The effect of demographic and clinical characteristics toward ocular surface squamous neoplasia (OSSN) recurrence after tumor excision surgery in Dr. Soetomo General Hospital, Indonesia: A literature review

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ABSTRACT

An essential component of the ocular surface is the conjunctiva. The most common non-pigmented malignancy that can affect the conjunctiva is ocular surface squamous neoplasia (OSSN). Despite the vast investigations on this deadly organism, certain elements related to demographics, clinical traits, and recurrence remain unclear. The objective of this review was to explore OSSN in depth. OSSN is classified into several types based on its clinical morphology, such as nodular, plaque, and diffuse OSSN. Plaque types can be classified into gelatinous, leucoplaikia, and papilliform. Histopathological classification of OSSN consists of benign, pre-invasive, and invasive types. The OSSN tumor stadium can be classified using the TNM criteria by the American Joint Committee on Cancer (AJCC). OSSN management can be divided into medical and surgical management based on classification and tumor stadium. Despite the advances in the treatment of OSSN, there are still variances and conflicting results in the recurrence after surgery, which certain demographic and clinical types of OSSN might cause. Further study is needed to confirm the significance of the recurrence of each demographic and clinical characteristic of each OSSN tumor.

INTRODUCTION

On the surface of the eye, ocular surface squamous neoplasia (OSSN) is the most typical non-pigmented malignancy. Despite being uncommon, these tumors need to be identified since they have the potential to result in systemic and even ocular morbidity and fatality. A wide range of illnesses, including precancerous and cancerous lesions involving aberrant proliferation of dysplastic squamous epithelial cells in the conjunctival, limbal, and corneal epithelium, are included in the term “ocular surface squamous neoplasia.”¹,² The most frequent non-pigmented malignancy of the cornea and conjunctiva is ocular surface squamous neoplasia (OSSN), which is also known as dysplasia, corneal and conjunctival intraepithelial neoplasia, and squamous cell carcinoma.³ The most popular treatment for OSSN has been surgical excision using a no-touch technique, although this has been associated with side effects include conjunctival scarring, symblepharon, conjunctival hyperemia, and a loss in limbal stem cells.⁴

Topical chemotherapies have become popular medical treatments as worthwhile alternatives to surgical surgery in recent years. These topical treatments offer the advantage of addressing subclinical conditions that, in the absence of treatment, may have recurrence rates as high as 56% following surgical excision with positive margins. The creation of anterior segment high-resolution optical coherence tomography (HR-OCT) technology is another recent development. HR-OCT is an excellent method for identifying and managing OSSN because it provides rapid, non-invasive, and high-resolution pictures of the ocular surface.⁵ Based on those explanations, this review aimed to discuss OSSN in a comprehensive review.

EPIDEMIOLOGY

In the United States and Australia, the incidence of ocular surface squamous neoplasia ranges from 0.03 to 1.9 per 100,000 persons per year, but it is 3.5 per 100,000 persons per year in Uganda. The prevalence of ocular surface squamous neoplasia is higher in white men. Caucasians living close to the equator who are 60 to 70 years old may have an incidence that is up to five times greater than average. Ocular surface squamous neoplasia, however, can afflict younger individuals and have a propensity toward more clinically aggressive behavior in Africa and some regions of Asia.⁶

The incidence of OSSN is greater in men than in women globally, according to statistics from the IARC (International Agency for Research on Cancer), although this difference is minor (Figure 1). Ocular surface squamous neoplasia can develop...
slowly in older men, 70–80% of whom have an average age of 60, in regions with temperate temperatures. On the other hand, young women under the age of 30 have the highest frequency in tropical nations, particularly in East and South Africa (around 50–70%). This might be ascribed to the location of African nations where HPV (Human Papilloma Virus) and HIV (Human Immunodeficiency Virus) incidence is highest, which can raise the risk of OSSN in women.\(^1,2\)

Because it receives the most sunlight exposure, the limbal nasal region (limbal epithelial crypts) has the highest prevalence of OSSN at about 75%. Conjunctival precancerous, malignant, and 4% of all other lesions are CIN. Invasive SCC occurs far less often, with incidence rates ranging from 0.02-3.5/100,000 people. According to a research from Iran, out of 274 people evaluated with ages ranging from 14 to 90, neoplasm epithelium conjunctiva accounted for the majority (40.8%) of lesion-invasive SCC cases. Young-onset OSSN is typically accompanied with HIV illness and xeroderma pigmentosa, which affects people between the ages of 5 and 28.\(^7-11\)

