

Clinical outcomes of Z-shaped incision without epithelial resection in pterygium surgery: A multicenter study

SATORU KASE¹, SHINKI CHIN², RIKI KIJIMA², CHIAKI YOKOYAMA²,
JUNICHI FUKUHARA², YUSUKE AIHARA², RINA KANAYA^{2,3},
MICHİYUKI SAITO², NOBUYOSHI KITAICHI³ and SUSUMU ISHIDA²

¹Department of Ophthalmology, Nara Medical University, Kashihara, Nara 6348521, Japan; ²Department of Ophthalmology, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Hokkaido 0640802, Japan;

³Department of Ophthalmology, Health Science University of Hokkaido, Sapporo, Hokkaido 0028072, Japan

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Abstract. Our previous study reported a novel technique for pterygium surgery: A Z-shaped incision without epithelial resection (non-resection technique). This technique is characterized by reduced intraoperative bleeding and easy conjunctival-flap creation. The present multicenter, retrospective, observational study aimed to determine the clinical outcomes of the non-resection method in patients with pterygia. Patients who underwent pterygium surgery using the non-resection technique and were followed-up >6 months were included. A total of 127 eyes from 117 patients (56 men and 61 women) with pterygia were included. Clinical data such as patient sex, age, pterygium size and postoperative recurrence were retrieved from the medical records of seven ophthalmic centers. The pterygium size was divided into four grades based on the pupillary coverage by the pterygial tissues. The mean age of the patients at the time of surgery was 73 years. Pterygia were located at the nasal, temporal and combined sites in 124, 0 and 3 eyes, respectively. Primary and recurrent pterygia were observed in 113 and 14 eyes, respectively. The mean pterygial size was grade 2.6. The follow-up duration ranged from 6 to 82 months (mean, 31 months), and postoperative recurrence was noted in 10 eyes (7.9%). The mean duration from surgery to recurrence was 20 months. Recurrence after surgery for recurrent pterygia was observed in 3 eyes from 3 patients, and the mean pterygial size was grade 3.4. The preoperative pterygium size was significantly greater in eyes with recurrence than in those without recurrence ($P<0.01$). No eyes exhibited tumor formation during the

follow-up periods. Although the non-resection method was not superior to previous methods for pterygial surgery in terms of postoperative recurrence rates, this procedure is simple and safe and requires no additional surgery.

Introduction

Pterygium is a common ocular surface disorder, characterized by a fibrovascular proliferative growth on the cornea. Pterygial tissues may cause visual disturbance because of corneal irregularities, corneal-surface flattening, and pupillary occlusion. Since pterygia can be misdiagnosed with ocular surface squamous neoplasia (OSSN) (1), careful observation of the proliferative tissues on slit-lamp examination is mandatory for accurate clinical diagnosis. Histopathological studies in Japanese patients have reported that pure pterygial tissues contained mildly proliferative multilayer epithelial cells without atypia together with subepithelial angiogenesis and inflammation (2-4). Although pterygial avulsion has been reported, it is extremely rare (5); therefore, treatment typically involves surgery to remove pterygial tissues followed by a pedunculated conjunctival flap, free conjunctival autograft, or amniotic-membrane transplantation (6). Moreover, chemical agents such as mitomycin c (MMC) and cyclosporine, an immunosuppressant, are used during or after surgery, to reduce postoperative recurrence (7,8). However, pterygium surgery is widely performed in not only ophthalmic institutes but also private clinics; therefore, a simple procedure that archives favorable clinical outcomes without the use of specific materials or agents is an unmet real-world need.

We reported a new technique for pterygium surgery: a Z-shaped incision without epithelial resection (non-resection method) in the Japanese literature approximately 10 years ago. This technique is characterized by reduced intraoperative bleeding and easy conjunctival-flap creation. Several ophthalmologists in different areas of Hokkaido, Japan, perform this procedure for the initial pterygial surgery, and our previous study reported a single-center prospective study on this non-resection method, in which 1 out of 10 pterygial patients showed recurrence (9). However, the major problem

Correspondence to: Professor Satoru Kase, Department of Ophthalmology, Nara Medical University, 840 Shijo-cho, Kashihara, Nara 6348521, Japan
E-mail: kaseron@naramed-u.ac.jp

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of that study was the limited number of participants owing to the single-center design and analyzing the clinical outcomes of the non-resection method in a relatively large number of patients is warranted. Therefore, this multicenter study aimed to clarify the clinical outcomes of the non-resection method in patients with pterygia. The present study differs from our previous study (9), especially in terms of study design, study periods and participants.

