Review

Applications of Mitomycin C in Cornea and External Disease

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Abstract

Isolated from *Streptomyces caespitosus*, mitomycin C (MMC) has various applications in the management of corneal and external disease due to its ability to modulate cellular proliferation. It has been employed in pterygium surgery, ocular surface neoplasia, and refractive surgery. Currently, there is no definite consensus on the treatment protocols for each of the aforementioned applications. Although its benefits in the management of corneal and external diseases are promising, MMC use has potential complications including endothelial cell loss, corneal perforation, scleral melt, secondary glaucoma, iritis, and endophthalmitis. This article will review the literature regarding the use of MMC in the field of cornea and external disease and describe protocols employed with corresponding outcomes.

Keywords: Mitomycin C, pterygium surgery, photorefractive keratectomy scar, post-PRK haze

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Introduction

Mitomycin C (MMC) is an antitumor antibiotic isolated from *Streptomyces caespitosus*.[1] MMC is an alkylating agent that covalently binds to DNA, resulting in an antitumoral effect.[2] MMC inhibits DNA synthesis primarily at the G1/S phase, resulting in a decrease in cell proliferation and migration.[3] MMC was introduced in ophthalmic surgery in 1963 as an adjunct to pterygium surgery.[4] MMC is also thought to elicit apoptosis of corneal epithelial, stromal, and endothelial cells as well as Tenon's capsule fibroblasts and ocular tumor epithelial cells.[5] In addition to its application in pterygium surgery, it has uses in ocular surface tumors, refractive surgery, glaucoma drainage surgery, oculoplastic surgery, and strabismus surgery.[3] In this manuscript, we broadly review the applications of MMC in the field of cornea and external disease. More comprehensive reviews exist in the literature on each subtopic covered in this work, and thus this manuscript aims to set the groundwork for interested readers.

Pterygium Excision

Pterygium is a wing-shaped benign fibrovascular overgrowth that centripetally involves the cornea.[6] Surgical excision may be performed to preserve visual acuity, achieve cosmetic improvement, or treat ocular surface symptoms. Recurrence rates (RRs) after pterygium surgery are variable, and adaptations have been developed to minimize this complication, including the use of supplemental MMC.[7] MMC use has been shown to decrease RRs when used as an adjuvant with a variety of surgical techniques, including bare sclera excision, excision with autografting, and excision with amniotic membrane transplantation. Furthermore, MMC may be used preoperatively, intraoperatively, or postoperatively in selected cases.[8]

Bare sclera technique

Surgical removal of pterygium using the bare sclera technique without any adjuvant treatment leads to an RR as high as 88%,[9] and for this reason the technique has been largely abandoned for alternative methods. MMC has been employed as an adjuvant treatment to bare sclera excision due to this high RR. Intraoperative application of MMC at concentrations ranging from 0.01% to 0.04% for durations ranging from 30 seconds to 5 minutes has led to a significant reduction in the RRs of pterygia when using the bare sclera technique. RRs ranged from 3.33% to 42.9% when using these dosages (Table 1).[10,11,12,13,14,15,16] Differences between the treatment regimens (concentration and duration) may explain some of the variability in recurrence. However, differences in age, race, and environmental factors may also contribute to variations in RRs.

MMC has also been used preoperatively with the bare sclera technique via subconjunctival injection at a dose of 0.1 mL of 0.015-0.02%. Using this approach 1 month or 1 day before pterygium surgery has led to an RR of 0-6% (Table 2).[11,17,18] Because of the small sample size, a direct comparison may not be suitable. Further studies on the preoperative use of MMC may help assess the relationship between dose, time, and efficacy. Authors observed that 0.1 mL of 0.015% concentration is similarly effective when employed as a subconjunctival injection 1 day before surgery (1/25 eyes recurred) and applied intraoperatively (2/25 recurred).[11]

Postoperative topical MMC has also been shown to decrease RRs in the bare sclera technique. Dosages for this approach have been reported to range from 0.02% to 0.04% MMC applied topically 2 to 4 times a day for 5 to 14 days (Table 3).[9,19,20,21] In some populations, postoperative use of 0.02% MMC twice daily for 5 days following bare sclera excision was shown to be as effective as conjunctival autografting in preventing recurrence (RR of 38% and 39%, respectively).[9]

