Original Article
Yonsei Med J 2025 Dec;66(12):857-865
https://doi.org/10.3349/ymj.2025.0032
Yonsei Medical Journal
YMJ
pISSN: 0513-5796 · eISSN: 1976-2437

Clinical Outcomes of Photodynamic Therapy for Choroidal Nevus with Subfoveal Fluid

Jin Yeong Kim and Christopher Seungkyu Lee
Institute of Vision Research, Department of Ophthalmology, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea.

Purpose: To evaluate the outcomes of photodynamic therapy (PDT) for choroidal nevus associated with subfoveal fluid.
Materials and Methods: Electronic medical records were reviewed for patients diagnosed with choroidal nevus and treated with PDT at a single center in Seoul, South Korea, from January 2019 to December 2023. Patient demographics, tumor characteristics, and clinical progress following PDT, including changes in foveal subretinal fluid (SRF) height, central subfield thickness (CST), corrected distant visual acuity (CDVA), tumor size, and fluid recurrence, were analyzed.
Results: Seven eyes of seven patients were included; all had SRF involving the foveal center and associated visual symptoms. The median diameter and thickness of tumors were 4.10 mm (range 3.2–5.5 mm) and 0.80 mm (range 0.6–1.4 mm), respectively. All patients received a single PDT session, with a mean follow-up of 20.6 months. Subfoveal fluid decreased in 6 patients (85.7%), with complete resolution in 4 eyes (57.1%); 1 patient showed no significant change after PDT. Consequently, the mean foveal SRF height decreased from 135.9±83.0 μm to 20.3±31.9 μm, and CST from 365.7±82.5 μm to 258.1±52.7 μm. CDVA improved in 1 patient (14.3%), remained stable in 3 (42.9%), and decreased in 2 (28.6%). Three of six patients with reduced subfoveal fluid experienced recurrence at 3 months, 3 months, and 21 months after PDT.
Conclusion: PDT demonstrated noticeable efficacy in reducing subfoveal fluid associated with choroidal nevus within 1 month of treatment. However, in some cases, the effect may be limited in long-term maintenance.

Key Words: Photodynamic therapy, subretinal fluid, nevus, choroid neoplasms, retrospective study

INTRODUCTION

Choroidal nevus is the most common benign intraocular tumor originating from melanocytes, with a reported prevalence ranging from 0.3% to 6.5%, depending on the race or age of the study population.[1,2] The transformation of choroidal nevus into malignant melanoma occurs in less than 1% of cases.[3,4] Risk factors for malignant transformation include a tumor thickness greater than 2 mm, the presence of subretinal fluid (SRF), symptoms such as vision loss, orange pigment, ultrasonographic hollowness, and a tumor diameter greater than 5 mm.[5-7] In most cases, choroidal nevus is asymptomatic and does not require treatment.[8,9] However, if the nevus is located near the fovea and is accompanied by SRF or choroidal neovascularization, it may cause symptoms such as visual impairment, visual field loss, or photopsia, necessitating treatment. Vision loss in patients with choroidal nevus is associated with subfoveal or juxtapapillary location, SRF, pigment epithelial detachment, and foveal edema.[1,9,10]

Various treatment modalities have been employed for symptomatic leaking choroidal nevi, including intravitreal injection of anti-vascular endothelial growth factor (VEGF), laser photocoagulation, transpupillary thermotherapy, and photodynamic therapy (PDT) with verteporfin.[11-22] PDT is a therapeutic approach that uses a photosensitizing agent to target abnormal blood vessels or tumor cells within the eye and has been applied in the treatment of neovascular age-related macular degeneration, polypoidal choroidal vasculopathy, central serous chorioretinopathy, circumscribed choroidal hemangioma, cho-

Received: March 18, 2025 **Revised:** May 4, 2025
Accepted: May 27, 2025 **Published online:** August 28, 2025
Corresponding author: Christopher Seungkyu Lee, MD, PhD, Institute of Vision Research, Department of Ophthalmology, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea.
E-mail: sklee219@yuhs.ac

•The authors have no potential conflicts of interest to disclose.

roidal osteoma, retinal capillary hemangioma, and choroidal melanoma.[23-25]

Although several studies have reported the use of PDT for choroidal nevi associated with choroidal neovascularization, SRF, or macular edema,[17-22,26] it is not yet considered a fully established treatment for choroidal nevus. Particularly in Asians, where the prevalence of choroidal nevus is known to be lower than in Caucasians, there is a lack of discussion on the effectiveness of PDT and its long-term outcomes. This study aimed to evaluate the outcomes and prognosis of PDT for choroidal nevus with subfoveal fluid.