Patients and methods

Patient demographics. This multicenter retrospective observational study was approved by the Institutional Review Board (IRB) of Hokkaido University Hospital (IRB number: 024-0068) as the central IRB. The study used an opt-out model in which patients were given the opportunity to refuse participation in the study through the website since this is a non-invasive retrospective observational study. Therefore, the requirement for written informed consent was waived. The study adhered to the tenets of the Declaration of Helsinki.

Patients with pterygial eyes treated with the non-resection method between January 1, 2018, and December 31, 2023, who were followed-up for >6 months were included. The exclusion criteria were eyes with OSSN (10), secondary pterygia after corneal dermoid resection (11), pterygium-like conjunctival nevus (12), and limbal stem-cell deficiency. In addition, patients who underwent other procedures, such as free conjunctival flap or non-Z-shaped pedunculated conjunctival flap with pterygium tissue resection, and eyes with insufficient clinical data including pterygial grade were excluded.

Patients underwent slit-lamp examination at a participating institution, and a definite diagnosis of pterygium was made. Primary pterygium was defined as a triangle fibrous proliferation towards the cornea with characteristic vasculatures without a history of pterygial surgery. Recurrent pterygium was defined as a secondary conjunctival fibrovascular proliferation following surgery for primary pterygium. Clinical data regarding patients' sex, age, pterygium size, and recurrence after surgery were retrieved from the medical records of seven ophthalmic centers [Hokkaido University Hospital (Sapporo, Japan), Health Science University Hospital of Hokkaido (Sapporo, Japan), Abashiri-Kosei Hospital (Abashiri, Japan), Sunagawa Hospital (Sunagawa, Japan), Hakodate Central Hospital (Hakodate, Japan), Furano-Kyokai Hospital (Furano, Japan) and Iwanai-Kyokai Hospital (Iwanai, Japan)] in Hokkaido, Japan. All ophthalmologists were board-certified doctor of ophthalmology who were members of the Japanese Ophthalmological Society. The choice of surgical procedure depended on the individual ophthalmologists' decision; therefore, this implies the cohort is consecutive among selected cases receiving this technique, but not consecutive among all pterygium surgeries, underlying a selection bias. Recurrence was defined as proliferation of epithelial and stromal vascular tissues after surgery, with invasion >2 mm from the corneal limbus, which could follow a previous study (13). A photograph of a typical recurrent pterygium with invasion >2 mm, directly measured in the Central Institute, was shared with all participating institutions. This helped standardize the evaluation of recurrence across different institutions and areas.

The preoperative size of the pterygium was divided into four grades based on the pupillary coverage by the pterygial tissues according to a previous study (14). Grade 1 included eyes with pterygium tissues located exclusively in the corneal limbus (Fig. 1A). Grade 2 showed growth beyond the corneal limbus but not until the pupil (Fig. 1C), and Grade 3 included eyes with tissue growth at the pupillary margin (Fig. 1E). Grade 4 included eyes with growth beyond the pupillary margin (Fig. 1G).

Surgical procedure. A schema of this procedure is presented in a previous paper (9). Briefly, after administrating sufficient eye-drop anesthesia, the pterygial head was carefully separated from the corneal surface, not to remove that. Next, the pterygial body was radially incised towards the conjunctiva (Fig. 2A), and a sub-Tenon injection of 2% lidocaine was administered. The remaining stromal tissue on the cornea was removed by curettage and the corneal bed was managed with Borman layer polishing using a crescent blade or golf knife. Ocular surface hemostasis was achieved using a built-in cataract surgery machine. The pterygial body was incised around the fornix to facilitating manipulation and suturing. The width of pterygial-tissue incision depended on the size of the pterygium (Fig. 2A, arrow). If the Tenon's capsule was thick, as in young patients, the subepithelial Tenon's capsule was trimmed to avoid damage to the epithelium. Cryopexy to the pterygial tissues was performed in selected eyes, similar to that for conjunctival tumors. Next, a sufficiently large Z- or reversed Z-shaped pedunculated conjunctival flap was created (Fig. 2B, arrows), and sutured to the lower/upper healthy conjunctiva (Fig. 2C, arrow). Thereafter, the pterygial tissue was sutured to the upper/lower space (Fig. 2D, arrow). However, in patients with conjunctival-flap overhang on the cornea, the center of the flap was sutured to the sclera to address the corneal overhang. Interrupted sutures were placed using 8-0 virgin silk, and tissue glue was not required. Finally, dexamethasone was injected into the conjunctiva and an antibiotic ointment was placed on the ocular surface. The detailed standard operating procedure was added as Table I. Postoperatively, antibiotic eye drops were administered thrice daily for 1 month, and low-dose corticosteroid eye drops 3-4 times per day were continued for at least 3 and 6 months in eyes with primary and recurrent pterygia, respectively. Suture removal was not required in most cases, and postoperative inflammation resolved at postoperative 3 months. However, sutures were removed in case of irritation or persistence beyond postoperative 3 months.

