

Clinical Management of Ocular Surface Squamous Neoplasia: A Review of the Current Evidence

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Received: June 12, 2018
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ABSTRACT

Ocular surface squamous neoplasia (OSSN) is the most common non-pigmented malignancy of the ocular surface and is represented in a wide range of histologic diagnoses, ranging from mild epithelial dysplasia to invasive squamous carcinoma. Although surgical excision is still the gold standard for OSSN treatment, interest in conservative medical approaches is steadily growing. We have reviewed all of the literature on OSSN published in English in the MEDLINE database up to May 2018, using the keywords “ocular surface squamous neoplasia,” “squamous conjunctival carcinoma,” and “conjunctival carcinoma in situ,” with the aim to provide a comprehensive review of the most recent evidence on this distinct clinical entity.

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Keywords: Conjunctival carcinoma; Ocular surface squamous neoplasia; Squamous conjunctival carcinoma

INTRODUCTION

First proposed in 1995 as a distinct clinical entity [1], ocular surface squamous neoplasia (OSSN) is an umbrella term which includes a broad spectrum of conjunctival malignancies, ranging from mild epithelial dysplasia to invasive squamous carcinoma (SCC) [2]. It is the most common non-pigmented malignancy of the ocular surface [3], with an incidence that ranges from 0.03–1.9 per 100,000/year in the Caucasian population [4–7], to 3–3.4 per 100,000/year in African ethnicity populations [8, 9].

Surgical excision is still the gold standard of treatment; however, due to the high rate of recurrence of the tumor, interest in conservative medical approaches has been progressively increasing in recent years [10]. The aim of this review was to report the most recent evidence on this entity, focusing on the latest data on the medical treatment for OSSN.

METHODS

A search of the MEDLINE database was performed using the keywords “ocular surface

squamous neoplasia,” “squamous conjunctival carcinoma,” and “conjunctival carcinoma in situ.” All reports published in English up to May 2018, including those available online ahead of print, were included. As such, this article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

RISK FACTORS AND PATHOGENESIS

The primary risk factor for OSSN is ultraviolet (UV) B radiation, with people chronically exposed to direct solar light and those involved in outdoor occupations being at the most risk [9]. According to an Australian population-based study [4], Individuals with fair skin, light iris color and/or susceptible to sunburn, those who spent > 50% of time outdoors during the first 6 years of life, and those living within 30° of the equator carry the greatest risk for developing the tumor.

Non-modifiable risk factors include male gender and age [11–13]. A longitudinal study published in the USA in 2018 reported that U.S. men had a 12-fold higher incidence rate than U.S. women and that this rate was stable in a follow-up of 4 years [14]. Conversely, in populations in African countries, OSSN prevalence peaks at a relatively younger age and there is no gender predilection; in addition, the epidemiologic trend is increasing [15, 16]. Modifiable risk factors are cigarette smoking [1, 11], vitamin A or retinol deficiency [17], chronic trauma or inflammation [18], and exposure to petroleum products; more recently, the use of topical voriconazole has been proposed as a predisposing factor [19, 20].

Infectious diseases such as human immunodeficiency virus types 1 and 2 (HIV-1 and -2) [21–24], human papillomavirus (HPV) serotypes 16 and 18 [25], and hepatitis B and C virus [26] play a putative role in the pathogenesis of OSSN.

HIV has been associated with a eightfold increased risk of OSSN [27], with the highest rate of incidence in the first 2 years of acquired

immunodeficiency syndrome (AIDS) [28]. As OSSN can be the first presenting sign of HIV/AIDS in 50–86% of cases [23, 29–32], screening for the presence of the virus should be always performed in atypical cases or in endemic regions. HIV infection has been associated with younger age at presentation of OSSN [31, 33], female or no gender predilection [16, 34, 35], more severe course [36, 37], bilaterality [38], worse prognosis [32], and increased risk of recurrence [39]. Immune dysregulation syndromes other than AIDS, including iatrogenic immunosuppression post-organ transplantation [39], non-Hodgkin’s lymphoma [40], asthma/eczema/atopic diseases [41–44], ocular cicatricial pemphigoid [45], xeroderma pigmentosum [46], and Papillon–Lefèvre syndrome [47], can also predispose to OSSN.

