Journal of Rawalpindi Medical University

Open Access Original Article

DOI: 10.37939/jrmc.v29i2.2668

Effectiveness of 5-Fluorouracil Chemotherapy in Preventing Recurrence of Ocular Surface Squamous Neoplasia

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Abstract

Objective: Ocular surface squamous neoplasia (OSSN) encompasses a spectrum of malignancies affecting the conjunctival and corneal tissues, including conjunctival intraepithelial neoplasia (CIN) and squamous cell carcinoma (SCC). High recurrence rates for OSSN necessitate effective treatment strategies, particularly in low-resource settings.

Methods: This prospective case series, conducted from March 2023 to March 2024 at the Department of Orbit and Oculoplastics, Alshifa Trust Eye Hospital, Rawalpindi, included 34 eyes from 34 patients with biopsy-confirmed OSSN. Patients underwent surgical excision with a 4 mm clear margin, followed by applying 1% 5-fluorouracil (5-FU) for 90 seconds and cryotherapy using a double freeze-thaw cycle. Post-surgical patients received topical 5-FU in cycles: one week on and three weeks off, for three to five months. Outcomes were documented through clinical examination and anterior segment optical coherence tomography (OCT). Primary outcomes were recurrence of clinical lesions. The secondary outcome was detecting the presence of HIV in patients by using an HIV antibody titres assay.

Results: The mean age of patients was 53.3 years. 73.5% were males, and 26.5% were females. The majority (76.5%) were diagnosed with full-thickness dysplasia. Treatment was predominantly post-excision. Chemoreduction prior to surgery was done in 4 patients. Most had 3 cycles of 5-FU (52.9%). During follow-up, not a single recurrent lesion occurred. Logistic regression indicated a positive, though non-significant, association between the number of 5-FU cycles and reduced recurrence ($\beta = 0.2598$, $p = 0.321$).

Conclusion: This study demonstrates that using 5-FU with cryotherapy significantly reduces OSSN recurrence in low-resource settings. Further research with larger cohorts is recommended to confirm these findings and refine treatment protocols.

Keywords: 5-Fluorouracil, Cryotherapy, chemotherapy protocols, Squamous Cell neoplasm, Conjunctival disease

Introduction

Ocular surface squamous neoplasia (OSSN) is an umbrella term used to describe conjunctival intra-epithelial neoplasia, squamous cell carcinoma in situ, and invasive squamous cell carcinoma.[1] OSSN is a common ocular tumour, with an incidence ranging from 0.03 to 1.9 per 100,000 persons per year.[1] OSSN cannot be taken lightly or observed for long because of its high potential to cause ocular and systemic morbidity. Our geographical distribution has shown to be more aggressive and targeting a younger population.

A Canadian epidemiological study revealed an age-standardized incidence rate of 0.45 cases per million individuals per year, with an average annual per cent increase in incidence of 4.5%.[2] The prevalence of ocular tumours in Asia differs from that in European countries. Recent literature indicates that basal cell carcinoma (BCC) is less common, occurring in 11 to 65% of cases, while squamous cell carcinoma (SCC) occurs in 5 to 48%, and sebaceous gland carcinoma (SGC) in 7 to 56%, more frequently than in Western countries.[3,4]

A study by Hollhumer et al. established a statistically significant correlation between HIV and OSSN, with a prevalence of HIV of 74% ($p < 0.001$). The study also identified distinct features among OSSN

Contributions:
S.U, - Conception of study
- Experimentation/Study Conduction
S.U, - Analysis/Interpretation/Discussion
S.U, - Manuscript Writing
S.U, A.M, F.T[4], F.T[5] - Critical Review

All authors approved the final version to be published & agreed to be accountable for all aspects of the work.

