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Review Article

# Ocular surface squamous neoplasia: A comprehensive and updated review

**Anuradha Raj[1]*, Sahil Jain[1], Anurag Singla[1], Easther Dazine[1]**

[1]Dept. of Ophthalmology, All India Institute of Medical Sciences, Bathinda, Punjab, India

## Abstract

Ocular Surface Squamous Neoplasia (OSSN) represents a spectrum of dysplastic and neoplastic epithelial disorders affecting the conjunctiva and cornea. Although OSSN is relatively rare compared to other ocular malignancies, its significance lies in its potential for ocular surface morbidity, recurrence, and, in rare cases, systemic spread. Over the past few decades, considerable advances have been made in diagnostic modalities, particularly with non-invasive imaging techniques such as anterior segment optical coherence tomography (AS-OCT) and confocal microscopy. Concurrently, therapeutic strategies have expanded beyond surgical excision to include topical chemotherapeutic and immunotherapeutic agents, resulting in better preservation of ocular anatomy and function. This review aims to provide a detailed analysis of the epidemiology, pathogenesis, clinical features, diagnostic approaches, management strategies, and recent innovations in the field of OSSN.

**Keywords:** Ocular surface squamous neoplasia, Mitomycin C, Interferons, Anterior segment optical coherence tomography

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## 1. Introduction

Ocular Surface Squamous Neoplasia (OSSN) refers to a continuum of epithelial malignancies involving the conjunctiva, cornea, and limbal area. The term was first consolidated by Lee and Hirst in 1995, who unified a broad array of terminologies like conjunctival intraepithelial neoplasia (CIN), carcinoma in situ, and invasive squamous cell carcinoma under a single spectrum.[1,2] Though relatively rare, OSSN is the most common non-pigmented malignancy of the ocular surface.

The disease can significantly impact the visual and anatomical integrity of the eye, particularly when diagnosis is delayed or inadequate management occurs. Traditional management has focused on wide surgical excision. However, emerging medical therapies and imaging techniques have shifted the paradigm toward more conservative, vision-preserving strategies.[1]

OSSN can be classified into benign (e.g., pseudotheliomatous hyperplasia), preinvasive (e.g., conjunctival/corneal intraepithelial neoplasia grades I–III), and invasive types (e.g., squamous carcinoma, mucoepidermoid carcinoma), according to Lee and Hirst's comprehensive classification.[2]

In this review, we present an updated, comprehensive synthesis of the current understanding of OSSN, emphasizing diagnostic advancements and modern therapeutic approaches.

### *1.1. Epidemiology and risk factors*

The global incidence of OSSN exhibits marked geographical variation, closely paralleling exposure to ultraviolet (UV) radiation. Studies have reported incidences ranging from 0.03 to 1.9 cases per 100,000 individuals annually. Areas close to the equator, such as Africa, Australia, and South America, demonstrate the highest incidence rates. Templeton's study in Uganda during the 1960s provided some of the earliest epidemiologic data, highlighting UV exposure as a major environmental risk factor. [3,4]

*Corresponding author: Anuradha Raj
Email: dranuradha_sagar@yahoo.com

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*1.2. Age and gender*

OSSN predominantly affects older individuals, with the mean age of presentation around 60 years. A slight male preponderance has been consistently observed, attributed in part to greater outdoor occupational exposure.[1,2]

*1.3. Ultraviolet radiation exposure*

Chronic UV-B exposure leads to direct DNA damage, particularly in limbal stem cells, resulting in mutations such as those affecting the p53 tumor suppressor gene. UV-induced immunosuppression may also promote tumorigenesis.[2]

*1.4. Human papillomavirus (HPV) infection*

High-risk HPV types, particularly 16 and 18, have been implicated in OSSN pathogenesis. Viral oncoproteins E6 and E7 disrupt cellular apoptosis pathways, facilitating malignant transformation.[2,5]

*1.5. Human immunodeficiency virus (HIV) infection*

HIV infection markedly increases the risk of OSSN, with studies showing up to a 12-fold increased incidence. Immunosuppression reduces tumor surveillance, allowing malignant cells to proliferate unchecked.[6]

