

BÖLÜM 6

OCULAR SURFACE SQUAMOUS NEOPLASIA: EPIDEMIOLOGY, DIAGNOSIS, AND EVOLVING THERAPEUTIC STRATEGIES

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ABSTRACT

Ocular surface squamous neoplasia (OSSN) encompasses a spectrum of premalignant and malignant epithelial disorders of the conjunctiva and cornea, ranging from conjunctival intraepithelial neoplasia to invasive squamous cell carcinoma. Although relatively uncommon worldwide, it represents the most frequent non-melanocytic ocular surface malignancy. Incidence varies by geography and demographics, with the highest rates reported in equatorial regions, particularly in areas of intense ultraviolet exposure. Additional risk factors include chronic ocular irritation, viral infections such as human papillomavirus, immunosuppression, and genetic disorders affecting DNA repair. Clinically, OSSN often presents as a unilateral, elevated, gelatinous, or leukoplakic lesion at the limbus, frequently accompanied by redness, irritation, or foreign body sensation. Diagnosis is based on slit-lamp examination and confirmed with histopathology, although non-invasive modalities such as impression cytology, anterior segment optical coherence tomography, and in vivo confocal microscopy are increasingly valuable for early detection and monitoring. Management depends on disease extent and ranges from surgical excision with cryotherapy to medical therapies including topical interferon alpha-2b, Mitomycin C, and 5-Fluorouracil. Advanced disease with intraocular or orbital invasion may require enucleation or exenteration. Prognosis is generally favorable when detected early, although recurrence remains a concern, necessitating long-term follow-up. Ongoing advances in imaging, molecular

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apies.⁴⁶ Clinical trials assessing checkpoint inhibitors, vaccine-based therapies, and gene-targeted drugs are warranted to determine their role in OSSN management.

9.4 Randomized Controlled Trials

There is a notable paucity of high-level evidence comparing topical agents for OSSN. Future randomized trials are needed to establish optimal drug regimens, treatment durations, and safety profiles. Additionally, studies focusing on recurrence prevention, especially in immunosuppressed patients, are crucial to improving long-term outcomes.

CONCLUSION

Conjunctival squamous cell carcinoma and the broader spectrum of ocular surface squamous neoplasia represent uncommon but vision-threatening malignancies. Early detection, supported by clinical suspicion and non-invasive imaging, plays a vital role in improving outcomes. Surgical excision remains the first-line treatment, especially when combined with cryotherapy and reconstruction techniques. However, topical therapies—interferon alpha-2b, mitomycin C, and 5-FU—offer highly effective, minimally invasive alternatives with favorable safety profiles.

Advanced disease, including intraocular or orbital extension, significantly worsens prognosis and necessitates radical interventions. Continued advancements in imaging, artificial intelligence, molecular diagnostics, and immunotherapy are expected to improve patient stratification, guide therapy, and ultimately reduce morbidity and recurrence.

Comprehensive patient care must include long-term surveillance, particularly in high-risk groups such as immunocompromised individuals. Future research should focus on comparative effectiveness trials, biomarker-guided therapy, and access to advanced diagnostics in underserved regions to mitigate the global burden of OSSN.

REFERENCES

1. Lee, G. A., & Hirst, L. W. (1995). Ocular surface squamous neoplasia. *Survey of Ophthalmology*, 39(6), 429–450. [https://doi.org/10.1016/S0039-6257\(05\)80105-2](https://doi.org/10.1016/S0039-6257(05)80105-2)
2. Shields, C. L., & Shields, J. A. (2004). Ocular surface squamous neoplasia: The 2004 review. *Survey of Ophthalmology*, 49(1), 3–24. <https://doi.org/10.1016/j.survophthal.2003.10.008>
3. Gichuhi, S., Sagoo, M. S., Weiss, H. A., & Burton, M. J. (2013). Epidemiology of ocular surface squamous neoplasia in Africa. *Tropical Medicine & International Health*, 18(12), 1424–1433. <https://doi.org/10.1111/tmi.12203>
4. Basti, S., & Macsai, M. S. (2003). Ocular surface squamous neoplasia: A review. *Cornea*, 22(7),

