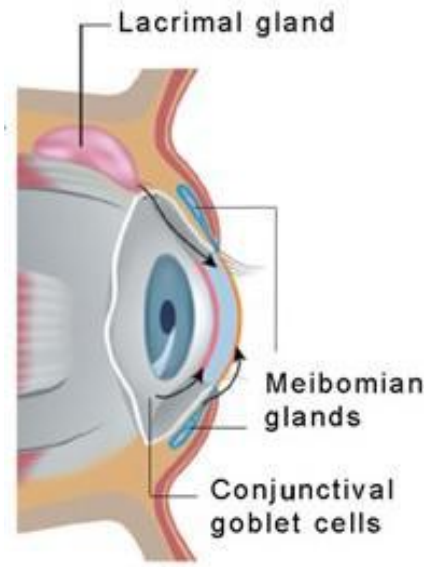


Fig 6 : Meibomian glands

The Meibomian glands are yellow round glands which are secluded by blood vessel arches of tarsal plate of the upper and lower eyelids. Their duct run perpendicular to the lid margin.

The nonkeratinized portion of the lid is seperated from keratinized portion by a Hydrophobic strip of lipid. These lipids come from the meibomian glands. The tarsal conjunctiva strongly attached to tarsal plate, hence corneal surface appears to be smooth.

The Tear film meniscus air–fluid border determines the Position of mucocutaneous junction. The mucocutaneous junction moves posteriorly in case of ectropion and moves anteriorly in case of entropion.

There are many grooves present in between tarsal groove and eyelid margin.These ridges communicates to the invagination surfaced with goblet cells of the conjunctiva. These crypts are few in number during childhood period and most of them develops at the time of puberty. “Above 50 years these crypts are identified in about one-third of conjunctival specimens. Crypts are usually more in number near the medial portion of the conjunctiva and in plica semilunaris”.

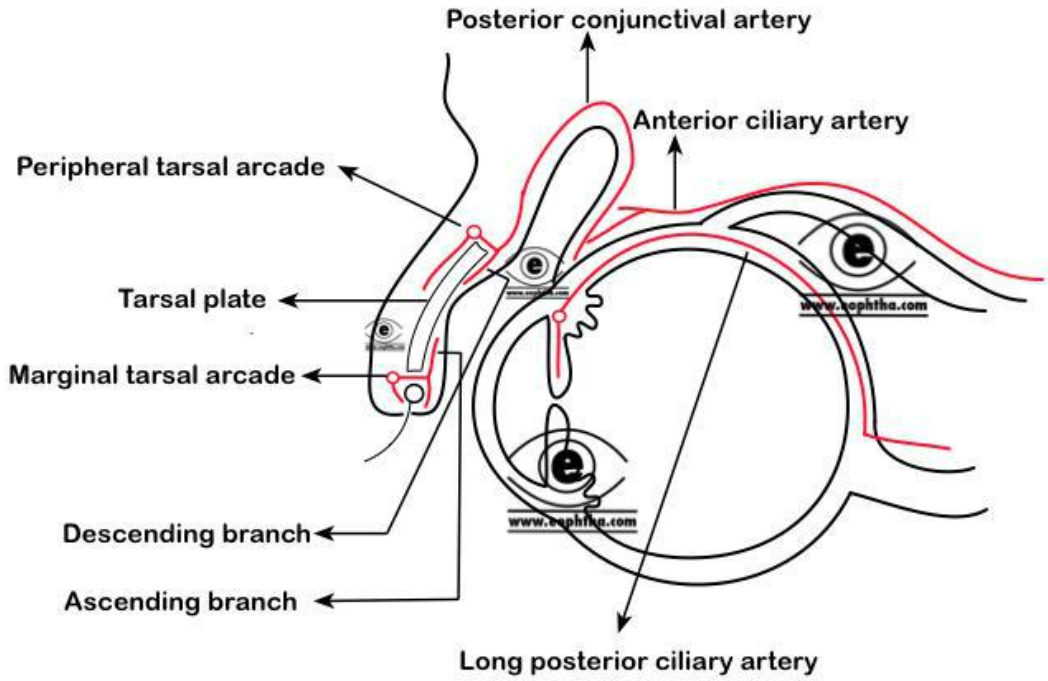


Fig 7 : Blood supply of conjunctiva

Anterior ciliary arteries supply blood to the Bulbar conjunctiva. The tarsal conjunctiva is supplied by 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 is supplied by the ciliary arteries through the anterior conjunctival arteries. A vascular watershed area lies between the anterior and posterior vascular territories which is approximately 3 or 4 mm away from the limbus. The conjunctiva is innervated by 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 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.

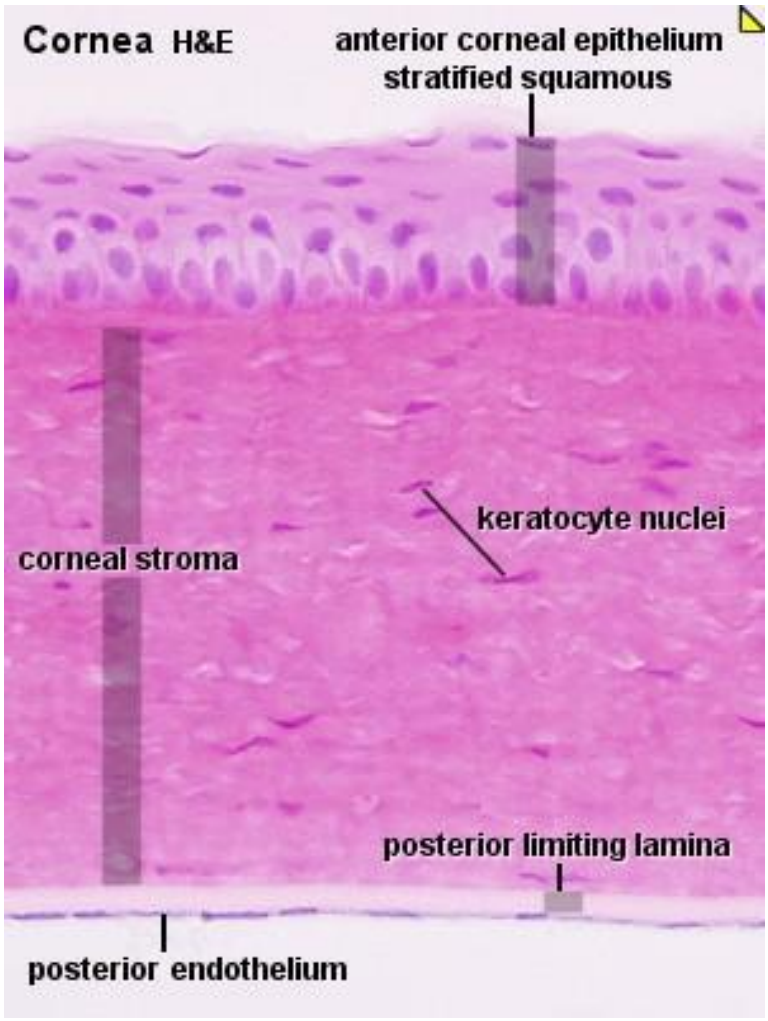


Fig 8 : Histology of Cornea

The anterior surface of cornea is derived from surface ectoderm and is lined by nonkeratinising stratified squamous epithelium whose basal columnar layer by hemi desmosomes 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 hemi desmosomes 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.

LIMBUS:

Limbus is the zone where the peripheral cornea and the anterior sclera transforms. 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. Familiarity with these landmarks is important to the surgeon performing cataract surgery or a glaucoma- filtering operation.

Ocular surface squamous neoplasia :

The first case of OSSN was described by Von graefe. In 1995 Lee and Hirst coined the term ocular surface squamous neoplasia[1]. It includes a Spectrum of conjunctival and corneal neoplasia.

Ocular surface squamous neoplasia are important because if it is not detected early it may lead to severe morbidity and death. If treated properly these consequences can be prevented.

Incidence:

Incidence of OSSN is about 0.13 to 1.9 / 1,00,000[1] population all over the world. It is more common in Males. The presenting age is from 60 to 70 years. It is usually unilateral and the most common site is Limbus. It predominantly affects dark skinned Caucasians. Patients of HIV and xeroderma pigmentosa are affected in earlier age group.

Risk Factors:

1. Ultraviolet irradiation
2. HPV infection.
3. HIV positivity
4. Immunosuppression
5. Old age
6. Male sex
7. Smoking
8. Exposure to petroleum products

9. Vitamin A deficiency
10. Exposure to chemicals such as trifluridine and arsenicals
11. Xeroderma pigmentosum
12. Exposure to dust
13. Ocular trauma
14. Solar keratosis.

UV-B Radiation:

UV-B Radiation cause DNA damage which leads to production of pyrimidine dimmers. It is also found to be the cause for p53 gene mutation which intern leads to OSSN. Incase of xeroderma picmentosa there will be failure or delay in DNA repair mechanism which leads to OSSN[2].

Human Papiloma Virus:

Genotypes of HPV 6 and 11 are found to be involved in papilomas and dysplastic and malignant lesions of Cornea and Conjunctiva. HPV 16 and 18 are demonstrated in cases of conjunctival intra epithelial neoplasia

(CIN)[2].The E6 region of HPV 16 and 18 codes a protein which forms a complex with protein coded by p53 tumour suppressor gene in the host.

HIV:

OSSN is associated with HIV in most of the patients. In Africa there was an increase in the number of cases of OSSN followed by a huge pandemic of HIV infection[2]. It showed a 10 fold increased risk in HIV infected individuals in Uganda (Waddell et al. 1996).

OSSN is found to be more aggressive in those patients who are infected with HIV. Those patients are get affected in the younger age itself and require enucleation or even exenteration.

Xeroderma Pigmentation:

It is an autosomal recessive disorder, where the defect is in DNA repair mechanism. It can cause aggressive OSSN even in younger patients. A study was conducted at National Eye Institute where 87 patients having xeroderma pigmentosa were studied, which revealed 10% patients had OSSN.

Immunosuppression:

Those who underwent corneal grafting, developed OSSN because of local immune suppression. HPV or Neoplastic cells from the donor's corneal epithelial cells may be the reason for the development of OSSN.

Clinical Manifestations:

OSSN presents as a growth over the ocular surface which may lead to symptoms such as foreign body sensation, irritation and decrease in vision which may be due to high Astigmatism or Visual access involvement. Usually OSSN starts in the conjunctiva and may extend towards Cornea. If cornea is involved it will be in pearly grey in color with tufts of vessels which are termed as sentinel vessels with or without well defined borders.

Grades of OSSN:

Benign dysplasia

Pseudotheliomatous hyperplasia

Papilloma

Benign herediatary intraepithelial dyskeratosis

Preinvasive OSSN

Conjunctival/corneal carcinoma in situ

Invasive OSSN

Squamous carcinoma

Mucoepidermoid carcinoma

Papilloma:

Papilloma can present either as pedunculated or sessile lesion.

Pedunculated Papilloma:

Pedunculated form looks like a stalk which is found to be a fibro vascular core. It is common in children and associated with HPV. The inferior fornix is the most common site of origin. It can get regressed spontaneously.

Fig 9 : Pedunculated Conjunctival Papilloma

Sessile papilloma:

`Usually Sessile papillomas are present near the corneo scleral junction. The stalk is absent in these type of lesions. It is related to HPV 16 & 18 infection. It is more common adults and the chances for dysplastic changes are high.