MATERIALS AND METHODS

Study participants

This retrospective study was based on the medical records of all patients diagnosed with choroidal nevus and treated with PDT at Severance Hospital in Seoul, South Korea, between January 2019 and December 2023. The study was approved by the Institutional Review Board of Yonsei University Severance Hospital (IRB no. 4-2023-1405) and conducted in accordance with the tenets of the Declaration of Helsinki. Patients with a history of ocular surgeries other than cataract surgery or those with other ocular diseases, such as corneal opacity, glaucoma, or other retinal diseases, were excluded. Additionally, patients with a follow-up period of less than 3 months or those with missing patient information, examination results, or treatment records were excluded from the analysis.

Data collection and analysis

Collected clinical data and ophthalmic examination records included patient age, sex, medical history, ophthalmic history, ocular treatment records, corrected distant visual acuity (CDVA), and ophthalmic imaging such as fundus photography, Spectralis spectral-domain optical coherence tomography (OCT, Heidelberg Engineering, Heidelberg, Germany), fluorescein and indocyanine green angiography, and ultrasonography. The location and size of nevus were reviewed, and tumor diameter and thickness were measured using OCT.[27,28] Central subfield thickness (CST) and foveal SRF height were obtained to objectively and quantitatively assess changes in subfoveal fluid. CST measurement was performed automatically by the built-in software, which analyzed the OCT scan data and calculated the average retinal thickness within a 1-mm diameter circle at the center of the Early Treatment Diabetic Retinopathy Study grid.

The number of PDT sessions, dosage (standard-dose, half-dose, or modified double-dose), and presence of additional treatment beyond PDT were reviewed. Standard-dose PDT involved administering 6 mg of verteporfin (Visudyne®, Novartis, Basel, Switzerland) per square meter of body surface area (BSA), while half-dose PDT used half this dosage. A diode laser with a wavelength of 689 nm and an intensity of 600 mW/cm^2 was applied for 83 seconds, delivering a total energy of 50 J/cm^2. In the modified double-dose protocol, one vial (15 mg) of verteporfin was infused, and the dose per square meter was calculated based on the patient's BSA. Additional irradiation time was then calculated to compensate for the difference in dose relative to the double dose and added to the standard 83 seconds to achieve a doubling effect.[29] All PDT procedures were performed by one of the authors (C.S.L.). Fig. 1 presents representative multimodal images with the PDT-treated area indicated.

To evaluate the outcomes and prognosis of PDT in symptomatic choroidal nevus with subfoveal fluid, we analyzed changes in subfoveal fluid, CST, CDVA, and tumor size at baseline, 1 month after PDT, and at the last visit. A decrease in CST of more than 20 μm compared to baseline was considered a clinically significant reduction in subfoveal fluid. Improvement or deterioration in visual acuity was defined as a difference of 0.2 logMAR or more in CDVA. The course of subfoveal fluid was monitored until the last visit, and the interval from PDT to any recurrence of fluid was recorded.

RESULTS

Baseline characteristics of patients and choroidal nevus

A total of seven patients underwent PDT in one eye diagnosed with choroidal nevus in the macular area. Among them, 4 were women (57.1%), with a mean age of 45.0±18.6 years at diagnosis. Six of the seven patients had subfoveal fluid at their initial visit. However, one patient, who initially had no symptoms or SRF, developed subfoveal fluid approximately 9 years later.

At the time of PDT, all patients had SRF involving the foveal center and associated ocular symptoms such as central scotoma, decreased visual acuity, or metamorphopsia. Before PDT, CDVA ranged from 0.1 to 1.4 logMAR, with a median CDVA of 0.40 logMAR. The median diameter of the choroidal nevus was 4.10 mm (range: 3.2–5.5 mm), and the median thickness was 0.80 mm (range: 0.6–1.4 mm).

All patients exhibited focal or diffuse leakage at the lesion site on fluorescein angiography, and indocyanine green angiography consistently revealed well-demarcated hypofluorescent blockage corresponding to the choroidal mass. OCT showed irregularity or disruption of the retinal pigment epithelium and thinning of the choriocapillaris overlying the nevus in most cases. No choroidal neovascularization was identified on multimodal imaging.

A single session of PDT was performed as the primary treatment for nevus-associated subfoveal fluid in all patients, none of whom had received any prior interventions, including anti-VEGF injections. Five patients underwent standard-dose PDT, one received half-dose PDT, and one underwent a modified double-dose protocol. The mean follow-up period after PDT was 16.8 months. Baseline characteristics and pre-treatment

