

# Recurrent Pterygium: A Review

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## Abstract

**Purpose:** To summarize the recent evidence regarding different aspects of pterygium recurrence.

**Methods:** Human-based studies from PubMed, Scopus, and Google Scholar were identified using the following keywords: conjunctival disease, pterygium, recurrent pterygium, pterygium recurrence, pterygium management/surgery, conjunctival autograft (CAU), amniotic membrane graft/transplant, and adjuvant therapy (January 2009 to February 2021). We reviewed risk factors associated with the recurrence of pterygium, timing of recurrence, medical treatments to prevent from recurrence, and nonsurgical and surgical alternatives for management of recurrence.

**Results:** Dry eye disease, black race, and young age are considered definite risk factors for recurrence. However, fleshy appearance of the pterygium and preoperative size remain controversial. Surgical techniques such as excessive suturing, insufficient conjunctival graft size, thick conjunctival graft with remained Tenon tissue, and postoperative graft retraction are considered possible risk factors for recurrence. Using fibrin glue instead of sutures can further reduce recurrence rates. Although recurrence could occur even after many years, most recurrences happen in the first 3–6 months after surgery. Multiple kinds of adjuvant medications are used before, during, or after the operation including mitomycin C (MMC), 5-fluorouracil (5-FU), corticosteroids, and anti-vascular endothelial growth factors (anti-VEGFs). Multiple weekly subconjunctival 5-FU injections are shown to be safe and effective in halting the progression of recurrent pterygium. Although topical bevacizumab is found to inhibit the growth of impending recurrent pterygium, the effect is mostly temporary. CAU is superior to amniotic membrane transplantation in the treatment for recurrent pterygia.

**Conclusions:** There is yet to be a panacea in treating recurrent pterygium. Currently, there is not a globally accepted recommendation for treating recurrent pterygium with anti-VEGFs or 5-FU as a nonsurgical treatment. We strongly recommend using MMC as an adjunct to surgery in recurrent cases, with consideration of its specific complications. CAU is the most effective surgical treatment for recurrent pterygium, and other new surgical therapies need further investigation.

**Keywords:** Adjuvant therapy, Amniotic membrane graft/transplant, Conjunctival autograft, Conjunctival disease, Pterygium, Pterygium management, Pterygium recurrence, Recurrent pterygium, Risk factor

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## INTRODUCTION

Pterygium is an abnormal growth of epithelial and fibrovascular tissue invading toward cornea. Impaired vision, induced astigmatism, and recurrent inflammation are among common complications. Pterygium management is mainly surgical. However, the main issue in pterygium management is recurrence,

which is still challenging regarding prevention and management. A better understanding of the recurrence risk factors may lead to a better prophylaxis plan and better medical or surgical treatment. The main proven risk factors for primary pterygium are cumulative ultraviolet (UV) light exposure, prolonged sunlight exposure (more than 5 h per day), having an outdoor occupation,

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aging, dry eye disease (DED), male gender, and genetic factors such as p53 tumor suppressor gene and ethnicity.<sup>1-8</sup> However, only some of these risk factors may be responsible for the development of a recurrent pterygium. Incomplete control of postoperative inflammation, surgical techniques such as excessive suturing and incomplete removal of the primary pterygium, young age, surgeon experience, higher morphologic grade (fleshiness of pterygium), heavy vascularization of the primary pterygium, and black race are other risk factors for recurrence of the pterygium.<sup>9-22</sup> In addition, the precise pathogenesis of recurrence is under debate. Also, basic science studies have shown that changes in the limbal stem cells and fibroblasts have a role in pterygium formation and pathogenesis.<sup>2,9</sup>

The purpose of this narrative review is to summarize the recent evidence regarding different aspects of pterygium recurrence, which can provide new insights and perspectives for better management of this common disease by ophthalmologists. We will review risk factors associated with the recurrence of pterygium, timing of recurrence, and the medical treatments we could use to prevent from recurrence. In addition, nonsurgical and surgical alternatives for management of recurrence are discussed.

## METHODS

Human-based studies from PubMed, Scopus, and Google Scholar were identified using one or more of the following keywords: Conjunctival disease, pterygium, recurrent pterygium, pterygium recurrence, pterygium management, pterygium surgery, conjunctival autograft (CAU), amniotic membrane graft/transplant, adjuvant therapy, risk factors, and predicting factors. Restrictions on sex, age, language and journal or article type were not applied. Only articles published from January 2009 to February 2021 were included for final review. The inclusion criterion was recurrent pterygium.

## RESULTS

One hundred and twenty-nine articles were gathered from the search engines initially including 77 original investigations (29 retrospective, 48 prospective), 23 clinical trials, 14 narrative reviews, 8 systematic reviews/meta-analysis, and 7 case reports/series. The articles were independently analyzed by two of the authors (L.G., N.A.) for eligibility according to our inclusion criteria. Finally, 26 articles that were not relevant to the review topic (reports of complications of pterygium surgery, including only primary pterygium cases, publication before January 2009) were eliminated, and 103 articles were included in the study. Table 1 summarizes the prospective studies on pterygium, covering the risk factors, treatment options, and options to improve the surgical outcomes and decrease the recurrence rate.

### **Risk factors for recurrence**

#### **Basic mechanisms**

Reports published before 2009 found an overexpression of different biomarkers like matrix metalloproteinases (MMPs)

and p53 in fibroblasts from primary pterygium head and were usually based on immunohistochemical (IHC) studies.<sup>8,23</sup> However, investigative studies in recurrent pterygium were less reported or just clinical observations were revealed. An *et al.* found that the level of MMP-1 in serum-free supernatant of cultured primary and recurrent human pterygium fibroblast (HPF) was higher compared to normal ones.<sup>23</sup> This finding was consistent with other reports that showed human pterygium tissues exhibit an enhanced MMP-1 expression detected by IHC analysis. They showed that the levels of MMP-1 and MMP-3 in supernatant secreted by primary HPFs exhibit a different pattern from recurrent HPFs. This means that different pathogenesis may exist between primary and recurrent pterygia.<sup>23</sup> Therefore, the process of pterygium recurrence is accelerated by induction of pre-inflammatory cytokines, growth factors, and different molecular biomarkers like excessive levels of stromal cell-derived factor 1, angiogenin, transcription factor specificity protein 1, and collagen I, which all are considered to be associated with higher recurrence rates.<sup>8,24,25</sup>