*1.6. Xeroderma pigmentosum*

Individuals with xeroderma pigmentosum, a genetic disorder characterized by defective DNA repair mechanisms, are at significantly higher risk for OSSN, especially in sun-exposed regions. Additionally, populations of British, Austrian, and Swiss ancestry show increased susceptibility, likely due to fair skin and hypopigmented iris.[6]

*1.7. Other risk factors*

1. Exposure to petroleum products and cigarette smoking.
2. Vitamin A deficiency impairs epithelial differentiation.
3. Chronic ocular surface inflammation due to trachoma or allergic conjunctivitis.

*1.8. Pathophysiology*

The pathogenesis of OSSN is a complex interplay of environmental factors, viral oncogenesis, and host immunologic status.[1]

*1.9. Ultraviolet (UV) radiation*

UV-B radiation (wavelength 280–315 nm) is particularly harmful to limbal epithelial stem cells, inducing DNA mutations. UV exposure leads to the formation of cyclobutane pyrimidine dimers, which, if not adequately repaired, result in mutations in tumor suppressor genes like p53. Mutated p53 impairs apoptosis, allowing abnormal epithelial cells to survive and proliferate.

UV-B exposure not only induces p53 mutations but also reactivates latent HPV infection, compounding the risk of oncogenesis. [2]

*1.10. Viral oncogenesis*

High-risk HPV strains, especially HPV 16 and 18, are implicated in OSSN development. HPV E6 protein promotes the degradation of p53, while E7 inactivates the retinoblastoma (Rb) protein, disrupting normal cell cycle control. This leads to dysregulated epithelial cell growth and neoplastic transformation.[2,5]

*1.11. Immunosuppression*

HIV infection dramatically increases the incidence and aggressiveness of OSSN. The loss of immune surveillance permits unchecked proliferation of dysplastic cells. Other forms of immunosuppression, such as organ transplantation, similarly predispose individuals to OSSN.

*1.12. Chronic inflammation and other carcinogen*

Prolonged ocular surface inflammation can induce oxidative DNA damage, further contributing to dysplasia. Chemical exposure, such as to petroleum products and tobacco smoke, may add additional mutagenic insults.

Histologically, OSSN lesions exhibit a continuum:

1. Dysplasia: Involves disordered maturation limited to the lower epithelial layers.
2. Carcinoma in situ: Full-thickness epithelial dysplasia without invasion of the basement membrane.
3. Invasive squamous cell carcinoma: Neoplastic cells breach the basement membrane and invade the substantia propria. [2]

## 2. Clinical Features

The clinical presentation of OSSN is notoriously variable, often mimicking benign conditions like pterygium or chronic conjunctivitis. Therefore, a high index of suspicion is necessary.[1]

1. Symptoms
   a. Ocular irritation or foreign body sensation
   b. Chronic redness
   c. Tearing (epiphora)
   d. Visual disturbance if the visual axis is involved
   e. Occasionally, visible mass or cosmetic concerns.
2. Signs
   a. Location: Typically found at the limbus, particularly at the interpalpebral fissure.
   b. Appearance:
      i. Gelatinous Lesion: Elevated, translucent to opaque mass with feeder vessels. (**Figure 1**a)
      ii. Papillomatous: Lobulated, sessile, cauliflower-like surface. (**Figure 1**b)
      iii. Leukoplakic: White plaque due to keratinization.

c. Feeder Vessels: Prominent vascularization supplying the lesion.
d. Surface Keratinization: Suggests dysplasia or carcinoma.
e. Fixed, immobile lesions: Suggest deeper scleral or intraocular invasion.

