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Phase I/II clinical study of next-generation photodynamic therapy (L-PDT) using talaporfin sodium (*Laserphyrin*®) for cervical intraepithelial neoplasia: Efficacy, safety, and fertility preservation

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ABSTRACT

Background: PDT using Photofrin® (P-PDT) has been applied to over 900 gynecologic tumor cases since 1989, demonstrating excellent efficacy and fertility preservation; however, post-treatment photosensitivity has limited its clinical application for CIN and cervical cancer. This study aimed to establish a safe, effective, and fertility-preserving alternative to cervical conization.

Methods: To overcome photosensitivity, we conducted a prospective Phase I/II clinical study to evaluate the safety, efficacy, oncological control, and fertility outcomes of L-PDT using talaporfin sodium (Laserphyrin®) and a diode laser for CIN grades 2–3. Forty-three women with biopsy-confirmed CIN2–3 were enrolled. Phase I determined the optimal light dose (50, 75, or 100 J/cm^2), and Phase II assessed efficacy and safety at 100 J/cm^2. Talaporfin sodium (40 mg/m^2) was administered intravenously 4 hours before laser irradiation under colposcopic guidance.

Results: Complete response (CR) was achieved in 95% (95% CI: 89.1–100%) at 3 months and 98% (95% CI: 93.2–100%) at 6 months after treatment. Original high-risk human papillomavirus clearance was 92.5% at 3 months and 95% at 12 months. Adverse events were mild and transient, including abdominal pain and low-grade fever. No recurrences occurred during a median follow-up of 66.4 months among patients achieving CR. Among women desiring pregnancy, the conception rate was 74% (23/31) and the live birth rate was 79% (27/34), with a low preterm birth rate of 3.7% (1/27). Conclusions: These results suggest that L-PDT is a safe and highly effective non-excisional treatment for CIN that may contribute to fertility preservation; however, potential advantages over conventional conization and laser vaporization need to be confirmed in comparative studies.

1. Introduction

Cervical cancer remains one of the most common gynecologic malignancies worldwide, particularly in low- and middle-income countries. It is estimated that in 2022 alone, over 600,000 new cases and 340,000 deaths occurred globally, with the vast majority of cases attributable to persistent infection with high-risk types of human papillomavirus (HPV) [1]. In high-income countries, the incidence and mortality of cervical cancer have significantly declined owing to the widespread implementation of cytological screening and HPV vaccination programs. However, in Japan, the situation remains concerning. National screening rates for cervical cancer remain below 50%, and public trust in HPV vaccination was undermined for years following suspension of governmental recommendations in 2013—leading to persistently low vaccination uptake among young women until recently [2]. As a result, the prevalence of cervical intraepithelial neoplasia (CIN), particularly CIN2 and CIN3, remains high, especially among women in their 20s and 30s—coinciding with peak reproductive age [3]. Concurrently, social trends such as delayed childbearing have led to an increase in pregnancies among women aged 35 and older [4], heightening the clinical demand for uterine-preserving treatments that do not compromise future fertility. There is an urgent need for effective conservative

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management strategies for high-grade CIN and early-stage cervical cancer that combine oncologic safety with fertility preservation, particularly in Japan where HPV vaccination uptake and screening rates remain suboptimal.

Currently, cervical conization remains the standard treatment for high-grade CIN and microinvasive cervical carcinoma (FIGO stage Ia1) [5]. This surgical technique allows for complete excision of the lesion and histopathological confirmation of disease extent. However, conization is not without drawbacks. Multiple studies have documented that excisional procedures of the cervix are associated with significant obstetric complications, including an increased risk of second-trimester pregnancy loss and preterm delivery, due to cervical shortening and insufficiency [6]. A landmark meta-analysis published in The Lancet reported that women undergoing cervical conization had a significantly elevated risk of preterm birth (odds ratio of cold knife conization: 2.59; 95% CI: 1.80–3.72; odds ratio of LLETZ: 1.70; 95% CI: 1.24–2.35) compared to the general population [7]. This association was even more pronounced in women who underwent repeat procedures or had large tissue resections. As fertility preservation becomes a priority in the management of CIN among young women, the development of effective non-surgical alternatives to conization has become an important research focus.