It is thought that the breakdown of the human body’s immune surveillance against the tumor creates a “permissive environment” for other risk factors to trigger malignant transformation of the epithelial cells [39]. For example, HPV infection, which is associated with HPV-induced inhibition of the tumor-suppressor protein retinoblastoma (Rb), may interact synergistically with sunlight exposure, which can cause UV radiation-related DNA damage, including the formation of pyrimidine dimers (CC > TT) and epigenetic changes in the p16 gene promoter [48], and lead to triggering of the neoplastic transformation of the cell lineage.

There is no clear genetic mutation associated with OSSN [49]. However, one of the key events reported are mutations affecting the tumor suppressor gene p53, with a high percentage of CC > TT alterations, which confirms the causative role of solar rays in the etiology of the tumor [50]. Moreover, Scholz et al. identified mutations in the telomerase reverse transcriptase (TERT) gene promoter—a marker of other systemic cancers [51] and a sign of worse prognosis [52, 53]—in 44% of the 48 samples of conjunctival OSSN included in their study [54]. Finally, hyper-expression of matrix metalloproteinases MMP-9 and MMP-11 and hypo-expression of clusterin seem to be a hallmark in the tumor cell transcriptome [55].

CLINICAL PRESENTATION

The usual presentation of OSSN is a unilateral vascularized limbal mass located in the interpalpebral fissure; it can also present as a bilateral/multifocal mass, albeit rarely [1]. Even more rarely, the tumor can involve the tarsal conjunctiva or it can be associated with pterygia or other benign conditions; both presentations make the correct diagnosis more challenging [56].

According to its morphology, OSSN can be classified into nodular, nodulo-ulcerative [57], gelatinous, leukoplakic, placoid, or papillary forms. The macroscopic appearance is a yellow-pink lesion with tortuous dilated feeder vessels, sometimes with keratinized plaques on its surface [58]. In dark-skinned people, the mass is commonly pigmented. HIV-related lesions are often larger, with forniceal extension, and feature more areas of leukoplakia with pronounced feeder vessels [16, 59]. The tumor may also have a less obvious appearance, such as opalescence on the cornea or chronic conjunctivitis [60], leading to a considerable delay in the correct diagnosis. The most common signs and symptoms are a red eye, ocular irritation, and the appearance of a new mass in the eye; in very advanced cases, necrotizing scleritis, associated with severe pain and visual loss, have been described [37, 61].

At the microscopic level, OSSN presents as a range of cellular dysplasia, from mild, moderate, to severe; distinctly neoplastic cells with an intact basal membrane are characteristic of the carcinoma in situ. When the basal membrane is involved, the tumor acquires features that are characteristic of invasive SCC. Some changes suggestive of this malignant transformation include a diffuse or multifocal configuration [62], brown pigmentation, median basal diameter of > 10 mm, and thickness of > 1 mm [63].

DIAGNOSIS

The gold standard for the diagnosis of OSSN remains histopathologic evaluation following an incisional or excisional biopsy [62]. However, in the past three decades, technological

innovations have led to the introduction of less or non-invasive methods of diagnosis, including impression cytology [64], in vivo confocal microscopy (IVCM) [65, 66], and high-resolution or ultra-high-resolution anterior segment optical coherence tomography (HR-OCT) [67]. Impression cytology [64] or exfoliative cytology [68, 69] are two methods that can be used to identify superficial dysplastic lesions, but they cannot assess the potential invasive growth of these lesions; moreover, they require a dedicated preparation and immediate analysis after tissue sampling.

Examination by IVCM reveals such OSSN features as pleomorphic epithelial cells, hyperreflectivity of the epithelium, demarcation line between normal and neoplastic area, enlarged nuclei with prominent nucleoli in the basal epithelium (“starry sky” appearance), and loss of limbal dendritic cells [65, 66, 70–72]. Similar characteristics are discernible non-invasively using HR-OCT [73, 74]. However, the diagnostic sensibility of this latter imaging modality is dependent on the training level of the users and ranges from 94 to 100%, with a specificity of up to 100% [67, 75, 76]. HR-OCT also allows for detection of treatment response and subclinical recurrence. The main limitation of HR-OCT is the impossibility to perceive deep invasion of the tumor or the histologic grade. Another diagnostic imaging modality, ultrasound biomicroscopy (UBM), has the considerable advantage of detecting the infiltration of adjacent structures due to its higher penetration and capability to achieve a better resolution of the posterior margin of the lesions [77, 78]. Examination using UBM reveals a hyperechoic tumor surface with a generally hypoechoic tumor stroma; this pattern differs from the hyperechoic orbital tissues, and is easily identifiable in cases of orbital invasion [77]. However, UBM is time-consuming and highly operator-dependent, and requires direct contact with the eye.