Conjunctival Autograft Technique

The conjunctival autograft technique has been employed in pterygium surgery with RRs as high as 39% in the absence of MMC.[9] MMC has been utilized intraoperatively as an adjunct to conjunctival autografting in concentrations ranging from 0.015% to 0.04%, leading to pterygium RRs ranging from 0% to 15.6% (Table 4).[18,22,23,24,25,26,27,28]

In most studies, MMC has been utilized intraoperatively when performing conjunctival autografting, although some authors have also reported utilizing MMC preoperatively or postoperatively. Gupta et al.[18] used 0.1 mL of 0.02% MMC via subconjunctival injection 1 month before surgery and achieved an RR of 3.3%. Similarly, Fakhry[22] used 0.1 mL of 0.015% MMC 1 month before surgery, observing an RR of 5.0%. Cardillo et al.[27] described the use of MMC in concentrations of 0.02-0.04%, either intraoperatively for 3 minutes or postoperatively via topical solution 3 times daily for 7 or 14 days. In this study, the RR for intraoperative MMC ranged from 4.08% to 6.66%, while postoperative MMC yielded an RR that ranged from 4.26% to 4.44%. Since no significant difference in RR reduction was observed between intraoperative or postoperative use, the authors suggested that intraoperative use should be favored since it is not subject to patient misuse or lack of compliance.[27]

While most studies report a significant decrease in RR when using MMC, a study performed in Saudi Arabia reported an RR of 15.6% when performing conjunctival autografting with 1 minute of intraoperative 0.02% MMC, versus an RR of 15.8% when performing conjunctival autografting alone, indicating some variability in practice patterns and surgical outcomes.[24] As seen in Table 4, the use of MMC generally appears to decrease RR. However, a protocol for optimal dosing and timing has not yet been established due to the differences in the populations studied and the power of the results from individual studies.

Amniotic Membrane Grafting Technique

Utilizing amniotic membrane grafting (AMG) alone without MMC to treat pterygium has led to RRs ranging from 13.8% to 72%.[29,30] MMC has been employed as an adjuvant in this technique to further reduce RR. Intraoperative use of 0.02% MMC for 2 and 3 minutes has led to an RR of 34.5% and 10.9%, respectively.[31,32] Rosen[33] reported an even lower RR of 5.8% when using 0.02% MMC intraoperatively for 60-90 seconds. As 0.5% of the eyes treated with this protocol developed scleral thinning, the exposure time was reduced to 20-30

Table 1. Intraoperative use of mitomycin C in pterygium excision using the bare sclera technique

Application time (min)	Concentration	Recurrence rate in control group (%)	Recurrence rate in treatment group (%)	Reference
0.5	0.02%	----	7.9-19.2	Cheng et al.[10]
3	0.015%	----	8	Zaky and Khalifa[11]
3	0.02%	75	42.9	Lam et al.[12]
3	0.04%	75	22.9	Lam et al.[12]
5	0.01%	38.8	3.33	Cano-Parra et al.[13]
5	0.02%	57.8	21	Yanyali et al.[14]
5	0.02%	75	8.3	Lam et al.[12]
5	0.02%	45	5	Frucht-Pery et al.[15]
5	0.02%	----	6.35-25	Avisar and Weinberger[16]
5	0.04%	75	8.6	Lam et al.[12]

seconds, after which no further cases of scleral thinning were noted.[33] Despite data indicating that MMC reduces recurrence after AMG, we cannot draw any definitive conclusions since none of the aforementioned studies had a control group. Ma et al.[34] directly compared AMG alone and AMG with intraoperative 0.025% MMC for 3 minutes and noted no significant decrease in recurrence (RR was 12.5% in the AMG alone group and 12.8% in the MMC group). Further well-designed studies are required to better understand if there is any combination of concentration and exposure time to lessen the RR of pterygium when employing the AMG technique.

