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Topical 5-fluorouracil 1% as primary treatment for ocular surface squamous neoplasia

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Abstract

Purpose—To determine the efficacy of topical 5-fluorouracil 1% (5FU) as a primary treatment of ocular surface squamous neoplasia (OSSN).

Design—Retrospective study.

Participants—Topical 5FU was used as primary therapy in 44 patients with OSSN.

Methods—5FU 1% administered topically four times a day for a week followed by a drug holiday of 3 weeks. Patients were identified through pharmacy database. Patients were excluded if 5FU was used as adjuvant therapy, did not complete therapy, or were still in active treatment for their OSSN at the time of last follow up.

Main outcome measure—The primary outcome measures were the frequency of complete resolution with topical 5FU treatment and the rate of OSSN recurrence.

Results—Of the 44 patients identified, 32 were males and 12 were females. The mean age was 68 years. Complete resolution of OSSN was noted in 82% (36/44) patients; and, 18% (8/44) were considered treatment non-responders. Patients were treated a median of 4 cycles (range 2-9). Nasal location was the only risk factor identified for nonresponse to therapy ($p=0.04$). The median follow up after resolution was 10 months (range 2-77). In the 36 patients with complete resolution, 4 had tumor recurrence. Recurrence rates at 1 and 2 years were 6% and 15% respectively using Kaplan-Meier survival analysis. At least one side effect from the medication was reported by 61% (21/44) of patients, but only 1 patient discontinued the medication due to intolerance. The most common side effect was pain ($n=17$, 39%) followed by tearing ($n=10$, 23%), photophobia ($n=6$, 14%), itching ($n=4$, 9%), swelling ($n=2$, 5%), and infection ($n=1$, 2%). No long-term complications were reported.

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Conclusion—5-fluorouracil is efficacious and well tolerated as a primary treatment for OSSN, with 82% of tumors completely responding to therapy.

Introduction

Ocular surface squamous neoplasia (OSSN) is a term that encompasses a spectrum of epithelial squamous malignancies, ranging from dysplasia to invasive carcinoma.¹ It represents the most common non-pigmented tumor of the ocular surface.² Traditional treatment for OSSN involves excision using a no-touch technique, with adjuvant alcohol and cryotherapy.³⁻⁶ Unfortunately, recurrences do occur after surgery, presumably due to microscopic disease beyond the clinically-identified lesion.⁷ Even with clear margins on pathology, recurrences of up to 33% have been reported.⁷ Furthermore, extensive surgical intervention carries the risk of subsequent limbal stem cell deficiency and symblephara formation.

In order to potentially avoid these risks and treat the entire ocular surface, medical treatment as a primary therapy for OSSN has increased in popularity.^{8, 9} Chemotherapeutic agents used for treatment of OSSN include interferon-alpha-2b (IFN), mitomycin-C (MMC), and 5-fluorouracil (5FU), and all have been shown to be effective.^{4, 6, 9-16} IFN is an endogenous protein with anti-viral and anti-neoplastic properties.^{17, 18} It is often the first choice of therapy in OSSN given its favorable side effect profile. Adverse reactions to topical IFN drops are uncommon and if present, usually mild.¹⁹ A literature search of primary treatment of OSSN with IFN (as opposed to adjuvant therapy after surgical removal), identified six studies with a total of 137 patients of which 92.5% of patients had successful resolution of their OSSN.²⁰⁻²⁶

MMC is a potent antimetabolite that was first used as a surgical adjunct before being adapted as a primary treatment for OSSN.^{6, 27} It has an unpleasant side effect profile, which includes pain in the majority of patients and rare but serious sequelae such as corneal and scleral melts.¹⁹ Of 10 studies with 212 patients treated with MMC as primary therapy, 90% of patients had successful resolution of their OSSN.^{11, 20, 28-35}

5FU is a structural analogue of thymine, which inhibits DNA formation by blocking the enzyme thymidylate synthetase. Rapidly multiplying cells, such as tumor cells, require more DNA and RNA than normal cells and therefore take up larger amounts of 5FU, allowing selective targeting of cancerous lesions.³⁶ Solutions of 5FU are stable for several weeks at 25 °C, and therefore it does not need refrigeration.³⁷