**ETIOLOGY OF OSSN**

Various factors influence the cause of OSSN, but it is unclear how the interaction and which factors are the most at risk of occurrence. The increasing incidence of OSSN in recent decades can be driven by an increase in the prevalence of suspected OSSN, among others, exposure ray ultraviolet B (UV-B), status immunocompromised (infection HIV and infection HPV), smoking, exposure to petroleum derivatives and xerophthalmia (vitamin A deficiency).\(^1,2\)

**EXPOSURE TO ULTRAVIOLET B (UV-B) RAYS**

Several epidemiological studies identified exposure to ultraviolet-B light (UV-B) as the biggest etiological factor in the pathogenesis of OSSN. The National Institutes of Health/American Association of Retired Persons (NIH-AARP) Diet and Health Study in the United States found a lower risk of OSSN in those who live >35° compared to <35° from the equator.

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**Figure 1.** Mapping of the occurrence level of OSSN worldwide for 1998-2002. Boys are shown in blue and girls in red. The merging of male and female is shown in purple.\(^1\)

**Figure 2.** Mechanism of DNA damage.\(^11\)
latitude. Based on IARC data, there was a 49% decrease in the incidence of OSSN in areas with enhancement line latitude of as much as 10 degrees. Because of a reduction of ultraviolet radiation, OSSN is most commonly affected in the interpalpebral regions exposed to sunlight, particularly in the nasal or temporal areas.1–2

Outdoor work may be linked to OSSN, perhaps related to exposure to solar radiation. Spending more than 50% of time outdoors for 6 years can induce UV-B. In Uganda, those who work outdoors have a higher risk of OSSN than those who work indoors, with a percentage of 74% of 133 workers. In Japan, exposure to petroleum products is also associated as a risk factor for OSSN.2

Ultraviolet-B radiation causes DNA damage directly through cross-linking and forms Cyclobutane Pyrimidine Dimer (CPD) and 6–4 photoproducts (6–4 PPs). CPD and 6–4 PP damage the Deoxyribonucleic Acid (DNA) structure and interfere with DNA synthesis (Figure 2). DNA damage will cause genomic instability and stem cell function and cause mutations. Mutations can occur in oncogenes or tumor suppressor genes, especially mutations in p53. The role of p53 is to control the cell cycle, DNA repair and the apoptotic pathway. Mutations in p53 will cause the loss of normal function of p53 so that cell proliferation becomes uncontrolled. The inability to repair DNA, as in xeroderma pigmentosa, can also cause OSSN.2,13,14

**HUMAN IMMUNODEFICIENCY VIRUS (HIV) INFECTION**

HIV is one of the major risk factors for OSSN, and there is a close correlation between the two. At the beginning of the HIV epidemic in the US, the growing prevalence of OSSN was noted. In individuals with HIV infection in HIV-endemic nations, notably in Africa, OSSN is present in 50–86% of cases. With the highest risk in the first two years of AIDS, HIV raises the chance of developing OSSN by 8–19 times. HIV patients with ocular surface squamous neoplasia typically had bigger lesions; 71% of these lesions have a
REVIEW

Figure 5. UHR-OCT of the OSSN image shows A. Sharp delineation between normal and abnormal epithelium and B. Thickened and hyperreflective epithelium hypoechoic stroma.10

Figure 6. Typical pictures taken using in-vivo confocal microscopy. Confocal microscopy on OSSN shows many varieties of aberrant squamous epithelial cells in vivo. In three patients with CIN diagnoses, (a) Squamous epithelial cells that are abnormally hyperplastic, disordered, and pleomorphic (blue arrows); (b) cellular anisocytosis and anisonucleosis; (c) enlarged nuclei and unclear cytoplasmic borders.20

Figure 7. An SCC patient’s 20 MHz UBM picture demonstrates blunting of the anterior chamber angle (arrow), which is consistent with anterior chamber angle invasion on histology. Conjunctival intraepithelial neoplasia, 20 MHz transverse, longitudinal, and ultrasound biomicroscopy sections, revealing hyperechoic tumor surface (arrows) and hypoechoic stroma.10

unilateral OSSN in individuals with bilateral conjunctival HPV DNA, the presence of HPV in the conjunctival tissue, and persistent HPV infection many years after OSSN eradication are all indications that ambiguous HPV is an etiological factor. This shows that HPV is unlikely to cause the illness on its own, necessitating the involvement of additional cofactors including HIV infection and UV-B radiation exposure.1,2