Conflicts of Interest: None
Financial Support: None to report
Potential Competing Interests: None to report

Institutional Review Board Approval
ERC-47/AST-23
15-03-2023
Al-Shifa Trust

Review began 02/08/2024
Review ended 21/06/2025
Published 30/06/2025

How to cite this article: Khan SA, Ullah S, Manzoor A, Taimur F, Tahir F, Sameen M. Effectiveness of 5-Fluorouracil Chemotherapy in Preventing Recurrence of Ocular Surface Squamous Neoplasia. JRMC. 2025 Jul. 2;29(2). https://doi.org/10.37939/jrmc.v29i2.2668

patients, including vascularization, leukoplakia, and pigmentation.[5] Another study by Odendaal et al. revealed that 66.7% of individuals with confirmed OSSN tested positive for HPV. It was found that 88.9%of those had HIV. Almost half of these patients had a CD4+ count of <200 cells/µL. Lower CD4+counts had a more invasive lesion.[6] A 10-year epidemiological study from Japan reported that the major malignant ocular tumours were malignant lymphoma in 74 cases, SGC in 28 cases, BCC in 15 cases, and SCC in 8 cases.[7]

Literature has identified several risk factors for OSSN, including UV light exposure, smoking, vitamin A deficiency, inflammatory disease, and immunosuppression.[8-10] In a study from Pakistan, 61.5% of patients with OSSN were male, and fifty-nine (90.8%) patients presented with chronic irritation.[11] Most patients were treated with excisional biopsy with mitomycin application (33.7%) or excision with corneo-sclerectomy with mitomycin (21.6%). This study also noted that 21 patients (32.2%) developed recurrence.[11]

Numerous ocular surface imaging techniques are in use for the early detection, management and follow-up of confirmed OSSN, including anterior segment optical coherence tomography (AS-OCT), confocal microscopy and ultrasound. Preferred treatment methods globally include surgical and pharmacological management, with a recent trend towards primary and adjunctive pharmacotherapy.

At the moment, no universal guidelines exist to advise on management approaches. Surgical excision is considered the rule of thumb for OSSN treatment.[12] However, it has been found that surgery alone may leave preclinical tumours and have a higher recurrence rate. Gustavo Savino et al. described in their results that multifocal disease ($p = 0.0039$), location at lower tarsal conjunctiva ($p = 0.0428$), histological diagnosis of high-risk squamous cell carcinoma ($p = 0.0264$), involved surgical margins ($p = 0.0434$), and excision biopsy (EB) alone ($p = 0.0005$) were found to have more chance of recurrence.[13] Lesions with involved margins have been shown to return with full-blown pathology in as high as 56% of patients. This rate is reduced to almost half, almost 33% with negative margins biopsies.[14] Changes to no-touch technique and adjuvant perop treatments like cryotherapy, postoperative topical mitomycin C, and postoperative topical interferons have shown lower recurrence rates of almost 21% in patients with positive margins.[15-17] Research has also shown that tumours treated with primary 5FU at a concentration of 1% had more complete resolution.[18] To minimise recurrence, treatment with postoperative chemotherapy should be more standardised.

The objective of this study was to investigate whether topical chemotherapy with a protocol following excision could effectively prevent the recurrence of ocular surface neoplasia or not.

Materials And Methods

This study was a prospective case series conducted over 1 year from March 2023 to March 2024. It aimed to evaluate the effectiveness of topical chemotherapy following surgical excision in preventing the recurrence of ocular surface squamous neoplasia (OSSN).The research was carried out at the Department of Orbit and Oculoplastics at Alshifa Trust Eye Hospital, Rawalpindi. This tertiary care facility is well-equipped with comprehensive ophthalmic services and a dedicated ophthalmic oncology unit, making it an ideal setting for this study.Patients presenting with clinically suspicious ocular lesions, such as flat, pedunculated, raised plaque-like, or pigmented lesions, were recruited for the study. Inclusion criteria required these lesions to be clinically suspected of OSSN and confirmed through histopathological examination. This included primary presenters as well as those with a previous history of surgery and treatment with antimetabolites such as MMC, Interferon alpha 2a and 5fluorouracil. Participants were recruited consecutively based on these criteria and informed consent and contact details were obtained from all patients before inclusion in the study.

The study included a total of 34 eyes from 34 patients with biopsy-confirmed OSSN. The sample size was determined based on the number of patients presenting to the hospital with suspected OSSN during the study period and meeting the inclusion criteria.

All patients underwent surgical excision of the lesion using a no-touch technique to prevent contamination and reduce recurrence rates. A 4 mm clear margin around the lesion was excised, and the excised tissue was sent for histopathological evaluation to confirm the diagnosis and assess surgical margins. Following excision, a 1% 5-fluorouracil (5-FU) formulation was applied to the lesion base for 90 seconds to eradicate any remaining malignant cells. Cryotherapy was then performed using a double freeze-thaw cycle to treat the excision margins. The corneal edge of the lesion was treated with wet cautery.