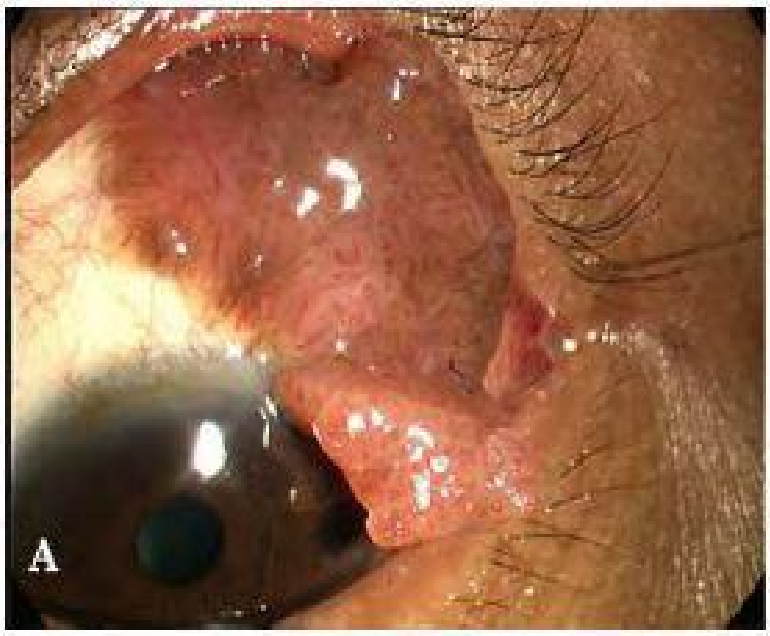


Fig 10 : Sessile Conjunctival Papilloma

CONJUNCTIVAL - CORNEAL INTRAEPITHELIAL

NEOPLASIA:

Grades of CCIN:

Based on the level of epithelial involvement, it can be classified as 3 grades.

Grade 1- The tumour cells are limited to the lower 1/3 of epithelium.

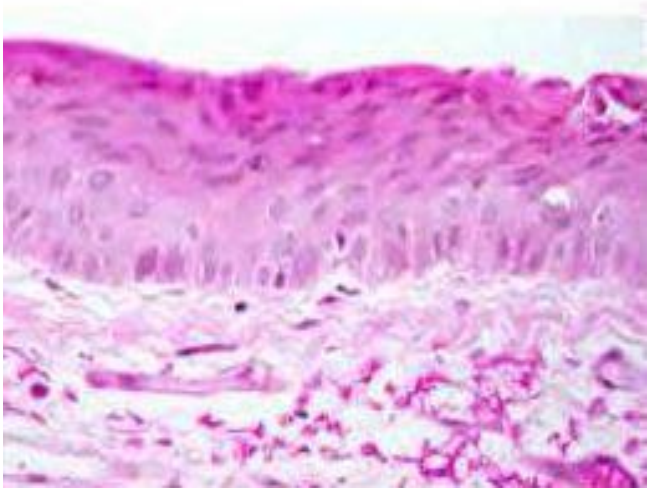


Fig 11 : Grade 1

Grade 2 : The tumour cells are involve upto 2/3 of the epithelium.

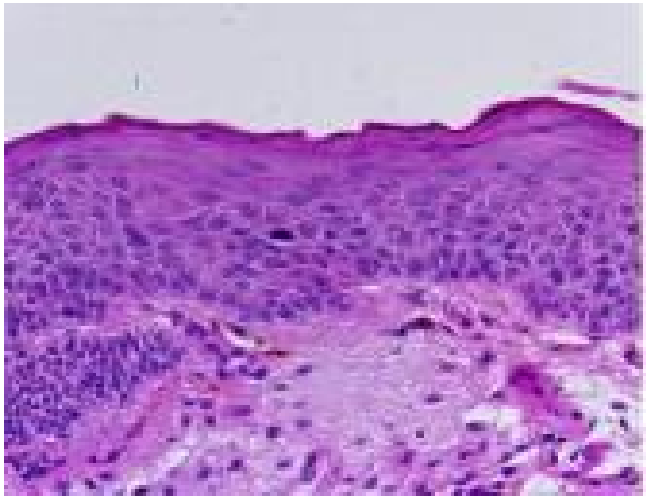


Fig 12 : Grade 2

Grade 3: The tumour cells are present up to the full thickness of the epithelium. However the basement membrane is not breached here.

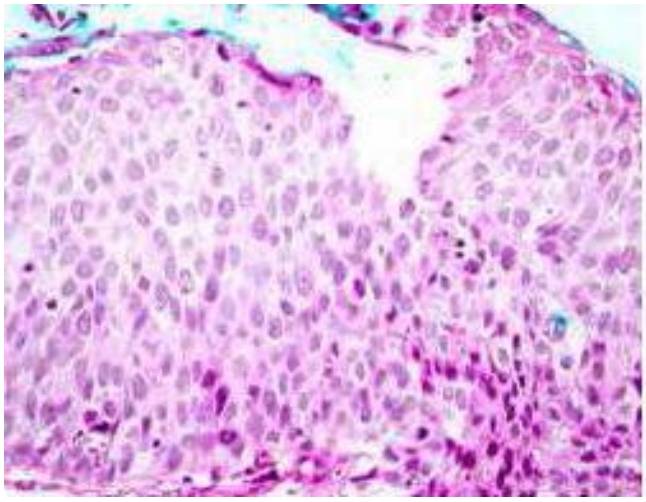


Fig 13 : Grade 3

Morphological Types:

There are three types of conjunctival - corneal intraepithelial neoplasia

- Gelatinous
- papilliform
- leukoplakic

Gelatinous Type: It is the most common type and it has as an ill defined borders with translucent appearance. (Fig 14)

Variants of gelatinous type:

Circumscribed - Most common

Nodular - Rapidly growing and Metastasis rate is high. Diffuse type - Slow growing and resembles conjunctivitis.

Both benign and malignant lesions look alike, hence it is very difficult to differentiate.

Papilliform type:

They present as strawberry like exophytic growth like lesion with well defined borders.Usually they are avascular.Recurrence is more common in this type.They are are often benign and highly vascular. (Fig 15)

Leukoplakic type:

It appears as a focal thickening of stratified squamous epithelium. Limbus is the most common site of origin .The often have pigmentations and resembles as malignant melanoma (Shields et al. 2008)". (Fig 16)

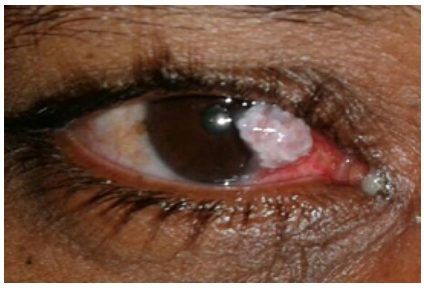


Fig 14 : Gelatinous Type

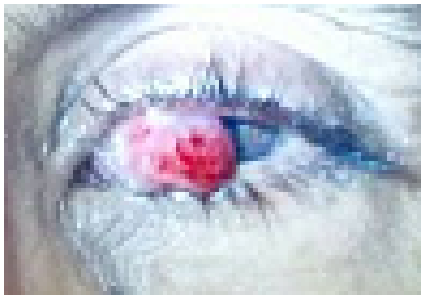


Fig 15 : Papilliform Type

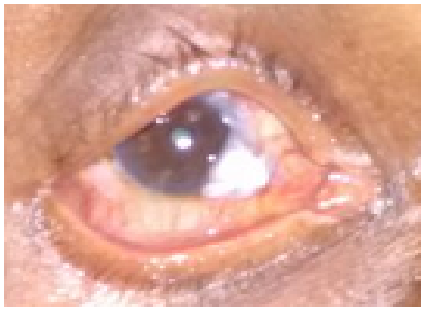


Fig 16 : Leukoplakic Type

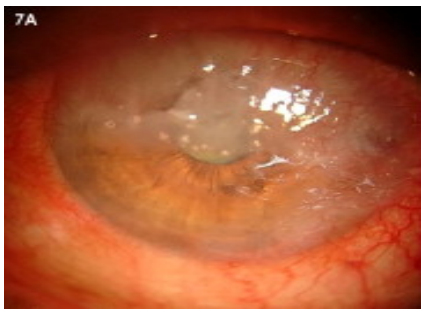


Fig 17 : Corneal Type

Corneal ossn :

Corneal OSSN (Fig 17)often occurs by extension from conjunctival lesions. They appear as greyish white with a well demarcated borders and they have finger like projections. Usually they are avascular.Recurrence is more common in this type. “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 squamous cell carcinoma:

In this type tumour cells breach the basement membrane and invades the stroma of the conjunctival epithelium. Tumour spreads by local invasion which is the most common mode of spread.

Glaucoma, Uveitis, RD and globe rupture can occur if it spreads intraocularly. However metastasis is uncommon. Regional lymphnodes are the extraocular structures which are most commonly involved. There are two types of cells associated with tumour cells Spindle type cells and mucoepidermoid cells. Intra orbital spread is more common in Mucoepidermoid type.

Mucoepidermoid carcinoma is very uncommon and it is common in elderly patients. Wide excision is necessary since this type is more aggressive.

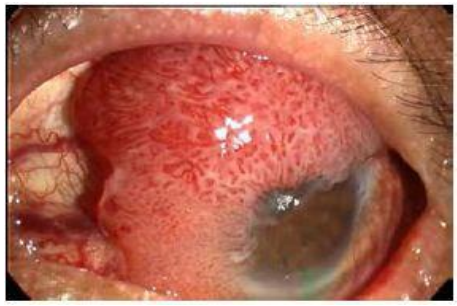


Fig : 17 Invasive squamous cell carcinoma

Differential diagnosis:

Differential diagnosis of OSSN are as follows:

1. Actinic disease
2. Pinguecula
3. Pannus
4. Vitamin A deficiency
5. Pterygium
6. Pyogenic granuloma
7. Malignant melanoma and nevi
8. Keratoacanthoma
9. Pseudoepitheliomatous hyperplasia
10. Necrotising scleritis