ESTABLISHING THE DIAGNOSIS

On the basis of the clinical picture (Figure 3), the diagnosis of OSSN was originally made. Using clinical criteria to identify OSSN yielded a 54% positive predictive value, according to a large African investigation. The choices for treating OSSN are expanding, and they now include non-invasive diagnostic procedures in addition to histopathological analysis. Cytology Impression, Ultra High-Resolution Optical Coherence Tomography (UHR-OCT), Confocal Microscopy, Ultrasound Biomicroscopy (UBM), and Vital dye are a few further diagnostic techniques.15–17

HISTOPATHOLOGY

An excisional biopsy specimen’s histological examination is the gold standard for diagnosing OSSN. After being immediately immersed in 10% formaldehyde solution and set in paraffin wax that had been sliced 5 mm perpendicular to the conjunctival surface, the specimen was stained with hematoxylin-eosin (Figure 4). All specimens underwent anatomical pathology examination. A biopsy excision has the benefit of providing a histology sample for the whole model.18

Excisional biopsy, however, may not be able to remove all of the tissue from big, diffuse lesions with unclear margins, and it may also raise the risk of scarring, limbal stem cell shortage, and symblepharon in cases of large or recurrent lesions.15,17,18

HUMAN PAPILLOMAVIRUS (HPV) INFECTION

There are conflicting findings about how HPV and OSSN are related. Several research links subtype HPV with OSSN, whereas several other studies are unable to support this link. The existence of testing in patients with young-onset HIV OSSN.1,6,15

IMPRESSION CYTOLOGY

A nitrocellulose membrane is used to treat superficial conjunctival and corneal cells, causing them to adhere to the ocular surface. These cells are then
REVIEW

Figure 8. Conjunctival lesions before and after staining with 0.05% toluidine blue. Image in A before coloring and image B after coloring. Figures A and B show moderately differentiated SCC (G2) with a dark blue staining appearance.1

Figure 9. Spectrum of epithelial dysplastic changes.11

Figure 10. OSSN description: A. gelatinous type, B. nodular type, C. diffuse type, D. leukoplakia type, E. papilliform type, F. Corneal involvement in OSSN, G. mucoepidermoid appearance: high risk of intraocular entry.2

collected and removed from the eye to be fixed, stained, and then put on a slide for analysis. According to Nolan et al., dysplastic keratinized cells, which are frequently associated by hyperkeratosis, were present in 55% of intraepithelial OSSN cases identified by SI, large syncytial-like clusters were present in 35%, and nonkeratinized dysplastic cells predominated in 10% of cases. Given the shallow cell sampling, cytology impression inspection cannot distinguish between intraepithelial lesions and invasive SCC, which limits the use of SI in invasive disease diagnosis. This SI examination can be used to diagnose recurrent OSSN, track the effectiveness of topical chemotherapy, and distinguish between clinically similar pathological conditions like limbal stem cell failure, pannus, and OSSN. It has been demonstrated that this SI examination correlates with the histopathological examination in 77–80% of cases.10,12

ULTRA HIGH-RESOLUTION OPTICAL COHERENCE TOMOGRAPHY (UHR-OCT)

For visualizing different eye sections, optical coherence tomography (OCT) is a fantastic tool. Low-coherence interferometry is used in optical coherence tomography to provide a two-dimensional picture of the light scattering. High-resolution pictures may be created with the current OCT technology, namely UHR-OCT. With an axial resolution of around 2 microns, ultra high-resolution optical coherence tomography is an OCT designed to assess the diseased appearance of the cornea. On the OSSN, epithelial thickening and enhanced reflectivity are identified and are given a general overview using ultra high-resolution optical coherence tomography (Figure 5). The reflectance look of normal and diseased epithelium often differs significantly. Additionally, it might help in locating the tumor margins precisely during excision. One of the other diagnostic procedures that can also identify subclinical recurrences at an early stage is ultra high-resolution optical coherence tomography. With this UHR-OCT, the patient is checked while sitting erect and comfortably, and it’s simple for the operator to operate. However, because
this technology is expensive to buy and maintain, not all medical facilities have access to it.