Advanced disease can involve corneal infiltration, anterior chamber inflammation, secondary glaucoma, or orbital extension. [2]

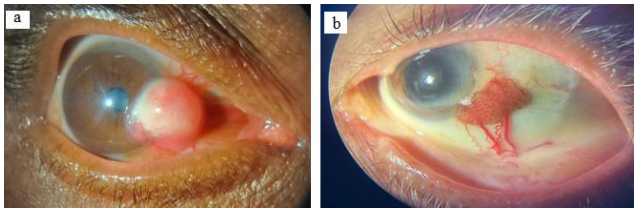


**Figure 1: a:** Showing elevated, globular mass; **b:** Demonstrating sessile cauliflower-like lesion

*2.1. Diagnostic modalities*

Early and accurate diagnosis is crucial to minimize ocular morbidity.

*2.2. Clinical examination*

Detailed slit-lamp bio microscopy remains the cornerstone of OSSN detection. Use of vital dyes like rose bengal can help demarcate abnormal epithelium.[1]

*2.3. Impression cytology*

This non-invasive technique uses cellulose acetate paper or biopore membranes to collect superficial epithelial cells. Cytologic features supporting OSSN include:

1. High nuclear-to-cytoplasmic ratio
2. Nuclear hyperchromasia
3. Irregular nuclear membranes
4. Presence of dyskeratotic cells

Although helpful for initial assessment, impression cytology cannot determine the depth of invasion. [2,7]

*2.4. Anterior segment optical coherence tomography (AS-OCT)*

AS-OCT offers high-resolution, cross-sectional imaging of the ocular surface. OSSN typically shows:

1. Thickened, hyperreflective epithelial layer
2. Abrupt transition from normal to abnormal tissue
3. Well-demarcated borders

OCT is particularly useful for non-invasive monitoring of treatment response.[8]

*2.5. In vivo confocal microscopy*

Confocal microscopy provides microscopic detail of epithelial and subepithelial tissues. Features suggestive of OSSN include:

1. Hyperreflective pleomorphic cells
2. Prominent nucleoli
3. Disruption of normal epithelial architecture.[9]

*2.6. Ultrasound biomicroscopy (UBM) and magnetic resonance imaging (MRI)*

UBM assesses the depth of scleral or intraocular invasion for large or suspicious lesions. MRI is invaluable for evaluating orbital extension, especially with gadolinium enhancement highlighting tumor tissue.[1]

*2.6.1. Microscopic examination*

The excised lesion with safe margins shows an abrupt transition of the epithelial lesion from the adjacent uninvolved conjunctiva.

*2.7. Depending on the level and thickness, OSSN is classified as*

Mild -When the lower one-third of the epithelium shows abnormal transformation.

Moderate -When the lower two-thirds of the epithelium shows abnormal transformation.

Severe -When the abnormality involves more than 2/3rds of the epithelial thickness, however, surface maturation is preserved, the lesion is termed as severe dysplasia.

Carcinoma in situ -Involvement of the full thickness of epithelium, however, with retained integrity of the epithelial basement membrane.

As the lesion progresses from mild to severe dysplasia, the cells differentiate less and less, gradually losing their squamous features until eventually the full thickness of epithelium is made of undifferentiated/immature atypical cells, which can even have a basaloid-like appearance.[10]

Though there are no standard protocols, the following has been suggested as a treatment guideline by Basti et al.[2]

Suspected OSSN < 3 clock hours: Excision biopsy + base, edge cryotherapy + alcohol epitheliectomy is done. If the margins are free of tumor cells, quarterly follow-up for a year is recommended. Thereafter, 6-monthly follow-up should suffice. If margins are involved, topical chemotherapy should be added with monthly follow-up and quarterly by impression cytology for a year to evaluate recurrence. If disease-free for one year, a 6-month follow-up is suggested.

Suspected OSSN 3 – 6 clock hours: As there is a risk of producing limbal stem cell deficiency, excision biopsy + cryotherapy is better avoided. A diagnostic biopsy is

required. In pre-invasive lesions, topical chemotherapy is likely to achieve tumor resolution. If invasive, surgery + cryotherapy is done after chemoreduction with 4 to 6 cycles of topical chemotherapy.

