

Treatment Outcomes of Ocular Surface Squamous Neoplasia with Surgery and Adjunctive Mitomycine C: Retrospective Case Series

ISSN : 2578-0360



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Submission: 📅 March 8, 2021

Published: 📅 March 26, 2021

Volume 3 - Issue 2

How to cite this article: Hülya Gökmen Soysal. Treatment Outcomes of Ocular Surface Squamous Neoplasia with Surgery and Adjunctive Mitomycine C: Retrospective Case Series. *Med Surg Ophthal Res.* 3(2). MSOR. 000557. 2021. DOI: [10.31031/MSOR.2021.03.000557](https://doi.org/10.31031/MSOR.2021.03.000557)

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Abstract

Aim: To present the clinical features and therapeutic outcomes of Ocular Surface Squamous Neoplasia (OSSN) cases which were treated with surgery and adjunctive Mitomycine C (MMC).

Materials and Methods: The records of 38 eyes which were treated for OSSN were reviewed retrospectively. Patients in stages T1 and T2 were treated with 'no touch' technique complete excision, cryotherapy and adjunctive MMC. Two patients in stages T3 and T4 disease underwent exenteration.

Results: The pathological diagnoses were Conjunctival Intraepithelial Neoplasia (CIN) in 22, carcinoma *in situ* in 6, and invasive Squamous Cell Carcinoma (SCC) in 10 eyes. Tumor was primary in 28 and recurrent in 10 eyes. The rates of previously recurrent cases were highest in invasive SCC group and lowest in CIN group. No serious complications associated with MMC occurred. A recurrence was observed in only one eye out of 36 eyes in stages T1 or T2. One patient in stage T4 that was treated with subtotal exenteration presented with preauricular lymphadenopathy after 19 months.

Conclusion: Recurrences and treatment complications can still be seen today despite the new developments and facilities regarding the treatment of the OSSN. These recurrences and side effects impair the success rate by increasing morbidity. We recommend a complete excision followed by cryotherapy and routine postoperative adjuvant MMC application to decrease the risk of unsuccessful results.

Keywords: Conjunctiva; Squamous neoplasia; Ocular surface; Mitomycine C

Abbreviations: CIN: Conjunctival Intraepithelial Neoplasia; Ocular Surface Squamous Neoplasia; SCC: Squamous Cell Carcinoma; MMC: Mitomycine-C

Introduction

The term Ocular Surface Squamous Neoplasia (OSSN) includes neoplastic squamous epithelial abnormalities ranging from mild dysplasia to invasive carcinoma of conjunctiva and cornea. Its incidence is estimated to be 17 to 20 cases per million people per year [1]. Proposed risk factors are human papilloma virus, exposure to ultraviolet light, cigarette smoking, human immunodeficiency virus, petroleum products, age, and male sex [1,2]. Symptoms may include foreign body sensation, redness and irritation. The most common localization is the interpalpebral area of perilimbal conjunctiva. Its clinical appearance may be described as gelatinous, papilliform, leucoplakic, and diffuse [3]. Occasionally some lesions may contain a dark pigmentary area occasionally. The lesions are often well demarcated from the normal tissue and frequently accompanied by a feeder vessel. Diffuse type is the least common, and may masquerade as chronic conjunctivitis [4].

Simple surgical excision as a traditional treatment method has a reported recurrence rate as high as 33% despite clear margins and incomplete resection results in recurrence rates up to 56% [3]. In 1994 Shields et al. described a method involving wide surgical excision that avoids contact with the tumor (no-touch technique), accompanied by double freeze-thaw cryotherapy to the edge of conjunctiva and alcohol application to the corneal edge [4]. Further studies confirmed that this technique is more effective in preventing recurrences [5-7]. Because of the relatively high recurrence rate of OSSN after surgery, topical chemotherapy agents have been studied as adjuvant therapy or monotherapy as an alternative to surgery. Three main agents shown to be effective are Mitomycine-C (MMC) [8-10], 5-Fluorouracil (5-

FU) [11,12] and interferon- α 2b (INF- α 2b) [13,14]. Other treatment modalities include subconjunctival ranibizumab [15] and external beam radiation therapy [16,17]. Unsuccessful treatment and invasive disease may require enucleation or orbital exenteration [18,19]. The purpose of this study is to report clinical features, recurrence rates, outcomes and complications in the management of OSSN by surgery and adjuvant MMC.