https://doi.org/10.3349/ymj.2025.0032

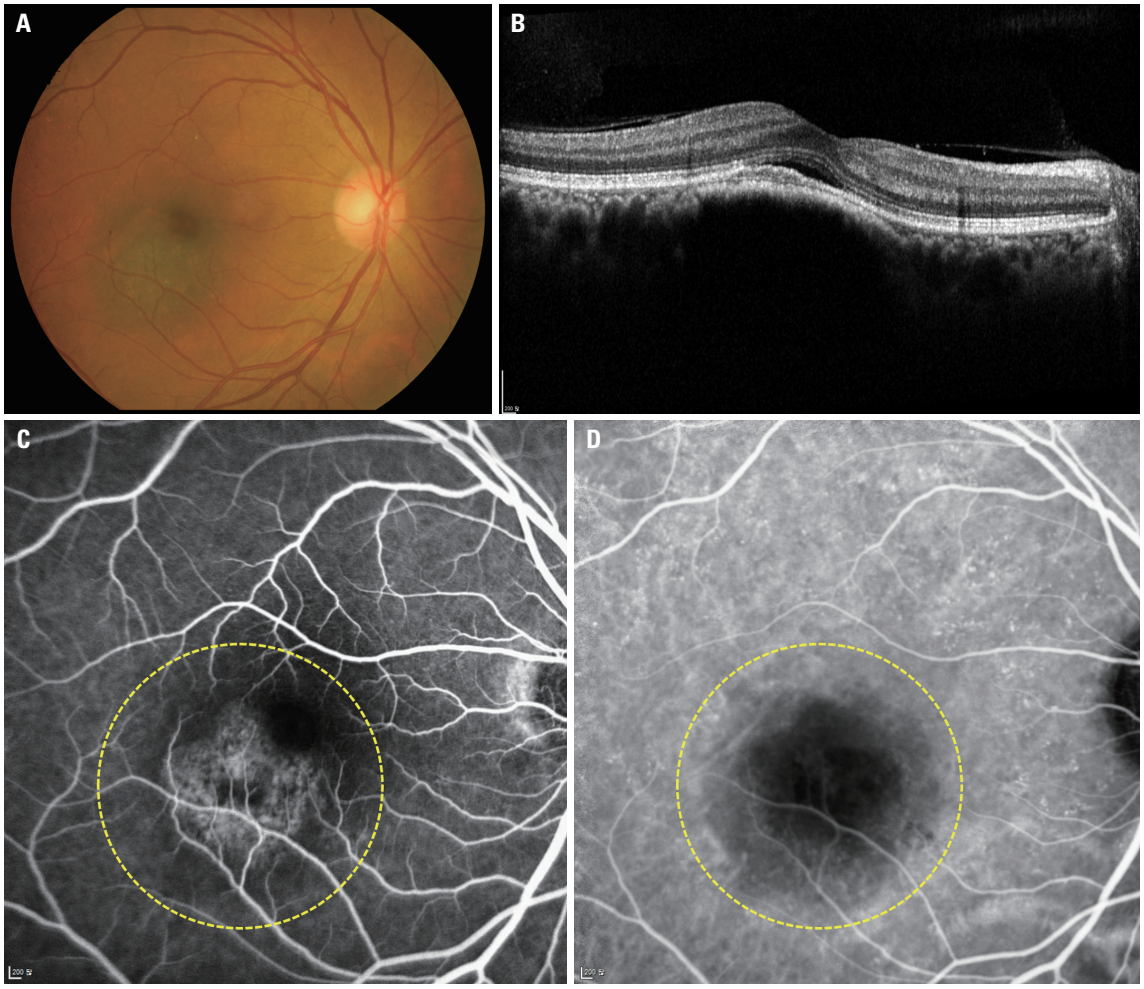

Fig. 1. Representative images of Patient 5 before PDT. (A) Fundus photography showing an elevated pigmented lesion at the macula. (B) Optical coherence tomography demonstrating subfoveal fluid with an underlying hyporeflective choroidal mass. (C) Early-phase fluorescein angiography showing diffuse leakage at the lesion site. (D) Mid-phase indocyanine green angiography revealing blockage corresponding to the choroidal nevus. The yellow dashed circles in (C) and (D) indicate the PDT spot area, with a diameter of 4400 μm. PDT, photodynamic therapy.

Table 1. Baseline Characteristics, PDT Regimen, and Anatomical/Visual Parameters of Seven Patients

Case no.	Sex/ Age (yr)	Tumor diameter (mm)	Tumor thickness (mm)	Risk factors of malignant transformation	No. PDT sessions/dose	CST (μm)	Foveal SRF height (μm)	CDVA
1	F/75	5.5	1.4	4	1/Modified double	250	75	20/500 1.40 logMAR
2	M/58	4.1	1.2	3	1/Standard	392	189	20/50 0.40 logMAR
3	M/32	3.2	0.6	1	1/Standard	519	253	20/25 0.10 logMAR
4	M/30	3.9	0.8	2	1/Half	315	38	20/25 0.10 logMAR
5	F/59	3.6	0.7	3	1/Standard	343	80	20/50 0.40 logMAR
6	F/31	4.9	1.2	3	1/Standard	377	219	20/66 0.52 logMAR
7	F/30	4.2	0.8	2	1/Standard	364	97	20/28 0.15 logMAR

PDT, photodynamic therapy; CST, central subfield thickness; SRF, subretinal fluid; CDVA, corrected distant visual acuity.
Visual acuity is presented in both Snellen equivalent and logMAR formats.

parameters for each case are summarized in Table 1.