- 687–704. <https://doi.org/10.1097/00003226-200310000-00015>
5. McKelvie, P. A., Daniell, M., McNab, A., Loughnan, M., & Santamaria, J. D. (2002). Squamous cell carcinoma of the conjunctiva: A series of 26 cases. *British Journal of Ophthalmology*, 86(2), 168–173. <https://doi.org/10.1136/bjo.86.2.168>
6. Patel, U., Karp, C. L., & Dubovy, S. R. (2021). Update on the management of ocular surface squamous neoplasia. *Current Ophthalmology Reports*, 9(1), 7–15. <https://doi.org/10.1007/s40135-020-00260-y>
7. Gichuhi, S., Macharia, E., Kabiru, J., Zindamoyen, A. M., Rono, H., Ollando, E., Wachira, J., Munene, R., Maina, J., Onyuma, T., Sagoo, M. S., Weiss, H. A., & Burton, M. J. (2016). Topical fluorouracil after surgery for ocular surface squamous neoplasia in Kenya: A randomised, double-blind, placebo-controlled trial. *The Lancet Global Health*, 4(6), e378–e385. [https://doi.org/10.1016/S2214-109X\(16\)30052-3](https://doi.org/10.1016/S2214-109X(16)30052-3)
8. Newton, R. (1996). A review of the aetiology of squamous cell carcinoma of the conjunctiva. *British Journal of Cancer*, 74(10), 1511–1513. <https://doi.org/10.1038/bjc.1996.581>
9. Gichuhi, S., Macharia, E., Kabiru, J., Zindamoyen, A. M., Rono, H., Ollando, E., Wachira, J., Munene, R., Onyuma, T., Jaoko, W. G., Sagoo, M. S., Weiss, H. A., & Burton, M. J. (2016). Risk factors for ocular surface squamous neoplasia in Kenya: A case-control study. *Tropical Medicine & International Health*, 21(12), 1522–1530. <https://doi.org/10.1111/tmi.12792>
10. Ateenyi-Agaba, C., Franceschi, S., Wabwire-Mangen, F., Arslan, A., Othieno, E., Binta-Kahwa, J., van Doorn, L. J., Kleter, B., Quint, W., & Weiderpass, E. (2010). Human papillomavirus infection and squamous cell carcinoma of the conjunctiva. *British Journal of Cancer*, 102(2), 262–267. <https://doi.org/10.1038/sj.bjc.6605466>
11. Galor, A., Karp, C. L., Chhabra, S., Barnes, S., & Alfonso, E. C. (2010). Topical interferon alpha 2b eye-drops for treatment of ocular surface squamous neoplasia: A dose comparison study. *British Journal of Ophthalmology*, 94(5), 551–554. <https://doi.org/10.1136/bjo.2008.153197>
12. Kalamkar, C., & Radke, N. (2016). Bilateral ocular surface squamous neoplasia in a child with xeroderma pigmentosum. *BMJ Case Reports*, 2016, bcr2016215814. <https://doi.org/10.1136/bcr-2016-215814>
13. Gichuhi, S., Ohnuma, S., Sagoo, M. S., & Burton, M. J. (2014). Pathophysiology of ocular surface squamous neoplasia. *Experimental Eye Research*, 129, 172–182. <https://doi.org/10.1016/j.exer.2014.10.015>
14. El-Abaseri, T. B., Putta, S., & Hansen, L. A. (2006). Ultraviolet irradiation induces keratinocyte proliferation and epidermal hyperplasia through the activation of the epidermal growth factor receptor. *Carcinogenesis*, 27(2), 225–231. <https://doi.org/10.1093/carcin/bgi220>
15. Kiire, C. A., & Dhillon, B. (2006). The aetiology and associations of conjunctival intraepithelial neoplasia. *British Journal of Ophthalmology*, 90(1), 109–113. <https://doi.org/10.1136/bjo.2005.077305>
16. McGee-Avila, J. K., & Mbulaiteye, S. M. (2024). Conjunctival squamous cell carcinoma in people with HIV in South Africa: Time to renew efforts for novel oncogenic virus discovery? *Journal of the National Cancer Institute*, 116(2), 186–188. <https://doi.org/10.1093/jnci/djad147>
17. Birkholz, E. S., Goins, K. M., Sutphin, J. E., Kitzmann, A. S., & Wagoner, M. D. (2011). Treatment of ocular surface squamous cell intraepithelial neoplasia with and without mitomycin C. *Cornea*, 30(1), 37–41. <https://doi.org/10.1097/ICO.0b013e3181d43ac6>
18. Chauhan, S., Sen, S., Sharma, A., Tandon, R., Kashyap, S., Pushker, N., Vanathi, M., & Sharma, N. (2014). American Joint Committee on Cancer staging and clinicopathological high-risk predictors of ocular surface squamous neoplasia: A study from a tertiary eye center in India. *Archives of Pathology & Laboratory Medicine*, 138(11), 1488–1494. <https://doi.org/10.5858/arpa.2013-0353-OA>
19. Karp, C. L., Moore, J. K., & Rosa, R. H., Jr. (2001). Treatment of conjunctival and corneal intraepithelial neoplasia with topical interferon alpha-2b. *Ophthalmology*, 108(6), 1093–1098. [https://doi.org/10.1016/S0161-6420\(01\)00577-2](https://doi.org/10.1016/S0161-6420(01)00577-2)
20. Nolan, G. R., Hirst, L. W., Wright, R. G., & Bancroft, B. J. (1994). Application of impression