DIFFERENTIAL DIAGNOSIS

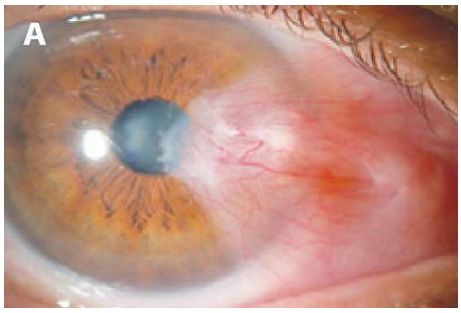


Fig 18 : Pterygium

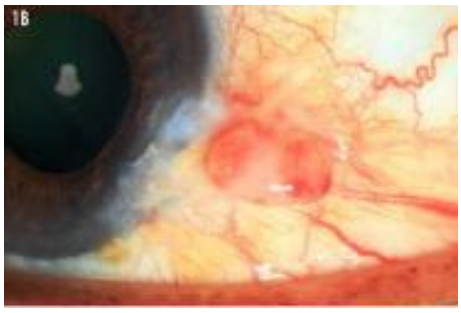


Fig 19 : Pyogenic granuloma

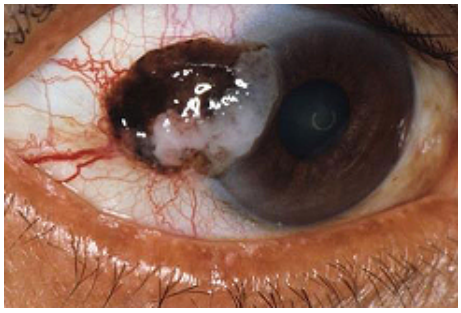


Fig 20 : Melanoma

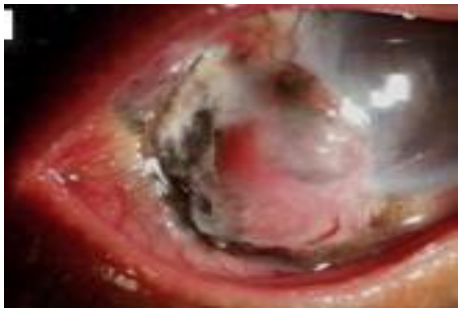


Fig 21 : Necrotising Scleritis

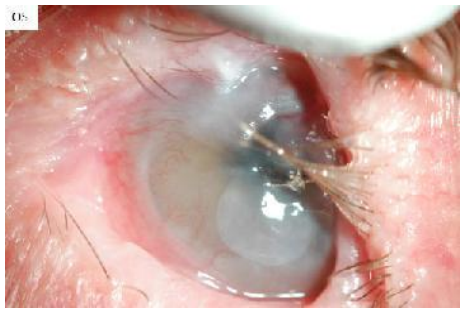


Fig 21 : Pannus with ankyloblepharon of upper lid

DIAGNOSIS AND INVESTIGATIONS:

Clinical assessment include slit lamp examination to look for,

- Type of lesion
- Site
- Dimension
- Location
- Extension
- Corneal involvement
- Feeder Vessel
- Blood vessels

Dilated fundus examination

Gonioscopy

Regional lymph node examination to look for cervical metastasis.

CYTOLOGY:

Cytology includes two methods :

1) **Exfoliative cytology** - This test is performed using spatula or cytobrush.

2) **Impression cytology-** Special devices are used in this technique.

EXFOLIATIVE TECHNIQUE:

Tumor cells are collected using cytobrush, because adhesion between the tumour cells are lost.

Advantages:

- very easy.
- Helps to detect recurrences.

Disadvantages:

- Patients have Discomfort.
- Drying artifacts
- Cells may overlap.

Impression Cytology:

Impression cytology is a simple and rapid technique[3]. Here the associations between the cells are maintained. However the specimens have to be processed without delay. It is widely used as a non- invasive technique for the diagnosis of suspected cases of OSSN.

Cellulose acetate paper is used for specimen collection. IC using biopore membrane has high accuracy[4]. In IC cellulose acetate paper pore size range from 0.025 – 0.45 micron or other devices such as nitrocellulose filters or polyether sulfone filters.

Advantages :

- It is a non-invasive procedure which is simple for both diagnosing and review of patients.
- Collecting samples from epithelium are relatively easy.
- Less discomfort to the patient
- can be performed as a OP procedure
- exact localization
- Cellular association is maintained.

Modification of the Bethesda system in cervical cytology used in classifying Squamous cell abnormalities (Solomon et al.2002)"

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

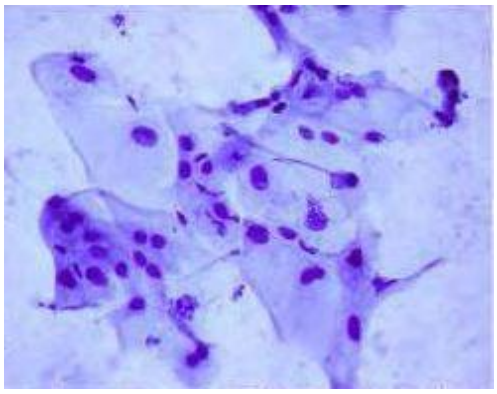


Fig 23

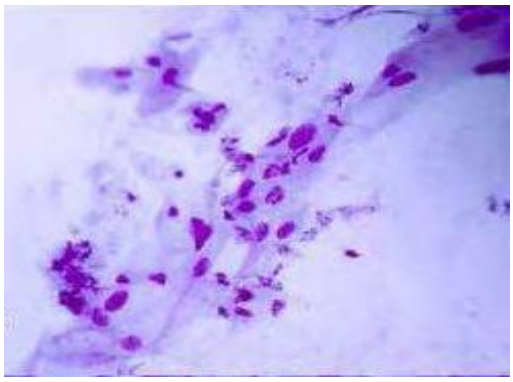


Fig 24

Figures 23 & 24 showing High grade squamous intraepithelial lesions (HSIL), including moderate to severe dysplasia & carcinoma in situ (CIS).

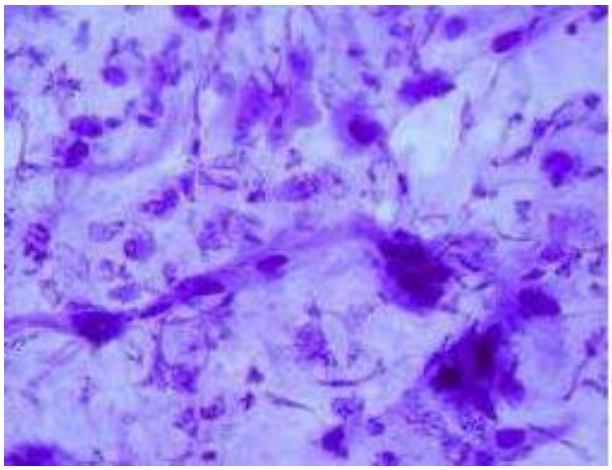


Fig 25 Squamous cell carcinoma

ULTRASOUND BIOMICROSCOPY:

These devices help in imaging of deep lying ocular structures completely by reflecting high energy sonic waves. It also used to detect presence of Glaucoma, to determine lens status and pathologies of intraocular tumours. They operate using frequencies up to 50MHz, which detect depths of 8mm or more. It also helps to rule out scleral extension of ocular surface squamous neoplasia.

Advantages:

- High penetration in large lesions

Disadvantages:

- Low resolution

- Difficult to evaluate epithelial and subepithelial lesions.

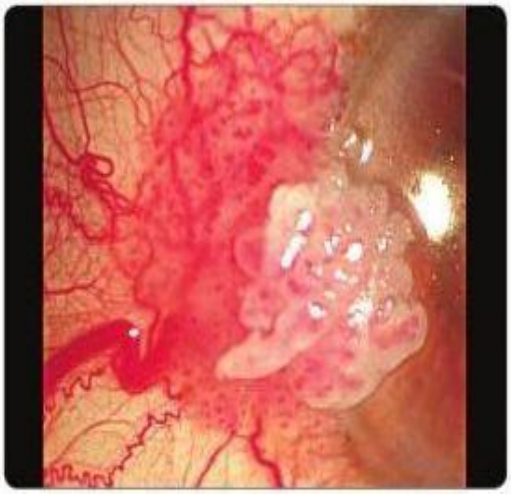


Fig 26 : Lesion seen from outside

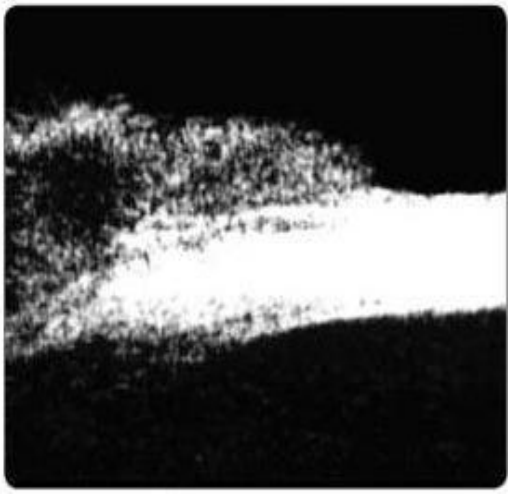


Fig 27 : UBM image of the tumor

ANTERIOR SEGMENT OCT:

ASOCT helps in in vivo examination of the morphologic and even histological features of the tissues. UHR OCT is a non-invasive , non contact technique where there will be high axial resolution of imaging to detect various anterior segment pathologies.

Fig 28 : Anterior Segment OCT Device

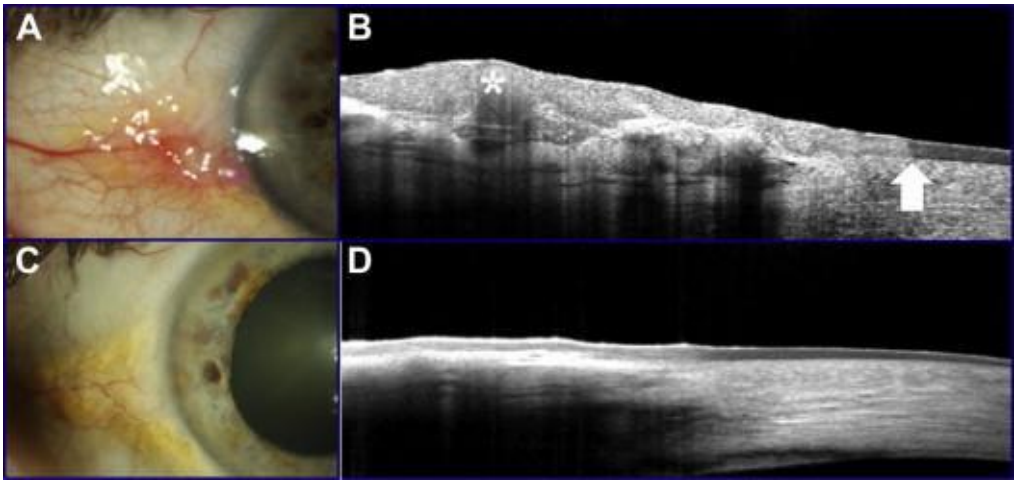


Fig 29 : Images of Anterior Segment in ASOCT

Here sharp demarcation is seen between the reflectivity of normal and diseased epithelium. This allows exact localization of the tumour margins. It is also helpful to delineate the tumour and helpls in early detection of 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 performed as an OP procedure and less invasive. There is no pain during course of the procedure.
- It helps the pathologists in the diagnosis of cytological picture
- Confocal microscopy can differentiate carcinoma in situ from invasive tumour.
- Helps to assess the subtypes
- Can detect recurrence tumours and
- Follow-up.

Disadvantages:

- Confocal microscopy provides a transverse view when compared to UHROCT
- By this method upto 500µm of depth can be studied.

HISTOPATHOLOGIC EXAMINATION:

Histopathologial examination is the Gold standard investigation to diagnose OSSN. Mode of treatment can be planned based on the report.

Excisional biopsy is ideal for Small tumours with minimal limbal involvement or ≤ 15 mm. For larger lesions Wedge biopsy is considered.

Negative margin shows an abrupt transition of the epithelium from the adjacent uninvolved normal conjunctival epithelium.Both margin and base of the lesion have to be studied. Architectural and cytological atypia should be noted.

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 main purpose of the treatment of OSSN is complete excision of the tumor with wide tumour free margin. Following which the double freeze-thaw cryotherapy for the conjunctival margin and alcohol epitheliectomy for the corneal component of the lesion has to be performed.