Table 2. Preoperative use of mitomycin C in pterygium excision using the bare sclera technique

Dosage*	Time of application	Recurrence rate (%)	Reference
0.1 mL of 0.015%	1 day	4	Zaky et al.[11]
0.1 mL of 0.015%	1 month	6	Donnenfeld et al.[17]
0.1 mL of 0.02%	1 month	0	Gupta et al.[18]

*Administered via subconjunctival injection

Ocular Surface Tumors

Ocular Surface Squamous Neoplasia

Ocular surface squamous neoplasia (OSSN) often involves both the cornea and the conjunctiva, and includes a spectrum of four pathologies: dysplasia, intraepithelial neoplasia, carcinoma in situ, and squamous cell carcinoma.[35] MMC has been used to treat OSSN as a primary treatment, intraoperative adjuvant, and postoperatively for lesions that were not entirely resected during excision.[36,37] Topical MMC concentrations as low as 0.002% have resulted in regression of primary and recurrent tumors,[38] although dosages ranging from 0.02% to 0.04% MMC are most often used.[39,40] Typically, MMC drops are instilled 4 times a day either until resolution or in different regimens of on and off weekly cycles.[38,39,40] Prabhasawat et al.[38] reported the results of treating 7 patients with 0.002% MMC 4 times a day until tumor regression, which was observed at a mean treatment duration of 5.2 weeks. Ballalai et al.[39] described the use of 0.02% MMC 4 times a day for 28 consecutive days, achieving complete tumor regression in all patients, of which only 1 out of 23 recurred. MMC has also shown promising results in

Table 3. Postoperative use of mitomycin C in pterygium excision using the bare sclera technique

Concentration	Regimen	Recurrence rate in control group (%)	Recurrence rate in treatment group (%)	Reference
0.02%	Twice daily for 5 days	88	38	Chen et al.[9]
0.02%	Twice daily for 5 days	32	7	Hayasaka et al.[19]
0.02%	Twice daily for 5 days	---	2.6	Rachmiel et al.[20]
0.04%	Three times daily for 7 days	32	11	Hayasaka et al.[19]
0.04%	Four times daily for 14 days	60	0	Mahar and Nowakara[21]

Table 4. Use of mitomycin C in pterygium excision using the conjunctival autografting technique

Application period	Application regimen	Concentration	Recurrence rate in control group* (%)	Recurrence rate in treatment group (%)	Reference
Preoperative	0.1 mL SC injection	0.02%	----	3.3	Gupta et al.[18]
	0.1 mL SC injection	0.015%	21.1	5	Fakhry[22]
Intraoperative	1 min	0.02%	13.3	0	Frucht-Pery et al.[23]
	1 min	0.02%	15.8	15.6	Alsarhani et al.[24]
	1 min	0.025%	18	9	Wong and Low[25]
	2 min	0.02%	----	0	Wagdy et al.[26]
	3 min	0.02%	29.27	6.66	Cardillo et al.[27]
	3 min	0.04%	29.27	4.08	Cardillo et al.[27]
	5 min	0.02%	----	3	Young et al.[28]
Postoperative	Three times daily for 7 days	0.02%	29.27	4.26	Cardillo et al.[27]
	Three times daily for 14 days	0.04%	29.27	4.44	Cardillo et al.[27]

SC: Subconjunctival
*Control group was conjunctival autografting alone

achieving chemoreduction of OSSN, and a mean of 4 cycles (4 times daily with 7 days on and 7 days off) was able to reduce tumor burden by 57%. This approach made the subsequent resection of the tumor less challenging and simplified ocular surface reconstruction.[40]

Primary Acquired Melanosis and Melanoma

Primary acquired melanosis (PAM) with atypia is a melanocytic lesion of the conjunctival epithelium that may potentially evolve into melanoma,[41] and MMC has been utilized to treat this pathology. Treatment regimens have consisted of 0.04% MMC drops 4 times a day with 14-day cycles,[42] as well as 0.02% MMC 4 times a day for 2 weeks followed by 2 weeks of 0.04% MMC 4 times a day and ending with 3 months of 0.02% MMC twice a day.[43] Kurli et al.[44] reported using MMC both as an adjuvant to excision and cryotherapy or as primary treatment for PAM with atypia and conjunctival melanoma. The authors used 0.04% MMC 4 times a day, either for 28 days for primary treatment or 7 days when used as an adjuvant. In this study, the overall RR was 50% in both groups.[44] In addition, the authors reported a higher incidence of recurrence for multifocal tumors, among which 70% recurred.[44]