OSSN > 6 clock hours: A diagnostic biopsy is required. In pre-invasive lesions, topical chemotherapy is quite likely to achieve tumor resolution. If invasive, surgery + cryotherapy is done after chemoreduction with 4 to 6 cycles of topical chemotherapy. If there is no response to chemotherapy, palliative radiotherapy or extensive surgery like enucleation/exenteration may be required.[11]

### *2.8. Management strategies*

The management of OSSN has evolved considerably, shifting from a primarily surgical excision approach to a multidisciplinary approach that involves surgery, topical chemotherapeutic agents, and immunotherapy. The choice of treatment depends on the size, location, depth of invasion, and whether the lesion is focal or diffuse.[1]

## 3. Surgical Management

### *3.1. No touch surgical technique*

Proper outlining of the borders of the tumour is done with Rose Bengal staining and excision of the lesion with margins of 2-3 mm is required[12]. Bowman's membrane should be preserved if there is a tumour in the corneal epithelium. If invasion beyond the corneal epithelium partial keratectomy is required. Frozen sections of lesions have been used to assess horizontal tumour spread, not vertical. This method is poor for deep surface sampling. Exposed sclera should be treated with 99% ethanol to devitalize cells. The involved cornea should be removed following treatment with 99 % ethanol. During excision of the tumour, any contact with the instruments is avoided to stop tumour seedings. Tissue superficial to Bowman's membrane comes as a single sheet. Cryotherapy is used in combination with surgical excision. It destroys the cell initially by thermal effect, then by obliteration of microcirculation, resulting in infarction & immunological response to cellular antigens which help to reduce the chances of recurrence. Rapid freeze & slow thaw is done for cellular destruction. Superficial cryotherapy for one second is better as it destroys small islands of tumour cells. Extensive freezing for 4-5 seconds leads to severe corneal reaction due to toxic, inflammatory & immune response. Cryotherapy is never done for peripheral cornea >2mm. Recurrence rate after this ranges from 7-22%. Side effects include iritis, corneal scarring, sectoral iris atrophy, thermal inflammatory edema, ablation of peripheral retina, ectropion and decreased or increased IOP. [13]The chances of limbal stem cell deficiency (LSCD) are there due to larger excision. Autologous limbal transplantation can rehabilitate the eyes very well if the cornea is involved. Separate instruments are required for ocular surface reconstruction. Reconstruction with either autologous conjunctiva or buccal mucous membrane transplantation did not result in adequate corneal clarity as it attracts more corneal vascularisation. Recurrence can occur within one year. Surgery helps in histopathologic confirmation of diagnosis, evaluation of invasion depth, and immediate debulking of the tumor mass.[11]

### *3.1. Enucleation and orbital exenteration*

This is reserved for cases with intraocular invasion or extensive orbital extension. Exenteration is rarely required nowadays, thanks to early diagnosis and less aggressive disease at presentation.

### *3.2. Limitations*

If margins are positive, the risk of recurrence and the potential for limbal stem cell deficiency and symblepharon formation is very high.

### *3.3. Medical management*

Medical therapy, particularly topical chemotherapy and immunotherapy, has gained favor due to its ability to treat diffuse or multifocal OSSN while preserving limbal stem cells as shown in **Table 1**.

### *3.4. Topical chemotherapeutic agents*

Primary treatment with chemotherapeutic agents for OSSN is largely limited to localized OSSN. Mitomycin C (MMC) and 5-fluorouracil (5-FU) have also been used as adjuvant therapy for recurrent lesions. Extensive OSSN with a mean diameter of 40 mm has shown 57% reduction in tumor base after chemoreduction with MMC. MMC is an alkylating agent with oxygen tension-dependent cytotoxic effects on cells. It is used in the concentration of 0.02-0.04% four times a day with one week on and one week off in an alternate cycle for a maximum of 8 weeks. The one week on, one week off regime prevents damage to more slowly dividing cells. MMC is highly effective, but ocular surface toxicity (punctal stenosis, dry eye, limbal stem cell deficiency) can occur.[2] 5-Fluorouracil (5-FU) is a pyrimidine analog that inhibits thymidylate synthase, interfering with DNA synthesis. It is used topically as a 1% solution, typically applied four times daily for one week, followed by a three-week drug-free period. It has a lower toxicity profile than MMC and is cost-effective.[14]