A thin strip of sclera should be excised when the tumor is attached to the globe. And “No touch” tecnique has to be followed to avoid tumour seeding.

IMMUNOHISTOCHEMICAL ANALYSIS:

Normal to low grade Squamous Intraepithelial lesions to high grade Squamous Intraepithelial Lesions show increase in Number of Ki-67 positive cells in conjunctival SCC and CCIN. Therefore Ki-67 can be used as a diagnostic indicator for OSSN.

Recent ongoing studies on Non Invasive techniques to diagnose OSSN:

1) Expression of glucose transporter protein -1 (GLUT -1) in OSSN.

2) Expression of p63 in conjunctival intraepithelial neoplasia and squamous cell carcinoma.

3) Identification of ocular surface squamous neoplasia by invivo staining with methylene blue.

4) Diagnosis of OSSN using 1% toluidine blue eye drops.

5) Ultra high resolution OCT in the diagnosis of OSSN.

REVIEW OF LITERATURE:

1. **American academy of ophthalmology; ophthalmic pathology and intraocular tumors (2014-2015) page 62-63**

OSSN most commoly arises at the limbal region ,overl an already existing pingicula.Ultra violet light (UV) exposure , in light skin pigmented individuals ,is a major risk factor for OSSN, its prevalence is higher in equatorial regions of the world. UV associated mutations in tumor suppressor p53 gene mutation have been demonstrated in OSSN ,and hereditary defect of DNA repair in xeroderma pigmentosum increases the risk of OSSN formation. OSSN is also common with HPV infection (subtypes 16 and 18) as well as in HIV infection.HIV associated OSSN is most common in subsaharan Africa ,and HIV must be suspected in patients with OSSN in younger age group .Other immunosuppressive conditions are also risk factors for OSSN.

2. **American academy of ophthalmology ; External disease and cornea (2014-2015) page -19**

Impression cytology is basically a research tool which allows to evaluate the squamous epithelium of ocular surface.Sheets of conjunctival epithelium and corneal cells are obtained using a filter paper. After which they are examined for morphological and histological presentation.Impression cytology of conjuctiva is used to monitor the progressive ocular surface changes,starting with reduced goblet cell density and followed by squamous metaplasia and keratinization in later stages.

3. **Scholars Journal of Applied Medical Sciences (SJAMS) ISSN 2320-6691 Sch. J. App. Med. Sci., 2014; 2(1D):461-465**

Impression cytology is a simple and non-invasive method with a high correlation rate in the diagnosis of OSSN. It can be used as a routine test in patients who are suspected for the presence of OSSN. It is helpful to check for recurrence in patients who underwent surgical excision biopsy. Expertisation of the ocular surface cytology and awareness of limitations such as negative results in hyperkeratotic dysplastic lesions helps to accurately diagnose OSSN.

4. Br J Ophthalmol 2001;85:154-158 doi:10.1136/bjo.85.2.154 Reliability of impression cytology for the diagnosis of ocular surface squamous neoplasia employing the Biopore membrane

Ocular surface impression cytology was first introduced by Egbert et al in the year 1977.They used cellulose acetate filter paper to collect the superficial layer conjunctival cells. This technique was later modified by other authors to investigate dry eyes, conjunctival squamous metaplasia staging,to diagnose ofvitamin A deficiency, limbal stem cell failure, microbiological infections, and to diagnose of OSSN.

The application of impression cytology was first introduced by Nolan et al using CAP for to conjunctival neoplasms. Recently Thiel et al described the use Biopore membrane device (Millicell-CM 0.4 μm PICM 012550, Millipore Corp, Bedford, MA, USA) to scrape conjunctival cells to diagnose superficial viral infections. It provides the quicker and easy method to be used as a clinical routine. The device is stable enough to allow sampling from the ocular surface. The cells adhere well to the Biopore membrane , hence a large layer of cells can be easily obtained. The membrane is very transparent if it is wet and this allows a detailed examination of cytology. Impression cytology has a role in the diagnosis of OSSN.

5. Br J ophthalmology 2005; 89;1655-1659

Egbert et al used millipore filters to harvest conjunctival cells. They are dried in air and stained with hematoxylin and periodic acid sciff(PAS) and Tseng modified the technique of collecting the cells and stained with both PAS and papanicolaou stains .Maskin and Bode studied the acquired cells using electron microscopy.

6. **"Barros and co workers** used a scoring index by modifing Bethesda system which showed a predictive index score of ≥4.5 to diagnose SCC using Impression cytology. The sensitivity was 95%, specificity was93%, positive predictive value was 95% and negative predictive value was 93%.(Barros et al. 2009)" But cytologist require skill and experience to interpretation of the Impression cytology specimens.

AIM :

To analyse the non invasive techniques in diagnosing ocular surface squamous neoplasia.

OBJECTIVE:

To evaluate the accuracy of impression cytology in the diagnosis of ocular surface squamous neoplasia by correlating with histopathological examination.

MATERIALS AND METHODS :

STUDY CENTER : Regional institute of ophthalmology and Govt Ophthalmic Hospital, Chennai .

STUDY DESIGN : Prospective study

STUDY DURATION : 5 months

SAMPLE SIZE **:** 50 patients

INCLUSION CRITERIA : Patients with elevated conjunctival limbal lesions accompanied by feeding blood vessels and of age 30-70 years.

EXCLUSION CTITERIA :

1. Patients with age less than 30 years.
2. Patients with Pterygium
3. Patients with severe dry eye
4. Patients with scleral involvement.
5. Patients with recurrence
6. Patients with severe debilitation.
7. Patients with HIV and other immunocompromised diseases.
8. Pregnant women.

METHODS & METHODOLOGY:

50 Patients with elevated conjuntival limbal mass were were included in this study. A detailed history on symptoms , duration, progression and exposure to risk factors were taken.

Clinical examination included were as below:

1) Visual acuity (Both corrected and uncorrected)

2) Evaluation of lesion for its shape, size, extent ,laterality,mobility under slit lamp were done.The presence keratinisation , feeder vessel, pigmentation, corneal invasion were noted.

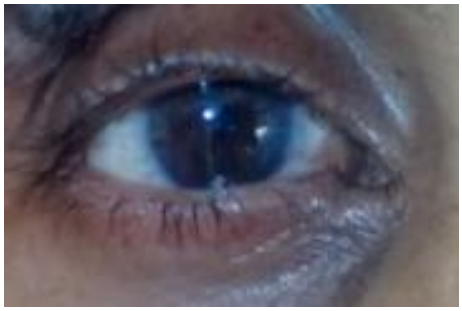


Fig 30 : Right Eye

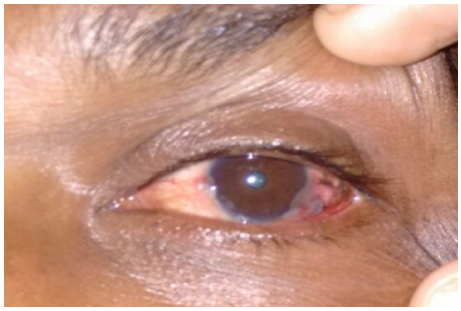


Fig 31 : Left eye

3) Ocular surface staining was done with Rose bengal.

4) Schirmer's test were performed to rule out dry eye.

5) Fundus Examination with IDO.

6) Gonioscopy was performed to rule out angle invasion.

7) Regional lymph node examination.

INVESTIGATIONS:

1. Routine laboratory work up

Random blood sugar

Complete hemogram

ESR

VCTC

VDRL

Mantoux.

2. UBM to rule out scleral invasion.

3. Chest xray - To rule out metasasis.

4. Impression cytology was done before excision biopsy.

5. MRI orbit - To rule out orbital invasion.

Types of lesions encountered during our study :

Fig 32 :Leukoplakic type

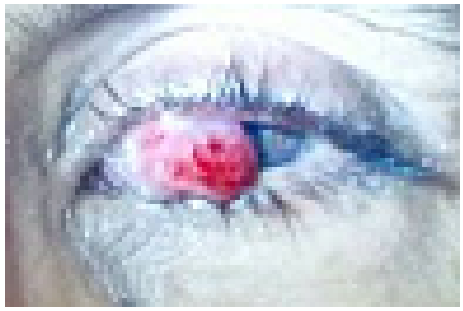


Fig 33 : Papilliform type

Fig 34 : Gelatinous type

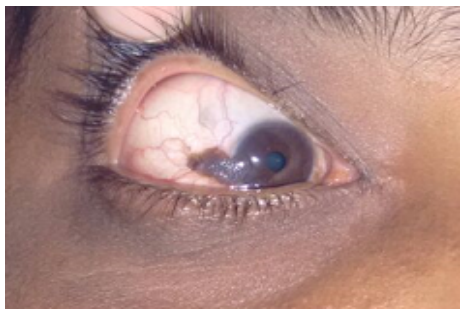


Fig 35 : Pigmented type

IMPRESSION CYTOLOGY TECHNIQUE:

A drop of 4% xylocaine was instilled to anaesthetise. Then a cotton bud was tightly pressed over the lesion for about 5 to 10 seconds and the bud was against the glass slide. After which it was fixed with 95% alcohol for half an hour. The specimen was studied under light microscope for the presence of dysplastic changes after staining with haematoxylin and eosin stains.

Fig 36 : Impression Cytology Being Performed

SURGICAL PROCEDURE :

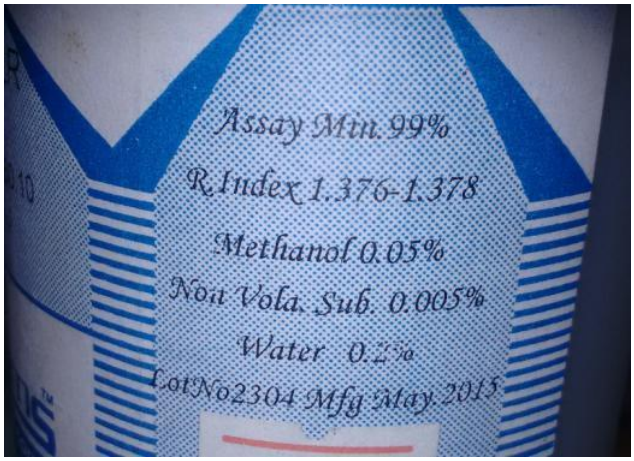


Fig 37 : Alcohol used in this technique

Excision biopsy technique : Alcohol epitheliectomy (2mm margin)

↓

Conjunctivo tenonectomy (4mm margin)

↓

Lamellar sclerectomy

↓

Double freeze thaw cryotherapy

↓

Amniotic membrane grafting

↓

Specimen sent for HPE.

No touch technique was followed during excision to avoid the spread of tumor to other areas .

SPECIMEN SENT FOR HPE AFTER PROPER MARKING OF THE BORDERS.