Due to the specific drawbacks of non-invasive imaging techniques, histopathology is still fundamental to the early identification of potential corneal, scleral, intraocular or orbital invasion of the tumor. Regional and systemic investigations by ultrasound, computed tomography, or magnetic resonance imaging

are often necessary for the correct staging and to plan the appropriate treatment (see “Treatment”).

TREATMENT

The management of OSSN includes surgical resection [79] and medical or para-surgical treatments, namely, topical chemotherapy (mitomycin C [MMC], 5-fluorouracil [5-FU]), topical/local immunomodulation with interferon alpha-2b (IFN- α 2b), topical antiviral medications (cidofovir) [80, 81], and photodynamic therapy [82]. Treatment with anti-vascular endothelial growth factor has also been tried, with inconsistent results [83, 84].

Surgical removal of conjunctival lesions is carried out following the Shields’ “no touch” technique to avoid the potential risk of seeding. This technique incorporates large macroscopically tumor-free margins (at least 4 mm) in the bioptic piece to increase the likelihood of clear margins [79]. Cryotherapy is then applied to the conjunctival and limbal margins in a “double freeze slow thaw” technique, which achieves the rupture of tumor cell membranes and the occlusion of the blood vessels [85, 86].

Corneal components are removed through alcohol keratoepitheliectomy leaving at least 2-mm tumor-free margins [79], while scleral invasion is addressed with partial lamellar sclerectomy [87]. Eucleation or orbital exenteration is reserved for cases with intraocular or periocular invasion, respectively [88, 89]. Extensive surgical excision of limbar OSSN (dissection duration of ≥ 6 clock-hours) carries the risk of limbal stem cell deficiency (LSCD), while the removal of large conjunctival tissue may lead to scarring and symblepharon, despite the use of cryopreserved amniotic membrane to cover the resulting defect [90, 91]. LSCD can be prevented with intraoperative limbal epithelial transplantation, which has shown promising results [92, 93]. Alternatively, to minimize the amount of tissue removed, a modified Mohs technique with intraoperative control of surgical margins has also been suggested [87, 94].

As surgery carries with it undeniable complications, as discussed above, the option of medical therapy has gained increasing popularity in the treatment of OSSN and is considered to be superior to invasive approaches in the treatment of subclinical and microscopic disease [95].

MMC is a potent alkylating agent used topically as a primary treatment [96] or with the adjunction of surgical resection—before (chemoreduction), intraoperatively, or after (chemopreventive) the procedure—to reduce the risk of recurrence [97–104]. Both the regimens of 1 drop of MMC 0.02% three times daily for at least two 1-week courses [101] and 1 drop of MMC 0.04% four times daily for at least two 1-week courses [105] have been demonstrated to be effective. The treatment is limited by MMC-related side effects, including photophobia, dry eye, punctal stenosis, persistent epithelial defects, LSCD, and allergic reactions, all of which are very common [106].

5-FU is a structural analog of thymine and inhibitor of the enzyme thymidylate synthetase. It impairs DNA and RNA synthesis in both normal and tumor cells, but as the amount of nucleic acids synthesis is higher in tumoral cells, the drug has a relative selectivity for the cancerous lineage [107, 108]. 5-FU has been delivered topically as a 1% 5-FU formulation four times/day for 4 weeks [109] or for 1 week followed by a drug holiday of 3 weeks [110], depending on the study. As primary therapy for OSSN, 5-FU has shown an efficacy of 85–100% [109–111], with a tumor recurrence rate ranging from 1.1 to 43% [112].

Interferons are natural glycoproteins with antiviral and antimicrobial properties that are released by several types of immune cells secondary to tumors or viral infections [113, 114]. Their role as antineoplastic agents is due to their anti-proliferative, anti-angiogenic, and cytotoxic effects, as well as to their property of being a potential inducer of the host antitumor immunosurveillance [115]. The first evidence of the efficacy of topical INF in the regression of limbal epithelial dysplasia was published in 1994 [116]. Since then, recombinant human IFN- α 2b has been used as the primary agent (immunotherapy) for small corneal or

conjunctival tumors (i.e., basal diameter < 20 mm, extension < 6 clock-hours) [117–123], as a neoadjuvant agent (immunoreduction) for diffuse tumor (i.e., basal diameter > 20 mm, extension > 6 clock-hours) to facilitate surgical excision; [124, 125], and as adjuvant therapy (immunoprevention), in the presence of positive margins after resection [126–129]. According to the most recently published analysis (Table 1), the drug has demonstrated a high rate of resolution, an acceptable rate of recurrence, and minimal toxicity when used in primary immunotherapy [117, 130–132].