p53 is a known important tumor suppressor protein that plays a role in regulating cellular proliferation and apoptosis. There have been published reports of abnormal levels of p53 protein in the epithelium of both primary and recurrent pterygium.<sup>26,27</sup> Zhang *et al.* found that 45% of primary pterygium and 50% of recurrent pterygium cases were positive for p53 expression, whereas this protein was not expressed in normal human conjunctiva.<sup>26</sup> However, another investigation by Nuhoglu *et al.* found no connection regarding the abnormal expression of p53 with recurrence.<sup>28</sup> Another molecular biomarker under investigation is vascular endothelial growth factor (VEGF) which has been introduced responsible for pterygium recurrence.<sup>29</sup> It has been documented that the expression of VEGF receptor 2 (VEGFR-2) may have a predictive value in the recurrence of pterygium.<sup>30</sup>

Familial cases of pterygium have been reported and indicate that genetic factors are significantly involved in the pathogenesis of the primary disease.<sup>1</sup> Rykov *et al.* found that carriers of BRAFV600 mutation had an 8-fold increased risk of recurrence during the first year after pterygium surgery.<sup>31</sup> In addition, viruses such as HSV, EBV, CMV, and HPV can be other risk factors for recurrence.<sup>31</sup>

#### **Clinical risk factors**

It was known from the earliest reports that the incidence of pterygium is higher in areas closest to the geographical equator, which was considered due to the effect of UV light.<sup>2</sup> Previous studies have not found gender among the proven nonsurgical risk factors for recurrence.<sup>28</sup> However, younger age was found to be associated with a higher risk of recurrence, and patients under the age of 45 have a 3.5-fold increase in their risk of recurrence.<sup>17,28</sup> Possible explanations for higher recurrence in younger subjects are rapid re-epithelialization, aggressive collagen synthesis, rapid angiogenesis, more robust and vigorous inflammatory response, and increased outdoor activity with high exposure to the dusty atmosphere and UV light.<sup>17,28,32</sup>

In addition, preoperative ocular surface inflammation is associated with higher postoperative recurrence rates.<sup>28</sup> Therefore, ocular surface inflammation has a significant role in pterygium recurrence, and early clinical recognition of factors leading to pre or postoperative inflammation with the application of appropriate treatment is recommended.<sup>33,34</sup> Ocular demodicosis is another strong perpetuating factor for increased ocular surface inflammation in association with chronic blepharitis, blepharoconjunctivitis, rosacea blepharitis, meibomian gland dysfunction, and keratitis.<sup>20,35-37</sup> In a retrospective study done by Huang *et al.*, ocular demodicosis is introduced as an overlooked risk factor for pterygium recurrence.<sup>20</sup> Although previous studies have not shown gender as the main risk factor for recurrence,<sup>28</sup> Huang *et al.* showed that male gender is a risk factor not only for pterygium development, but also for postoperative recurrence. This might be also due to the higher rates of ocular demodicosis in male patients.<sup>20</sup> African-Americans are also at increased risk of recurrence.<sup>28</sup>

### **Pterygium characteristics and surgical techniques**

The impact of preoperative size, fleshiness, and histology of pterygium on recurrence rate are areas of controversy.<sup>17</sup> However, in previous studies (1990s) some researchers emphasized the importance of a healthy limbal epithelium in the prevention of recurrence.<sup>5,15,17</sup> Some studies have confirmed a positive association between preoperative size of the pterygium and its recurrence<sup>8,38-41</sup>. Others fail to establish such a relationship.<sup>17,18,32,42</sup> Samadi *et al.* showed in their case series that the vertical size of the pterygium more than 6.7 mm is a risk factor for recurrence.<sup>17</sup> Kim *et al.* also confirmed the same finding.<sup>43</sup> In contrast, in a prospective study of 190 patients, larger preoperative size of the pterygium was confirmed as a protective factor against recurrence following CAU or limbal conjunctival autograft (LCAU) surgeries.<sup>18</sup> It is important to mention that published studies in this aspect differ substantially not only in methodological aspects but also in their observation period, the usage of adjuvant medication, sample size, and measuring approach.<sup>17</sup> Anguria *et al.* did not show an association between the fleshiness of pterygium and recurrence.<sup>18</sup> They showed that fleshiness of pterygium protected older patients from pterygium recurrence after excision, and they concluded that fleshiness was not an important factor for the recurrence. Mushtaq *et al.* found a significant relationship between histology of resected pterygium and recurrence rate.<sup>44</sup> The presence of Fuchs spots in pathologic evaluation is related to a high degree of inflammation, vascularization, and fibrinoid changes in pterygium tissue. Nuhoglu *et al.* did not find a positive association between histology and recurrence.<sup>28</sup> In addition, they could not find any significant difference in inflammation intensity, degree of vascularization, or fibrinoid change between the primary pterygium and the recurrent pterygium group.

Some authors of earlier publications believed that the surgical technique used for primary pterygium resection is probably the single most important factor influencing postoperative

recurrence.<sup>28,34,44</sup> Inadequate peripheral dissection, insufficient conjunctival graft size, preparation of a thick graft with remained Tenon tissue, and graft retraction due to inadequate fixation are among possible risk factors for recurrence.<sup>34</sup> CAUs have been shown to reduce recurrence rates in both primary and recurrent pterygia to as low as 5%.<sup>34</sup> However, later it was found that CAU preparation from the superior or inferior conjunctiva does not have a role in the final recurrence rate.<sup>45-47</sup> The amount of fibrovascular tissue removal during initial surgery is considered an important factor in reducing recurrence rates.<sup>28</sup> There have been reports of increased recurrence rates when polyglactin sutures are used, which implies conjunctival reaction in the early postoperative period.<sup>7,48</sup>