Statistical analysis. Age and pterygial size were compared between eyes with and without recurrence using Mann-Whitney U test. To account for within-subject correlation (clustering of both eyes from the same patient) and adjust for center effects, multivariate logistic regression was performed using Generalized Estimating Equations (GEE) with an exchangeable correlation structure (Tables II and III). To address the wide variation in follow-up duration and avoid bias from crude proportions, Kaplan-Meier survival analysis (log-rank test) and robust Cox proportional hazards regression were performed. Statistical significance was set at $P < 0.05$.

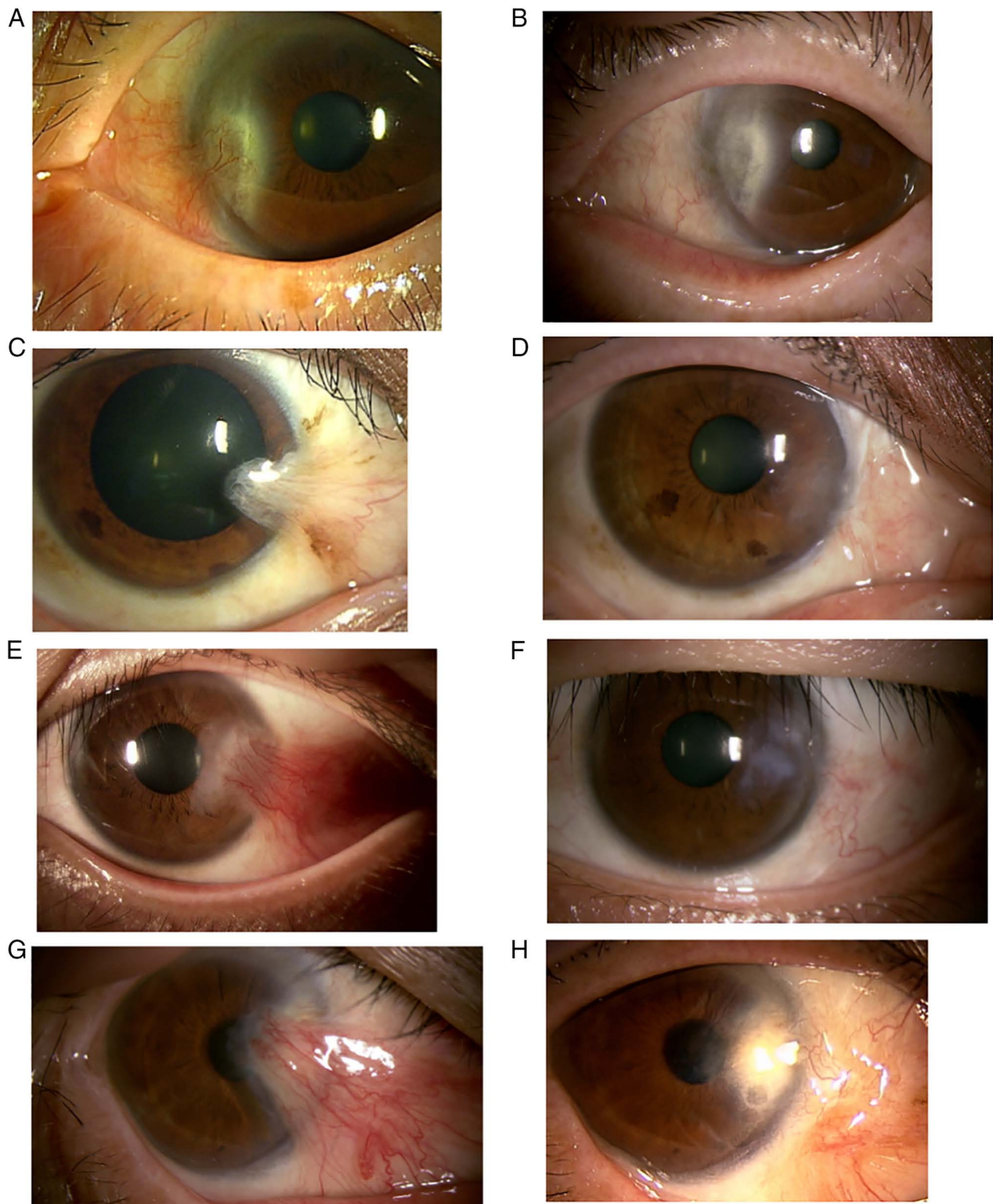


Figure 1. Preoperative and postoperative findings in pterygium treated using the non-resection method. (A) Pterygium adjacent to the corneal limbus (grade 1). (B) Recurrence was not observed; however, corneal stromal opacity remained. (C) Pterygium with pigmentation beyond the corneal limbus (grade 2). (D) Recurrence was not observed, while the tumor volume was reduced. (E) Pterygium around the pupillary margin (grade 3). (F) There was no recurrence after surgery. (G) Pterygium with hyperemia beyond the pupillary margin (grade 4). (H) There was no recurrence after surgery, while remission of hyperemia was noted, although corneal stromal opacity remained.

Results

Clinical demographics. This study included 127 eyes from 117 patients (56 men and 61 women) with pterygia. The

mean age of the patients at the time of surgery was 73 years. Pterygia were observed at nasal, temporal, and combined sites in 124, 0, and 3 eyes, respectively. Patients' complaints included hyperemia, visual disturbances, proliferative tissues

Table I. Non-resection method of pterygial surgery.

Step	Description
1	Separation of the pterygial head from the cornea
2	Radical incision of the body
3	Sub-Tenon injection of 2% lidocaine
4	Removal of the remaining stromal tissue on the cornea
5	Polishing the corneal bed
6	Creation of the upper/lower conjunctival flap using a Z-shaped incision
7	Suture of the conjunctival flap to the lower/upper conjunctiva
8	Suture of the pterygial head to the conjunctival epithelium in the upper/lower space
9	Dexamethasone injection into the conjunctiva with an antibiotic ointment on the ocular surface