IFN- α 2b is prescribed either topically as drops or locally as perilesional subconjunctival injections [133]. There is as yet no consensus on the dosage of local IFN- α 2b to be injected, and dosages ranging from 3 million international units (MIU)/0.5 cc [130, 134] upwards to 9 MIU/0.5 cc [129] or downwards to 3 [125, 126], 5 [120], 10 [127, 135] MIU/cc once a month have been reported. For focal lesions, the entire injection is given in only one location; for multifocal disease, the injection is distributed over all of the involved areas. There is relatively more consensus on the dosage of topical IFN- α 2b, as it is given at a standard dose of 1 MIU/mL one drop 4 times/day, even though a dose of 3 MIU/mL one drop 4 times/day has also been reported, with no difference in efficacy [72, 119, 133]. The vial must be kept refrigerated and is replaced every 2 weeks. Median resolution time ranges from 1.5 to 6 months of treatment [44, 72]. After macroscopic clinical regression, the drug is often continued for additional cycles to prevent recurrences, even though the total length of the treatment varies among the different studies, ranging from 1 to 4 months [10, 72, 120, 136].

Being an endogenous molecule, INF is better tolerated than chemotherapeutic agents. Perilesional injections of IFN- α 2b are associated with transient flu-like symptoms, while topical drops are associated with irritation, conjunctival hyperemia [129], reactive lymphoid hyperplasia [137], and follicular conjunctivitis [135]; side effects usually resolve with treatment

discontinuation. One of the limitations of IFN- α 2b with respect to surgery is the economic burden, even though the availability and affordability of the medical drug has been improving in recent years. A 10-MIU/mL vial costs \$179–235 in the USA, for a total of > \$700 for a 4-month cycle of injective therapy and a total of \$1074–1440 for a 6-month cycle of topical treatment. In other countries outside the USA (e.g., India), the cost-effectiveness of IFN- α 2b is much more favorable [120].

While an efficient immune system has been advocated as a requisite for IFN- α 2b efficacy [138, 139], the presence of HPV infection does not seem to influence the response to the treatment [140]. In case of HIV-related immunosuppression, clinicians should prefer non-immunomodulating agents, such as 5-FU or MMC, in association with the highly active anti-retroviral therapy (HAART) protocol, even though the role of HAART in OSSN regression is still being debated [37, 141]. Conversely, there are very few studies investigating the prognostic signs able to predict the response to IFN- α 2b. Zarei-Ghanavati and associates found a borderline difference in the number of limbal dendritic cells after 1 month of topical IFN- α 2b between responders and non-responders, in favor of responders [72]. Invasion of the epithelial basement membrane and the Bowman's layer do not seem to be a negative prognostic factor [135], while the size of the tumor at baseline has been associated with a longer treatment [142].

Cidofovir is an antiviral agent with activity against double-stranded DNA viruses, including HPV. The antitumor activity of cidofovir, independent of the virus infection status of the patient, is due to the incorporation of the molecule into replicating DNA, where it causes direct DNA damage and promotes cellular apoptosis. A dose of 2.5 mg/mL topical cidofovir has shown encouraging efficacy as secondary treatment in multi-refractory OSSN [80].

Finally, in selected cases of invasive disease, brachytherapy [58, 143] or proton-beam radiotherapy [144, 145] can be used in the attempt to salvage the eyeball.

Table 1 Rate of resolution, rate of recurrence, and toxicity of interferon- α 2b used in primary immunotherapy for ocular surface squamous neoplasia