### **Time of recurrence**

The recovery of the conjunctival goblet cell population after CAU surgery in the pterygium may require more than 1 year.<sup>49</sup> Short durations of follow-up in most studies published before 2009 was a major limitation for the contribution of results in routine clinical practice.<sup>7,15,17,44,50</sup> Furthermore, since the loss to follow-up is common in the postoperative period, the validity of the reported recurrence rates is under debate. Therefore, the exact time of pterygium recurrence cannot be accurately calculated as most patients are followed up for only 1 year and it may not be long enough in some eyes. In conclusion, to evaluate pterygium recurrence properly, the postoperative follow-up assessment should be at least 12 months.<sup>8,11,17</sup> It has been noticed that most recurrences occur within the first 3–6 months after surgery.<sup>28</sup>

Some researchers believe that if later recurrences are taken into account, there may be a significantly greater recurrence rate than previously reported.<sup>17</sup> There are studies with a median follow-up of 12 years<sup>51</sup> or even up to 18 years.<sup>43</sup> Kucukerdonmez *et al.* showed that all recurrences occurred within 1 year after surgery.<sup>52</sup> They found that the meantime to recurrence in the fibrin glue treated group was not significantly different from the suture group (6.3 vs. 7.6 months). In another study by Toker *et al.*, patients were followed up for one year, as nearly all postoperative recurrences occurred within that time.<sup>12</sup> This was in agreement with another study showing that 87.5% of recurrences happened in the first postoperative year.<sup>17</sup> In a study using preserved limbal allograft and amniotic membrane transplantation (AMT) for recurrent pterygium by Ono *et al.*, the results showed that the mean period to recurrence was 16.3 months (range, 5–33 months) after surgery.<sup>53</sup> The authors reinforced that the recurrence rate in the previous studies would have been much higher if the follow-up period was long enough. In the study by Nuhoglu *et al.*, the meantime to recurrence was  $4.3 \pm 2.1$  months in the primary pterygium group compared to  $4.1 \pm 2.2$  months in the recurrent pterygium group, which was not statistically significant.<sup>28</sup> In eyes without demodicosis, recurrence occurred within 6 months after surgery, but this period was longer in eyes with demodicosis, suggesting that

demodiosis might contribute to conjunctival recurrence by a pathologic process that may last for a longer period.<sup>20</sup>

In addition, survival analysis is important in estimating the meantime to recurrence. Hence, studies without survival curves may underestimate true recurrence rates.<sup>6,17,38,50</sup> Using Kaplan–Meier analysis, Samadi *et al.* found that the pterygium recurrence is not limited to immediate postoperative period.<sup>17</sup> Therefore, they suggested longer follow-up to determine the true rate of the recurrence. Many authors believe that 97% of recurrences after surgery happen within the first 12 months.<sup>6,31,52-56</sup>

**Prevention of recurrence**

The same protective measures recommended for the avoidance of development of primary pterygium, like sunlight, wind, and dust, wear UV light protecting sunglasses and hats, may prevent recurrence of pterygium. The importance of the protective effect of sunglasses, especially for high-risk individuals, is clearly demonstrated in multiple studies.<sup>4,57</sup> Ocular Demodex infestation has recently been identified as an overlooked risk factor for pterygium recurrence. Therefore, control of inflammation incited by ocular demodiosis before and after surgery is an important strategy for reducing recurrences.<sup>20,33</sup> However, as mentioned earlier, considerations in the first operation have an absolute prognostic value in the rate of recurrence. The preventive considerations are generally categorized as medical methods (mitomycin C [MMC] application) or surgical methods (CAU, AMT).<sup>58</sup>

It was proposed initially that pterygium is a chronic degenerative process and its removal activates subconjunctival fibroblasts, inducing the proliferation of fibroblasts and vascular cells. There is the deposition of extracellular matrix proteins, which contribute to pterygium recurrence.<sup>10</sup> However, later the main idea of pterygium development and recurrence changed to be an inflammatory condition.<sup>2,44,47</sup> Some authors thought that excising the Tenon tissue under the edge of the conjunctiva during dissection can reduce recurrence rates.<sup>34</sup> However, the complete removal of the subconjunctival fibrovascular tissue is sometimes impossible, especially in recurrent pterygium cases.<sup>11</sup> Therefore, the ophthalmic surgeons decided to use multiple kinds of medications before, during, or after the operation to reduce the hyperproliferation of fibrovascular tissue and thereby reduce the recurrence rate. MMC,<sup>58-60</sup> 5-fluorouracil (5-FU),<sup>19,59,61</sup> corticosteroids,<sup>61</sup> and anti-VEGFs are the most popular agents. Daunorubicin and doxorubicin have also been used as adjuvants to prevent recurrences and have shown preliminary promising results in some studies.<sup>62</sup> Furthermore, Wagdy *et al.* showed that augmenting CAU with Ologen implantation is effective in the management of recurrent pterygium with mild nonvision-threatening postoperative side effects comparable to that of MMC.<sup>63</sup> It should be noted that a combination of different adjunct therapies is much better than single adjunct therapy in reducing the rate of recurrence.<sup>64</sup>

In multiple studies, the surgical technique used for primary pterygium removal is proven as an important risk factor for

**Table 1: Summary of prospective studies on pterygium, covering the risk factors, different treatment options, and ways to improve the surgical outcomes and decrease the recurrence rate**