While 5FU has been used as an adjunct to surgery³⁸, literature reporting primary topical 5FU as a treatment for OSSN is more limited than that evaluating MMC and IFN. For primary treatment, only 37 cases in literature report successful resolution of OSSN ranging from 85% to 100%, mean 95.6% in these reports.^{4, 15, 39-41}

5FU has several theoretical advantages over IFN and MMC including a lower cost of treatment, no need for refrigeration³⁷, and less frequent dosing regimen. Given a limited amount of data on the use of 5FU as primary treatment in OSSN, we performed this study to evaluate the efficacy and side effect profile of 5FU as a primary treatment in OSSN.

Methods

Study population

The institutional review board of the University of Miami approved this retrospective study, and the methods adhered to the tenets of the Declaration of Helsinki and were compliant with the Health Insurance Portability and Accountability Act. Pharmacy records identified 64 patients who received 5FU as a treatment for OSSN between May 2004 and March 2015. Of those, patients were excluded because they were prescribed topical 5FU as adjuvant surgical therapy (n=3), did not complete therapy (n=14), or were still in active treatment for their OSSN at the time of last follow up (n=3), leaving 44 patients for analysis.

Topical 5FU—All patients were treated with topical 5FU at a concentration of 1%. The drops were administered 4 times daily for one week, followed by a drug holiday for 3 weeks. This monthly cycle was continued until clinical resolution, after which the drops were discontinued. Patients were initially seen on a 2-month basis to assess treatment response. No punctal plugs were used.

Data extracted—Patient records were reviewed for demographic information (age, race, ethnicity), OSSN risk factors (skin cancer, HPV, HIV, smoking), and prior history of OSSN. Characteristics of the current lesion were also documented including the involved eye, tumor location, tumor size and involved ocular structures (conjunctiva, cornea, limbus, orbit), uni- vs. multi-focality, and appearance (leukoplakic, gelatinous, papillomatous, flat/nodular) based on descriptions and photographs. The tumor size and location provided the basis for American Joint Committee on Cancer (AJCC) clinical stage of the tumor.⁴² Of the 16 patients that underwent biopsy, pathologic grading of the tumor (mild, moderate, severe, carcinoma in situ, or invasive squamous cell carcinoma) and margin positivity were also recorded. Treatment information documented included modality of treatment, and for medical therapy included the dose, frequency, and length of treatment.

Main outcome measures—The main outcome measure was the frequency of OSSN clinical resolution and recurrence rates after treatment. A secondary outcome was the frequency of complications associated with each therapy during the follow-up period.

Response information was recorded in terms of time to complete resolution of the lesion (defined clinically). Recurrence was defined as a reappearance of a lesion, in a similar location as the original tumor, after complete resolution of the original tumor. Follow up was carried out from the time of clinical resolution of the lesion until the last visit. Documented complications included those volunteered by the patient as well as those elicited by the examiner during the clinic visit. Complications recorded included redness, pain, irritation, itching, flu-like symptoms, infection, limbal stem cell deficiency, symblepharon, and diplopia.

Statistical analyses—Statistical analyses were performed using the SPSS 20.0 (SPSS Inc, Chicago, IL) statistical package. Frequencies of demographic and clinical variables were calculated for each group. Categorical variables were compared using a Chi square analysis; continuous variables were compared using the student t-test. Time-to-event curves

were generated using the Kaplan-Meier method. Cox proportional hazards analysis was employed to evaluate factors associated with disease recurrence.

Results

Demographics of the study population are presented in Table 1. As in previous studies, the majority of patients were white males in their 7th decade of life (Table 1).

Resolution of OSSN

Of the 44 eyes, 36 lesions (82%) completely resolved with 5FU therapy (Figure 1 and 2). Of these, the median number of cycles was 4 (range 2 to 9, mean 3.8).

Non-resolution of OSSN

Treatment non-response was seen in 4 patients after the tumor failed to resolve after the full 4 or more cycles of 5FU; 4 patients were considered partial non-responders as they were switched to a different therapy after receiving between 1 and 3 cycles of therapy for various reasons.