### *3.5. Topical immunotherapy*

#### *3.5.1. Interferon Alpha-2b (IFNα-2b)*

Antitumor and antiviral cytokine used topically (1 million IU/mL) or as subconjunctival injections and the treatment courses may last for 2–4 months. The minimal ocular toxicity makes it particularly useful in cases where ocular surface preservation is critical. This is highly efficacious, even in recurrent and extensive OSSN.[15]

**Table 1:** Showing the various drugs used in OSSN treatment[16]

| Drugs | Type | Mechanism of Action | Dosage | Adverse Effects |
|---|---|---|---|---|
| MMC | Alkylating agent | Under aerobic condition generates free radicals →<br>Cytotoxicity →<br>Lipid peroxidation →<br>• Inhibition of DNA and protein synthesis<br>• Inhibits cell migration and production of extracellular matrix | Topical 0.02–0.04% | • Conjunctival hyperemia<br>• Blepharospasm<br>• Corneal punctate erosion<br>• Punctal stenosis<br>• Limbal stem cell deficiency |
| 5-FU | Pyrimidine analog | • Inhibits thymidylate synthetase<br>• Inhibits production and incorporation of thymidine into DNA<br>• Inhibits RNA synthesis | Topical 1% | • Eyelid erythema<br>• Conjunctival hyperemia<br>• Corneal punctate erosion |
| IFN α-2b | Type 1 IFN | • Immune-mediated suppression of IL-10<br>• Stimulates IL-2 and IFN-γ mRNA<br>• Anti-proliferative<br>• Anti-viral | Topical or intralesional:<br>• 1 million IU/ml<br>• 3 million IU/ml<br>• 10 million IU/ml | • Superficial punctate keratopathy<br>• Follicular conjunctivitis<br>• Systemic flu-like syndrome<br>• Fever/myalgia |

**Abbreviations:** OSSN: Ocular surface squamous neoplasia; IFN α-2b: Interferon alpha 2b; 5-FU: 5-fluorouracil; IL: Interleukin; MMC: Mitomycin C.

*3.6. Emerging therapies*

Pegylated Interferon offers a longer half-life and reduced dosing frequency.[2] Anti-VEGF Agents show an adjunctive role in highly vascularized tumors, but are still under exploration.

*3.7. Choosing between surgery and medical therapy*

Surgery is preferred for nodular, localized, well-circumscribed lesions without extensive corneal involvement. Topical therapy is favored for diffuse, multifocal, or recurrent lesions and for patients at higher surgical risk. Many centers now use a combination approach: surgical excision followed by adjuvant topical therapy to reduce the risk of its recurrence.

*3.8. Recent advances and future directions*

Recent years have witnessed tremendous innovation in OSSN diagnosis and management.

*3.9. Advances in imaging*

Ultra-High Resolution AS-OCT (UHR-OCT): It enhances the ability to differentiate OSSN from benign lesions like pterygium or papilloma. OCT Angiography (OCT-A) offers detailed vascular mapping of tumors without dye injection.[8]

*3.10. Molecular and genetic insights*

The Immunohistochemical markers such as p16 (a surrogate marker for HPV infection) provide prognostic information. Studies into p53, Ki-67, and surviving expression patterns could further refine risk stratification.[2]

*3.11. Emerging therapies*

Immune Checkpoint Inhibitors: Early studies suggest that systemic immunotherapies (such as anti-PD-1 agents) could have a role in refractory or metastatic OSSN. Gene Therapy is useful in future treatment and may involve targeting specific molecular defects, such as p53 mutations. Prophylactic vaccination against oncogenic HPV strains holds promise for OSSN prevention, particularly in high-risk populations.[17]

*3.12. Artificial intelligence (AI) and telemedicine*

Automated image analysis of AS-OCT and slit-lamp photographs using AI algorithms may facilitate earlier OSSN diagnosis, especially in resource-limited settings.[2]

## 4. Conclusion

OSSN, while rare, represents a significant ophthalmic pathology due to its potential for vision loss and ocular surface morbidity. Early diagnosis is key to effective management and improved prognosis. Advances in non-invasive diagnostic imaging and the development of topical chemotherapeutic and immunotherapeutic agents have shifted the treatment paradigm toward eye-sparing, vision-preserving strategies.