Subfoveal fluid, tumor size changes and visual outcome after PDT

At 1 month post-PDT, 6 of 7 eyes (85.7%) responded to treatment. Four eyes (57.1%) achieved complete resolution of subfoveal fluid, 2 eyes (28.6%) showed partial resolution, and 1 eye exhibited no significant change. Detailed case-by-case information on anatomical response and visual acuity changes after PDT is summarized in Table 2. The mean CST significantly decreased from 365.7±82.5 μm at baseline to 258.1±52.7 μm following 1 month of PDT. The only non-responding eye, which maintained a CST of 310 μm from a baseline of 315 μm, had been treated with half-dose PDT. Foveal SRF height also showed a mean reduction from 135.9±83.0 μm to 20.3±31.9 μm at 1 month post-PDT. PDT did not substantially alter tumor diameter or thickness in any of the seven eyes throughout the follow-up period.

At the 1-month follow-up, 1 eye (14.3%) showed an improvement in visual acuity by more than 0.2 logMAR, 4 eyes (57.1%) maintained stable visual acuity, and 2 eyes (28.6%) experienced a decline. The median CDVA was 0.15 logMAR (range: 0.1–1.7 logMAR) at 1 month and 0.30 logMAR (range: 0.05–2.0 logMAR) at the last visit. Although subfoveal fluid was significantly reduced in some cases, this did not necessarily result in improved visual acuity. Among the four cases in which subfoveal fluid completely resolved, one showed visual acuity improvement, two remained stable, and one experienced a decrease.

Recurrence of subfoveal fluid

The mean follow-up period from PDT to the last visit was 20.6±19.7 months (median: 12.2 months, range: 3.2–50.3 months). Among the six patients who initially responded to PDT, 3 (50%) experienced a recurrence of previously decreased fluid at 3 months (two cases) and 21 months (one case) post-treatment, with an average time to recurrence of 9.1 months. Representative images of treatment response in two cases are presented in Figs. 2 and 3. While Patient 7 showed complete and sustained resolution of subfoveal fluid after PDT, Patient 6 exhibited partial recurrence at 3 months.

At the last visit, the mean CST was 310.4±82.4 μm, representing an increase of 52.3 μm compared to the 1-month post-PDT measurement, although still lower than the baseline CST of 365.7 μm. Importantly, in all three recurrent cases, neither the foveal SRF height nor the CST exceeded pre-treatment values (Table 2). Patient 2 received four intravitreal injections of triamcinolone acetonide (Maqaid®, Wakamoto Pharmaceutical Co., Ltd., Tokyo, Japan) for worsening subfoveal fluid and macular edema during follow-up after PDT. Although macular edema persisted, the subfoveal fluid was completely reabsorbed following the third injection. No additional interventions, including repeat PDT, were administered to the remaining patients during the follow-up period.

DISCUSSION

In this study, we evaluated the treatment outcomes of PDT in choroidal nevus associated with subfoveal fluid. A total of seven eyes underwent PDT, and 6 (85.7%) responded within a month, showing a reduction in subfoveal fluid. Subfoveal fluid completely resolved in 4 eyes (57.1%), while two exhibited a partial reduction without full resolution. The only patient

Table 2. Summary of Clinical Outcomes and Follow-Up Data after PDT

Case no.	PDT response in subfoveal fluid	1 month after PDT			Last visit			Recurrence of fluid (months)	Follow-up period after PDT (months)
		CST (μm)	Foveal SRF height (μm)	CDVA	CST (μm)	Foveal SRF height (μm)	CDVA		
1	Partial resolution	209	26	20/1000 1.70 logMAR	213	10	20/2000 2.00 logMAR	No	12.5
2	Complete resolution	225	0	20/100 0.70 logMAR	327	0	20/100 0.70 logMAR	3	50.3
3	Partial resolution	334	86	20/28 0.15 logMAR	472	203	20/40 0.30 logMAR	21	47.8
4	No response	310	30	20/28 0.15 logMAR	338	74	20/25 0.10 logMAR	N/A	3.2
5	Complete resolution	277	0	20/25 0.10 logMAR	285	0	20/22 0.05 logMAR	No	12.2
6	Complete resolution	192	0	20/66 0.52 logMAR	271	120	20/50 0.40 logMAR	3	6.1
7	Complete resolution	260	0	20/28 0.15 logMAR	267	0	20/33 0.22 logMAR	No	12.1