Author/year	Design/total participants male, n (%)	Ethnicity/age (range)	Treatment/ adjuvant therapy (MMC, 5-FU, none)	Follow-up time (months)	First recurrence time (months)	Risk factor for recurrence	Suggestion for recurrence reduction
Srinivasan <i>et al.</i> , 2009 <sup>13*</sup>	Prospective trial/40 (42)	NM/47 (32-72)	CAU (suture vs. fibrin glue)/none	3	NR	NR	Fibrin glue instead of suture
Zhao <i>et al.</i> , 2013 <sup>9</sup>	Prospective cohort/2695 (42)	Chinese/55 (40-83)	No treatment, only observation	120	NR	Rural region of habitation, lower fasting blood glucose	NR
Türkyılmaz <i>et al.</i> , 2013 <sup>16</sup>	Prospective/74 (63)	Turkish/50 (31-59)	Bare sclera/none	18	NR	Dry eye disease	NR
Al Favez, 2013 <sup>22</sup>	Prospective trial/205 (96)	Caucasian/36 (29-44)	CAU versus LCAU/ none	62	NR	NR	LCAU is superior to CAU in recurrent pterygium surgery
Katircioglu <i>et al.</i> , 2015 <sup>10</sup>	Prospective trial/55 (62)	Turkish/57 (32-81)	AMT versus CAU/ MMC	27	NR	AMT without MMC	NR
Anguria <i>et al.</i> , 2014 <sup>18</sup>	Prospective trial/190 (18)	African/46 (22-65)	CAU versus LCAU/ none	6	1-6	Young age	NR
Toker and Eraslan, 2016 <sup>12</sup>	Prospective trial/65 (52)	Turkish/51 (20-80)	AMT versus CAU (with fibrin glue)/ none	12	2-8	Early graft retraction, ocular surface inflammation	Fibrin glue instead of suture, CAU is superior to AMT
Chen <i>et al.</i> , 2017 <sup>11</sup>	Prospective trial/82 (45)	Chinese/55 (42-66)	LCAU versus AMT/ MMC	12	3	Ocular surface inflammation	LCAU combined with MMC results in a better cosmetic appearance and lower recurrence

\*Superscript numbers are related cited reference numbers. NR: Not reported, CAU: Conjunctival autograft, AMT: Amniotic membrane transplantation, LCAU: Limbal CAU, MMC: Mitomycin C, 5-FU: 5-fluorouracil



pterygium recurrence. Simple bare sclera resection alone has the highest rate of recurrence and was associated with 6 times higher odds of pterygium recurrence.<sup>10,52</sup> Simple bare sclera excision is not encouraged as a method of primary pterygium removal in the current era.<sup>10</sup> The recent meta-analysis published in Cochrane favored using CAU for participants with primary and recurrent pterygia to reduce recurrence at the first 6 months of follow-up.<sup>65</sup> In the comparison of fixation of graft with sutures versus fibrin glue, graft retraction is the most common drawback when sutures are used.<sup>66</sup> Therefore, using fibrin glue instead of sutures is another surgical modification. There are several studies which reported a recurrence rate of 0%–4.5% with fibrin glue.<sup>12,40,67-71</sup> Prospective randomized controlled studies showed lower long-term recurrence rates with fibrin glue in comparison to polyglactin or nylon sutures.<sup>12,67,70</sup> It can be due to less postoperative inflammation and an immediate adherence of the graft, which plays a crucial role in inhibiting fibroblast ingrowth, encouraging earlier graft vascularization, and reducing the recurrence.<sup>19,66,72</sup> Romano *et al.* pointed out the benefits of using fibrin glue versus sutures in terms of recurrence rate.<sup>66</sup> However, Kucukerdonmez *et al.*<sup>52</sup> did not confirm the superiority of fibrin glue. They compared the results of AMT using fibrin glue versus vicryl sutures in pterygium surgery. The results showed that there is no difference in the recurrence rate and cosmetic outcomes between groups.

### Mitomycin C

MMC is one of the popular adjunctive medications used during pterygium surgery since the 1980s to decrease the recurrence rate. MMC is used in three main methods: Preoperative and intraoperative application or use as a postoperative drop. However, initial studies of postoperative MMC drops reported higher risk of complications and therefore are rarely used nowadays.<sup>15,59,62</sup> The more the MMC is exposed to bare sclera, the more the likelihood of MMC-induced complications, which may include scleritis, secondary glaucoma, corneal edema, corneal perforation, corectopia, iritis, sudden-onset mature cataract, scleral calcification, incapacitating photophobia, and pain.<sup>10,58,62</sup> Some of these complications occur later in the follow-up period. Therefore, long-term evaluation after surgery is necessary in cases treated by MMC.

In recent years, preoperative and intraoperative MMC applications have been considered the mainstay of therapy in pterygium surgery. Some authors believe that subconjunctival injection of MMC before the operation helps with the exact titration of drug delivery to the activated fibroblasts and minimizes corneal epithelial toxicity.<sup>73</sup> Khalifa *et al.* showed that preoperative subconjunctival injection of low dose MMC (0.1 ml of 0.15 mg/ml) 1 day before excision of recurrent pterygium is an effective modality for the management of recurrence.<sup>73</sup> They included fifty eyes with recurrent pterygium and randomly divided their subjects to two groups: The preoperative MMC injection group (25 eyes) and the intraoperative MMC application group (25 eyes). The results were not different between groups 1 year after

the operation. Fakhry *et al.* used the preoperative injection of MMC (0.1 mL of MMC 0.15 mg/mL) 1 month before LCAU surgery in 30 eyes with recurrent pterygium and found significantly less recurrence (5%) in comparison to LCAU surgery alone (21%).<sup>74</sup>

The rationale for using intraoperative MMC after removal of the pterygium is its inhibitory effect on DNA replication, then slowing down fibrovascular tissue regrowth. Another advantage of MMC is its relatively low cost and technical ease of use during surgery. It has been shown that increasing the duration of intraoperative bare sclera exposure to MMC reduces recurrence and improves outcomes in the expense of increasing complications.<sup>15,62</sup> Kaufman *et al.* evaluated 51 studies and confirmed this finding in an Ophthalmic Technology Assessment paper.<sup>15</sup> Most of the published studies have used MMC with a range of 0.01%–0.04% intraoperatively. The most common technique is applying MMC 0.02% for 2–3 min.<sup>10</sup> Pterygium excision and CAU using fibrin glue to secure the graft combined with intraoperative MMC was found to be a safe and effective surgical option for treating recurrent pterygium.<sup>71</sup> Chen *et al.* compared the outcomes of an LCAU with those of an AMT to treat recurrent pterygium.<sup>11</sup> The authors used intraoperative 0.02% MMC for 3 min before carrying out LCAU or AMT. They found LCAU with intraoperative 0.02% MMC is as efficacious as AMT with the same dose of MMC. One year later, about 2% of cases in the LCAU group in comparison to 11% of cases in the AMT group developed recurrence ( $P = 0.19$ ). Furthermore, the surgical site showed a better appearance in the LCAU group. Katircioglu *et al.* reported their finding on recurrent pterygium cases treated with AMT combined with 0.02% MMC for 1 min or CAU combined with the same dose of MMC.<sup>10</sup> They found a similar recurrence rate in both groups. These various rates of recurrence have been attributed to different concentrations and patching times of the MMC cotton applicator, as well as to the surgical technique used.