CONFOCAL MICROSCOPY

Using in vivo confocal microscopy, a cytological study of the ocular surface provides a quick, secure, and largely non-invasive diagnostic procedure. Nevertheless, treating OSSN patients seldom involves using this evaluation. This test is used to evaluate the degree of dysplasia based on cellular morphology, nuclear atypia, and nuclear to cytoplasmic ratio, and it can help in making the first diagnosis of OSSN. Depending on how far the damaged epithelium has extended, the OSSN grading judgment is also regarded as excellent. Confocal microscopy in vivo can help detect recurrences and assess how OSSN patients respond to topical chemotherapy drugs. The limitation of this examination is that the maximum examination depth only reaches 500 micrometers where this depth is insufficient to detect tumors that resemble the inner eye (Figure 6).

ULTRASOUND BIO-MICROSCOPY (UBM)

When a tumor invasion of the cornea or sclera is suspected, an ultrasound examination called ultrasound biomicroscopy (UBM) is performed. UBM can also offer high overall image quality and tumor imaging, as seen by the enhanced posterior margin resolution, resolution for pigmented tumors, iris pigment epithelial cysts, and ciliary body lesions (Figure 7). UBM has been used to

<table>
<thead>
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<th>Clinical Stage</th>
<th>Definition</th>
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<tr>
<td>Primary Tumor (T)</td>
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<tr>
<td>T0</td>
<td>There are no tumors.</td>
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<tr>
<td>T (is)</td>
<td>CIN tumors (carcinoma in situ)</td>
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<tr>
<td>T1</td>
<td>Tumor with largest basal diameter &lt;5mm</td>
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<tr>
<td>T2</td>
<td>Tumor with the largest basal diameter &gt;5mm doesn’t invade adjacent structures.</td>
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<tr>
<td>T3</td>
<td>Tumor invades adjacent structures, except orbit.</td>
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<tr>
<td>T4</td>
<td>Tumor invades orbit, with or without widespread extension.</td>
</tr>
<tr>
<td>T4a</td>
<td>Tumor invades the soft tissues of the orbit but not the bone.</td>
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<tr>
<td>T4b</td>
<td>Tumor invades bone</td>
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<tr>
<td>T4c</td>
<td>Tumor invades the surrounding paranasal sinuses.</td>
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<tr>
<td>T4d</td>
<td>Tumor invades the brain.</td>
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<tr>
<td>Regional lymph nodes (N)</td>
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</tr>
<tr>
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<td>No metastases to lymph nodes were found.</td>
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<tr>
<td>N1</td>
<td>Metastases to lymph nodes found.</td>
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<tr>
<td>Distant metastases (M)</td>
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<td>GX</td>
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<tr>
<td>G3</td>
<td>Difficult to be differentiated</td>
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diagnose OSSN, and it has proven to be the most accurate method for determining the extent of intraocular tumors and the existence of metastases.2,10

**VITAL DYE**

Vital dye is an additional low-cost diagnostic test that is particularly effective in diagnosing OSSN. It is common practice to stain and determine the degree of OSSN lesions using diagnostic stains like lissamine green and rose bengal. However, it is hard to utilize this dye effectively to diagnose OSSN since it is non-specific and stains too much of the other ocular surfaces. Toluidine blue (ToB) and methylene blue are two further essential paints that are frequently utilized.10,12

Acidophilic dyes toluidine blue and methylene blue stain aberrant tissue a dark blue color. They breakdown more often in benign tissues because they have a predilection for the nucleic acids of malignancies that have weak cell-to-cell adhesion and a rapid rate of mitosis. In comparison to histology, investigations have indicated that ToB and methylene blue stains have high sensitivity (97%) but low to moderate specificity (50%) for the diagnosis of OSSN. Since relatively few OSSN lesions do not stain with these dyes, ToB and methylene blue are effective first screening methods (Figure 8).10,12

**CLINICAL MANIFESTATIONS**

Initially, patients are often unaware of OSSN lesions because they do not cause pain and decrease vision in the eye. As it grew, OSSN began to cause discomfort. The complaint most often obtained on OSSN is the feeling of a lump or sensation of a foreign body in the eye, irritation, reddish, And growth lesions on the surface ball of the eye. It is often unilateral and grows slowly but may occur bilaterally in the immunsuppressed patient. Symptoms ranged from 2 weeks to 2 months or more than 6 months.1,2,6,11,17,21