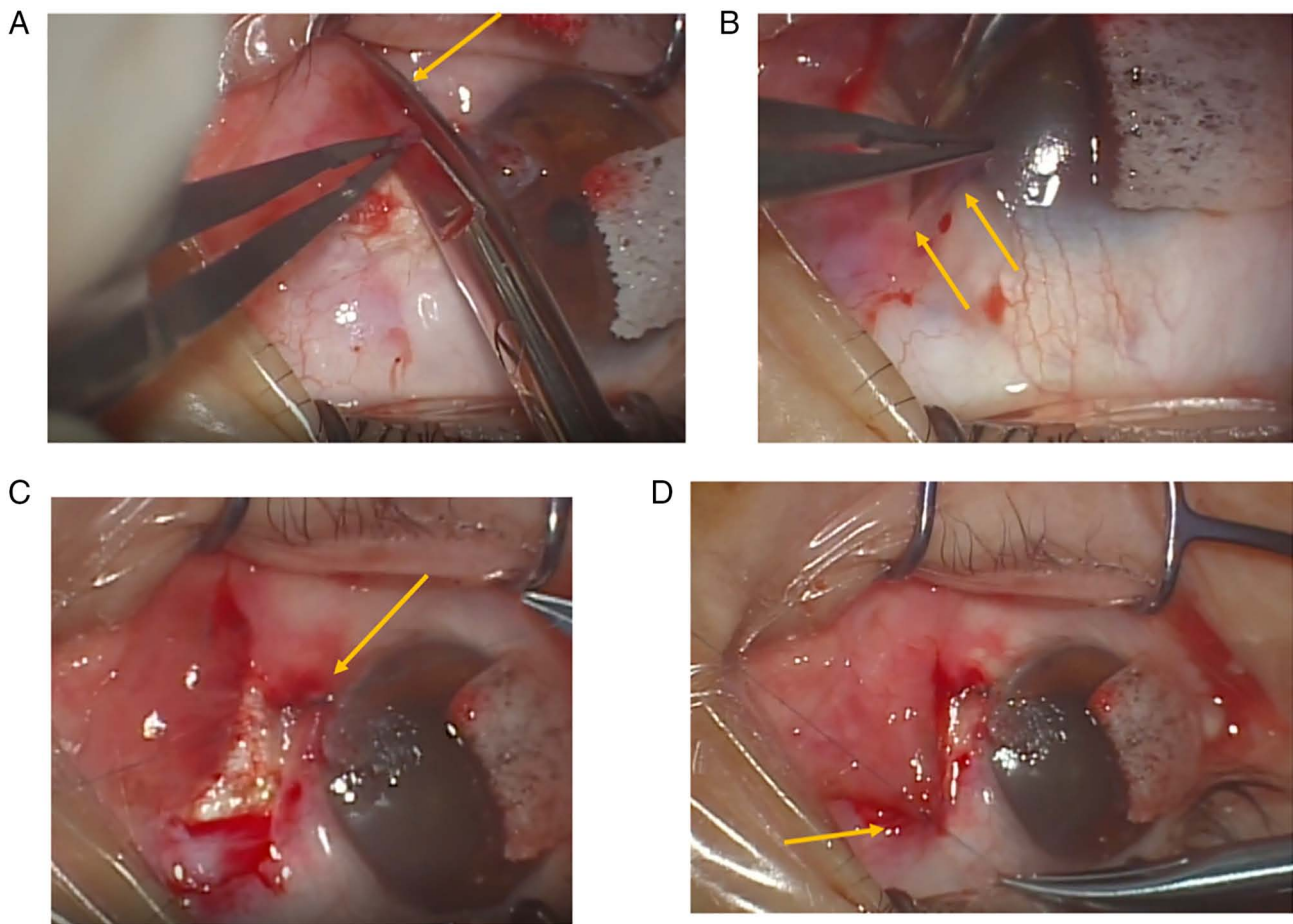


Figure 2. Non-resection method of pterygial surgery. (A) The pterygial head was separated from the cornea and the body was radially incised (arrow). (B) An upper conjunctival flap was created using a Z-shaped incision (arrows). (C) The conjunctival flap was sutured to the lower conjunctiva (arrow). (D) The pterygial head was sutured to the conjunctival epithelium in the upper space (arrow).

on the ocular surface, and conjunctival inversion or elevation; however, diplopia was not reported by any patient. Primary and recurrent pterygia were observed in 113 and 14 eyes, respectively. The Grades 1, 2, 3, and 4 pterygia were observed in 3, 49, 65, and 10 eyes, respectively, and the mean size was Garde 2.6. The follow-up duration ranged from 6 to 82 months (mean, 31 months). In most cases, the conjunctival flap at the corneal limbus presented a smooth surface with fine coloration (Fig. 1B, D, F and H); however, corneal stromal opacity