### Corticosteroids

Uncontrolled postoperative inflammation is a well-established risk factor for recurrence of pterygium.<sup>14,58,75</sup> Furthermore, since most recent studies confirmed the inflammatory nature of recurrence after pterygium surgery, corticosteroids remained the cornerstone in controlling this important risk factor.<sup>8,17,34,59,62,75</sup> Ophthalmic surgeons used corticosteroids intraoperative or postoperatively; however, the postoperative topical steroid is the most common current method. Most of the studies focusing on the role of corticosteroids are published before 2009, but large randomized clinical trials to evaluate an optimal postoperative steroid treatment are still lacking. Different topical steroid regimens have been suggested to control inflammation after pterygium surgery; however, none of them has been confirmed.<sup>59</sup> Hirst *et al.* used topical prednisolone acetate for a period of 4–6 weeks.<sup>76</sup> Hirst published his results for 1000 pterygium extended removal followed by extended conjunctival transplant (P. E. R. F. E. C. T.) surgery in a series of primary and recurrent pterygia removal.<sup>76</sup> He used topical

prednisolone acetate every 2 h for 3 weeks and then increased the interval to four times daily for an additional 6 weeks. This was consistent with low recurrence rate, which was one case of recurrence in the 1000 surgeries (0.1%). Postoperative use of subconjunctival triamcinolone has shown some benefits in decreasing conjunctival inflammation, granuloma formation, and fibrovascular proliferation, therefore leading to the prevention of disease recurrence.<sup>62,75</sup>

Considering all these studies, there is still no large randomized controlled clinical trial to confirm the efficacy of local intraoperative steroid treatment in decreasing the rate of recurrence.

### **Dry eye disease management**

Few studies before 2009 have investigated the effect of DED on pterygium recurrence. Generally, they have been small-scale studies with a short duration of follow-up (1–6 months) which found no difference in the parameters of ocular surface like Schirmer test before and after pterygium surgery.<sup>77</sup> However, later tear film status has been investigated widely in eyes with pterygium, and greater abnormalities have been found in cases with recurrent pterygium. Decreased tear breakup time (TBUT),<sup>77-79</sup> lower Schirmer test results<sup>79</sup> and higher tear osmolarity<sup>79,80</sup> have been reported in pterygium patients. Tan *et al.* showed a bilateral correlation between DED and pterygium recurrence.<sup>14</sup> They found that the Schirmer test result was significantly lower in patients with recurrence compared to those without recurrence. Tear osmolarity showed deterioration in patients with pterygium recurrence. While pterygium removal was associated with an improved Schirmer test value.<sup>77</sup> Ozsutcu *et al.* evaluated the differences in tear film parameters between pterygium-affected and healthy eyes. They showed that pterygium is associated with tear hyperosmolarity and abnormal tear film function.<sup>79</sup> Türkylmaz *et al.* found abnormal tear film function and osmolarity in primary pterygium cases, which improved after pterygium excision.<sup>16</sup> However, tear osmolarity deteriorated again when recurrence happened. Kampitak and colleagues have been publishing multiple studies regarding the ocular surface changes in pterygium patients pre and postoperatively. In 2014, they published the results showing that the size of pterygium did not correlate with TBUT and Schirmer test results.<sup>78</sup> However, decreased TBUT, but normal Schirmer test results, could be found in pterygium cases. Kampitak *et al.* demonstrated a reduction in recurrence rate by 50% through additionally applying lubricant eye drops after steroid drops instillation for a postoperative period of 3 months, highlighting the importance of an adequate ocular surface problems management following pterygium resection.<sup>75</sup> They concluded that using artificial tears as adjunctive drug to topical corticosteroid could lower the risk of pterygium recurrence. DED perpetuates ocular surface inflammation in the postoperative period, and this inflammation may increase the rate of recurrence.<sup>14,77</sup> Proper and early diagnosis and management of DED in the perioperative period could reduce the risk of recurrence.<sup>14,34</sup>

As there is no definite recommendation or guideline for use of adjuvant treatments, and future studies are needed to standardize dosage, time, and ways of administration. It is important to consider the side effects associated with adjuvant treatment and make the final decision based on the benefit-risk ratio for each patient. This risk assessment begins during the preoperative setting, and risk factors for recurrence must be addressed thoroughly.

### **Nonsurgical management of recurrence**

#### **5-fluorouracil**

5-FU is a pyrimidine analog that stops the process of DNA and RNA synthesis. The anti-proliferative and anti-fibroblastic effects have caused this agent to be useful in the field of ophthalmology. Several small studies have been performed to evaluate the role of perioperative 5-FU with or without concomitant corticosteroids in the management of recurrent pterygium since 2001.<sup>19,64</sup> The initial results have been promising. 5-FU was adopted as a routine in the treatment of pterygium by some authors.<sup>8,15</sup> In the Said *et al.* study, multiple weekly subconjunctival intraslesional 5-FU injections, 0.1–0.2 ml (2.5–5.0 mg) started within 1 month of recurrence, have been shown to be safe and effective in halting the progression and inducing regression of recurrent pterygium.<sup>19</sup> Another study assessed the changes in pathological parameters of the ocular surface before and after 10 intraslesional injections of 5-FU in recurrent pterygium cases.<sup>49</sup> They reported an increase in the number of epithelial cells and density of goblet cells, reduction in the squamous metaplasia, and changing in abnormal cytology to normal in these injected eyes. Patients also reported lower conjunctival redness and less eye dryness after 5-FU injection.<sup>49</sup> Malik *et al.* compared the mean change in corneal astigmatism, visual acuity, and clinical appearance between the primary versus recurrent pterygium after four weekly injections of intraslesional 5-FU.<sup>81</sup> They concluded that 5-FU improved the cosmesis in both primary and recurrent pterygium group, but did not have a significant effect on astigmatism.