More than 95% of the lesions are found in actively mitotic limbal areas and are often seen in the sun-exposed interpalpebral zone and can extend across the limbus to reach the cornea. Regarding the cornea, decreased vision due to high astigmatism or involvement of the visual axis can also be complained about.1,2,6,11,17,21

The typical features of OSSN on macroscopic clinical examination are generally divided into nodules, plaques and diffuse (Figure 9, Figure 11). Description clinical nodular obtained a well-defined, rapidly growing lesion with a high probability of lymph node metastases and is frequently seen in cases of Invasive SCC. The plaque type usually occurs over a long period and is less aggressive than the nodular type.5,11,12

Plaque type is subdivided into three patterns: gelatinous, leukoplakic, and papilliform. Picture of a thick mass in the limbal area can be accompanied by a feeder vessel. This gelatinous picture is the most common form found. The appearance of leucoplakia is usually pre-invasive, and the papilliform appearance is shaped like red-speckled strawberries and is exophytic.5,11,12

The diffuse form of OSSN is the least common and is frequently misdiagnosed because it clinically resembles chronic conjunctivitis. This type also tends to metastasize to regional lymph nodes, making it difficult to differentiate between benign and malignant lesions.5,11,12

Histologically, OSSN can be classified into 3 forms, namely, benign, pre-invasive and invasive (Table 1). OSSN usually excludes benign and invasive forms denoting infiltration through the conjunctival epithelial basement membrane into the stroma. OSSN pre-invasive lesions were classified as mild, moderate, or severe, based on the extent of epithelial replacement by less mature dysplastic cells normally. Dysplasia mild (CIN grade I) is dysplasia confined to the lower third of the epithelium. In moderate dysplasia (CIN grade II), the abnormal cells extend into the middle third from the epithelium. Severe dysplasia (CIN grade III), cells extending to the superficial third of the epithelium and when involving
the entire thickness of the epithelium and loss of all normal cells with intact basement membranes, as well known as CIS (Carcinoma in Situ) (Figure 10).1,6

**OSSN CLASSIFICATION BASED ON TUMOR STADIUM**

Tumor classification, which is based on tumor stadium, can be assessed by using the TNM (Tumor, Node, and Metastasis) criteria as stated in the eighth edition of the American Joint Committee on Cancer (AJCC), with T representing the primary tumor, N representing regional gland involvement, and M representing metastatic spread (Table 2).23

**ANCILLARY EXAMINATION**

Imaging examinations are often needed to determine the stage of the disease and plan the right treatment, one of which is Magnetic Resonance Imaging (MRI). In OSSN, MRI can be used if there has been intraorbital invasion or metastases. This is common in patients with older age and SCC located near the limbus corneoscleral with a history of one or more recurrences after excision. The tumor may extend throughout the orbital cavity in some more advanced cases. Both local and distant invasions can result in patient mortality. Therefore, MRI can be used to provide anatomical information, determine the extent of disease, delineate the exact location and detect the involved orbital compartment (Figure 12).23–27

**MANAGEMENT OF OSSN**

Management of OSSN can be divided into two main groups, namely surgical and medical procedures. Surgical action by excision is the action most often used in OSSN cases. Topical chemotherapy can be an alternative therapy for possible complications of excision procedures using antimetabolite class drugs, namely Mitomycin-C (MMC), 5-fluorouracil (5FU) and interferon α-2b (IFN-α-2b). The combination of excision and cryosurgery techniques and radiotherapy as an adjuvant can also be used for OSSN management.1,6,12,29
Figure 15. A. Slit lamp photo of the left eye showing OSSN with a gelatinous appearance on the temporal side of the conjunctiva and limbus (arrow). B. UHR-OCT images of the inferior temporal conjunctiva and limbus showing thickened, hyperreflective epithelium (asterisks) and transition between normal and abnormal epithelium (arrows). C. Slit lamp photo of left eye after 2 months (two cycles) of topical 5-FU treatment with clinical tumor resolution. D. UHR-OCT images of inferior temporal conjunctiva and limbus showing resolution of the tumor with thin epithelium (asterisks) after 2 months (two cycles) of topical 5-FU treatment.