- cytology to the diagnosis of conjunctival neoplasms. *Diagnostic Cytopathology*, 11(3), 246–249. <https://doi.org/10.1002/dc.2840110309>
21. Nanji, A. A., Sayyad, F. E., Galor, A., Dubovy, S., & Karp, C. L. (2015). High-resolution optical coherence tomography as an adjunctive tool in the diagnosis of corneal and conjunctival pathology. *The Ocular Surface*, 13(3), 226–235. <https://doi.org/10.1016/j.jtos.2015.02.001>
22. Alzahrani, Y. A., Alahmadi, A. S., Alahmadi, A. M., Alsarhani, W. K., & Alzahrani, Y. M. (2022). Diagnostic tools for ocular surface squamous neoplasia: A review. *Frontiers in Oncology*, 12, 955449. <https://doi.org/10.3389/fonc.2022.955449>
23. Napora, C., Cohen, E. J., Genvert, G. I., Presson, A. C., Arentsen, J. J., Eagle, R. C., & Laibson, P. R. (1990). Factors associated with conjunctival intraepithelial neoplasia: A case-control study. *Ophthalmic Surgery*, 21(1), 27–30. <https://doi.org/10.3928/1542-8877-19900101-07>
24. El-Hadad, C., Zaghoul, M. S., Farid, M., Khafagy, W., & Ezzat, A. (2014). Conjunctival squamous cell carcinoma: Clinicopathological characteristics, treatment outcomes, and prognostic factors. *Clinical Ophthalmology*, 8, 79–86. <https://doi.org/10.2147/OPTH.S54588>
25. Mittal, R., Rathore, A., Meel, R., Singh, P., Dahiya, R., Pushker, N., Bajaj, M. S., Sen, S., & Kashyap, S. (2019). Ocular surface squamous neoplasia: An overview of pathogenesis, molecular biology, clinical features, diagnosis and management. *Indian Journal of Ophthalmology*, 67(9), 1389–1399. https://doi.org/10.4103/ijjo.IJO_1240_19
26. Nagata, K., Maruyama, F., Araki-Sasaki, K., Nakajima, A., & Ogata, N. (2014). Immunohistochemical expression of EGFR and Ki-67 in ocular surface squamous neoplasia. *PLOS ONE*, 9(4), e93164. <https://doi.org/10.1371/journal.pone.0093164>
27. Galor, A., Feuer, W., Lee, Y., Dubovy, S., Kovalyshyn, I., & Karp, C. L. (2018). Tumor size and clinical outcomes for ocular surface squamous neoplasia: A proposal for the American Joint Committee on Cancer staging system. *Ophthalmology*, 125(6), 859–868. <https://doi.org/10.1016/j.ophtha.2017.12.020>
28. Erie, J. C., Campbell, R. J., & Liesegang, T. J. (1986). Conjunctival and corneal intraepithelial and invasive neoplasia. *Ophthalmology*, 93(2), 176–183. [https://doi.org/10.1016/S0161-6420\(86\)33764-3](https://doi.org/10.1016/S0161-6420(86)33764-3)
29. Shields, J. A., Shields, C. L., & De Potter, P. (1997). Surgical approach to conjunctival tumors. *Archives of Ophthalmology*, 115(6), 808–815. <https://doi.org/10.1001/archophth.1997.01100150810025>
30. Tabin, G., Levin, S., Snibson, G., Loughnan, M., Taylor, H., & McCarty, C. (2005). Late recurrences and the necessity for long-term follow up in corneal and conjunctival intraepithelial neoplasia. *Cornea*, 24(3), 297–300. <https://doi.org/10.1097/01.icc.0000151496.93372.64>
31. Kiire, C. A., Srinivasan, S., & Karp, C. L. (2010). Ocular surface squamous neoplasia. *International Ophthalmology Clinics*, 50(3), 35–46. <https://doi.org/10.1097/IIO.0b013e3181e246e5>
32. El-Hadad, C., Abdelbaky, S. H., Eltanamly, R. M., & Ezzat, W. F. (2021). Prognostic factors for orbital exenteration, local recurrence, metastasis, and death from disease in conjunctival squamous cell carcinoma. *Ophthalmic Plastic and Reconstructive Surgery*, 37(3), 279–285. <https://doi.org/10.1097/IOP.0000000000001814>
33. Nanji, A. A., Sayyad, F. E., & Karp, C. L. (2013). Topical chemotherapy for ocular surface squamous neoplasia. *Current Opinion in Ophthalmology*, 24(4), 336–342. <https://doi.org/10.1097/ICU.0b013e3283622a13>
34. Sripawadkul, W., Reyes-Capo, D., Zein, M., Wylegala, A., Albayyat, G., Galor, A., & Karp, C. L. (2023). Long-term study of topical interferon α -2b eye drops as primary treatment of ocular surface squamous neoplasia. *The Ocular Surface*, 28, 108–114. <https://doi.org/10.1016/j.jtos.2022.12.009>
35. Frucht-Pery, J., Rozenman, Y., & Pe'er, J. (1997). Mitomycin C therapy for corneal intraepithelial neoplasia. *American Journal of Ophthalmology*, 124(3), 303–309. [https://doi.org/10.1016/S0002-9394\(14\)70814-6](https://doi.org/10.1016/S0002-9394(14)70814-6)
36. Joag, M. G., Sise, A., Murillo, J. C., Sayed-Ahmed, I. O., Wong, J. R., Bouchard, C. S., Karp, C. L., & Galor, A. (2016). Topical 5-fluorouracil 1% as primary treatment for ocular surface squamous