#### **Anti-vascular endothelial growth factor**

It has been known that angiogenesis and vascular proliferation is a part of the pterygium pathogenesis.<sup>82</sup> Several studies have shown that in the natural history of pterygium formation and recurrence, expression of basic fibroblast growth factor, VEGF, transforming growth factor- $\beta$ , and platelet-derived growth factor are increased.<sup>24,83,84</sup> Before 2009, medical adjunctive approaches to prevent neovascularization and future recurrence of pterygium included therapy with beta radiation, MMC, 5-FU, and corticosteroids in routine practice.<sup>2,8,15</sup> However, later, the value of anti-VEGFs was noticed by some authors, as these class of adjunct medications did not have significant ocular side effects like MMC or 5-FU.<sup>84,89</sup> Therefore, in recent years, anti-VEGF agents such as bevacizumab and ranibizumab have been studied widely in primary and recurrent pterygium treatment as adjunctive therapy to surgical excision or as a nonsurgical treatment alone.<sup>58,85-93</sup> Different routes and doses

of administration have been evaluated in multiple studies. Subconjunctival and topical application are the most popular administration techniques. Subconjunctival administration has a shorter half-life than intravitreal injection resulting in a more frequent need for injection of the drug which may cause more side effects and limit the effect of these medications. Many authors have evaluated the use of anti-VEGF drugs as an adjuvant treatment after surgical resection. These studies did not show any benefit of bevacizumab injection on recurrence rates.<sup>87</sup> Studies that were evaluating the efficacy of bevacizumab injections on the day before surgery were unable to conclude beneficial effects or to find a significant decrease in the rate of recurrence.<sup>88</sup> Briefly, multiple injections seem to have greater efficacy and longer duration of action in comparison to a single injection. However, as there is no clear evidence that ranibizumab is superior to bevacizumab in this area, bevacizumab is still considered the first-line choice by many authors because of the lower cost. Table 2 summarizes the studies evaluating the effect of topical, subconjunctival, or subtenon bevacizumab/ranibizumab on impending recurrent pterygium.

Anti-VEGF treatments have different results with regard to recurrent pterygium regression. One hypothesis is that these drugs affect neovascularization instead of old and organized vessels. This emphasizes the importance of early administration of these drugs. This can also explain why anti-VEGF treatments were not as much effective as in primary pterygium or as an adjunct to surgical treatment for recurrent pterygium with fibrotic elements. Up to now, there is not a globally accepted recommendation for treating recurrent pterygium with anti-VEGFs, but some authors recommend these drugs as an alternative to surgery in selected patients. Monitoring the patients closely after a single injection to repeat the injection in cases of minimal response is recommended.

### **Surgical management of recurrence**

As for primary pterygium, there are different surgical techniques for the management of recurrent pterygium. Recurrent pterygia are more difficult to remove because of the scarring from the previous surgery. The most important question regarding the surgical management of recurrent pterygium is choosing between AMT and CAU. CAU represents the current gold standard treatment for primary pterygium. It seems to have a lower risk of recurrence when patients with recurrent pterygium receive CAU surgery compared with AMT.<sup>94</sup> Multiple studies carried out before 2009 suggest that CAU might be a better surgical choice for the treatment of recurrent pterygia than AMT. It has been documented that the use of AMT alone had a higher recurrence rate than the use of CAU alone in cases of surgery for recurrent pterygium. However, AMT has its specific advantages, which eliminates the need for harvesting a large CAU and minimizing iatrogenic injury to the rest of the healthy conjunctival surface, are the worthiest ones. Therefore, later authors look for an adjacent procedure/medication that could increase the success rate of using AMT for the treatment of recurrent pterygia.<sup>6,10,11,15</sup>

Due to a larger area of subconjunctival fibrosis in some cases, a larger conjunctival defect is created after the excision of recurrent pterygium. Therefore, a larger graft is needed to close this defect. This led to choosing AMT instead of CAU by some surgeons. However, studies show that the use of AMT without CAU in these kinds of pterygium, especially after recurrent pterygium surgery, may not be the right choice and may increase the chance of recurrence. Therefore, it is better to use it in combination with CAU. AMT combination with CAU after pterygium removal decrease the chance of postoperative inflammation and thereby, the recurrence rate.<sup>52</sup> This effect is likely due to rapid epithelialization of the amniotic membrane. Intraoperative techniques like “tucking-in” the amniotic membrane under the surrounding conjunctiva or pinching it together with the recipient conjunctiva have been suggested by some authors to achieve a good apposition.<sup>52,59</sup>

Hirst introduced a variation to the standard CAU technique in 2009. They named this technique as P.E.R.F.E.C.T. This technique included extensive tenectomy and pterygium resection followed by the transplantation of a large CAU, which led to very low recurrence rates (0.1% for 1000 patients) in primary and recurrent cases.<sup>50</sup> In 2015, Katircioglu *et al.* compared AMT to free CAU for the treatment of patients with recurrent pterygium. MMC was used as an adjuvant in both groups. They suggested that AMT-MMC is an acceptable method for the treatment of recurrent pterygium cases, with similar outcomes and complication rates.<sup>10</sup> Barbosa *et al.* conducted a study in which 39 eyes with recurrent pterygium underwent AMT associated with narrow-strip CAU. They suggested that CAU alone seems to be a proper surgical choice for the treatment of recurrent pterygia; however, combining it with AMT provides a good surgical alternative in cases where little conjunctival donor tissue is available.<sup>6</sup> There is controversial evidence that LCAU is more effective than CAU for treatment of recurrent pterygium. Chen *et al.* compared the outcomes of an LCAU with AMT followed by intraoperative 0.02% MMC to treat recurrent pterygium. With a 12-month follow-up, no difference was found in terms of the healing time for epithelial defect, conjunctival inflammation grade, or the frequency of complications. They concluded that surgeon’s preferences should determine the method of treatment.<sup>11</sup> Lee *et al.*<sup>95</sup> conducted a retrospective study to evaluate the efficacy and safety of pterygium excision using a large CAU for the treatment of recurrent pterygium. For each affected eye, pterygium excision with a large CAU was performed with a mean follow-up of 17 months. Most patients were satisfied with the cosmetic outcome. The postoperative recurrence rate was 4.0%, and the average recurrence period was about 7.5 weeks.<sup>95</sup> A randomized, prospective, parallel-group clinical trial conducted by Al Fayed<sup>22</sup> compared the safety and efficacy of LCAU and CAU for treating recurrent pterygium. They included 224 patients with advanced recurrent pterygium with a mean follow-up of 62 months. Ten percent of patients in the CAU group and only 1.0% of patients in the LCAU group developed recurrence. No sign of limbal stem cell deficiency