Materials and Methods

We retrospectively reviewed the records of cases that were operated as conjunctival tumor and diagnosed as OSSN by histopathological examination between 2007 and 2017. This study was approved by the Ethical Board of the Institutional Ethics Committee of Kafkas University, Kars/Turkey (80576354-050-99/105) and followed the tenets of the Declaration of Helsinki. Written informed consent was obtained from all patients. Of the 44 patients, 6 with xeroderma pigmentosum were excluded and 38 eyes of 37 patients were included in the study. All surgeries were performed by the same surgeon. Patients with a follow up time less than 6 months and patients treated with adjunctive chemotherapy other than MMC were not included in the study. Two patients were in stage T3 and T4 according to AJCC (American Joint Committee of Cancer) classification. Remaining patients that were in lower stages were treated with complete excision under local anesthesia using the 'no touch' technique with a -4mm margin of normal-looking epithelium. No touch technique is a gentle technique without touching the tumor, since cells from these friable tumors can seed into adjacent tissues. Adjacent corneal epithelium was removed by alcohol and crescent knife. In case of scleral invasion, superficial lamellar sclerectomy was performed. Cryotherapy was applied to the remaining conjunctival edges, and alcohol was applied to the base of lesion. Large conjunctival defects were reconstructed with Amniotic Membrane Transplantation (AMT) in patients with wide tumors. Patients with stage T1 and T2 tumors were further treated with 0.02% MMC four times a day on a week-on-week-off basis for 2-4 cycles according to clinical findings during follow-up.



Figure 1a: Advanced conjunctival carcinoma that invaded fornices.

Scar tissue and suspicious lesions involving whole surface were observed in one patient in stage T3 disease who has been

previously operated on 8 times. After topical MMC administration, a wide excision with AMT was performed. The lesions continued growing intraorbitally, so the patient was opted for subtotal exenteration (Figures 1a & 1b). The stage T4 tumor in the other patient involved fornices, resulting in absolute vision loss. Therefore subtotal exenteration was carried out. All patients were followed on increasing intervals and a complete eye examination performed at every visit. All treatment complications and recurrences were recorded. Statistical tests were mainly used to investigate the relationship between recurrence and histopathological subtype. Chi-square test was used to compare percentages, and statistical significance was set at $P < 0.05$. Statistical analysis was performed through SPSS Windows version 16 (SPSS, Inc., Chicago, IL).



Figure 1b: CT of the same patient.

Results

Thirty eight eyes of 37 patients were included in this study. Fourteen were female and 23 were male. Mean age of patients was 65.97 ± 14.03 (range: 29-90 years). Pathological diagnosis was conjunctival intraepithelial neoplasia in 22 eyes, Carcinoma *In Situ* (CIS) in 6 eyes and invasive squamous carcinoma in 10 eyes. Right eye was affected in 20 patients and left eye was affected in 16 patients. The disease occurred bilaterally two years apart in one patient. Localization of conjunctival lesion was at medial limbus in 27 eyes, at lateral limbus in 2 eyes, at multiple quadrants in 7 eyes and diffuse in 2 eyes. Tumor was primary in 28 eyes. Ten eyes had a history of surgery, where 5 patients were operated on once, one patient 4 times, and one patient 8 times for conjunctival tumor. Each of the remaining 3 patients had a history of pterygium surgery and there were no histopathology reports. Mean follow up time was 32.53 ± 21.45 (min:6, max:84) months. Data is shown at (Table 1). Clinical appearances of lesions were very diverse. (Figures 2a-2c) shows leucoplakic, papilliform and diffuse form of OSSN. A large gelatinous OSSN lesion with brown patches is shown in (Figure 3). Table 2 shows histopathological distribution according to status of primary or previously recurrent. Although statistically insignificant, previously recurrent cases are highest in invasive SCC group and lowest in CIN group (Table 2).

Table 1: Summary of patient characteristics.