- neoplasia. *Ophthalmology*, 123(7), 1442–1448. <https://doi.org/10.1016/j.ophtha.2016.02.034>
37. Kozma, K., Dömötör, Z. R., Csutak, A., Szabó, L., Hegyi, P., Erőss, B., Helyes, Z., Molnár, Z., Dembrovsky, F., & Szalai, E. (2022). Topical pharmacotherapy for ocular surface squamous neoplasia: Systematic review and meta-analysis. *Scientific Reports*, 12(1), 14221. <https://doi.org/10.1038/s41598-022-18545-6>
38. Shields, C. L., Ramasubramanian, A., Mellen, P. L., & Shields, J. A. (2012). Intraocular invasion of conjunctival squamous cell carcinoma in five patients. *Ophthalmology*, 119(3), 558–563. <https://doi.org/10.1016/j.ophtha.2011.08.036>
39. Borella, Y., Lumbroso, L., Lévy, C., Gardrat, S., Klijanienko, J., Malaise, D., Dendale, R., Cas-soux, N., & Matet, A. (2024). Intraocular invasion by conjunctival squamous cell carcinoma: Clinical presentation, histopathological findings, and outcome. *Ocular Oncology and Pathology*, 10(1), 32–42. <https://doi.org/10.1159/000531983>
40. Rathi, S. G., Ganguly Kapoor, A., & Kaliki, S. (2018). Ocular surface squamous neoplasia in HIV-infected patients: Current perspectives. *HIV/AIDS (Auckland)*, 10, 33–45. <https://doi.org/10.2147/HIV.S120517>
41. Gurnani, B., & Kaur, K. (2025). Ocular surface squamous neoplasia. In *StatPearls [Internet]*. Treasure Island, FL: StatPearls Publishing. Retrieved from <https://www.ncbi.nlm.nih.gov/books/NBK573082/>
42. Tsatsos, M., Delimitrou, C., Tsinopoulos, I., & Ziakas, N. (2025). Update in the diagnosis and management of ocular surface squamous neoplasia (OSSN). *Journal of Clinical Medicine*, 14(5), 1699. <https://doi.org/10.3390/jcm14051699>
43. Gokharu, S., Arya, D., Chauhan, D., & Das, S. (2025). Ocular surface squamous neoplasia masquerades: Clinical profile and outcome. *Indian Journal of Ophthalmology*, 73(Suppl 3), S405–S409. https://doi.org/10.4103/IJO.IJO_3391_23
44. Greenfield, D. S., Jiang, Y., Madu, A., Hernandez-Aya, L. F., Sun, W., Karp, C. L., Dubovy, S. R., Lee, R. K., & Galor, A. (2025). Deep learning-based differentiation of ocular surface squamous neoplasia from pterygium and pinguecula using anterior segment optical coherence tomography. *American Journal of Ophthalmology*, 268, 45–54. <https://doi.org/10.1016/j.ajo.2024.10.012>
45. Ramberg, I. M. S. (2022). Human papillomavirus-related neoplasia of the ocular adnexa. *Acta Ophthalmologica*, 100(Suppl 272), 3–33. <https://doi.org/10.1111/aos.15244>
46. Esmaeli, B. (2023). Immune checkpoint inhibitor therapy for orbital and ocular adnexal squamous cell carcinomas: International Society of Ocular Oncology President's Lecture, 2022. *Investigative Ophthalmology & Visual Science*, 64(7), 29. <https://doi.org/10.1167/iovs.64.7.29>