PDT, photodynamic therapy; CST, central subfield thickness; SRF, subretinal fluid; CDVA, corrected distant visual acuity; N/A, not applicable.
Visual acuity is presented in both Snellen equivalent and logMAR formats.

https://doi.org/10.3349/ymj.2025.0032

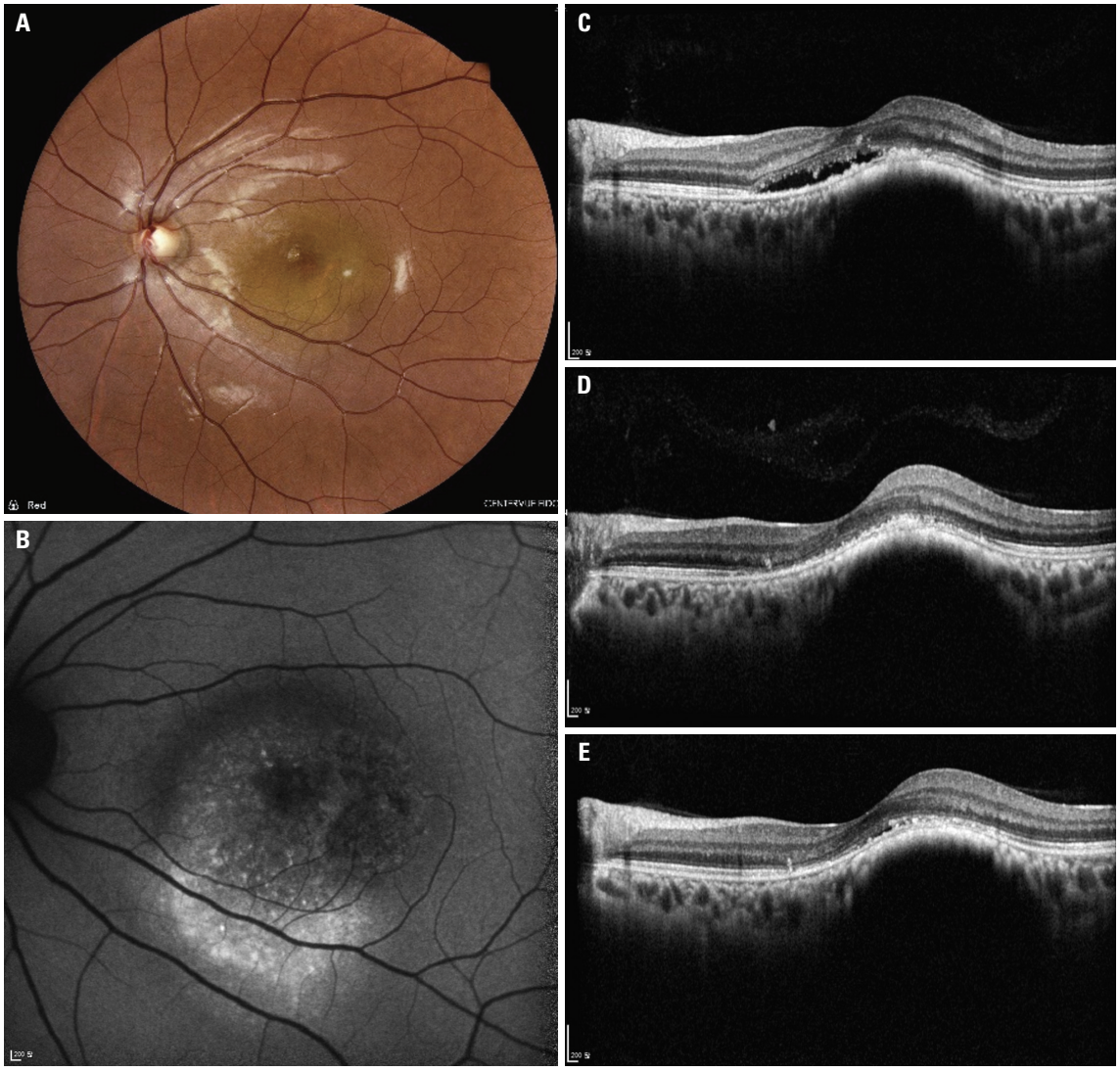

Fig. 2. Representative images of Patient 7. Fundus photography (A), fundus autofluorescence (B), and OCT before treatment (C), and OCT at 1 month (D) and 3 months (E) after PDT, showing complete resolution of subfoveal fluid 1 month after PDT with sustained stability thereafter. OCT, optical coherence tomography; PDT, photodynamic therapy.

who did not respond was the one who had received half-dose PDT. Although this is a single case, it may suggest that half-dose PDT is insufficient for resolving nevus-related SRF. Standard-dose PDT effectively reduced subfoveal fluid in patients with choroidal nevus. However, a significant improvement in visual acuity was observed in only one patient, and no significant change in tumor size was noted in any case. Among the four eyes with complete fluid resolution, two experienced recurrence at 3 months after PDT, while the other two maintained stable progress up to 12 months. Of the 2 eyes with partial resolution, one remained stable for 12 months, whereas the other showed an increase in subfoveal fluid at the 21-month follow-up.