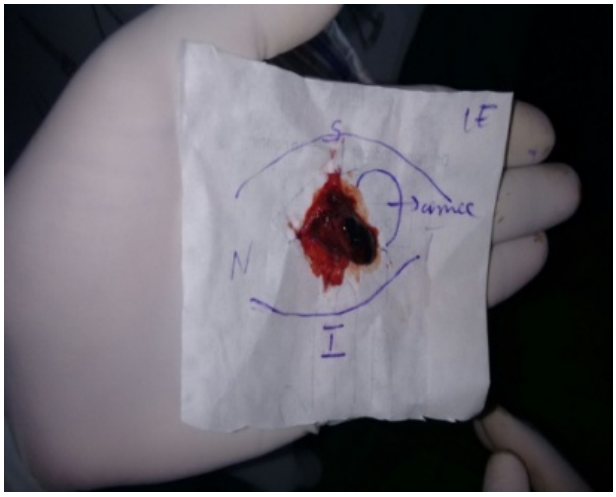


Fig 37 : Specimen Sent For Hpe After Proper Marking Of The Borders to evaluate for extension of the tumor spread

Correlation of Impression cytology and Histopathology specimens:

Both the specimens of impression cytology and that of excisional biopsy werestudied under electron microscope for the presence of dysplastic cells.

DIAGNOSTIC CRITERIA FOR OSSN - IMPRESSION CYTOLOGY

1) Nuclear enlargement with raised nuclear-cytoplasmic ratio

2) Hyperchromasia with coarsely clumped nuclear chromatin.

3) Irregular nuclear membrane

4) Nuclear pleomorphism

5) Prominent nucleoli.

GRADES OF OSSN ON HISTOPATHOLOGY

Mild dysplasia: Dysplastic cells restricted to the lower one-third of the epithelial layer.

Moderate dysplasia: Dysplastic cells occupying two thirds of the thickness of epithelium.

Severe dysplasia / Carcinoma-in-situ: Complete involvement of the epithelium including surface layer without breach of the basement membrane.

Invasive squamous cell carcinoma: Breach of the basement membrane with involvement of substantia propria by tumor cells .

RESULTS AND STATISTICAL ANALYSIS

AGE DISTRIBUTION:

Age group	No. Of patients	Percentage
30-50	**16**	**32%**
51-70	**34**	**68%**
Total	**50**	**100%**

TABLE 1 showing Age Distribution

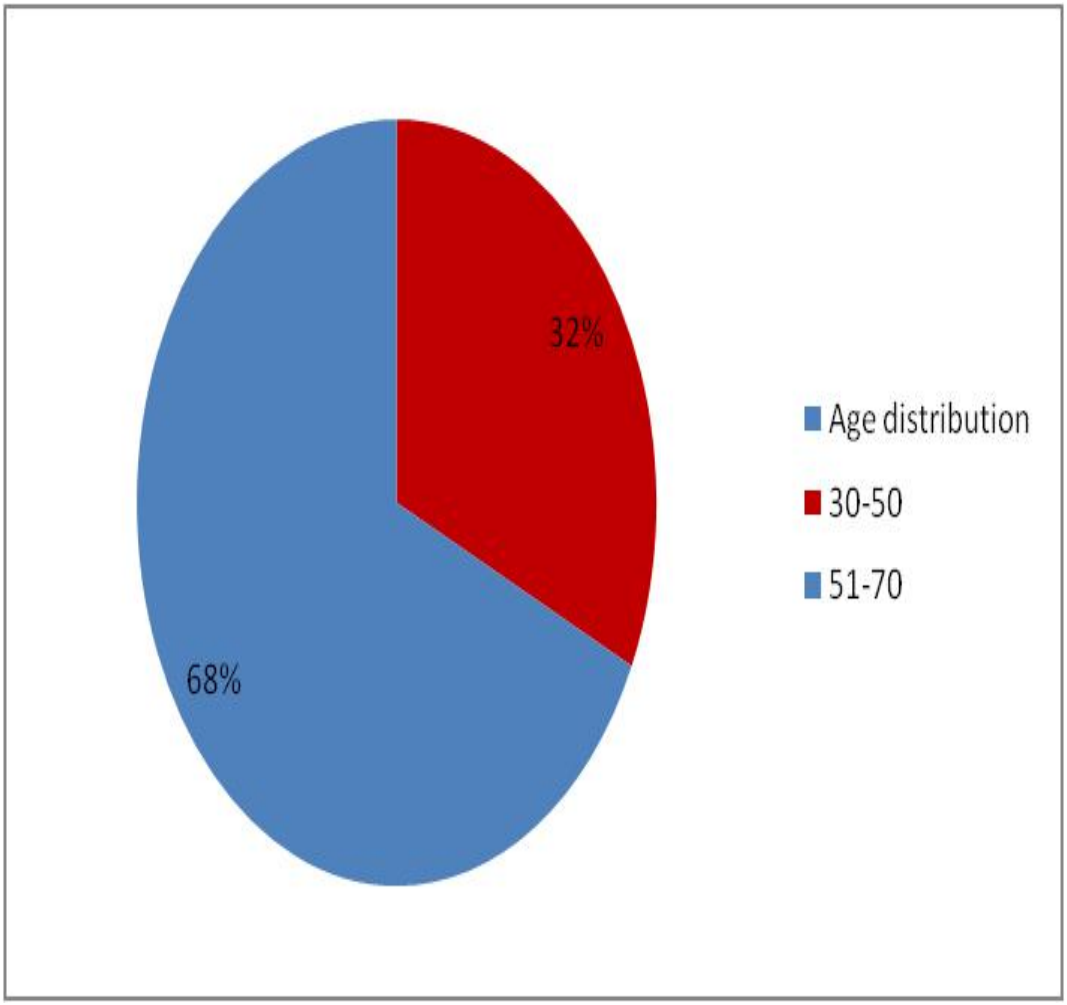


Chart 1 : Pie chart showing age distribution

In our study group the maximum percentage of patients were in the age group of 50 to 70.

SEX DISTRIBUTION:

SEX	NO. OF PATIENTS	PERCENTAGE
MALE	36	72%
FEMALE	14	28%
TOTAL	50	100%

Table 2 showing Sex Distribution

SEX DISTRIBUTION:

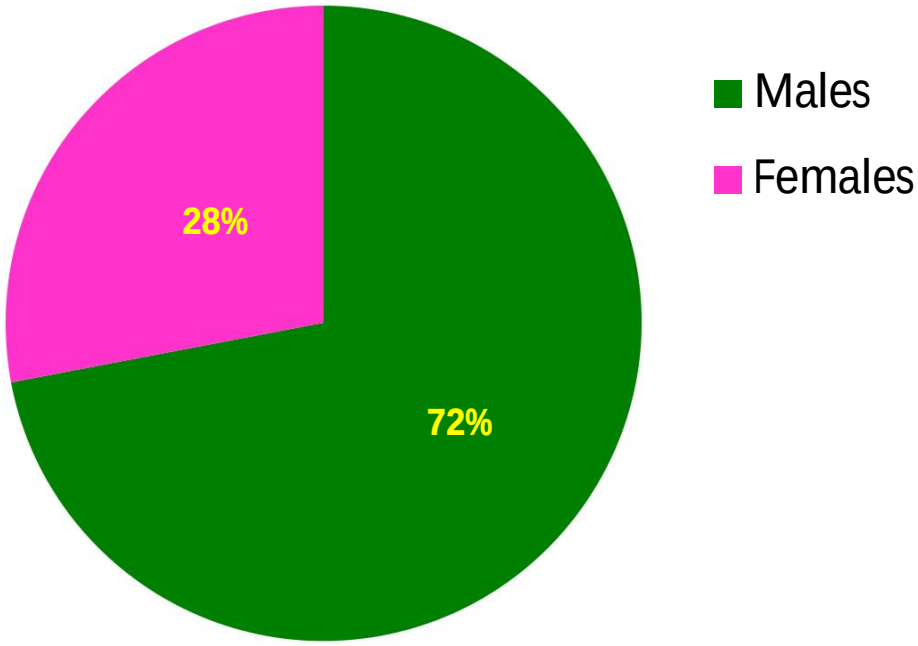


Chart 2 Pie chart showing Sex Distribution

In our study group the majority of patients were males .

LATERALITY:

EYE AFFECTED	NO. OF PATIENTS	PERCENTAGE
RIGHT EYE	22	44%
LEFT EYE	28	56%
TOTAL	50	100%

Table 3 showing Laterality of involvement

LATERALITY:

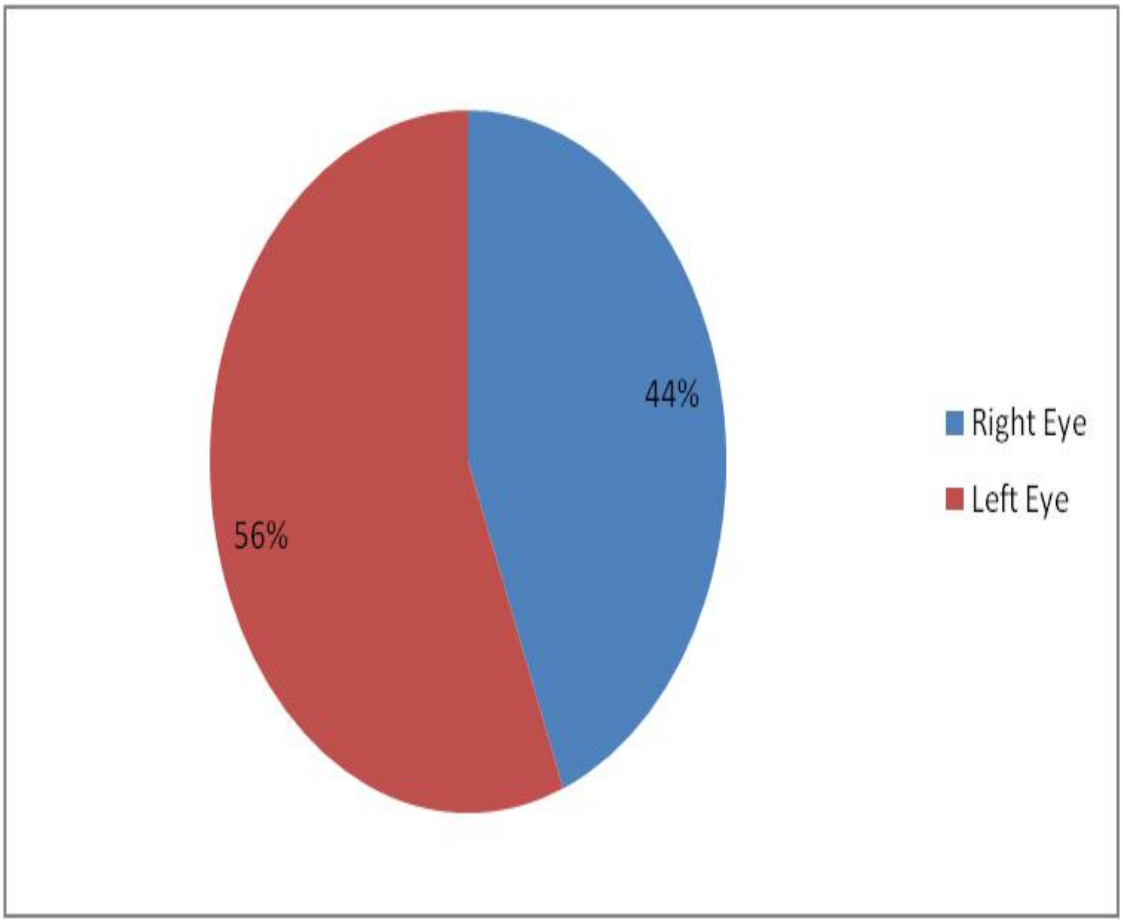


Chart 3 : Pie chart showing Laterality of eye

In our study group patients presented with lesion almost equally in both eyes.