Combining partial and total treatment non-responses, we examined which patient and tumor characteristics were associated with them. Patients whose tumor completely resolved on 5FU were older than those in which treatment failed [71 years, standard deviation (SD) 11 versus 55 years, SD 14, $p=0.002$]. Gender, race, and ethnicity were not associated with treatment non-response. Tumors located nasally were likely show non-response to 5FU (30% non-response, $n=5$) compared to those not in a nasal location (4% non-response, $n=3$), Fisher exact $p=0.04$.

Squamous cell carcinoma

Three patients had pathologically confirmed squamous cell carcinoma. In this subset, 1 patient had full resolution with 3 cycles of 5FU, 1 patient was a non-responder to treatment after 6 cycles, and 1 patient was given only two cycles of 5FU before being switched to another treatment modality.

OSSN recurrences after treatment

A total of 4 recurrences were seen in the 36 patients who initially responded to therapy; one of which was in a patient with squamous cell carcinoma. One recurrence was at 3.7 years, another at 1.4 years, and two at 3 months. Using Kaplan-Meier survival analysis, the 1 and 2 year recurrence rates were 6% and 15%, respectively (Figure 3). The presence of nodularity increased the risk of recurrence approximately 11 fold (95% confidence interval (CI) 0.97 to 122, Cox proportional hazards $p=0.05$). None of the other demographic or clinical factors associated with recurrence.

Treatment complications

A total of 27 patients (61%) experienced at least one medication related side effect. The most common side effect was pain ($n=17$, 39%) followed by tearing ($n=10$, 23%), photophobia ($n=6$, 14%), itching ($n=4$, 9%), swelling ($n=2$, 5%), and infection ($n=1$, 2%).

Limbal stem cell deficiency from 5FU was not seen in any patients. Only one patient discontinued treatment after 3 cycles of 5FU, due to self-reported intolerable side effects. There were no long-term complications associated with the use of 5FU.

Discussion

5FU was first reported as a treatment for OSSN in 1986.³⁹ Since then, a few case series and small reports have been published with an overall response frequency ranging from 57-100% for 5FU treatment which seems rather low.^{15, 39-41} However when examining only cases treated with 5FU as an exclusive, primary therapy (as opposed to adjuvant therapy after surgical removal), the response frequency improves and ranges from 85% to 100%.^{4, 15, 39-41} In our study, representing the largest group of patients treated with 5FU as primary therapy, we found that 82% of patients experienced complete resolution of OSSN. Our response frequency of 82% for 5FU is similar to what has been reported in larger series of IFN and MMC treated patients.^{11, 20-26, 28-35}

One issue in comparing treatment response between 5FU studies is that varying regimens have been used to treat OSSN. Nutt et al. reported that only 10 of 24 (41.6 %) tumors completed resolved with 5FU as primary therapy but in this series, no patient received more than 4 cycles.⁴³ Some authors favor continuous administration of 1% 5FU 3 or 4 times a day, for 4 weeks.^{4, 39-41, 15} Yeatts et al administered 1% 5FU 4 times a day for 2-4 days and then repeated it after an interval of 30-45 days with success.¹⁵ A series by Parrozzani et al that included 41 patients of which 22 patients were treated primarily with 5FU 4 times a day daily, for a month.⁴¹ In these patients, all tumors completely resolved after mean of 1.9 monthly cycles (range 1-5.), however 3 patients (7.3%) developed early recurrence. In our series there were 4 recurrences and 2 were noted within 3 months following cessation of therapy. These early recurrences likely represent persistent subclinical disease (incomplete treatment) and not true recurrences. In more recent years, we use high resolution optical coherence tomography (HR-OCT) imaging to guide length of treatment, a practice that may decrease the frequency of premature termination of medical therapy.⁴⁴

Our side effect profile is also similar to what has been reported in the literature. A large review comparing data from all three topical treatments reported side effects for 5FU from a total of 26 patients, of whom 11 (42%) had both hyperemia and keratitis.¹⁹ Encouragingly, a confocal microscopy study showed no long-term differences between the treated and control (fellow) eyes after treatment with 5FU.⁴¹