persisted in few cases (Fig. 1B and H). No complications such as infection, persistent inflammation/hyperemia, Dellen, corneal/sclero-conjunctival ulcers, suture-related problems, granuloma formation or motility restriction were observed. No patient required suture removal after surgery.

Pterygium recurrence after surgery. Postoperative recurrence was observed in 10 eyes (7.9%) of 10 patients (mean age, 71 years). Of these, five eyes each were from men and women,

Table II. Multivariate Cox proportional hazards regression analysis.

A, Model A: Full model (adjusted for patient clusters and facilities)

Variables	Hazard ratio	95% CI	P-value
Age	0.98	0.94-1.03	0.504
Sex (male vs. female)	1.97	0.52-7.54	0.321
Laterality (right vs. left)	0.79	0.24-2.60	0.695
Recurrence at operation	2.40	0.46-12.37	0.297
Grade	4.42	1.33-14.67	0.015 ^a
Cryopexy	8.89	0.80-98.75	0.075

B, Model B: Parsimonious model (major clinical variables only)

Variables	Hazard ratio	95% CI	P-value
Recurrence at operation	1.68	0.41-6.91	0.476
Grade	4.57	1.73-12.09	0.002 ^a
Cryopexy	10.94	2.19-54.71	0.004 ^a

^aP<0.05.

Table III. Generalized estimating equations logistic regression analysis.