Photodynamic therapy (PDT) represents a promising minimally invasive and fertility-sparing treatment for cervical neoplasia. PDT involves the administration of a photosensitizer that preferentially accumulates in neoplastic tissues, followed by irradiation with light of a specific wavelength. This activation triggers the generation of singlet oxygen and reactive oxygen species, leading to selective cytotoxic effects on dysplastic cells while preserving surrounding normal tissues [8]. Our institution was among the first to develop a protocol for porfimer sodium (Photofrin®)-based PDT (P-PDT) for cervical lesions, and we have applied this method in over 900 cases of CIN and early cervical cancer. In these clinical applications, P-PDT has demonstrated robust efficacy in inducing complete remission (CR) of high-grade lesions while maintaining cervical anatomy and functionality—key factors for successful future pregnancies [9,10]. Moreover, the safety profile of P-PDT has been favorable, with relatively few systemic side effects or long-term sequelae. However, P-PDT is associated with several logistical limitations: it requires hospitalization for drug administration and light shielding due to prolonged photosensitivity (up to four weeks), and the laser equipment (e.g., excimer dye laser or YAG-OPO systems) is large and requires specialized maintenance [11]. These constraints have limited the broader adoption of P-PDT, especially in smaller clinics and outpatient settings.

To overcome the limitations of P-PDT, second-generation photosensitizers such as talaporfin sodium (Laserphyrin®) have been developed. Talaporfin has a favorable pharmacokinetic profile, characterized by rapid clearance from the body and a significantly shorter photosensitivity window—allowing patients to resume normal indoor lighting exposure after just two weeks [12]. In Japan, Laserphyrin has been approved for PDT in early-stage lung cancer (2003) [12], malignant brain tumors (2013) [13], and recurrent esophageal cancer (2017) [14], demonstrating efficacy comparable to that of Photofrin but with reduced adverse effects. Furthermore, the semiconductor diode laser used with talaporfin sodium is compact (approximately 14 kg), portable, and easy to operate, facilitating the expansion of PDT to outpatient and resource-limited settings [14]. Despite its promising characteristics, clinical trials of Laserphyrin-PDT (L-PDT) for cervical dysplasia in Japan have been limited, and its efficacy and safety for this indication remain under-investigated. Notably, Photolon—a structurally similar chlorin e6 derivative—has been widely used in countries such as Russia and Belarus for the treatment of CIN, with reported complete response rates exceeding 90% and HPV clearance in more than half of cases after three months [15].

To address this gap, we conducted a Phase I/II prospective clinical trial to evaluate the safety, efficacy, and long-term outcomes of L-PDT in women with histologically confirmed high-grade cervical intraepithelial neoplasia (HSIL). Specifically, we aimed to assess the complete response rate and the rate of high-risk HPV clearance at 3 and 6 months post-treatment, gynecological and obstetric outcomes during long-term follow-up, including the recurrence rate, and pregnancy and preterm birth rates. This study represents the first systematic clinical evaluation of L-PDT for CIN with long-term follow-up in Japan and provides important evidence for its potential as a next-generation, fertility-preserving therapeutic option. The findings may offer a clinically meaningful alternative to conization for reproductive-age women diagnosed with CIN2/3, particularly those wishing to avoid surgical excision and its associated reproductive risks.

2. Materials and methods

2.1. Study design and ethics

This study was a single-institution, open-label, phase I/II clinical trial evaluating the safety and efficacy of photodynamic therapy (PDT) using talaporfin sodium (TS) and a diode laser in patients with cervical intraepithelial neoplasia (CIN) grade 2 or 3. The study was conducted in accordance with the Declaration of Helsinki and the Ethical Guidelines for Clinical Research of the Japanese Ministry of Health, Labour and Welfare (MHLW). The protocol was approved by the Institutional Review Board of our institution and registered in the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN000022113).

2.2. Patients

2.2.1. Eligibility criteria

Participants were eligible if they met the following criteria: (1) female patients aged ≥20 years; (2) histologically confirmed CIN2 or CIN3 lesions according to the 2012 Japanese guidelines; (3) Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1; (4) adequate organ function including: WBC ≥4,000/mm^3, hemoglobin ≥10.0 g/dL, platelets ≥100,000/mm^3, AST and ALT ≤2× institutional upper limit, total bilirubin ≤2.0 mg/dL, and creatinine and BUN within institutional normal range; (5) refusal to undergo standard treatments such as conization and provided written informed consent; (6) able to be hospitalized as required.