Figure 16. A. Slit lamp photo of the right eye showing OSSN with piliform features in the temporal conjunctiva and limbus (arrow). B. UHR-OCT images of temporal and limbal conjunctiva showing thickened, hyperreflective epithelium (asterisk) and transition between normal and abnormal epithelium (arrows). C. Slit lamp photo of the right eye 4 months after being given IFN α-2b 1 MIU/mL four times a day with a clinical picture of tumor resolution. D. UHR-OCT images of the temporal and limbal conjunctiva showing resolution of a tumor with thin and normal epithelium (asterisks) after 4 months of topical IFN α-2b treatment.

SURGERY

Surgical procedures for OSSN can be performed from simple excision to exenteration. Factors that affect surgical technique include the size and extent of the lesion, clinical invasiveness and location of the lesion, as well as the health and age of the patient. Surgical excision has long been the gold standard for OSSN. The main method of surgical excision for OSSN is the ‘no touch’ technique, which avoids touching the tumor with instruments with a wide margin of 3-4 mm from the tumor margins to keep the operative field dry to prevent potential tumor cell seeding (Figure 13).

Cryotherapy can be performed on the conjunctival margin of the excised area, as well as the limbus and cornea, if the margins are extended. Closing the wound with amniotic membrane tissue and fibrin glue can be very helpful because defects of any size can be closed, but direct suturing can be done if the wound is small.

The advantage of surgery is the hope for a faster resolution than medication. However, surgery has a recurrence rate of up to 56% with positive margins. In addition, surgical excision can also cause sequelae such as conjunctival scarring, symblepharon, conjunctival hyperemia and limbal stem cell deficiency.

CRYOTHERAPY

Treatment with surgery alone for OSSN has a recurrence rate that is enough for cryosurgery to treat eyelid tumors and eyeball surfaces. Cryotherapy techniques are often used with eye surgery by destroying remaining tumor tissue outside the margins of surgical excision. The combination of excision and cryotherapy can reduce the number of recurrences to 0-12%. Cryotherapy role with effect thermal which can destroy tumor cells and inhibit microcirculation, causing ischemic on the network, fine network normal nor network tumor targeted. Side effects of this therapy include iritis, changes in ball pressure eyes, inflammation, corneal oedema, scarring and corneal vascularization, limbal stem cell deficiency, sectoral iris atrophy, detachment of the peripheral retina, and ectropion.

TOPICAL CHEMOTHERAPY

Medical therapy, the more lots used along with height number recurrence from OSSN can use antimetabolite class drugs, namely mitomycin-C (MMC) and 5-fluorouracil (5-FU) or interferon α-2b (IFN-α-2b). The advantage of this medical therapy is that it can cover the entire surface of the eye and treat diseases microscopically and sub-clinically. Indications for using topical chemotherapy for OSSN are described in Table 3.

MITOMYCIN-C (MMC)

Mitomycin-C (MMC) is an anti-tumor antibiotic that inhibits DNA synthesis in
Table 3.  Indications for giving topical chemotherapy

1.  >3 quadrants of conjunctival involvement
2.  >180 degrees of limbal involvement
3.  Increasing corneal lesions reach the pupillary axis
4.  Positive margin after surgical excision
5.  The patient is not ready for surgery

G1 and S phases. MMC can also cause apoptosis and necrosis in cell tissue. In OSSN, MMC is generally used as topical eye drops at a 0.02-0.04% dose. The use of MMC is also highly effective, with high-resolution rates ranging from 76% to 100% and low recurrence rates ranging from 0% to 20% (Figure 14). The drawback of using MMC is the intensity of its side effects. MMC has more side effects than IFN α-2b and 5-FU, including itching, pain, corneal erosion, hyperemia, punctal stenosis and limbal stem cell deficiency. Patients are usually instructed to use steroid eye drops and artificial tears during treatment to reduce side effects and prevent toxicity.

5-FLUOROURACIL (5-FU)

5-fluorouracil is an anti-cancer drug that inhibits DNA replication and cell growth, which was first used to treat OSSN by de Keizer et al. 5-FU is generally used as a topical eye drop at a concentration of 1% and given in 'cycles' four times daily for 1 week, followed for 3 weeks without treatment, with repeated cycles until resolution. These studies have shown 5-FU to be highly effective in treating OSSN, with a high-resolution rate of 82%-100% and a low recurrence rate of 10%-14% (Figure 15). The side effects of 5-FU are generally mild and well tolerated compared to MMC, including eye pain, hyperemia, eyelid oedema and keratopathy.