Our response frequency of 82% for 5FU is similar to what has been reported in larger series of IFN and MMC treated patients. The side effects from 5FU are worse than with IFN but better than those of MMC. For IFN, success for primary treatment ranges 82% to 100%^{20, 22-26}, has minimal reported side-effects such as follicular conjunctivitis and mild irritation.⁴⁵ MMC, on the other hand, has a similar response frequency, ranging from 76% to 100%^{11, 20, 28-35}, with a much higher frequency of adverse reactions, in approximately 76% of patients.¹⁹ These range from acute effects such as conjunctival hyperemia, ocular allergy, superficial punctate keratitis, ocular pain, and epiphora, to long term effects such as recurrent corneal erosion, limbal stem cell deficiency and punctal stenosis.⁴⁵ Punctal plugs

are used routinely with MMC but not required in 5FU. Punctual stenosis has not been reported with topical 5 FU use.

As with all studies, our findings must be considered in light of its limitations, which include its retrospective nature, limited patient numbers, small number of SCC lesions, and evolving management of OSSN. For example, we now give patients 4 cycles of 5FU prior to declaring nonresponse to treatment. However, when first using 5FU, some patients switched to an alternative therapy prior to completing 4 cycles. In addition, ultra-high resolution anterior segment OCT (HR-OCT) has altered the way we diagnose and manage tumors. We suspect that the two recurrences we had at 3 months had sub-clinical disease and premature termination of therapy. We are now better able to follow the complete resolution of the tumor with the HR-OCT to ensure normalization before cessation of therapy. The effect of this imaging modality on recurrence rates, however, is not yet known. Finally, the ideal dosing regimen is still unknown, and other protocols might have different outcomes.

Despite these limitations, this study adds important knowledge regarding the role of topical 5FU as a primary treatment of OSSN. In our institution, topical IFN remains our first choice of medical therapy given its high tolerability. There are a few considerations, however, when 5FU is our preferred choice. These include (1) an inadequate or incomplete response to IFN; (2) economic considerations as 5FU (\$40/month) is much less costly than IFN (\$240/month) and MMC (\$190/month); (3) refrigeration issues as both IFN and MMC need to be kept refrigerated at all times but not 5FU; and (4) when patients prefer a cycling regimen as the ease of one week per month is easier than the daily dosing of IFN. This study demonstrated that topical 5FU is a good choice in these circumstances as it has a similar efficacy as both IFN and MMC and a side effect profile in the middle of the two agents. It is interesting, that although the response frequencies appear similar between the 3 topical agents, there are some patients who respond to one agent and not the other.^{46, 47} As these agents have different mechanisms of action, more research is needed to predict which patient is most likely to respond to which treatment modality.

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References

1. Lee GA, Hirst LW. Ocular surface squamous neoplasia. *Surv Ophthalmol.* 1995; 39(6):429–50. [PubMed: 7660300]
2. Shields CL, Demirci H, Karatza E, Shields JA. Clinical survey of 1643 melanocytic and nonmelanocytic conjunctival tumors. *Ophthalmology.* 2004; 111(9):1747–54. [PubMed: 15350332]
3. Shields JA, Shields CL, De Potter P. Surgical management of conjunctival tumors. The 1994 Lynn B. McMahan. *Lecture Arch Ophthalmol.* 1997; 115(6):808–15. [PubMed: 9194740]
4. Midena E, Angeli CD, Valenti M, et al. Treatment of conjunctival squamous cell carcinoma with topical 5-fluorouracil. *Br J Ophthalmol.* 2000; 84(3):268–72. [PubMed: 10684836]