**Table 2: Summary of prospective studies evaluating the effect of topical, subconjunctival, or subtenon bevacizumab/ranibizumab on impending recurrent pterygium**

Author/year	Design/ participants (n)	Method of treatment	Follow-up time (months)	Conclusion
Wu <i>et al.</i> , 2009 <sup>89*</sup>	Case report/1	2 months after pterygium surgery with bare sclera and MMC: Topical bevacizumab eyedrops (25 mg/mL) 4 times daily for 3 weeks	6	Topical bevacizumab may be effective to prevent recurrence in a patient with impending recurrent pterygium
Fallah <i>et al.</i> , 2010 <sup>60</sup>	Prospective trial/54	After pterygium surgery with bare sclera and MMC: 26 patients received bevacizumab eyedrops (5 mg/ml) twice daily and betamethasone eyedrops 4 times daily for 1 week; 28 patients received betamethasone only	3-6	Short-term topical bevacizumab helped with delaying the onset of recurrence in cases of impending recurrent pterygium
Lekhanont <i>et al.</i> , 2012 <sup>61</sup>	Prospective trial/80	A single intrascleral injection of bevacizumab in impending recurrent pterygium: 20 patients received 1.25 mg; 20 patients received 2.50 mg; 20 patients received 3.75 mg; 20 patients served as control	3-18	A single subconjunctival bevacizumab injection decreased conjunctival vascularization in a dose-dependent manner partially and transiently. The effect did not last >4 weeks even with 3.75 mg dosage
Ozgurhan <i>et al.</i> , 2013 <sup>85</sup>	Prospective trial/44	Starting from 1 month after recurrent pterygium surgery with CAU: 22 patients received bevacizumab eyedrops (5 mg/ml) 4 times daily for 2 months; 22 patients received artificial tear only	6	Topical bevacizumab therapy 1 month after surgical excision of recurrent pterygium is well tolerated and effective to prevent further neovascularization. However, the recurrence rate is not clinically lower than control group
Hurmeric <i>et al.</i> , 2013 <sup>91</sup>	Prospective case series/9	Single or multiple subconjunctival ranibizumab (0.5 mg/0.05 mL) injections within 6 months of recurrence diagnosis: 5 patients received 1 injection; 4 patients received 3 injections (basal, 2 and 4 weeks)	6	Multiple injections did not appear to be superior to a single injection with regards to conjunctival hyperemia
Stival <i>et al.</i> , 2014 <sup>86</sup>	Prospective case series/36	Single subconjunctival bevacizumab (2.5 mg/0.1 mL) injection (0.5 mL)	2	Subconjunctival bevacizumab injection is useful for the management of recurrent pterygium
Bayar <i>et al.</i> , 2014 <sup>90</sup>	Prospective case series/23	Starting from 1 month after pterygium surgery with CAU: Subconjunctival bevacizumab (2.5 mg/0.1 mL) injection (mean injection 2±0.78)	12-22	Repeated injections of bevacizumab may help to prevent the high recurrence rate of residual impending pterygium
Nava-Castañeda <i>et al.</i> , 2015 <sup>21</sup>	Prospective trial/38	Three subconjunctival bevacizumab (2.5 mg/0.1 mL) injections within 3 months of recurrence diagnosis: Basal, 2 and 4 weeks	12	This method was able to regress corneal and conjunctival neovascularization in early corneal recurrent pterygia
Kasetsuwan <i>et al.</i> , 2015 <sup>58</sup>	Prospective trial/22	After pterygium surgery with bare sclera: 12 patients received bevacizumab eyedrops (0.05%) 4 times daily for 3 months; 10 patients received placebo only	3	Short-term topical bevacizumab helped with lowering the trend for recurrence
Rose <i>et al.</i> , 2017 <sup>92</sup>	Prospective case series/8	Three monthly subtenon ranibizumab (0.5-2 mg) injections within 3-18 months of recurrence diagnosis: Basal, 1 and 2 months	9-26	In half of the cases, the recurrent pterygium growth was arrested

\*Superscript numbers are related cited reference numbers. MMC: Mitomycin C, CAU: Conjunctival autograft

was observed during follow-up.<sup>22</sup> A Cochrane review of 20 published studies on pterygium from eight countries worldwide found that in 6 months after surgery, CAU is associated with a lower risk of recurrence in comparison to AMT. This was true also for participants with recurrent pterygium.<sup>65</sup> Considering the 3-month rate of pterygium recurrence using each technique for both primary and recurrent pterygium, the recurrence rate ranged from 0% to 16.7% in the CAU and 4.76% to 26.9% in the AMT group.<sup>65</sup> There was a substantial reduction in the risk of recurrence for participants with recurrent pterygium who received CAU surgery in comparison to AMT surgery. It

should be noted that in most comparative studies, AMT had been used in combination with intraoperative MMC. However, in some studies, AMT was compared with CAU without using intraoperative MMC. Therefore, this may cause an important bias for reporting the efficacy of AMT.

Between novel surgical techniques, various studies evaluated the use of adhesives or sutures. Mashor *et al.* reported the safety and efficacy of fibrin glue in recurrent pterygium cases, which were treated with pterygium excision and CAU-MMC combination.<sup>71</sup> After a mean follow-up of 26.5 months, only one patient developed recurrence (3.6%). This method was



considered a safe and effective surgical option for treating recurrent pterygium. Reda *et al.* showed that the use of fibrin glue in pterygium surgery with AMT was safer, less toxic, and less time-consuming and resulted in fewer complications than graft surgery with sutures.<sup>96</sup> Therefore, fibrin glue can further reduce recurrence rates and surgery time.