Five of the seven patients received PDT within 1 month after subfoveal fluid was first detected. However, treatment was delayed for approximately 2 years in one case (Patient 6) due to the patient's initial refusal to undergo PDT. Another case (Patient 7) experienced a delay of 7.5 months due to the discontinuation of Visudyne® imports in Korea. Despite these delays, both patients achieved complete resolution of subfoveal fluid; however, the patient who postponed PDT for 2 years experienced a recurrence just 3 months post-treatment. Visual acuity remained stable in both cases through the last follow-up visit. One limitation is that there may be a significant discrepancy between the timing of clinical detection and the actual onset of subfoveal fluid. These findings are insufficient to establish a definitive causal relationship between the timing of PDT and subfoveal fluid response or recurrence.

In 2019, Shields, et al.[7] suggested six updated risk factors for malignant transformation of choroidal nevi, summarized in the mnemonic "To Find Small Ocular Melanoma Doing IMaging" (TFSOM-DIM): Thickness >2 mm, SRF, symptoms of visual

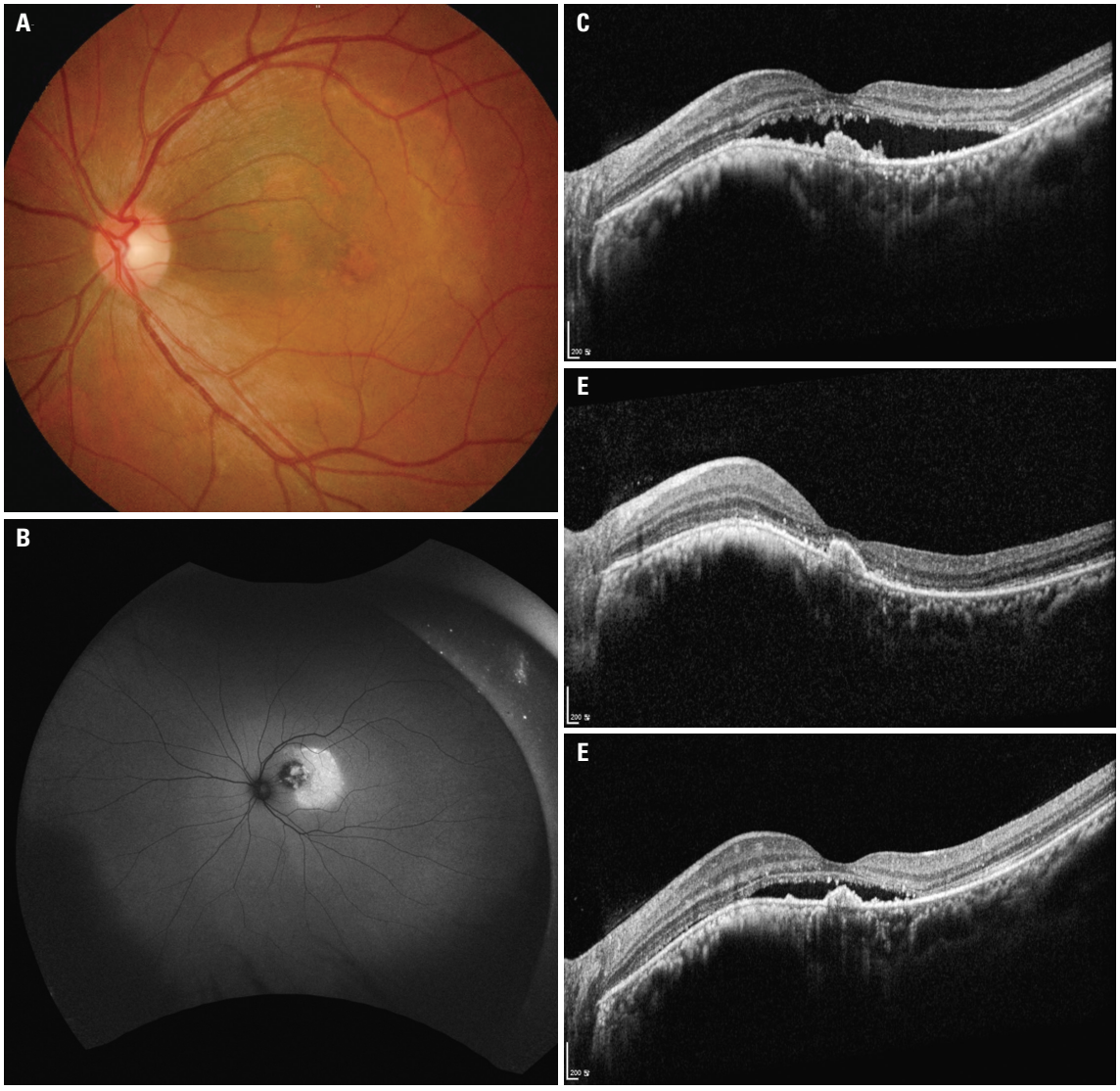

Fig. 3. Representative images of Patient 6. Fundus photography (A), wide-field fundus autofluorescence (B), and OCT before treatment (C), and OCT at 1 month (D) and 3 months (E) after PDT, showing resolution of subfoveal fluid 1 month after PDT with partial recurrence at 3 months. OCT, optical coherence tomography; PDT, photodynamic therapy.

acuity loss to 20/50 or worse, Orange pigment, Melanoma acoustic hollowness, and tumor DIaMeter >5 mm. Based on these criteria, all cases in our study shared the presence of SRF and had between one and four risk factors (Table 1). The single case that did not respond to PDT (Patient 4) had two risk factors. Among the three cases that initially responded but later experienced recurrence, the number of risk factors was one, three, and three, respectively. A patient with four risk factors (Patient 1) underwent modified double-dose PDT, which resulted in partial resolution of fluid without further deterioration. No consistent correlation was observed between the number of risk factors and the response to PDT, although this assessment is limited by the use of different treatment protocols. Furthermore, none of the patients in this study showed evidence of tumor growth or malignant transformation during the follow-up period.

In this study, while five patients received standard-dose PDT, one patient underwent modified double-dose PDT and another received half-dose PDT. The use of these different protocols presents a limitation in interpreting treatment efficacy. The choice of PDT protocol was determined by the treating physician, based on clinical factors such as patient age, baseline visual acuity, and the severity of subfoveal fluid. The patient who received modified double-dose PDT (Patient 1) was relatively older (75 years), had four risk factors for malignant transformation, and presented with poor baseline visual acuity (20/500), which contributed to the decision to administer a more aggressive approach. In contrast, the patient who received half-dose PDT (Patient 4) had the smallest amount of subfoveal fluid (foveal SRF height: 38 μm) and the best baseline visual acuity (20/25), which led to the choice of a more conservative regimen. However, Patient 1 showed only partial resolution of sub-