5. Peksayar G, Altan-Yaycioglu R, Onal S. Excision and cryosurgery in the treatment of conjunctival malignant epithelial tumours. *Eye (Lond)*. 2003; 17(2):228–32. [PubMed: 12640411]
6. Siganos CS, Kozobolis VP, Christodoulakis EV. The intraoperative use of mitomycin-C in excision of ocular surface neoplasia with or without limbal autograft transplantation. *Cornea*. 2002; 21(1): 12–6. [PubMed: 11805500]
7. Tabin G, Levin S, Snibson G, et al. Late recurrences and the necessity for long-term follow-up in corneal and conjunctival intraepithelial neoplasia. *Ophthalmology*. 1997; 104(3):485–92. [PubMed: 9082277]
8. Adler E, Turner JR, Stone DU. Ocular surface squamous neoplasia: a survey of changes in the standard of care from 2003 to 2012. *Cornea*. 2013; 32(12):1558–61. [PubMed: 24145630]
9. Stone DU, Butt AL, Chodosh J. Ocular surface squamous neoplasia: a standard of care survey. *Cornea*. 2005; 24(3):297–300. [PubMed: 15778602]
10. Ballalai PL, Erwenne CM, Martins MC, et al. Long-term results of topical mitomycin C 0.02% for primary and recurrent conjunctival-corneal intraepithelial neoplasia. *Ophthal Plast Reconstr Surg*. 2009; 25(4):296–9.
11. Frucht-Pery J, Sugar J, Baum J, et al. Mitomycin C treatment for conjunctival-corneal intraepithelial neoplasia: a multicenter experience. *Ophthalmology*. 1997; 104(12):2085–93. [PubMed: 9400769]
12. Galor A, Karp CL, Chhabra S, et al. Topical interferon alpha 2b eye-drops for treatment of ocular surface squamous neoplasia: a dose comparison study. *Br J Ophthalmol*. 2010; 94(5):551–4. [PubMed: 19493859]
13. Karp CL, Galor A, Chhabra S, et al. Subconjunctival/perilesional recombinant interferon alpha2b for ocular surface squamous neoplasia: a 10-year review. *Ophthalmology*. 2010; 117(12):2241–6. [PubMed: 20619462]
14. Karp CL, Galor A, Lee Y, Yoo SH. Pegylated interferon alpha 2b for treatment of ocular surface squamous neoplasia: a pilot study. *Ocul Immunol Inflamm*. 2010; 18(4):254–60. [PubMed: 20662655]
15. Yeatts RP, Engelbrecht NE, Curry CD, et al. 5-Fluorouracil for the treatment of intraepithelial neoplasia of the conjunctiva and cornea. *Ophthalmology*. 2000; 107(12):2190–5. [PubMed: 11097594]
16. Yeatts RP, Ford JG, Stanton CA, Reed JW. Topical 5-fluorouracil in treating epithelial neoplasia of the conjunctiva and cornea. *Ophthalmology*. 1995; 102(9):1338–44. [PubMed: 9097771]
17. Baron S, Tying SK, Fleischmann WR Jr, et al. The interferons. Mechanisms of action and clinical applications. *JAMA*. 1991; 266(10):1375–83. [PubMed: 1715409]
18. Bracarda S, Eggermont AM, Samuelsson J. Redefining the role of interferon in the treatment of malignant diseases. *Eur J Cancer*. 2010; 46(2):284–97. [PubMed: 19906524]
19. Poothullil AM, Colby KA. Topical medical therapies for ocular surface tumors. *Semin Ophthalmol*. 2006; 21(3):161–9. [PubMed: 16912014]
20. Besley J, Pappalardo J, Lee GA, et al. Risk factors for ocular surface squamous neoplasia recurrence after treatment with topical mitomycin C and interferon alpha-2b. *Am J Ophthalmol*. 2014; 157(2):287–93 e2. [PubMed: 24184223]
21. Hu FR, Wu MJ, Kuo SH. Interferon treatment for corneolimbal squamous dysplasia. *Am J Ophthalmol*. 1998; 125(1):118–9. [PubMed: 9437331]
22. Kusumesh R, Ambastha A, Sinha B, Kumar R. Topical Interferon alpha-2b as a Single Therapy for Primary Ocular Surface Squamous Neoplasia. *Asia Pac J Ophthalmol (Phila)*. 2015
23. Nanji AA, Moon CS, Galor A, et al. Surgical versus medical treatment of ocular surface squamous neoplasia: a comparison of recurrences and complications. *Ophthalmology*. 2014; 121(5):994–1000. [PubMed: 24411578]
24. Shields CL, Kaliki S, Kim HJ, et al. Interferon for ocular surface squamous neoplasia in 81 cases: outcomes based on the American Joint Committee on Cancer classification. *Cornea*. 2013; 32(3): 248–56. [PubMed: 22580436]
25. Sturges A, Butt AL, Lai JE, Chodosh J. Topical interferon or surgical excision for the management of primary ocular surface squamous neoplasia. *Ophthalmology*. 2008; 115(8):1297–302. 302 e1. [PubMed: 18294690]