Mean age	65.97±14.03
Mean follow up (Months)	32.53±.21.45
Gender	
Male	23 (62.2%)
Female	14 (37.8%)
Laterality	
Right	20 (52.6%)
Left	16 (41.1%)
Bilateral	1 (2.6%)
Primary	28
Recurrent	10
Localization	
Medial limbus	27 (71%)
Lateral limbus	2 (5.2%)
Multiple quadrants	7 (18.4%)
Diffuse	2 (5.2%)
Pathology	
CIN	22 (57.9%)
CIS	6 (15.7%)
SCC	10 (26.3%)



Figure 2b: Papillomatous type of OSSN.

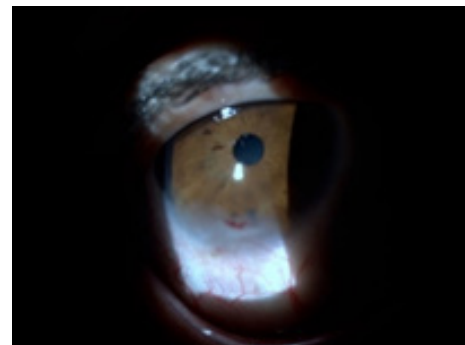


Figure 2c: Diffuse type of OSSN.



Figure 2a: Leukoplakic type of OSSN.

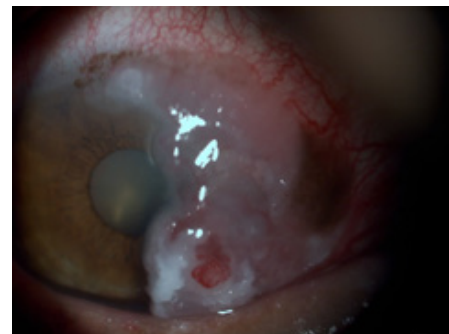


Figure 3: Large gelatinous OSSN lesion, with brown patches.

Table 2: Distribution of primary and recurrent cases according to histopathological stage. CIN: Conjunctival Intraepithelial Neoplasia, CIS: Carcinoma *In Situ*, SCC: Squamous Cell Carcinoma.

Pathology	Primary Cases (n-% in Pathological Subtype)	Recurrent Cases (n-% in Pathological Subtype)	Total
CIN	19-86.34%	3-13.63%	22
CIS	4-66, 6%	2-33.3%	6
SCC	5-50%	5-50%	10

In one case with sclerectomy, during postoperative period, scleral patch and AMT were needed because of scleral thinning. The tumor recurred in one patient after 6 years. Patient was reoperated and treated with postoperative topical MMC again. The patient with 8 previous surgeries was treated with preoperative MMC and wide excision with AMT. Upon failure, this was followed

by exenteration. No complications were observed in this patient. The patient treated with subtotal exenteration presented with preauricular lymphadenopathy after 19 months and was referred to the oncology department. Five patients suffered from side effects of the drug while being treated with postoperative adjunctive MMC. In these cases adjuvant therapy was chased until the signs

related to irritation healed. Afterwards, the treatment protocol was completed. This protected patients from serious side effects related to topical MMC treatment.

Discussion

Today, the treatment of choice for conjunctival malign tumors is a wide local excision accompanied by cryotherapy to the conjunctival edges. Cryotherapy and radiation therapy were used in order to decrease recurrence rates but alternative treatment methods have been searched due to high recurrence rates and serious complications. Radiation therapy is not preferred anymore due to complications such as dry eye syndrome, cataract, scleral ulceration and scar formation. In recent years, topical chemotherapeutic agents like INF- α 2b, MMC, 5-FU and cyclosporine for treatment of conjunctival neoplasia were searched and successful results were reported [12,13]. The recurrence rate was 2.7% in 36 noninvasive (stage T1 and T2) OSSN cases in this series. We routinely performed adjunctive cryotherapy and postoperative topical MMC. Recurrence rates for OSSN were reported to be as high as 53% with simple excision alone [3]. Combining cryotherapy to conjunctival edges resulted in a significant decrease in recurrence rates. Reported recurrence rates range from 0% to 12.3% after surgical excision combined with cryotherapy [5,6,7,20]. Sudesh et al. showed a 7.7% recurrence rate for excision combined with cryotherapy, compared to 28.5% for simple excision in primary tumors in their retrospective study [5]. Galor et al. [21] reported a 0.51 fold decrease in recurrence rate with adjuvant cryotherapy [21]. Current evidence supports that cryotherapy effectively destroys residual tumor cells that may be left behind and reduces recurrence rates.