https://doi.org/10.3349/ymj.2025.0032

foveal fluid following PDT, and Patient 4 demonstrated no anatomical improvement. In comparison, four of the five patients treated with standard-dose PDT achieved complete resolution of subfoveal fluid, and one showed partial resolution, indicating a favorable treatment response. These findings suggest that standard-dose PDT may be considered a primary treatment protocol; however, further large-scale studies using a consistent PDT protocol are needed.

In our study, although the median CDVA improved overall, only one patient showed significant improvement in visual acuity. Visual acuity remained relatively stable in four patients, while two patients experienced a decrease in vision following PDT despite a reduction in subfoveal fluid, with initial visual acuities of 1.4 and 0.4 logMAR, respectively. Thus, a reduction in subfoveal fluid following PDT did not necessarily translate into better visual outcome in all cases. This finding suggests that other factors, such as baseline visual acuity, the timing of PDT relative to fluid onset, and the extent of photoreceptor damage, may influence visual outcomes. Previous studies involving similar patient groups have also shown inconsistent visual outcomes following PDT.[19-22] Rundle, et al.[19] reported corresponding improvement in visual acuity in five out of seven patients. Amselem, et al.[20] observed that, among five patients, visual acuity remained stable in most cases, with one patient experiencing a decrease. Similarly, García-Arumí, et al.[21] reported that among 17 eyes, 11 eyes (65%) showed improvement in visual acuity, 4 eyes (23%) remained unchanged, and 2 eyes (12%) worsened. More recently, Pointdujour-Lim, et al. [22] reported that following PDT, visual acuity improved in 8 eyes (53%), remained stable in 6 eyes (40%), and worsened in 1 eye (7%). When SRF persists over time, both photoreceptors and the retinal pigment epithelium may sustain chronic damage, which can subsequently affect visual outcomes and treatment response. In a recent study by Yaghy, et al.,[30] the authors analyzed changes in photoreceptor morphology over time in cases of SRF associated with choroidal nevus. They reported that photoreceptor morphology evolved from normal to shaggy, then retracted, and eventually absent, as the duration of SRF increased, and that the presence of shaggy photoreceptors appeared to be more indicative of chronic SRF rather than malignant transformation. In our study, OCT performed prior to PDT revealed shaggy photoreceptors in two out of seven patients, and retracted photoreceptors in four patients. These photoreceptor changes may have contributed, at least in part, to the limited visual improvements observed even after subfoveal fluid resolution. Further research should explore whether subjective visual symptoms or vision quality, measured through methods beyond simple visual acuity, show improvement, and should also assess the long-term visual prognosis after PDT.