A tailored approach, considering lesion size, location, patient immune status, and resource availability, is essential for optimal outcomes. Continued research into molecular biology and innovative therapies promises to refine OSSN management further, offering hope for even better visual and anatomical results in the future.

## 5. Conflict of Interest

None.

## 6. Source of Funding

None.

## References

1. Lee GA, Hirst LW. Ocular surface squamous neoplasia. *Surv Ophthalmol*. 1995;39(6):429–50.
2. Basti S, Macsai MS. Ocular surface squamous neoplasia: a review. *Cornea*. 2003;22(7):687–704.
3. Gichuhi S, Sagoo MS, Weiss HA, Burton MJ. Epidemiology of ocular surface squamous neoplasia in Africa. *Trop Med Int Health*. 2013;18(12):1424–43
4. Templeton AC. Tumors of the eye and adnexa in Africans in Uganda. *Cancer*. 1967;20(10):1689–98.
5. Sen S, Sharma A, Panda A. Immunohistochemical localization of HPV in conjunctival neoplasias. *Indian J Ophthalmol*. 2007;55(5):361–3.
6. Mahomed A, Chetty R. Human immunodeficiency virus infection and p53 protein expression in OSSN. *Arch Ophthalmol*. 2002;120(5):554–8.
7. Nolan GR, Hirst LW. Cytomorphology of OSSN using impression cytology. *Cancer*. 2001;93(1):60–7.
8. Singh S, Mittal R, Ghosh A, Tripathy D, Rath S. High-Resolution Anterior Segment Optical Coherence Tomography in Intraepithelial Versus Invasive Ocular Surface Squamous Neoplasia. *Cornea*. 2018;37(10):1292–8.
9. Tanaka S, Kohanim S. The Role of Confocal Microscopy in Diagnosing Ocular Surface Tumors. *Int Ophthalmol Clin*. 2017;57(1):75–85
10. Mittal R, Rath S, Vemuganti GK. Ocular surface squamous neoplasia – Review of etio-pathogenesis and an update on clinico-pathological diagnosis. *Saudi J Ophthalmol.* 2013;27(3):177–16.
11. Radhakrishnan A. Ocular Surface Squamous Neoplasia:A brief review. *Kerala J Ophthalmol*. 2015;23(4):347–51.
12. Shields CL, Chien JL, Surakiatchanukul T, Sioufi K, Lally SE, Shields JA. Conjunctival Tumors: Review of Clinical Features, Risks, Biomarkers, and Outcomes--The 2017 J. Donald M. Gass Lecture. *Asia Pac J Ophthalmol (Phila)*. 2017;6(2):109–20.
13. Bowen RC, Soto H, Raval V, Bellerive C, Yeaney G, Singh AD. Ocular surface squamous neoplasia: outcomes following primary excision with 2 mm margin and cryotherapy. *Eye (Lond)*. 2021;35(11):3102–9.
14. Sun Y, Hua R. Long-Term Efficacy and Safety of Subconjunctival/Perilesional 5-Fluorouracil Injections for OSSN. *Drug Des Devel Ther*. 2020;14:5659–65.
15. Meel R, Dhiman R, Vanathi M, Sen S, Gupta N, Tandon R. Treatment outcome with interferon alpha 2b in ocular surface squamous neoplasia. *Oman J Ophthalmol*. 2021;14(1):27–32.
16. Bansal R, Honavar SG. Oncological principles in the management of ocular surface squamous neoplasia - A Review. *Indian J Ophthalmol*. 2025;73(2):173–90.
17. Zein M, De Arrigunaga S, Amer MM, Galor A, Nichols AJ, Ioannides T, et al. Therapeutic Response to Treatment of a Papillomatous Ocular Surface Squamous Neoplasia With Intramuscular Human Papillomavirus Vaccine. *Cornea*. 2024;43(8):1049–52.

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