Ono *et al.* reported a long-term follow-up of preserved limbal allograft and AMT for recurrent pterygium in 84 eyes. The mean follow-up period was 73 months, and pterygium recurred in about 12% of eyes within 16.5 months.<sup>53</sup> Mednick *et al.* proposed the simple limbal epithelial transplantation (SLET) technique as a novel way to treat recurrent pterygia. In their case series, they treated four patients who presented with recurrent pterygium and applied MMC 0.02% for 2–3 min subconjunctivally after excision. There was no recurrence after a mean follow-up period of 11 months.<sup>97</sup> Chung *et al.* randomized patients with primary or recurrent pterygia to LCAU alone and LCAU combined with the widening of the limbal incision to allow for pterygium removal.<sup>98</sup> In this technique, the surgeon widened the limbal incisions by 1 mm on both the superior and inferior limbal margins. They concluded that LCAU with the additional widening of the limbal incision was more effective in terms of reducing pterygium recurrence than CAU alone. In another recently published study, the clinical outcomes of surgery for recurrent pterygia using MMC, double AMT, and a large conjunctival flap were investigated.<sup>99</sup> This retrospective case series by Monden *et al.* included 31 eyes with recurrent pterygia and followed the patients for about 3.6 years. They showed that surgical pterygium excision with the application of MMC, double AMT, and placement of a large conjunctival flap was an effective treatment for recurrent pterygia.<sup>99</sup> The same team later published their results of surgery on 10 eyes with recurrent pterygium and severe symblepharon using the same technique with addition of cryopreserved limbal allograft transplantation and found the final results to be promising.<sup>100</sup> Expanded polytetrafluoroethylene (e-PTFE), known as Gore-Tex, is a fluoropolymer that can prevent adhesion of the wound area to adjacent tissues and promote epithelialization. In a study conducted by Kim *et al.*,<sup>101</sup> only patients with multi-recurrent pterygia were enrolled and all eyes underwent pterygium excision followed by application of MMC, AMT, and LCAU. In half of the eyes, multi-microporous e-PTFE was inserted between the transplanted amniotic membrane and the conjunctiva intraoperatively. They found that the implantation of multi-microporous e-PTFE led to significantly lower recurrence rates (3.3% vs. 25%), also reduced symblepharon, motility restriction, and even hyperemia.

## DISCUSSION

Recurrence of pterygium is always a concern for ophthalmologists as it diminishes the excellent surgical results. Knowing the risk factors of recurrence and in-time use of proper methods to decrease the recurrence rates in pre,

intra, and postoperative periods could be helpful in managing pterygium cases in a better way. Moreover, recurrent pterygium cases are more challenging and should be approached with more accurate knowledge than primary pterygium cases because of their invasive nature.

Among proposed risk factors, DED, black race, and young age are considered preoperative risk factors for recurrence.<sup>1–8</sup> Some molecular biomarkers and genetic factors have also been considered to increase the risk of recurrence. However, the fleshiness of pterygium and preoperative pterygium size are not the constant risk factors and therefore remain controversial.<sup>9–22</sup> Surgical techniques such as excessive suturing, inadequate peripheral dissection, insufficient conjunctival graft size, thick conjunctival graft with remained Tenon tissue, and postoperative graft retraction due to inadequate fixation are considered possible risk factors for recurrence.<sup>34</sup> Some studies have concluded that fibrin glue is superior to suturing techniques in terms of recurrence, but other studies failed to reach that result. In choosing between different surgical techniques, CAU reduced the recurrence rates in many studies.<sup>6,94,95</sup> Using preoperative or intraoperative MMC as an adjunct to surgery has decreased the recurrence rates. However, this anti-proliferative drug has its own complications that should be taken in mind when applied for patients. Incomplete postoperative inflammation control and uncontrolled UV light exposure can increase the risk of recurrence as well.

Concerning the time of recurrence, although most recurrences happen in the first 3–6 months after surgery, there is no clear cut-off period for recurrence, and it can occur even after many years.<sup>28</sup> It is recommended that studies, which aim to evaluate the recurrence, should consider their follow-up period at least 1 year.

Many surgical and nonsurgical methods have been mentioned to treat recurrent pterygium cases. Among nonsurgical methods, injection of 5-FU and anti-VEGFs has become popular in recent years. Multiple weekly subconjunctival intralesional 5-FU injections were shown to be safe and effective in halting the progression and inducing regression of recurrent pterygium.<sup>19</sup> Topical bevacizumab was found to inhibit growth of impending recurrent pterygium, but the effect was mostly temporary and just delayed the recurrence. Studies with multiple subconjunctival injections rather than a single injection of bevacizumab showed halting the progression of recurrence.<sup>90</sup> Up to now, there is not a global recommendation for treating recurrent pterygium with anti-VEGFs. Many authors recommend these drugs as an alternative to surgery in some patients. Monitoring the patients closely after a single injection to repeat the injection in cases with the minimal response is recommended.

In general, the most important question regarding the surgical management of recurrent pterygium is choosing between AMT and CAU. Multiple studies suggest that CAU might be a better surgical choice for the treatment of recurrent pterygia than AMT. Using fibrin glue instead of sutures can further reduce recurrence rates and surgery time. There is controversial

evidence that LCAU is more effective than CAU for the treatment of recurrent pterygium.

There are also some new methods in treating recurrent pterygium cases. Multimicroporous e-PTFE, preserved limbal allograft and AMT, the SLET technique, and LCAU combined with the widening of the limbal incision are among novel ways to reduce recurrence. It is important to remember that there is not enough evidence about these techniques and cited evidence are collected from small and single studies.

Recently, there have been significant advances in our understanding of nature, risk factors, and treatment of recurrent pterygium. Such advances in the treatment have not only continued to reduce the recurrence rate but also may enable us in using less invasive therapeutic options. Therefore, there is a need for ophthalmologists to update their knowledge regarding the current ongoing concepts of nature and risk factors of recurrent pterygium as well as the current treatment options to obtain better surgical results and improve patient satisfaction. In this narrative article, we reviewed the latest evidence on recurrent pterygium and its surgical and nonsurgical management. However, the literature is still updating with newer surgical and/or nonsurgical methods to decrease the recurrence and improve the cosmetic outcomes.

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### Conflicts of interest

There are no conflicts of interest.

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