Authors	Year of publication	Study design	Eyes (n)	Drug delivery	Treatment duration	Duration of follow-up (months)	Recurrence rate (%)	Complete recurrence rate (%)	Time to resolution	Previous treatment	Side effects
Singh et al. [123]	2018	Prospective	6	Topical	24 weeks	3.38	0	100	16 weeks	MMC	Foreign body sensation, follicular conjunctivitis
Chaugule et al. [122]	2018	Retrospective	5	Topical	3 months	8.8	0	100	3 months	None	Irritation, burning, dry eye
Pujari et al. [160]	2018	Case report	1	Topical	N/A	12	0	100	5 weeks	None	N/A
Meel et al. [148]	2017	Retrospective	26	Topical	N/A	16.15	N/A	65.38	8 weeks	MMC, excision biopsy	N/A
Kusumesh et al. [121]	2017	Retrospective	26	Local	N/A	22.2	3.85	69.23	6 weeks	None	N/A
Kusumesh et al. [121]	2017	Retrospective	26	Topical	N/A	22.2	3.85	89	3.1 months	None	Conjunctival hyperemia, burning sensation
Kaliki et al. [69]	2016	Retrospective	9	Topical	6 cycles ^a	9	0	92	3 cycles ^a	None	Conjunctival hyperemia
			13	Local and topical	7 cycles ^b				4 cycles ^b		Conjunctival hyperemia, flu-like syndrome
Kusumesh et al. [119]	2015	Retrospective	24	Topical	3.25 months	18.81	0	91.6	3.25 months	None	Conjunctival congestion, spontaneous intra-tumoral bleeding, foreign body sensation
Zarei-Ghanavati et al. [124]	2014	Prospective	5	Topical	8 weeks	10.2	0	100	8 weeks	One eye had excision + cryotherapy	None
Shah et al. [132]	2012	Retrospective	20	Topical	11 months	12	4	83	6 months	Excisional biopsy (39%), cryotherapy (9%), topical MMC (4%), topical interferon alpha-2b(13%)	Conjunctival hyperemia, follicular hypertrophy, giant papillary conjunctivitis, irritation, corneal epithelial defect, flu-like syndrome
Karp et al. [117]	2010	Retrospective	5	Local	6.6 cycles ^c	30.64	20	80	3-49 months	None	Local irritation, flu-like syndrome
			10	Local and topical	5.9 cycles ^c	84.06	0	90	1.89 months		

MMC Mitomycin C, N/A: not assessed

^a Topical interferon (INF)- α 2b, four times/daily for 1 month^b Monthly INF- α 2b injections^c INF- α 2b injections, three times weekly initially, then weekly

Table 2 Definitions of TNM (Tumor, Node, Metastasis) and histopathologic grade for ocular surface squamous neoplasia, according to the American Joint Committee on Cancer eighth edition cancer staging manual Adapted from [146]

TNM staging	Definition
Primary tumor (T)	
TX	Cannot assess the primary tumor
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor (< 5 mm in greatest dimension) invades through the basement membrane without invasion of adjacent structures ^a
T2	Tumor (> 5 mm in greatest dimension) invades through the basement membrane without invasion of adjacent structures ^a
T3	Tumor invades adjacent structures excluding the orbit
T4	Tumor invades orbit with or without further extension
T4a	Tumor invades orbital soft tissues without bone invasion
T4b	Tumor invades the bone
T4c	Tumor invades adjacent paranasal sinuses
T4d	Tumor invades the brain
Lymph node (N)	
NX	Regional lymph nodes cannot be assessed
N0	Regional lymph node metastasis absent
N1	Regional lymph node metastasis present
Systemic metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
Histopathologic grade (G)	
GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated

Table 2 continued

TNM staging	Definition
G4	Undifferentiated

^a Adjacent structures in all cases include the cornea, fornical/palpebral/tarsal conjunctiva, intraocular chambers, caruncle and plica semilunaris, lacrimal puncta and canaliculi, anterior/posterior eyelid lamellae, and eyelid margin

CLASSIFICATION

Tumor staging is assessed using the TNM (Tumor, Node, Metastasis) definitions, as stated in the American Joint Committee on Cancer (AJCC) recommendations, with T describing features of the primary tumor, N describing involvement of the regional nodes, and M describing the spread of distant metastasis. The eighth edition of the AJCC classification has been recently released, and the definitions for T1 and T2 differ from those in the seventh edition. In the seventh edition the definition of T1 and T2 was based solely on the tumor size, whereas in the eighth edition T classification is based both on the tumor size (≤ 5 or > 5 mm) and the invasiveness of the basement membrane and adjacent structures, namely the fornix, the plica semilunaris, the caruncle, the eyelid lamellae, the orbit, the sinuses bone, and the brain (Table 2) [146].