INTERFERONS Α-2B (IFN Α-2B)

Interferon (IFN) α-2b is a natural protein produced by immune cells with antiviral, antimicrobial and antineoplastic properties. IFN α-2b has been used to treat various diseases, including skin carcinoma, hepatitis, cervical intraepithelial neoplasia, Kaposi’s sarcoma, melanoma, hairy cell leukaemia, renal cell carcinoma and follicular lymphoma. IFN α-2b was first used to treat OSSN in 1994 and has since become one of the most commonly used topical chemotherapy for OSSN. Interferon α-2b can be used as topical eye drops, subconjunctival perilesional injection, or both (Figure 16). Both forms have shown great success in treating OSSN, with topical eye drops having a resolution rate of 81%-100% and injections having a resolution rate of 87%-100%. IFN eye drops also have a very low recurrence rate ranging from 0% to 4%.

Topical IFN α-2b eye drops are very well tolerated by patients and generally have no side effects. IFN α-2b injections are also well tolerated, but patients usually experience mild flu-like symptoms for about 24 hours after injection.

RADIOThERAPY

Radiotherapy can be used as adjuvant therapy in OSSN after surgical treatment, including proton, brachytherapy, orthovoltage external radiation, and stereostatic radiation. Radiotherapy with protons and orthovoltage is effective with satisfactory results. However, using these devices is still not widespread in various radiotherapy centers, and no long-term outcome data exists.

The option of brachytherapy has been used in recent years to treat OSSN. Brachytherapy can be an excellent alternative in cases limited to the surface layers of the eye, especially when there is residual scleral neoplasia after primary excision. In some instances of intraocular invasion, brachytherapy can effectively prevent the expansion of the invasion and can preserve the globe. However, when given at higher doses on the eye’s surface, it can cause more scarring and thinning of the sclera.

POSTOPERATIVE RECURRENCE

Tumors are still a significant problem in the eye because of their high morbidity and mortality rates and their resistance to intraocular invasion. Invasion Intraocular and metastases are rare in OSSN but can occur as a result of treatment late. The recurrence rate of OSSN after excision can occur in more than half of cases many years later. This usually represents a more aggressive state because the disruption
of the excised tumor tissue increases the ability of tumor cells to enter the eyeball. The recurrence or recurrence rate after excision ranges from 43-51%, with a high mortality rate of around 15-30% within 10 years.12,19,20

Recurrences in OSSN can grow rapidly and be more invasive. Therefore, they must be treated with aggressive medical, surgical or combined measures (Figure 17). Lee and Herst reported a recurrence rate of 17% after excision for conjunctival dysplasia, 40% for CIS and 30% for SCC. The use of medical therapy in OSSN for one year has a reduced risk of recurrence from 36% to 11%. Combining excision techniques, cryosurgery and radiotherapy as an adjuvant can be done to reduce the number of recurrences to 0-12%. Research by Li et al. showed a lower recurrence rate of 7.1% within 1-5 years. Repeated excision can lead to conjunctival scarring and limbal stem cell deficiency. Recurrence rates can be reduced to less than 5% with protocol-based therapy.16,12

Some of the factors that often lead to recurrence include the accuracy of determining the margin limit at the initial excision, age, sex, AJCC classification, post-excision positive tumor margins, histological grade of the lesion, location, corneal involvement, clinical appearance, multiple lesions, pathological findings, size larger size (>2 mm), high proliferation index and availability of adjunctive therapy, such as cryotherapy, immunotherapy or chemotherapy.23

CONCLUSION

Despite the advances in the treatment of OSSN, there are still variances and conflicting results in the recurrence after surgery, which certain demographic and clinical types of OSSN might cause. Further study is needed to confirm the significance of the recurrence of each demographic and clinical characteristic of each OSSN tumor.

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ETHICAL CONSIDERATION

This literature review has followed the COPE and ICMJE protocols regarding publication ethics. Ethical clearance number: 0968/LOE/301.4.2/VII/2022

CONFLICT OF INTEREST

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AUTHOR CONTRIBUTION

All authors have made a relatively equal contribution in writing the report on the results of this literature review.

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