TYPE OF THE LESION:

TYPE OF LESION	NO OF PATIENTS	PERCENTAGE
GELATINOUS	**29**	**58%**
PAPILLFORM	**16**	**32%**
LEUKOPLAKIC	**5**	**10%**
TOTAL	**50**	**100%**

Table 4 showing type of Lesion

TYPE OF THE LESION:

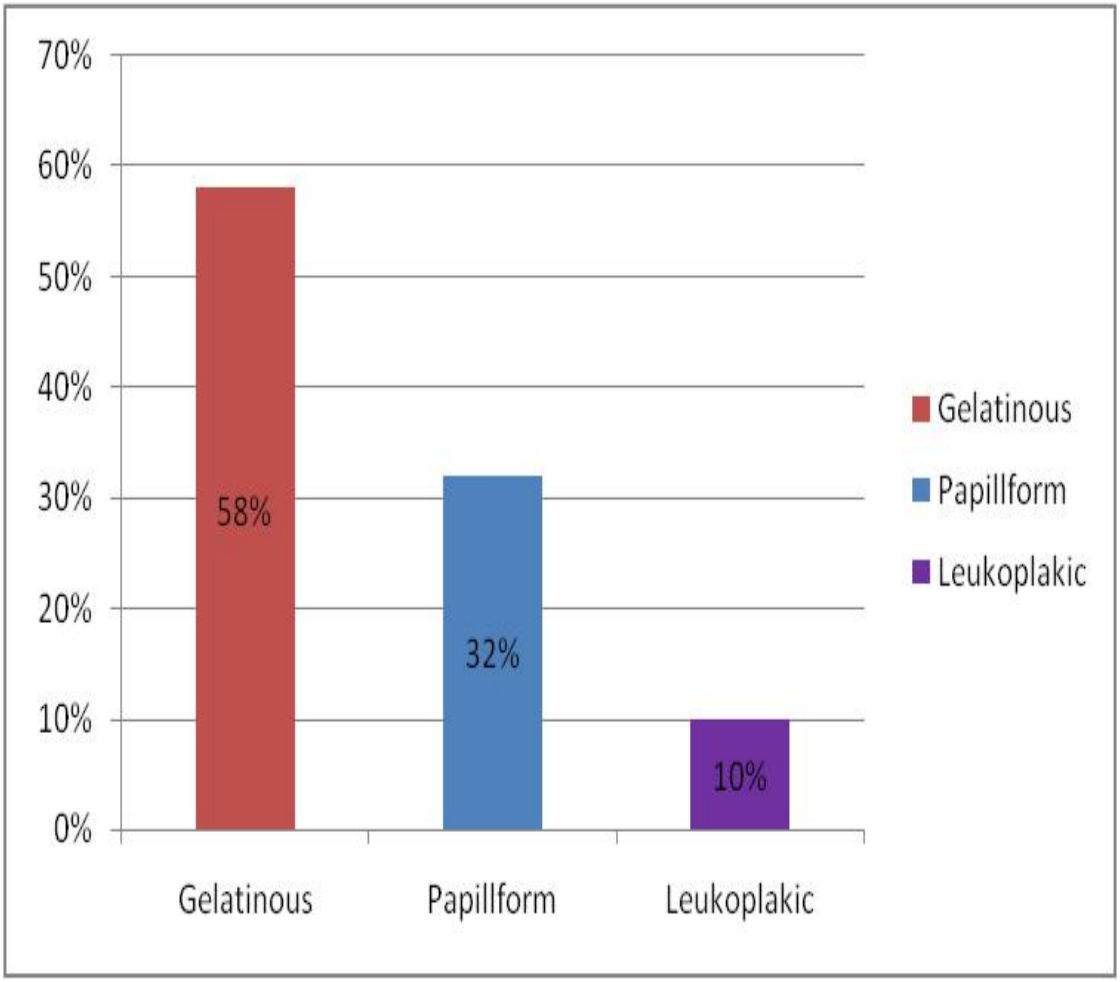


Chart 4 Bar chart showing type of Lesion

Most of the patients presented with gelatinous type lesion in our study.

CORNEAL INVOLVEMENT:

CORNEAL INVOLVEMENT	NO OF PATIENTS	PERCENTAGE
PRESENT	36	72%
ABSENT	14	28%
TOTAL	50	100%

Table 5 showing Corneal involvement

CORNEAL INVOLVEMENT:

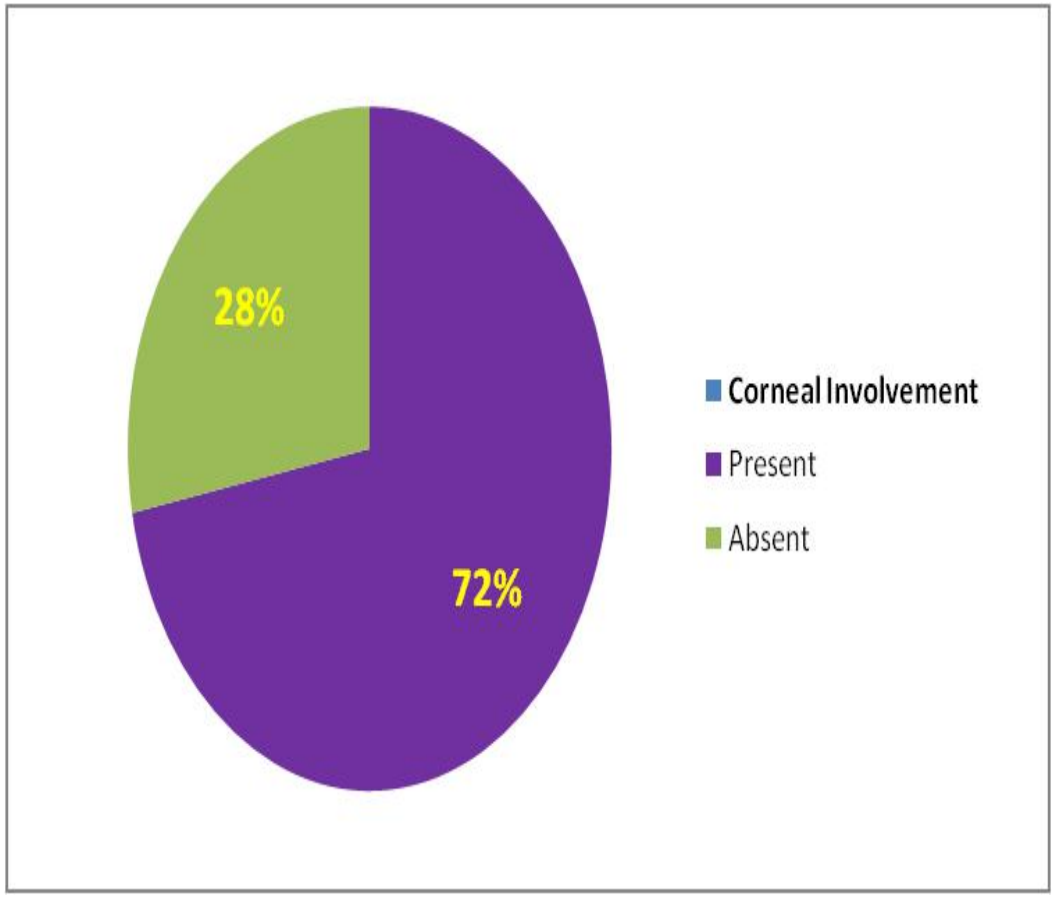


Chart 5 Pie chart showing Involvement of Cornea

About 72% of patients had corneal involvement encroaching from the limbus.

CORRELATION BETWEEN IMPRESSION CYTOLOGY AND HPE

Comments	Correlation	Non correlation
No of patients	47	3
Percentage	94%	6%

Total no. of patients - 50

CORRELATION:

Impression cytology

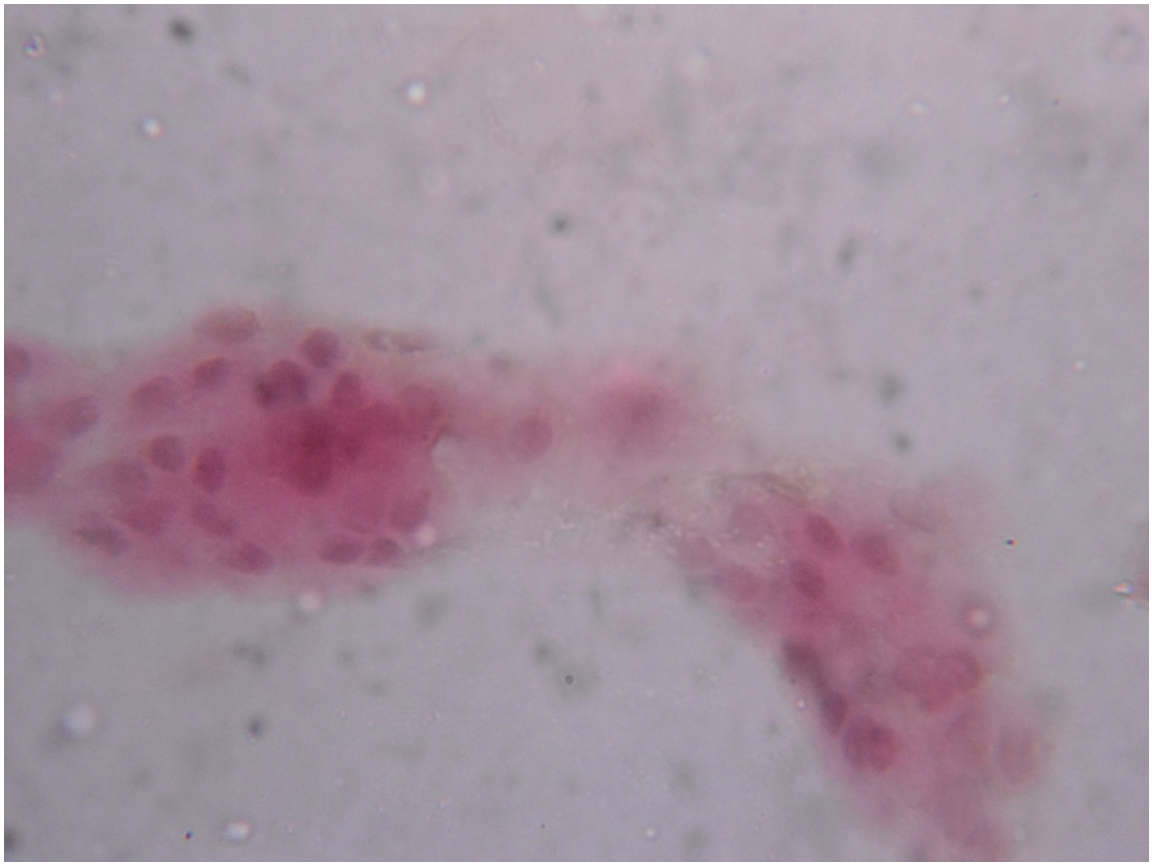


Fig 38 : **Impression cytology** - 40 x showing Severe dysplastic changes increased n:c ratio,nucleomegaly and irregular nuclear membrane