Patients who had a histopathology report indicating dysplasia were prescribed topical 1%5-FU chemotherapy for three months. The drops were prepared by mixing 1 cc of 5-FU with 4 ccs of normal saline and dispensed in labelled bottles. A standardised regimen was formulated. Drops were instilled 4 times a day. One drop every six hours for 1 week followed by a drug holiday for 3 weeks. The cycle of 4 times a day was repeated in the 5th week followed by another holiday of 3 weeks. In this way, it was 1 week on and 3 weeks off for 3 months. Detailed instructions on usage, dosage regimen, and disposal were provided to patients using diagrams and written instructions.

For patients with extensive lesions or higher grades of histopathology, the chemotherapy regimen was extended up to five months. Patients with lesions greater than 6 clock hours were treated with topical chemotherapy as a chemo-reduction strategy, which showed promising outcomes. The chemo reduction dosing schedule was 1 drop 4 times a day for 1 week and then a drug holiday

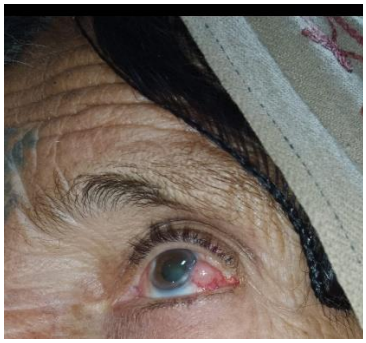
for 3 weeks. This cycle was repeated for a maximum of 3 months. After satisfactory reduction in size clinically, surgical excision with perop 5FU and cryotherapy was done, followed by a similar topical chemotherapy regimen.

The primary outcome of the study was the recurrence rate of OSSN following treatment. Secondary outcomes included the assessment of lesion size, depth of invasion, HIV screening and response to treatment using anterior segment optical coherence tomography (OCT). The variables collected for analysis included demographic data (age, gender, occupation), clinical characteristics of the lesion (size, shape, histopathological findings), treatment regimen, recurrence rates, and complications.Baseline assessments were conducted, including detailed ophthalmic examination, photography of the lesion, and anterior segment OCT to assess lesion depth and involvement. Post-operative follow-up visits were scheduled to monitor healing and detect any signs of recurrence. Anterior segment OCT was repeated post-operatively to evaluate deeper tissue penetration and detect recurrence. Recurrence was defined as the appearance of a new suspicious lesion at the site of the previous excision.

All clinical data, histopathology reports, and OCT images were documented in a standardized proforma. Data were analyzed using SPSS version 25. Categorical variables were expressed as frequencies and percentages, while continuous variables were presented as means with standard deviations. Recurrence rates between different treatment groups were compared using appropriate statistical tests. The study was approved by the Hospital Ethical Committee. Informed consent was obtained from all participants, ensuring adherence to ethical standards as per the Declaration of Helsinki.

Results

Data from 34 patients was taken in this study with a mean age of 53.3, exhibiting a broad range of 72 years (minimum age of 11.00 and maximum age of 83 years). There were 25 (73.5%) males and 9 (26.5%) females.



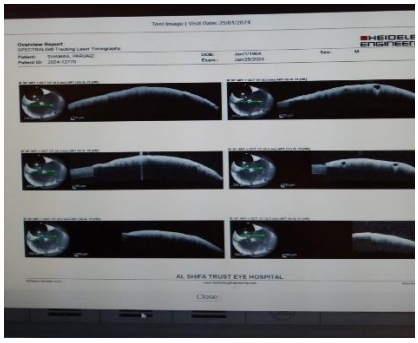


Figure 1. a-The image shows a close-up view of an eye with a red, inflamed conjunctiva, and a visible lesion on the outer corner, suggesting a possible case of ocular surface squamous neoplasia (OSSN).b -Anterior segment OCT

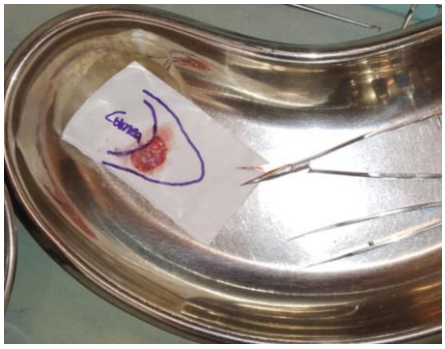


Figure2.The image shows the excised specimen with a limbal position marked ready to be sent to a laboratory

Most patients were diagnosed with OSSN (76.5%) and the majority were fresh cases (61.8%) (Figure 1. Table 1).