A retrospective study by García-Arumí, et al.[21] examined 17 patients with symptomatic choroidal nevus and SRF who underwent standard-dose PDT. Among 9 patients (53%) who showed complete resolution, two experienced recurrence at 21 months and 54 months, respectively. Although the timing and frequency of SRF recurrence observed in that study appeared later and less frequent than in ours, it is important to note that recurrence was assessed only among patients who had achieved complete SRF resolution. Among those, one patient achieved complete resolution after three PDT sessions, and another after two sessions. Furthermore, three patients failed to achieve complete resolution despite receiving two or three PDT sessions, which suggests that even with repeated PDT, there may be limitations in achieving sustained subfoveal fluid control. In another study, Pointdujour-Lim, et al.[22] reported that among the 15 patients, nine achieved complete resolution of subfoveal fluid after standard-fluence PDT. Of the 15, five patients underwent a second PDT session; among them, three achieved CR, one showed no significant change, and the remaining one experienced worsening of the subfoveal fluid. Although they did not report on subfoveal fluid recurrence or clarify whether the second PDT session was performed due to an insufficient initial response or a recurrence after initial improvement, the median interval between the first and second PDT sessions closely aligned with the recurrence interval observed in our study.

Taken together, the decision to perform repeat PDT in patients who show poor response to the initial treatment or experience recurrence remains a clinical challenge. In our case series, Patient 4 showed no subfoveal fluid response following PDT. Since a half-dose PDT was administered, an additional full-dose PDT session could have been considered. However, the patient was lost to follow-up 3 months after the initial treatment, precluding further interventions, including repeat PDT. For patients who initially responded to PDT but later experienced recurrence, additional PDT could be cautiously considered. Nevertheless, due to concerns about the long-term durability of PDT and the potential risk of photoreceptor damage, we adopted a conservative, observation-based approach, and no repeat PDT was performed during the follow-up period. Although alternative strategies, such as intravitreal anti-VEGF agents, may be considered, the current evidence is limited due to their modest efficacy and the potential concern regarding interference with malignant transformation.[31] Given these uncertainties, further studies are warranted to identify which patients are more prone to recurrence and who may benefit from additional treatment.

This study is the first to report the effectiveness of PDT for choroidal nevus-related subfoveal fluid in Asian patients, making direct comparisons with other studies challenging. Possible factors contributing to differing treatment responses in Asian populations may include genetic variations, pigmentation, and environmental influences. Further research with larger and ethnically diverse cohorts is needed to determine whether racial differences affect treatment outcomes and prognosis.

The major limitations of this study include its retrospective observational design and small sample size, due to the rarity of

the disease. Additionally, variables such as follow-up duration, PDT dose, and initial visual acuity make it difficult to derive definitive conclusions. Future studies with larger patient cohorts and longer follow-up periods are necessary. Further analysis of factors related to PDT outcomes, including fluid recurrence, will provide better insight into prognosis after PDT.

Despite these limitations, PDT appears to be a viable treatment option for choroidal nevus with subfoveal fluid, producing a significant reduction in subfoveal fluid at 1 month post-treatment, except in the patient who received half-dose PDT. However, one-third of the initially responsive patients experienced recurrence within 6 months, indicating that a considerable proportion face challenges in maintaining long-term fluid absorption. These findings, which were not fully addressed in previous studies, highlight the need for greater attention to patient education, treatment strategies, and long-term follow-up, even after complete fluid resolution.

ACKNOWLEDGEMENTS

This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) under RS-2023-00208518 (C.S.L.).

AUTHOR CONTRIBUTIONS

Conceptualization: Christopher Seungkyu Lee. Data curation: Jin Yeong Kim. Formal analysis: Jin Yeong Kim. Funding acquisition: Christopher Seungkyu Lee. Investigation: Jin Yeong Kim. Methodology: Jin Yeong Kim. Project administration: Christopher Seungkyu Lee. Resources: Christopher Seungkyu Lee. Software: Jin Yeong Kim. Supervision: Christopher Seungkyu Lee. Validation: Christopher Seungkyu Lee. Visualization: Jin Yeong Kim. Writing—original draft: Jin Yeong Kim. Writing—review & editing: Jin Yeong Kim and Christopher Seungkyu Lee. Approval of final manuscript: all authors.

ORCID iDs

Jin Yeong Kim https://orcid.org/0000-0001-9896-1851
Christopher Seungkyu Lee https://orcid.org/0000-0001-5054-9470

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