A, Model adjusted for major clinical variables and facilities

Variables	Odds ratio	95% CI	P-value
Recurrence at operation	2.10	0.28-15.95	0.470
Grade	3.85	1.08-13.75	0.038 ^a
Cryopexy	9.17	0.69-122.10	0.093

B, Model including major clinical variables only

Variables	Odds ratio	95% CI	P-value
Recurrence at operation	1.52	0.25-9.22	0.650
Grade	4.36	1.60-11.87	0.004 ^a
Cryopexy	7.15	1.05-48.68	0.045 ^a

^aP<0.05.

and recurrence after surgery for primary and recurrent pterygia was observed in seven, and three eyes, respectively. Kaplan-Meier analysis revealed no postoperative recurrence in all enrolled patients (Fig. 3A). The mean duration from surgery to recurrence was 20 months. The mean preoperative pterygial size was Grade 2.6 and Grade 3.4 in eyes without and

with recurrence, respectively. The preoperative pterygium size was significantly greater in eyes with recurrence than in those without recurrence (U=932.50, P=0.0052, Mann-Whitney U test). By contrast, age was not significantly different between eyes with and without recurrence (Mann-Whitney U test). All sutured pterygial tissues shrank with a pale coloration, and no eyes showed tumor formation during the follow-up period. No additional surgery was required for the eyes with pterygia after the initial surgery. In the GEE model, patient IDs were specified as cluster, and the facility was adjusted as a covariate. Even after accounting for clustering and facility effects, pterygium Grade remained a significant independent risk factor for post-operative recurrence [Odds ratio (OR), 3.85; 95% Confidence Interval (CI), 1.08–13.75; P=0.0376 in the facility-adjusted model; and OR, 4.36; 95% CI, 1.60–11.87; P=0.0039 in the clinical GEE model]. Recurrence occurred earlier and at a higher rate in higher-grade eyes, and the log-rank test revealed a statistically significant difference in recurrence between Grades 1-2 and Grades 3-4 (P=0.0253) (Fig. 3B).

Adjunctive cryopexy. There are no clear criteria for cryopexy in pterygium surgery. In 5 eyes of 5 patients with wide pterygial bodies or relatively young age, cryopexy was performed after separation of the pterygial tissues from the cornea regardless of the extent of corneal invasion by the pterygial head, because of potential high risks of recurrence. The patients' ages ranged from 49 to 76 years (mean: 68 years). Among these, two and three eyes had primary and recurrent pterygia, respectively. The mean grade was 2.8. Cryopexy was performed using a conventional cryopexy probe at -80°C for 2-3 sec, pressing from beneath the pterygial tissues for one cycle. Postoperative inflammation and hyperemia resolved 2-3 months after surgery. The follow-up duration of eyes that underwent cryopexy ranged from 19 to 45 months (mean, 32.8 months). The log-rank test revealed that addition of cryopexy was significantly associated with recurrence (P=0.0030, Fig. 3C). Moreover, addition of cryopexy was associated with a high hazard ratio for recurrence (hazard ratio, 10.94; 95% CI, 2.19–54.71; P=0.0036), which likely reflects a 'confounding by indication' bias, as cryopexy was selectively performed on eyes deemed by surgeons to have a high risk of recurrence.

Discussion

This study demonstrated that favorable clinical outcomes of the non-resection method for pterygial surgery with low recurrence rates, without the use of chemical agents such as MMC. Therefore, this procedure could be performed in various ophthalmic clinics, facilitating easy access to comprehensive pterygial surgery for ophthalmologists globally.

In this study, the preoperative size of the pterygium was mostly Grade 2 or 3, and 10 of 127 eyes had Grade 4 pterygia. The findings in this study suggest that this non-resection method is appropriate for pterygial growth around the pupil. Notably, the preoperative pterygium size was significantly greater in eyes with recurrence than in those without recurrence (P<0.01). Therefore, if the pterygial tissues are wide, a single Z-shaped incision might not be sufficient to reconstruct