Table 1. Diagnosis and Case Type

Diagnosis	Frequency (%)
Ocular Surface Squamous Neoplasia (OSSNdysplasia involving full-thickness	13 (38.2%)
Squamous Cell Carcinoma (SqCA)preinvasive	3(8.8%)
Recurrent Ocular Surface Squamous Neoplasia (OSSN)	14 (41.1%)
Conjunctival Intraepithelial Neoplasia (CIN)grade 1	4 (11.7%)

Table 2. Outcome of patients

Outcome	Frequency (%)
Improved and under follow-up	12 (35.3%)
No definitive Recurrence @6 months	22 (64.7%)

Treatments were evenly distributed between chemo reduction and post-excision. The most common number of cycles of 5-FU was three (52.9%), and the majority of patients experienced no recurrence (64.7%)

Discussion

This study highlights the importance of using postoperative 5-Fluorouracil (5-FU) in cycles after surgery with cryotherapy to reduce recurrence rates in histologically proven cases of ocular surface squamous neoplasia (OSSN) in low-resource regions like Pakistan. OSSN is a superset term that includes various histological conditions of surface tissues, ranging from mild dysplasia to full-thickness disease with basement membrane breach. Nomenclatures in use are namely: carcinoma in situ, squamous cell carcinoma (SCC), mucoepidermoid carcinoma etc.. The challenge with this pathology is a significant recurrence rate, with literature reporting rates up to 33% despite wide-margin resection and adjuvant treatments.[19] Such figures highlight the need for effective therapeutic strategies to improve patient outcomes.

The combination of 5-FU and cryotherapy has proven to be an effective approach in reducing OSSN recurrence. In this study, the application of 5-FU following wide excision and cryotherapy, and then postsurgically in cycles has demonstrated promising results, with the majority of patients achieving no recurrence. This strengthens previous research that has demonstrated the efficacy of 5-FU in treating OSSN.[20-21] By employing this combined treatment strategy, there is potential to increase the survival rates of patients and improve their quality of life.

Potent antimetabolite like 5-FU is particularly useful in low-resource areas due to its cost-effectiveness and feasibility. Unlike other treatments such as interferon alpha 2b (IFN), 5-FU does not require low-temperature refrigeration, and has a low price, making it more accessible for patients and hospitals alike in regions with limited healthcare resources.[21] Moreover, the topical application of 5-FU does the anticipated treatment of the entire ocular surface including very low-grade dysplastic changes It reduces the risk of systemic side effects with enhanced patient compliance.

Our results are consistent with the results of a meta-analysis that compared topical pharmacotherapy (including 5-FU, IFN, and mitomycin-C) with surgical excision. This meta-analysis concluded that topical treatments were as efficacious and well-tolerated as surgery alone in terms of tumour resolution and recurrence rates.[22] This further supports the use of 5-FU in conjunction with cryotherapy as a viable treatment option for OSSN, particularly in resource-limited settings.

Although Mitomycin C is chemically a more potent agent, it has adverse effects like concomitant thinning, limbal stem cell loss, and punctal stenosis. It also needs temperature maintenance which is not always possible at the patient's end.

Available interferon alpha formulation is alpha 2a which is currently not approved for OSSN.It also had a significantly higher recurrence rate and cost issues.[22]

Our analysis so far fully supports the use of 5-FU in conjunction with cryotherapy as an effective treatment strategy for OSSN, particularly in low-resource settings. This approach not only reduces recurrence rates but also offers a cost-effective and feasible treatment option for patients. However, we need case series with larger sample sizes and longer follow-up periods to give credence to these findings and optimize treatment protocols for OSSN in diverse clinical settings.

Conclusions

Ocular Surface neoplasia is a treatable cancer. However late presentation, poorer prognosis and lack of standardised treatment lead to increased morbidity.This study has demonstrated promising results by showing no recurrence after topical chemotherapy cycles of 5FU after excision. This combined treatment approach is cost-effective, feasible, and patient-friendly. Given the high recurrence rate of OSSN, adopting 5-FU and cryotherapy as standard treatment can be particularly beneficial in resource-limited regions. Further research with larger cohorts is recommended to confirm these findings and refine treatment protocols.

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