MMC employed to treat conjunctival melanoma appeared to be more effective when used as an adjuvant (50% RR) than primary treatment (100% RR).[44] Ditta et al.[45] described the use of MMC as an adjuvant for conjunctival melanoma with a treatment regimen of 3-week-long cycles of 0.04% MMC 4 times a day, separating cycles with 1 week of steroid drop use. Most patients (93%) underwent at least 3 cycles, and an overall recurrence of 33.3% was observed.[45] An observational case report documented the use of neoadjuvant 0.04% MMC 4 times a day for 3 weeks and post-excision adjuvant 0.04% MMC for another 4 cycles. This treatment approach was effective for the patient's conjunctival melanoma without any signs of recurrence after 32 months of follow-up.[46]

Photorefractive Keratectomy

Photorefractive keratectomy (PRK) is a surgical technique that uses an excimer laser to correct refractive error.[47] A common complication after PRK is the development of corneal haze due to aberrant corneal healing.[48] A recent meta-analysis of 3,536 eyes demonstrated that MMC helps reduce early and late-onset post-PRK haze.[49] A common protocol for MMC use in this application is intraoperative 0.02% MMC for 30 seconds, which has been primarily established for eyes with greater than 6 diopters (D) of myopia.[50] Virasch et al.[51] studied the relationship between MMC application time and the development of corneal haze and visual outcome. A concentration of 0.02% MMC was used for 12 seconds, 1 minute, or 2 minutes for eyes with a spherical equivalent of approximately -6.5 to -7.1 D of myopia. In this study, no difference was observed for haze scores or best-corrected visual acuity among the groups,[51] and shorter application times appeared to be as effective in haze prophylaxis as longer application times. Kaiserman et al.[52] analyzed the correlation between 0.02% MMC application time and corneal haze development in a retrospective study with 7,535 eyes. In the moderate myopia group, there was 0% incidence of haze in the group with application times ≥40 seconds versus 1.3% in the <40 seconds group (p=0.03).[52]

Thornton et al.[53] compared the use of 0.002% MMC and 0.02% MMC for application times of either 30 seconds or 2 minutes. In this study, 0.02% MMC had a higher efficacy in preventing postoperative haze than 0.002% MMC in cases of myopia ≥-6.00 D and ablation depths of ≥75 µm. In patients with lower degrees of myopia or ablation depths less than 75 µm, both concentrations appeared to be equally effective. This study also compared the degree of haze formation when applying 0.002% MMC for either 30 seconds or 2 minutes, but changing the exposure time did not appear to impact the degree of haze formation.[53] Shojaei et al.[54] used 0.02% MMC for 5 seconds in eyes undergoing PRK with ablation depths less than 65 µm and reported decreased haze formation in eyes receiving this treatment versus control eyes. At 6-month follow-up, 11.5% of control eyes had trace haze and 1.3% had 1+ haze, while 1.4% of treated eyes had trace haze and 0% had 1+ haze.[54] The findings from the studies above are summarized in Table 5.

Table 5. Use of mitomycin C (MMC) in photorefractive keratectomy

Concentration	Application time	Findings	Reference
0.02%	12 s	Short (12 s) and long (1-2 min) application times were equally effective in haze prophylaxis.	Virasch et al.[51]
	1 min		
	2 min		
0.02%	<40 s	Significantly higher incidence of haze formation in the shorter application time group (1.3% vs. 0%, p=0.03).	Kaiserman et al.[52]
	≥40 s		
0.002%	30 s	Different exposure times while using 0.002% MMC did not appear to impact the degree of haze formation.	Thornton et al.[53]
	2 min		
0.002%	30 s - 2 min	0.02% MMC was more effective than 0.002% MMC for haze prophylaxis in cases of myopia ≥-6.00 diopters and ablation depths of ≥75 µm. In cases involving less myopia or ablation depth, both concentrations were equally effective.	
0.02%			
0.02%	5 s	Trace haze occurred in 1.4% of treated eyes and 11.5% of untreated eyes. 1+ haze occurred in 0% of treated eyes and 1.3% of untreated eyes.	Shojaei et al.[54]

Phototherapeutic Keratectomy

Phototherapeutic keratectomy (PTK) is a surgical technique that utilizes an excimer laser to treat anterior stromal conditions.[55] Pathologies commonly treated with PTK include Reis-Bücklers dystrophy, granular dystrophy, macular dystrophy, Salzmann nodular degeneration, keratoconus nodules, and anterior stromal scars.[56] One of the main potential limitations of PTK is recurrence of the original pathology,[57] and MMC has been used in conjunction with PTK to decrease or delay recurrence.