Complications of cryotherapy include corneal scarring and pannus, iris atrophy, ocular hypotony and conjunctival scarring [22]. We didn't observe any transient or permanent complications related to cryotherapy. Main reason for such complications is excessive freezing. This should be avoided especially if it is applied to scleral bed. MMC for OSSN treatment was first described by Frucht-Perry et al. [23]. The complete cure rate ranges between 82% and 100% when used as a monotherapy or combined with surgical excision [24]. Birkholz et al. [25] reported a significantly reduced prevalence of recurrence with the adjunctive MMC (5.9% vs. 66.7%) in their retrospective review [25]. Gupta et al. [9] also showed no recurrence in 73 localized primary tumors treated with surgery and accompanied with cryotherapy and postoperative MMC in their prospective study [9]. In a previous study of Soysal et al. [10] 16 cases with tumor cells in at least one surgical margin were treated with postoperative adjuvant MMC. Throughout a mean follow up period of 29 months, no recurrences were observed [10]. In recent years, there has been a trend towards using topical chemotherapies in treating OSSN as an alternative to surgery. A survey in 2012 reported that 58% of ophthalmologists used topical monotherapy in OSSN, and an increase in the use of postoperative topical therapy was noted compared to 2003 survey [26]. We don't employ chemotherapy as a monotherapy. We think that it is more ideal to have a pathologic confirmation of the

disease with excisional biopsy. Sometimes it is difficult to evaluate invasiveness with imaging methods alone. Furthermore, surgical excision provides significant debulking of tumor that results in a shorter time for healing. Although very successful results have been reported, especially with interferon monotherapy, it requires a very long period of time, and has high cost, which adds to its disadvantage. On the other hand, postoperative MMC treats the whole surface of conjunctiva and presumably eliminates neoplastic cells in extralesional regions, thus decreases the recurrence rates [27].

Common side effects of MMC are usually transient and mild including allergy, epiphora, and punctate epithelial keratopathy. Serious complications due to limbal stem cell deficiency may be observed occasionally. We didn't observe any serious side effects during any of the follow up. This result may be due to the temporary interruption of topical chemotherapy when we observe slight side effects. We had 2 cases with local invasion. One of these patients had 8 previous surgeries. The other patient was a neglected case presented with absolute vision loss. Conjunctival squamous cell carcinoma tends to grow superficially first, but it can invade deeper structures if not treated. Sclera and Bowman's layer act as a barrier against invasion in most cases. Majority of the invasive cases in the literature are previously operated patients where these layers are impaired [26]. It should be noted that 3 of the 4 patients with scleral invasion had a history of surgical intervention in this case series. SCC rates are also higher as insufficient surgery facilitates transformation from intraepithelial stage to the invasive stage in recurrent cases (Table 2). Failure to differentiate from pterygium and eventually incomplete excision of the lesion is not uncommon. Therefore, all excised conjunctival lesions should be sent to histopathological evaluation. The patient with advanced squamous cell carcinoma (T4) that involved fornices causing absolute vision loss was treated with subtotal exenteration. However, the patient was presented with preauricular lymphadenopathy and was referred to oncology department 19 months later. For the other patient with 8 previous surgeries, we initially performed wide excision with preoperative and postoperative topical MMC. However, since the tumor continued to grow intraorbitally, an exenteration was carried out. Local tumor excision may be performed in some advanced cases, but intraocular invasion generally necessitates enucleation or exenteration. In the study of Miller et al., 71% of the 38 cases with SCC greater than stage T3 were treated with local tumor excision and 28% were treated with orbital exenteration [28]. Despite a 52% recurrence rate in the first group of patients, none were reported to require an orbital exenteration.

In conclusion, despite the new developments and facilities regarding the early diagnosis and treatment of the OSSN, recurrences and treatment complications still exist. These recurrences and side effects impair success rate by increasing morbidity. The course of the cases that have a history of previous surgery is more challenging. We recommend a complete excision followed by cryotherapy and routine postoperative adjuvant MMC application to decrease the number of unsuccessful results.

Acknowledgement

The authors declare that they have no conflict of interest. Informed consent was obtained from all individual participants included in the study.

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