Histopathology

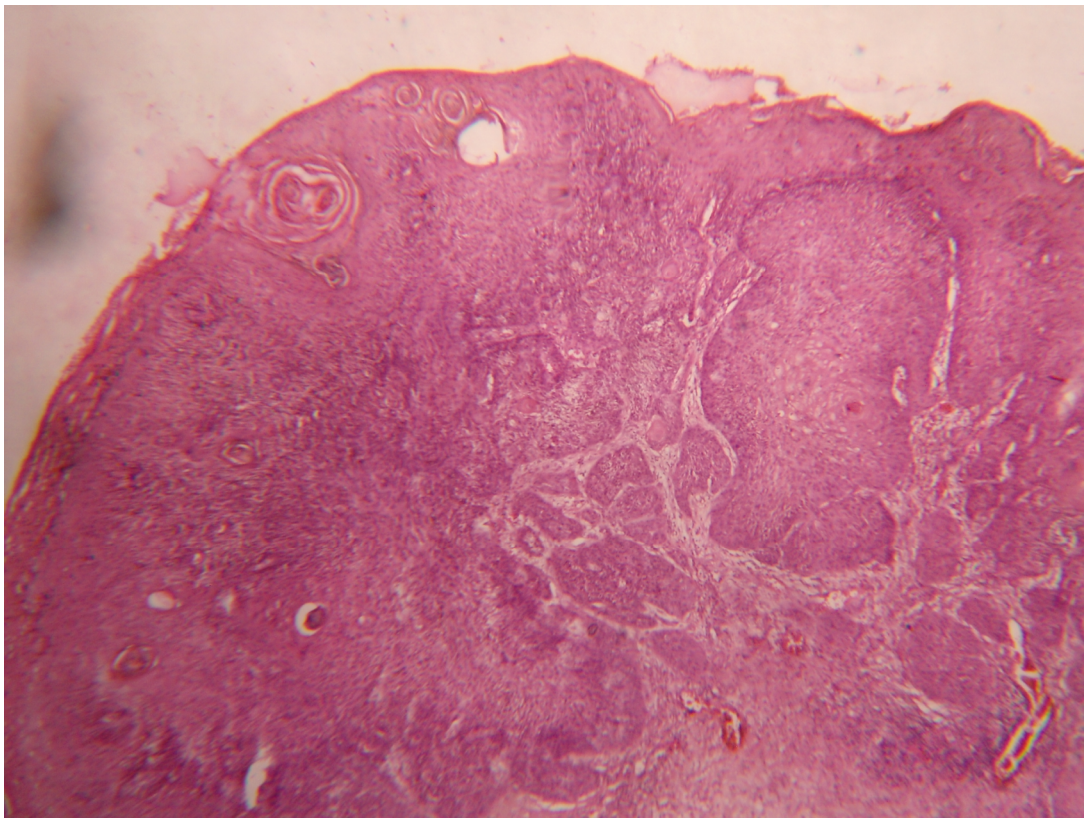


Fig 39 : **Histopathology** - 40x Showing Infitrating neoplasm-nests of polyhedral cells ,vesicular nuclei,prominent nucleoli,keratin pearls,abudant eosinophilic cytoplasm- well differentiated SCC

Out of 50 patients 40 patients showed correlation between Impression cytology and Histopathology.

NON CORRELATION:

Impression cytology

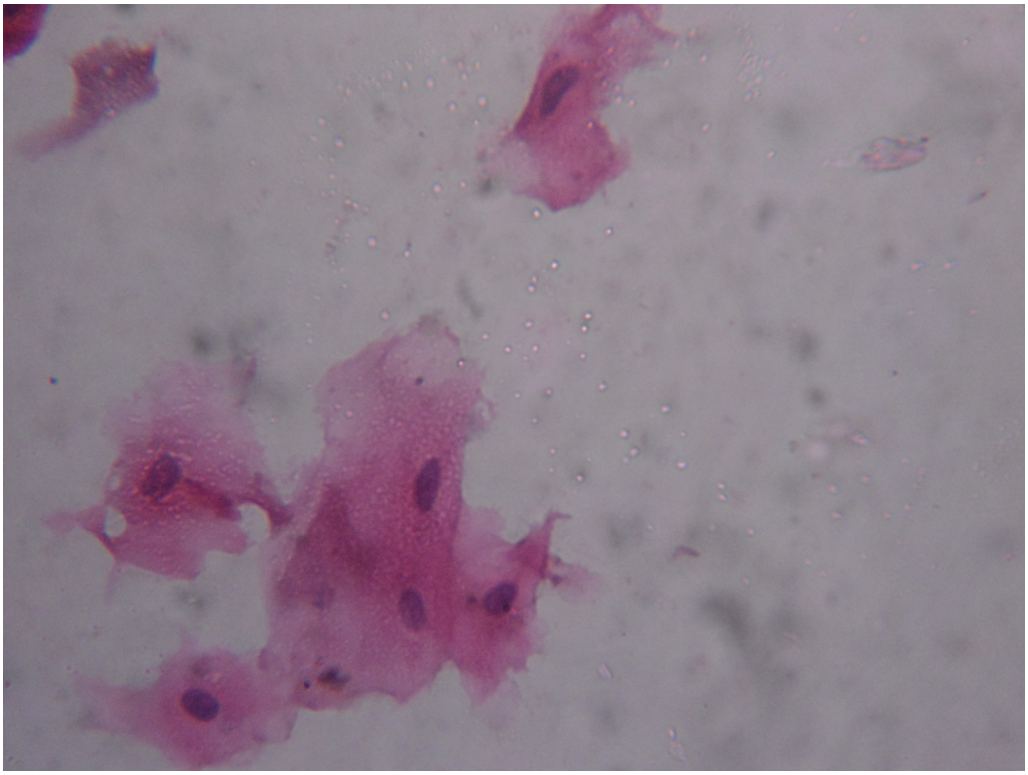


Fig 40 **Impression cytology - 40x** showing normal mature squamous epithelial polyhedral cells with centrally placed round to oval nuclei.

Histopathology

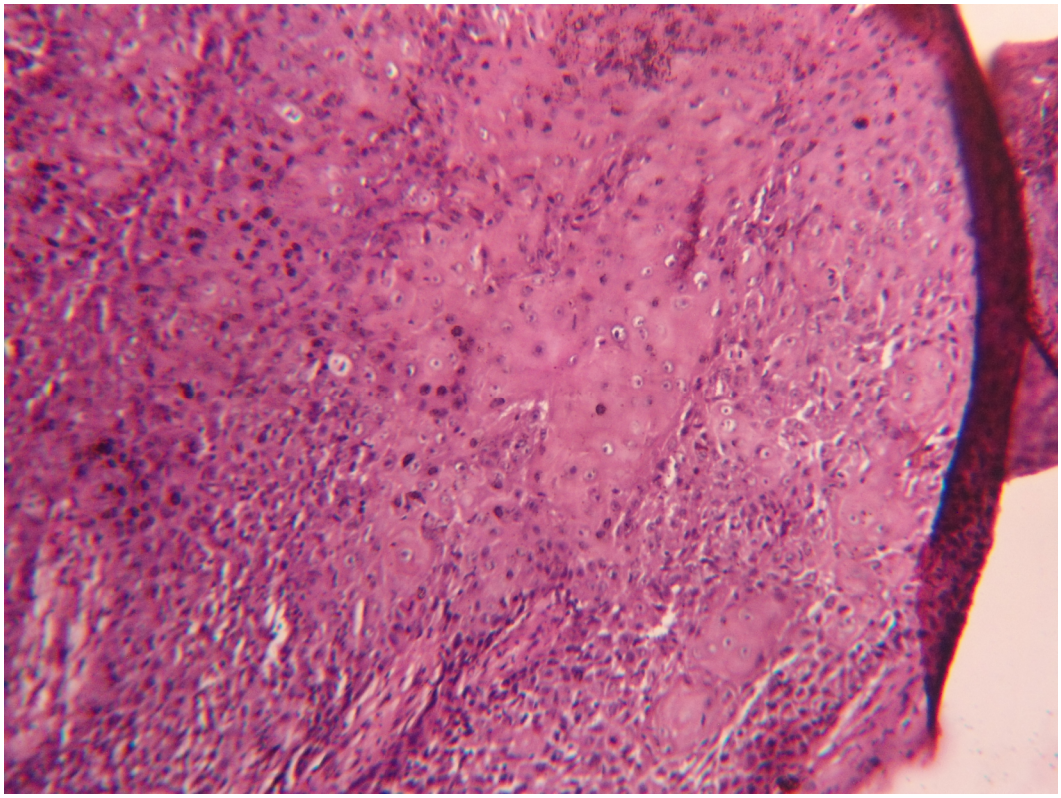
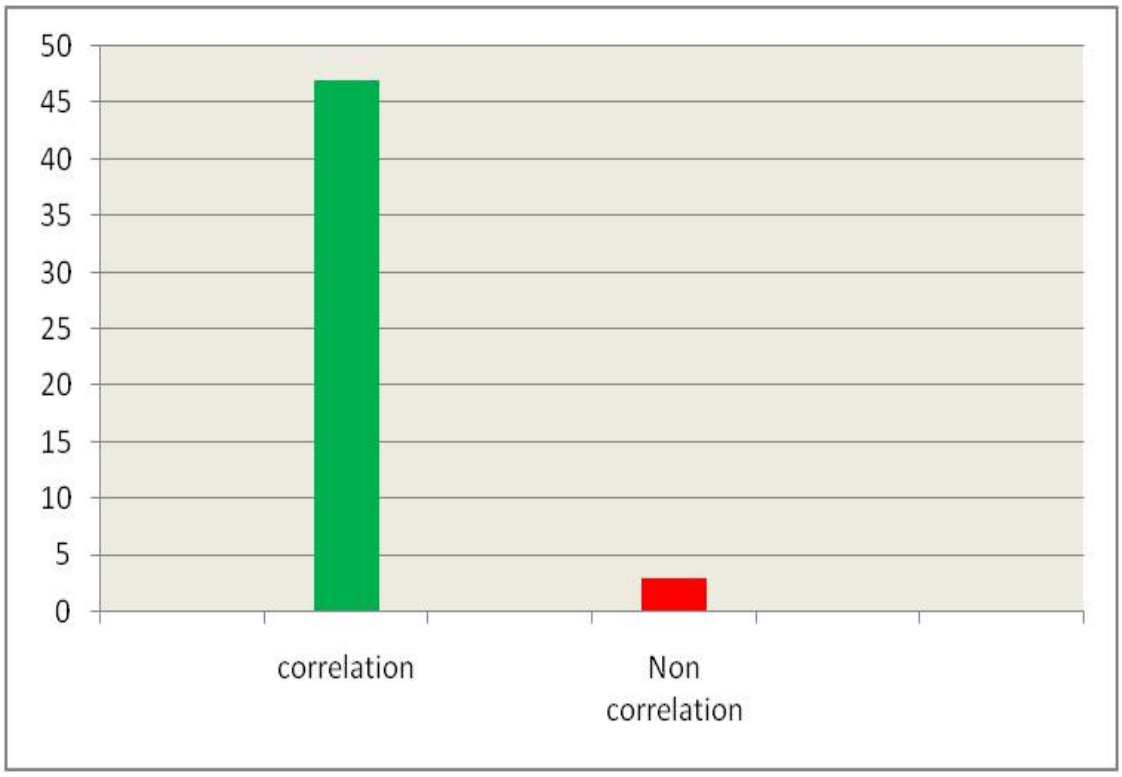


Fig 41 **Histopathology-40x -** Showing Severe dysplastic changes of squamous epithelia involving all layers with foci of microinvasion

Out of 50 patients 10 patients showed no correlation between Impression cytology and Histopathology.