Yousef et al. [147] evaluated 101 eyes with OSSN based on the classification of the AJCC seventh edition and reported that the majority of eyes were diagnosed in the Tis and T1 category, with only 1 and 2% in the T2 and T4 stages, respectively. Similarly, Galor et al. [133] classified 389 OSSN post-excisional cases into T1 (53%), T2 (36%), T3 (10%), and T4 (1%). To the contrary, more recent statistics based either on the seventh [135, 148] or the eighth edition [149] have revealed that only a few lesions presented as in situ, while the majority of the cases fell cumulatively in the T3 or T4 category. This disparity can be explained by the fact that

Table 3 New clinical classification proposed for ocular surface squamous neoplasia Adapted from [150]

Grade	Limbal involvement (clock-hours)	Maximal basal diameter (mm)	Treatment
Grade I: OSSN with no invasion into ocular coats clinically and on imaging ^a			
A (small)	≤3	≤5	Surgical excision with margin control
B (large)	>3 to < 6	>5 to < 15	Immunotherapy or immunoreduction
C (diffuse)	≥6	≥15	Immunoreduction
Grade II: OSSN with invasion into ocular coats (sclera/corneal stroma) on imaging ^a			
	Any	Any	Excision with lamellar sclerectomy or keratectomy + cryotherapy of margins and base
Grade III: OSSN with intraocular invasion			
	Any	Any	Enucleation
Grade IV: OSSN with intraorbital extension ^b			
	Any	Any	Exenteration

OSSN Ocular surface squamous neoplasia

^a Imaging in grade I and II relies on ultrasound biomicroscopy

^b Confirmed by computed tomography or magnetic resonance imaging

OSSN often grows with limbus involvement, shifting the lesion directly to the T3 category, notwithstanding a small dimension. Another limitation of the TNM classification is the inclusion of those lesions with intraocular extension into the T3 category, even though they require enucleation for tumor control, rather than local excision. To overcome these drawbacks of the TNM classification, a new clinical-based classification scheme has been proposed which provides general advice for tumor management (Table 3) [150].

PROGNOSIS

Overall, OSSN has a good/fair prognosis, with little tendency to metastasize and a low mortality rate; it is often linked to regional or distant metastases or intracranial invasion [151]. However, a recurrence risk of up to 39% after treatment has been reported in the literature [2, 152–154], and this rises to 43% in cases

treated exclusively with surgery or solely with topical agents [106, 107]. Recurrences take place most frequently within the first 6 months after resection, and the recurrence rate is closely dependent on the involvement of surgical margins [152], the presence of feeder vessels [149], the HIV infection status [33, 155, 156], histopathologic grade [157], and the availability of adjunctive therapies, as such as cryotherapy, immunotherapy or chemotherapy [37]. In terms of the T classification, in 2013, Shields et al. noted that the T classification, based on the AJCC seventh edition, was not predictive of surgical failure [135]; however, several following reports have correlated the recurrence rate to the T category, albeit reporting highly heterogeneous groups of patients [147, 149, 158, 159]. Recently, the overexpression of the tumor-suppressor gene p16^{INK4a} has been identified as a biomarker of diffuse growth pattern, early age of presentation (< 50 years), and metastatization in late T stages [48].

CONCLUSION

Ocular surface squamous neoplasia is a curable cancer with a low mortality rate, but it remains a considerable medical and economic burden in the peri-equatorial regions of the world. The improvements in non-invasive diagnostic techniques and treatment protocols have led to a considerable reduction in tumor-related morbidity. However, understaging and misdiagnosis of this condition often lead to a preventable loss of vision and the need for more aggressive treatments. HIV infection or predisposing conditions, such as xeroderma pigmentosum or atopic conjunctivitis, should be ruled out in all patients with a diagnosis of OSSN and atypical presentation (i.e., young age, bilateral or multifocal tumors, and history of rapid tumor growth) [24].

Surgical removal with or without cryotherapy is still considered the traditional treatment for OSSN. When there are positive margins or incomplete excision, local or topical IFN- α 2b represents the best cost-effective approach to minimize tumor recurrence [128]. Nevertheless, primary monotherapy with immunomodulant or chemotherapy agents is now earning increasing recognition and acceptance. Within this framework, systematic reviews and meta-analysis of the recently published literature will help to clarify the efficacy and the limitations of these novel therapeutic approaches to OSSN.

ACKNOWLEDGEMENTS

Funding. No funding or sponsorship was received for this study or publication of this article.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosures. Maria Vittoria Cicinelli, Alessandro Marchese, Francesco Bandello and Giulio Modorati have nothing to disclose.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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