PTK alone is associated with clinically significant RRs of 47% of eyes with Reis-Bücklers dystrophy, 23% of eyes with granular corneal dystrophy, 14% of eyes with lattice dystrophy, 14% of eyes with macular corneal dystrophy, and 15% of eyes with Salzmann nodular degeneration.[57,58,59] Due to the high recurrence of these corneal pathologies, PTK with the additional use of MMC has been employed.

Granular dystrophy and macular dystrophy have been treated with regimens consisting of PTK and MMC 0.02% for 30 seconds, after which significant recurrences occurred in 11.1% of treated patients in each group.[60] Reis-Bücklers dystrophy has been treated with 0.02% MMC for 2 minutes, and in a case report, this regimen resulted in no recurrence at 1-year follow-up.[61] Salzmann nodular degeneration has been treated with PTK and 0.02% MMC for 1-2 minutes to prevent recurrence and improve visual symptoms, mainly contrast sensitivity and higher-order corneal aberrations.[62,63] Reddy et al.[62] reported using 0.02% MMC for 60 seconds on 13 eyes with Salzmann nodules, none of which recurred in a follow-up time of 3 months. Avellino dystrophy has been treated with PTK and 0.02% MMC for 2 minutes. Kim et al.[64] reported on 4 patients treated with this approach. Two patients were homozygous for the Avellino corneal dystrophy mutation in the *BIGH3* gene, and both of them had a recurrence. However, the remaining 2 patients were heterozygous and showed no signs of recurrence.

Epithelial Ingrowth

Epithelial ingrowth is an uncommon complication of LASIK surgery in which epithelial cells proliferate between the LASIK flap and underlying stromal bed.[65] Wilde et al.[66] reported positive outcomes when using MMC to treat recalcitrant epithelial ingrowth in post-LASIK eyes. Four eyes were treated with 70% alcohol followed by 0.02% MMC, both on the stromal bed and under the flaps, after mechanical debridement of the epithelial ingrowth. The flap was then secured in place using fibrin glue. For all eyes, visual acuity improved and no recurrence was observed.[66] Taneri et al.[67] reported a case of a buttonholed LASIK flap that developed epithelial ingrowth. In this case, PTK was performed with application of 0.02% MMC on the corneal stroma for 1 minute. After treatment, no recurrence was seen.[67] In another case, severe post-LASIK epithelial ingrowth was treated with flap amputation followed by PTK and 0.02% MMC for 2 minutes. In this case, overall visual acuity improved and no complications were seen.[68] In all these reports it is unclear how much the MMC affected the recurrence of the epithelial ingrowth, but it most likely decreased the subsequent corneal haze or scarring.

Epithelial Downgrowth

Epithelial downgrowth is a complication of ocular trauma or surgery in which epithelial cells enter the anterior chamber and proliferate over intraocular tissue.[69] MMC has been used to treat cystic epithelial downgrowth following cataract surgery. Yu et al.[70] reported a case where cystic fluid from the epithelial downgrowth was aspirated, then a solution of 0.0002 mg/mL of MMC was injected into the lesion and left there for 5 minutes, after which the MMC was washed out of the cyst with balanced salt solution. The cyst decreased in size and vision improved, but the authors noted that this procedure should be performed with great care due to high-risk complications if MMC were to leak into the anterior chamber.[70]

Other Applications of MMC in Ocular Diseases

The use of MMC has been shown to increase the success rate of filtering procedures for the treatment of glaucoma. It is currently used in trabeculectomy, bleb needling, and ab-interno filtering procedures.[71] MMC at 0.02% has also proven useful when performing a dacryocystorhinostomy as it can prevent the development of scar tissue by decreasing the contraction and migration of fibroblasts that occurs in response to injury. Additionally, it seems to reduce the osteotomy closure rate.[72,73] In the case of strabismus surgery, MMC appears to decrease the formation of postoperative adhesions.[74,75]