26. Zarei-Ghanavati S, Alizadeh R, Deng SX. Topical interferon alpha-2b for treatment of noninvasive ocular surface squamous neoplasia with 360 degrees limbal involvement. *J Ophthalmic Vis Res.* 2014; 9(4):423–6. [PubMed: 25709765]
27. Frucht-Pery J, Rozenman Y. Mitomycin C therapy for corneal intraepithelial neoplasia. *Am J Ophthalmol.* 1994; 117(2):164–8. [PubMed: 8116744]
28. Papandroudis AA, Dimitrakos SA, Stangos NT. Mitomycin C therapy for conjunctival-corneal intraepithelial neoplasia. *Cornea.* 2002; 21(7):715–7. [PubMed: 12352093]
29. Tseng SH, Tsai YY, Chen FK. Successful treatment of recurrent corneal intraepithelial neoplasia with topical mitomycin C. *Cornea.* 1997; 16(5):595–7. [PubMed: 9294697]
30. Chen C, Louis D, Dodd T, Muecke J. Mitomycin C as an adjunct in the treatment of localised ocular surface squamous neoplasia. *Br J Ophthalmol.* 2004; 88(1):17–8. [PubMed: 14693762]
31. Gupta A, Muecke J. Treatment of ocular surface squamous neoplasia with Mitomycin C. *Br J Ophthalmol.* 2010; 94(5):555–8. [PubMed: 20447963]
32. Heigle TJ, Stulting RD, Palay DA. Treatment of recurrent conjunctival epithelial neoplasia with topical mitomycin C. *Am J Ophthalmol.* 1997; 124(3):397–9. [PubMed: 9439368]
33. Rozenman Y, Frucht-Pery J. Treatment of conjunctival intraepithelial neoplasia with topical drops of mitomycin C. *Cornea.* 2000; 19(1):1–6. [PubMed: 10631999]
34. Shields CL, Naseripour M, Shields JA. Topical mitomycin C for extensive, recurrent conjunctival-corneal squamous cell carcinoma. *Am J Ophthalmol.* 2002; 133(5):601–6. [PubMed: 11992855]
35. Wilson MW, Hungerford JL, George SM, Madreperla SA. Topical mitomycin C for the treatment of conjunctival and corneal epithelial dysplasia and neoplasia. *Am J Ophthalmol.* 1997; 124(3):303–11. [PubMed: 9439356]
36. Goette DK. Topical chemotherapy with 5-fluorouracil. A review. *J Am Acad Dermatol.* 1981; 4(6):633–49. [PubMed: 7016939]
37. Martindale, W. Martindale, The Extra Pharmacopoeia. 31st. London: Royal Pharmaceutical Society; 1996. p. 572-5.
38. Kenawy N, Garrick A, Heimann H, et al. Conjunctival squamous cell neoplasia: the Liverpool Ocular Oncology Centre experience. *Graefes Arch Clin Exp Ophthalmol.* 2015; 253(1):143–50. [PubMed: 25398663]
39. de Keizer RJ, de Wolff-Rouendaal D, van Delft JL. Topical application of 5-fluorouracil in premalignant lesions of cornea, conjunctiva and eyelid. *Doc Ophthalmol.* 1986; 64(1):31–42. [PubMed: 3582100]
40. Midena E, Boccato P, Angeli CD. Conjunctival squamous cell carcinoma treated with topical 5-fluorouracil. *Arch Ophthalmol.* 1997; 115(12):1600–1. [PubMed: 9400803]
41. Parrozzani R, Lazzarini D, Alemany-Rubio E, et al. Topical 1% 5-fluorouracil in ocular surface squamous neoplasia: a long-term safety study. *Br J Ophthalmol.* 2011; 95(3):355–9. [PubMed: 20693564]
42. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol.* 2010; 17(6):1471–4. [PubMed: 20180029]
43. Nutt RJ, Clements JL, Dean WH. Ocular surface squamous neoplasia in HIV-positive and HIV-negative patients and response to 5-fluorouracil in Angola. *Clin Ophthalmol.* 2014; 8:2435–40. [PubMed: 25506205]
44. Nanji AA, Sayyad FE, Galor A, et al. High-Resolution Optical Coherence Tomography as an Adjunctive Tool in the Diagnosis of Corneal and Conjunctival Pathology. *Ocul Surf.* 2015; 13(3):226–35. [PubMed: 26045235]
45. Nanji AA, Sayyad FE, Karp CL. Topical chemotherapy for ocular surface squamous neoplasia. *Curr Opin Ophthalmol.* 2013; 24(4):336–42. [PubMed: 23680759]
46. Holcombe DJ, Lee GA. Topical interferon alfa-2b for the treatment of recalcitrant ocular surface squamous neoplasia. *Am J Ophthalmol.* 2006; 142(4):568–71. [PubMed: 17011846]
47. Rudkin AK, Dempster L, Muecke JS. Management of diffuse ocular surface squamous neoplasia: efficacy and complications of topical chemotherapy. *Clin Experiment Ophthalmol.* 2015; 43(1):20–5. [PubMed: 24995542]