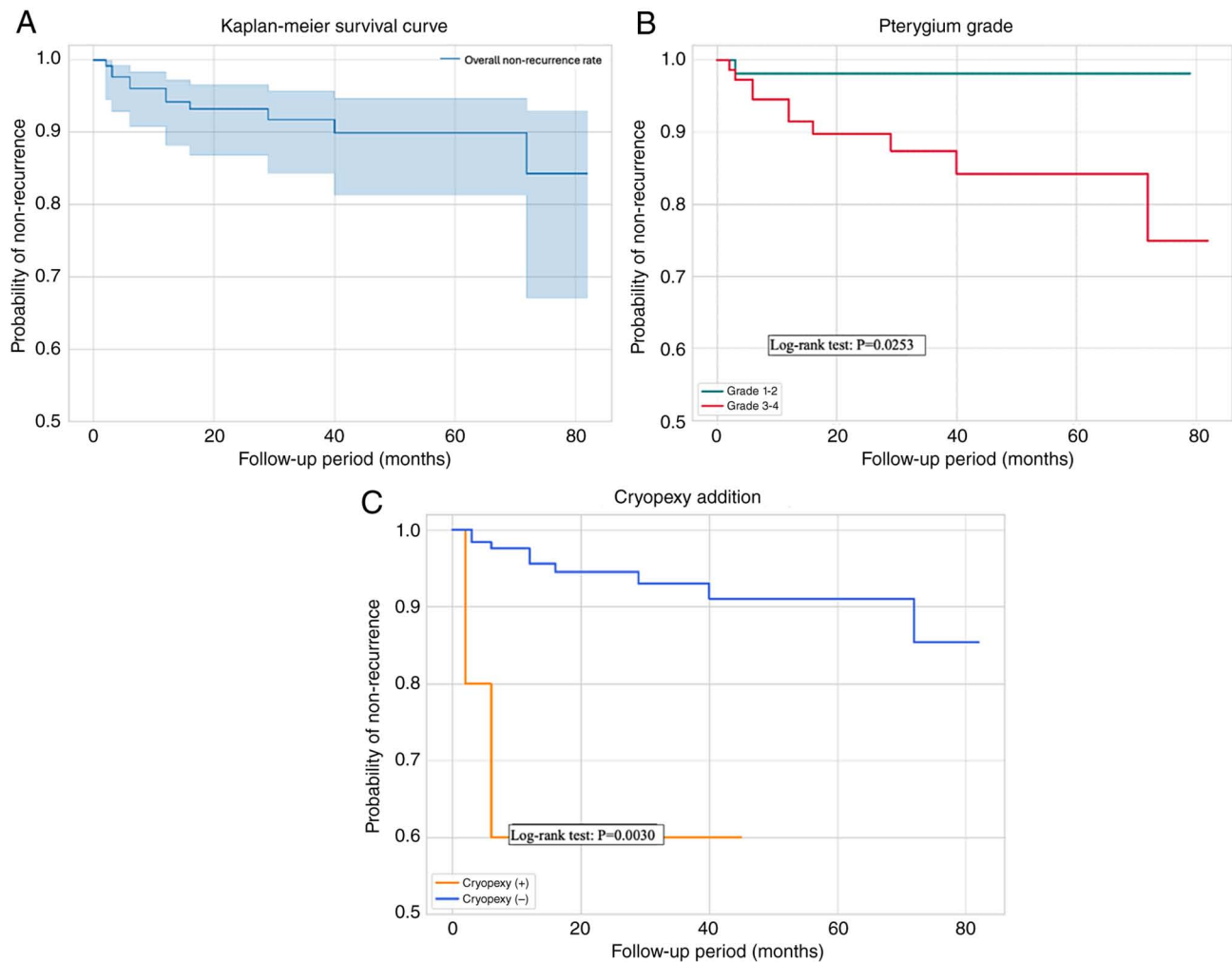


Figure 3. Kaplan-Meier analysis of patients with pterygia. The log-rank test was used to determine significant differences between groups. The mean follow-up period was 31 months. (A) Kaplan-Meier analysis of postoperative non-recurrence in all patients included. (B) Comparison between grade 1-2 and grade 3-4 groups using the log-rank test showed a statistically significant difference ($P=0.0253$). A faster and higher rate of recurrence was observed in higher-grade eyes. (C) The follow-up period of eyes with cryopexy ranged between 19 and 45 months. A significant difference was observed between the groups with and without addition of cryopexy (log-rank test; $P=0.0030$).

the corneal limbus. Particularly, if the recurrence is severe and adhesive to the skin of the eyelid, reconstruction of the conjunctival fornix using extensive free flaps is required. However, this non-resection method uses pterygium tissue as a reconstructive material; therefore, even if an additional flap or excision is needed during surgery, it is possible to switch to other methods. On the other hand, there would be a variability between surgeons when this method is used. Our finding suggest that the non-resection method is not a universal surgical procedure, but is a useful first-line approach in pterygium surgery.