Bar chart showing Correlation between Impression cytology & histopathology specimens



94% **6%**

Data Analysis :

Based on the results achieved the epidemiological indices were calculated. which are as follows.

Parameters	Values
Accuracy	**94%**
Sensitivity	**97.87%**
Specificity	**33.33%**
Positive predictive value	**95.83%**
Negative predictive value	**50%**

DISCUSSION:

50 Patients who presented during the study period with elevated conjunctival limbal mass were studied .Among these 50 patients about 68% belonged to the age group of 5^{th} to 7^{th} decade. Majority of them were males who gave history of outdoor activities.when considering laterality there was no significant difference noted between right and the left eye.56% of patients had involvement in their right eye and the remaining 44% had the lesion in their left eye.Reg2arding the morphological type of presentation Gelatinous (58%)type of lesion was the commonest type when compared with the papilliform (32%)and leukoplakic(10%) types.About 72% of the patients had corneal involvement which were found to be more aggressive.

The impression cytology specimens which were obtained preoperatively were correlated with the histopathological specimens which were otained through excisional biopsy. Out of 50 patients 47 patients (94%) had correlation.Among them 1 patient had normal epithelium in impression cytology and histopathology showed it as benign nevus. .The remaining 3 patients (6%) had no correlation between the samples of impression cytology and histopathology . In these 3 cases , 2 cases had dysplastic cells in impression

cytology but histopathology showed no dysplastic changes.The remaining 1 patient had normal epithelia in impression cytology and severe dysplasia in histopathology. The positive predictive value of this cytological test is quiet high which was about 95.83 % and the sensitivity was about 97.87%.

The ocular surface squamous neoplasia are rare entity but has to be picked up early since they have the potential to cause severe ocular and systemic morbidity as well as mortality.The treatment of ocular surface surface squamous neoplasia depends upon the stage of the tumor.However repeated biopsies can cause scarring, discomfort anatomical deformity and limbal deficiency.

In such situations impression cytology can be used as an alternative tool in the diagnosis of ocular surface neoplasms where surgery is not appropriate.It is especially useful in cases of HIV positive individuals who are more prone to such neoplasms.In these patients impression cytology found to be a safer means to diagnose the ocular surface tumors.

Impression cytology is a technique of obtaining the superficial layers of ocular surface using different devices.The cells adhere to the devices and can be removed and studied under the microscope for the presence of any dysplastic changes[4].

The main advantage of impression cytology is the easy collection of samples without much discomfort to the patient.It can be done as an outpatient procedure.It helps in more precise localisation of area which is studied.Moreover the cell to cell relationship is maintained here which allows one to see the cells the way they are present in vivo.

Another advantage of impression cytology is the preservation of limbal stem cells[5] which are responsible for renewal of corneal epithelium unlike excisional biopsy where they get damaged .It can also detect melanocytic tumors by the presence of atypical melanocytes.The predictability of impression cytology in pigmented lesions is about 73%.However this technique has its own limitations like it cannot detect kerototic lesions where surface keratin interfere with the results.

CONCLUSION:

Impression cytology is an easy and rapid non-invasive method which gives reliable information with minimal discomfort to the patient where Limbal stem cells are preserved . Based on this prospective clinical study the accuracy of Impression cytology in diagnosing OSSN is about 94% and sensitivity of 97.87%.Hence Impression cytology can be used as a Screening tool.It has a high positive predictive value. And there may be a role of impression cytology in the screening, initial assessment and follow up of patients with suspected OSSN. But always Histopathology remains The Gold standard technique in the diagnosis of ocular surface squamous neoplasia.

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PROFORMA

Name : Age / Sex :

OP / IP No : Occupation :

Address :

Chief Complaints :

History :

- H/o of Duration –
- H/o Photosensitivity –
- H/o Drug intake –
- H/o Joint Pain –
- H/o Infection –
- H/o Alcohol intake –
- H/o Progression-

Past History :

- H/o Similar complaints in the past –
- H/o previous treatment –
- H/o Hypertension, Diabetes, Asthma, Epilepsy, IHD –

Personal History

- Type of Diet

Family History –

General Examination

- Pallor –
- Icterus –
- Regional lymphadenopathy

Systemic Examination

- CVS –
- RS –
- CNS –
- BP –
- Pulse –

Ocular Examination

	Right Eye	Left Eye
• Visual Acquity		
UCVA –		
BCVA –		
• IOP –		

Slit lamp examination

- Site –
- Size –
- Shape –
- Borders –
- Extension –
- Mobility –
- Type of Lesion –
- Presence of feeder vessel –
- Presence of keratinisation –
- Presence of pigmentation –

Schimers test

Fundus Examination –

Gonioscopy –

Ultra biomicroscopy –

Impression cytology –

HPE –

MRI ORBIT –

MASTER CHART

S. No.	Age/Sex	Laterality	Type of lesion	Corneal involvement	Impression cytology	HPE	Correla-tion
1	55 / F	RE	Gelatinous	Present	dysplasia	SCC	Yes
2	42 / M	LE	Gelatinous	Absent	Dysplasia	No dysplasia	No
3	50 / M	LE	Leukoplakic	Present	Dysplasia	Moderate dysplasia	Yes
4	37 / F	RE	Papilliform	Absent	No dysplasia	Degenera-tion	Yes
5	70 / F	LE	Gelatinous	Absent	Dysplasia	SCC	Yes
6	33 / M	RE	Papilliform	Present	No dysplasia	Nevus	Yes
7	58 / M	LE	Gelatinous	Present	Mild dysplasia	Severe dysplasia	Yes
8	65 / M	RE	Gelatinous	Present	Severe dysplasia	SCC	Yes

9	38 / M	RE	Papilliform	Present	Mild dysplasia	Moderate dysplasia	Yes
10	53 / M	LE	Gelatinous	Present	Dysplasia	Moderate dysplasia	Yes
11	66 / M	RE	Papilliform	Absent	Dysplasia	Mild dysplasia	Yes
12	57 / M	LE	Gelatinous	Present	Severe dysplasia	SCC	Yes
13	51 / F	RE	Gelatinous	Present	Mild dysplasia	Moderate dysplasia	Yes
14	67 / M	LE	Leukoplakic	Absent	Dysplasia	SCC	Yes
15	50 / M	RE	Gelatinous	Present	Hyperkeratotic	Squamos hyperplasia	Yes
16	63 / F	LE	Gelatinous	Present	Severe dysplasia	Severe dysplasia	Yes
17	49 / M	LE	Gelatinous	Present	dysplasia	SCC	Yes
18	69 / F	LE	Papilliform	Absent	Mild dysplasia	No dysplasia	No
19	35 / M	RE	Papilliform	Present	Normal epithelia	Nevus	Yes
20	64 / M	LE	Gelatinous	Absent	Moderate dysplasia	SCC	Yes
21	41 / M	RE	Gelatinous	Present	Mild dysplasia	Mild dysplasia	Yes

22	69 / F	LE	Gelatinous	Present	Mild Dysplasia	Moderate dysplasia	Yes
23	56 / M	RE	Papilliform	Absent	Dysplasia	SCC	Yes
24	42 / M	RE	Leukoplakic	Present	Moderate dysplasia	Severe dysplasia	Yes
25	56 / M	LE	Gelatinous	Present	Mild dysplasia	Mild dysplasia	Yes
26	31 / M	LE	Papilliform	Present	Dysplasia	SCC	Yes
27	64 / M	RE	Papilliform	Present	Severe dysplasia	SCC	Yes
28	57 / F	LE	Gelatinous	Present	Moderate dysplasia	Severe dysplasia	Yes
29	65 / M	RE	Papilliform	Present	Dysplasia	SCC	Yes
30	62 / M	LE	Gelatinous	Present	Severe dysplasia	CIN	Yes
31	47 / M	RE	Papilliform	Absent	Mild dysplasia	Moderate dysplasia	Yes
32	54 / M	LE	Gelatinous	Present	Squamous papiloma	SCC	Yes
33	30 / F	RE	Papilliform	Present	Severe dysplasia	Severe dysplasia	Yes
34	53 / M	LE	Gelatinous	Present	Dysplasia	Severe dysplasia	Yes
35	55 / M	RE	Leukoplakic	Present	Mild	Severe	Yes

					dysplasia	dysplasia	
36	44 / F	LE	Gelatinous	Absent	Mild dysplasia	Severe dysplasia	Yes
37	68 / M	LE	Gelatinous	Present	Dysplasia	SCC	Yes
38	52 / M	RE	Papilliform	Present	Moderate dysplasia	Severe dysplasia	Yes
39	36 / F	LE	Gelatinous	Absent	Mild dysplasia	Mild dysplasia	Yes
40	52 / M	LE	Gelatinous	Present	Moderate dysplasia	Moderate dysplasia	Yes
41	70 / M	LE	Gelatinous	Present	Severe dsplasia	CIN	Yes
42	57 / M	LE	Papilliform	Present	Dysplasia	SCC	Yes
43	62 / M	LE	Gelatinous	Present	Mild dysplasia	Moderate dysplasia	Yes
44	68 / F	RE	Leukoplakic	Absent	Severe dysplasia	SCC	Yes
45	56 / F	RE	Gelatinous	Present	Mild dysplasia	SCC	Yes
46	53 / M	LE	Papilliform	Absent	Severe dysplasia	Severe dysplasia	Yes
47	65 / M	LE	Gelatinous	Present	Mild dysplasia	Mild dysplasia	Yes
48	61 / M	RE	Gelatinous	Present	Dysplasia	SCC	Yes

49	50 / F	LE	Papilliform	Absent	Normal epithelia	Severe dysplasia	No
50	68 / M	RE	Gelatinous	Present	Dysplasia	SCC	Yes

Informed consent form

Study title : **"Analytical study of Non invasive techniques for diagnosing ocular surface squamous neoplasia"**

Name of the Participant: _____

Name of the Principal (Co-Investigator): _____

I _____ have read the information in this form (or it has been read to me). I was free to ask any questions and they have been answered. I am over 18 years of age and exercising my free power of choice, hereby give my consent to be included as a participant in "Analytical study of Non invasive techniques for diagnosing ocular surface squamous neoplasia"I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

I hereby give permission to the investigators to release the information obtained from me as result of participation in this study to regulatory authorities, Govt. agencies, and Ethics Committee. I understand that they are publicly presented.

I have understand that my identity will be kept confidential if my data are publicly presented.

I have had my questions answered to my satisfaction.

I agree to take part in this study.

I am aware that if I have any question during this study, I should contact the investigator. By signing this consent form I attest that the information given in this document has been clearly explained to me and understood by me, I will be given a copy of this consent document.

_____	_____	_____
Signature/ Thumb impression subject	Subject Name	Date(dd/mm/yyyy)

If Patient is unable to read or write

Signature of LAR Legally Acceptable Representative	Name of LAR	Date(dd/mm/yyyy)
Signature of the Investigator	Investigator Name	Date(dd/mm/yyyy)
Signature of the witness	Witness Name	Date(dd/mm/yyyy)