Toxicities and Potential Complications of MMC

Although MMC has shown promising results in treating ocular disease, there are a variety of potential complications to consider. In pterygium surgery, complications reported include: corneal edema, corneal perforation, scleral stromal necrosis with possible infectious scleritis, secondary glaucoma, corectopia, iritis, cataract, and endophthalmitis.[76,77,78,79,80,81] Safianik et al.[79] documented two cases of scleral melt and one case of limbal perforation with iris incarceration after using 0.02% MMC for 3 minutes for pterygium surgery. These patients ultimately required a tectonic graft in the case of the limbal perforation, and conjunctival grafts for the scleral melts. Rubinfeld et al.[78] documented the possible complication of developing secondary iritis after pterygium surgery with postoperative 0.04% MMC drops 4 times a day. In another case in this series, a patient developed a scleral melt that led to a peaked pupil toward the side of the lesion.[78] Importantly, MMC has been associated with scleral necrosis decades after exposure, and therefore continued and regular follow-up of these patients is necessary.

MMC use in ocular surface surgeries has also been associated with endothelial cell loss. Bahar et al.[77] reported that employing intraoperative 0.02% MMC for 2 minutes in pterygium surgery resulted in an endothelial cell loss of 6% at 1 month after surgery, while no significant endothelial cell loss occurred in the control group. Avisar et al.[76] reported that employing 0.02% MMC for 5 minutes during pterygium surgery can lead to endothelial cell loss of 21.05%±3.2% at 3 months after surgery. In the case of epithelial downgrowth, Yu et al.[70]

reported a 13.3% decrease in endothelial cell density following the use of 0.0002 mg/mL MMC for 5 minutes. MMC usage in PRK has also been linked to endothelial cell loss. Some studies have reported that employing 0.02% MMC for 10-50 seconds correlated to a statistically significant decrease in endothelial cells compared to PRK alone.[82,83] However, the vast majority of studies regarding this potential toxicity report no statistically significant change in endothelial cell density when employing MMC with PRK.[54,84,85,86,87,88,89] Even studies with a larger number of subjects and longer follow-up periods did not find any correlation, suggesting a favorable safety profile with minimal, if any, risk of endothelial cell loss when employing MMC with PRK.[84,85]

Endophthalmitis after pterygium surgery with MMC is very rare. Peponis et al.[81] published a case report of a patient who developed endophthalmitis following the use of 0.02% MMC for 1 minute. In this case, the subject had a scleral melt 21 days after surgery with fungal endophthalmitis (*Fusarium* species). The patient was treated with antibiotics and antifungals, vitrectomy, scleral patch, tectonic graft, and finally enucleation.[81] Yi et al.[90] presented another case in which the subject developed endophthalmitis with *Serratia marcescens* which was treated with vitrectomy and antibiotics. This treatment led to the resolution of the infection, but the patient developed significant vision loss. The authors suggested that the impaired scleral barrier after surgery with MMC and the patient's immunosuppressed state may have played a role in the infectious process.[90]

MMC use in the other aforementioned applications has a less severe complication profile. MMC employed for OSSN has a risk of allergic reaction, epithelial surface toxicity, punctal stenosis, and limbal stem cell deficiency. These are managed with topical steroids, artificial tears, and punctal plugs.[91] Conjunctival hyperemia and lacrimation are well documented, in addition to delayed epithelial healing.[92,93] MMC use for PAM and melanoma may lead to keratoconjunctivitis, corneal abrasion, pannus, and corneal haze.[44] To minimize the risk of complications as a result of MMC, it may be beneficial to limit exposure times and use lower concentrations.[10,19,20]

Conclusion

MMC has demonstrated high utility in a wide array of ocular pathologies, especially in the field of cornea and external disease, due to its ability to alter tissue remodeling. Currently, there is a need to further establish the optimum treatment protocols for each aforementioned indication. Although MMC usage has promising results, it could lead to potentially vision-threatening complications, and judicious use is therefore warranted.

Ethics

Peer-review: Externally and internally peer reviewed.

Authorship Contributions

Concept: M.A.C., C.J.R., Z.A.S., Design: M.A.C., C.J.R., Z.A.S., Data Collection or Processing: M.A.C., C.J.R., Z.A.S., Analysis or Interpretation: M.A.C., C.J.R., Z.A.S., Literature Search: M.A.C., C.J.R., Z.A.S., Writing: M.A.C., C.J.R., Z.A.S.

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