In this study, the pterygium recurrence rate after non-resection method was 7.9%. A previous study reported that conjunctival autograft is superior to the scleral bare procedure in terms of postoperative recurrence rates (15). Recently, Aziza *et al* (7) reported that recurrence in one of 32 pterygial patients who underwent a scleral bare procedure with MMC application. Noguera *et al* (6) reported a recurrence rate of 1% in patients who underwent resection of pterygial tissues with transplantation of conjunctival autograft or amniotic membrane with MMC application. Moreover, a previous study reported

that the recurrence rate after other procedures was <10%. Therefore, the recurrence rate after non-resection method is comparable to those after other methods. However, the comparable rate was achieved without the use of chemical agents such as MMC or amniotic membranes. In fact, MMC-related scleral melt/defect is a serious complication, with a long-term implications for the postoperative managements of patients (16-18). Kim *et al* (19) reported that a low postoperative recurrence rate of 6% using conjunctival mini-flap technique without the use of MMC, whereas the recurrence rate after conjunctival autograft transplantation was 17%. The recurrence rate in this study might be comparable to that in the previous study (19), without any concerns regarding serious complications owing to the use of MMC.

In this study, the epithelium of the definitive pterygium, which contains columnar epithelium or squamous metaplasia without cellular atypia (3,4), was not resected. Therefore, the pterygial epithelium could be used as a reconstructive material, facilitating easy ocular-surface reconstruction. Because the indication for this non-resection method is a definitive pterygium, preoperative inspection of proliferative tissues on

slit-lamp examination is extremely important. Moreover, cryopexy of the pterygial tissues may contribute to the suppression of pterygial epithelial proliferation and angiogenesis (20), which potentially reduces recurrence in wide-edge pterygia. Conditions such as OSSN with pterygium, pterygium-like OSSN or pterygium-like conjunctival nevus (1,10,12), in which resection of proliferative tissues with extensive conjunctival reconstruction is recommended, are contraindications for this procedure.

This study had several limitations. First, this was a retrospective multicenter study; because choice of surgical procedure depended on the individual ophthalmologists' decision, the cohort included consecutive patients treated using this technique, but did not include all consecutive pterygium surgeries. Therefore, a selection bias could not be excluded. Furthermore, this study design had a single-arm design, not a randomized comparative study. A prospective head-to-head study is required to verify the usefulness of this procedure for pterygial surgery. Second, the sutured pterygial tissue was not histologically confirmed. Hence, pathophysiological mechanisms underlying shrinkage of the sutured tissues remain unknown; however, the presumed mechanism is contact inhibition between the pterygial epithelium and normal conjunctival epithelium (9). If the sutured tissues exhibit postoperative growth, ophthalmologists should consider biopsy of the tissues, for histopathological confirmation. Third, because of the multicenter nature of the study, surgeries were conducted by different ophthalmologists with different levels of experiences in pterygial surgery. The differences in skills and experiences might have affected recurrence rates. Forth, Tan's classification on pterygial morphology classifying as atrophic, intermediate and fleshy (21), could not be available in this multicenter analysis, because the slit-lamp photographs were not available in several participants and participating institutions. Fifth, the masked evaluators were not used in analysis of clinical data, and the duration of the pterygial surgery was unavailable in this study. Finally, visual and refractive outcomes cannot be fully examined in this cohort; therefore, further analyses are required to clarify the usefulness of this method.

In conclusion, although the non-resection method could be comparable to the previous methods for pterygial surgery in terms of postoperative recurrence rates, it might be safely and can be easily performed in any institute. Nevertheless, eyes with higher grades of pterygia exhibit a tendency for recurrence.

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Availability of data and materials

The data generated in the present study are not publicly available to protect potentially identifiable personal data but may be requested from the corresponding author.

Authors' contributions

SK wrote the manuscript and acquired the clinical data. SC reviewed the manuscript and interpreted the clinical data. MS, CY, YA, JF, SI, NK, RKi and RKa conducted critical revision and supervised data interpretation. RKi, CY, JF, YA, RKa and NK made substantial contributions to conception and design, and acquisition of clinical data. SI and NK performed evaluation and interpretation of data. MS conducted all the statistical analyses in the present study while remaining blinded to the clinical data. SK and MS confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was approved by the Institutional Review Board of Hokkaido University (IRB no. 024-0068; Sapporo, Japan) as the central institutional review board. The study protocol included all the participating institutions listed in the manuscript. Therefore, ethical approval from the other institutions was not required. The study adopted an opt-out approach. This means that enrolled patients were given the opportunity to refuse participation in the study through the website. Therefore, the requirement for written informed consent was waived.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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