Figure 1.

a: 71 year old male with extensive ocular surface squamous neoplasia of the right eye. **b:** High resolution optical coherence tomography revealed thickened hyperreflective epithelium (caliper) **c:** Dramatic resolution of tumor after 4 weekly cycles of 5 fluorouracil. **d:** High Resolution OCT shows smooth thin normal epithelium (caliper).

Figure 2.

a: 70 year old male with recurrent OSSN of the right eye. A conjunctival lesion (dashed arrows) is present as well as corneal component (solid arrows) **b:** Ultra high resolution OCT shows thickened hyperreflective epithelium (arrow) **c:** Resolved tumor after 4 weekly cycles of 5 fluorouracil 1% **d:** High resolution OCT shows thin, normal epithelium.

Figure 3. Kaplan Meyer survival curve shows disease free survival at 1 and 2 years to be 94% and 85% respectively.

Table 1

Demographic and clinical information in patients with ocular surface squamous neoplasia treated with 5-fluorouracil (5FU) eye drops.

Demographic and clinical factors	n (%)
Age in years, mean [SD] (n)	68 [13] (44)
Gender, male n [%]	32 [73%]
Race, white n [%]	24 [57%]
black n [%]	2 [5%]
other n [%]	16 [38%]
Ethnicity, Hispanic n [%]	23 [56%]
Current smoker, n [%]	4 [9%]
H/o skin cancer, n [%]	11 [26%]
Involved eye, right n [%]	27 [61%]
History of OSSN, n [%]	19 [43%]
Area, mm ² [SD] (range)	38 [48] (1-225)
Location, nasal [*] n [%]	20 [47%]
temporal	23 [52%]
superior	11 [25%]
inferior	13 [30%]
Corneal involvement, n [%]	41 [93%]
Clinical AJCC stage, T2 n [%]	3 [7%]
T3	40 [93%]
Multifocal tumor, n [%]	5 [11%]
Appearance [†] , leukoplakia, n [%]	14 [33%]
papillomatous	9 [21%]
nodular	5 [11%]
gelatinous	20 [46%]
Pathologic grade ^{**} , mild –severe dysplasia	6
CIS	7
SCC	3

n=number of individuals in group; OSSN= ocular surface squamous neoplasia; SD=standard deviation; CIS= carcinoma in situ; SCC=squamous cell carcinoma; AJCC= American Joint Committee on Cancer clinical stage³⁹ (Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 2010;17(6):1471-4.)

^{*} Tumors could involve more than one quadrant, e.g. a tumor involving the temporal and superior bulbar conjunctivae would appear both in the temporal and the superior location categories.

[†] Tumors could have more than 1 descriptor for appearance

^{**} For those that underwent biopsy (n=16)

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