2.2.2. Exclusion criteria

Patients were excluded for the following: (1) presence of glandular dysplasia, adenocarcinoma in situ, or invasive carcinoma; (2) unsatisfactory colposcopy findings (TZ type 3); (3) history of other cancers; (4) severe uncontrolled systemic illness; (5) prior cervical conization or PDT; (6) history of photosensitivity or use of photosensitizing drugs; (7) history of porphyria; (8) pregnancy or breastfeeding; (9) concurrent participation in another clinical trial; or (10) judged by the investigator to be unsuitable.

2.3. Phase I: Dose escalation study

In phase I, TS was administered intravenously at a fixed dose of 40 mg/m^2. Four hours post-administration, colposcopy-guided blue light excitation was used for photodynamic diagnosis (PDD) to assess TS uptake in lesions. Cervical biopsies were performed, and uptake was confirmed via fluorescence microscopy by detecting intracellular localization of TS.

The primary endpoint was the assessment of dose-limiting toxicities (DLTs) related to PDT. Secondary endpoints included adverse events, toxicity, and preliminary efficacy. Diode laser fluence was escalated in three levels: 50 J/cm^2 (step 1), 75 J/cm^2 (step 2), and 100 J/cm^2 (step 3), each with a fixed fluence rate of 150 mW/cm^2. A minimum of 3 patients per each step were enrolled. If no DLT was observed in 28 days, escalation proceeded. If 1 of 3 patients experienced a DLT, 3 more were added. The maximum tolerated dose (MTD) was defined when ≥2 of 3 or ≥3 of 6 patients experienced a DLT. The recommended dose (RD) was defined as the dose below MTD. If no DLT occurred at level 3, it was designated the RD for phase II.

2.4. PDT procedure

We have developed a new Laserphyrin PDT (L-PDT) protocol for CIN and cervical cancer, based on Photofrin PDT laser irradiation method established for uterine cervical cancer by Muroya, Sakamoto et al. (1999) [9–11] and Yamaguchi et al. (2005) [16], the Laserphyrin PDT protocol for lung cancer developed by Kato, Furukawa et al. (2003) [12], and the Laserphyrin PDT protocol esophageal cancer developed by Yano, Muto et al. (2012) [17].

TS (100 mg) was reconstituted in 4 mL of saline and administered slowly at 40 mg/m^2 intravenously. At 4–6 hours post-administration, lesions were irradiated with 664 nm wavelength diode laser.

2.4.1. Colposcopic irradiation

In the phase I study, the starting fluence was 50 J/cm2 (step 1), with a fixed fluence rate of 150 mW/cm2. Lesions were irradiated with diode laser at 50, 75, 100 J/cm^2 per 20mm circular spot using a straight type laser fiber under direct colposcopic visualization.

Circular spot irradiations were overlapped to fully cover the lesion, resembling the Olympic rings.

2.4.2. Cervical canal irradiation

A circumferential side-firing cervical probe was inserted along the cervical canal to a depth of 20 mm under colposcopy guidance. Cervical irradiation was performed twice, before and after the fiber was withdrawn 10 mm at a time.

2.5. Safety assessments

All patients underwent baseline physical examination, hematological and biochemical analyses, electrocardiogram, and chest X-ray. Post-PDT, adverse events were monitored weekly for 28 days using the CTCAE v4.0 criteria.

DLT was defined as any of the following: (1) persistent pain requiring opioid analgesia for ≥4 days; (2) grade ≥2 fever for ≥4 days despite antipyretics; (3) grade ≥3 cervical stenosis or hemorrhage without disease progression; (4) grade ≥4 non-hematological toxicity. Skin photosensitivity was assessed via artificial sunlight (25 J/cm^2, 2 cm × 2 cm), and erythema responses were scored on a 0–3 scale.

2.6. Efficacy assessments

Efficacy was evaluated via cervical cytology and punch biopsy 3 months after PDT. Responses were classified as:

CR (Complete Response): No lesion detected in cytology, colposcopy, or histopathology.

PR (Partial Response): Lesions improved but residual abnormalities persisted.

SD (Stable Disease): No significant change in lesion status.

PD (Progressive Disease): Worsening of any evaluation parameter.

Patients below PR were re-evaluated at 6 months. The CR rate was used as the primary efficacy outcome.

2.7. HPV genotyping

HPV genotyping was performed using the Linear Array HPV Genotyping Test (Roche Molecular Systems, USA) on residual cytology specimens. This PCR-based assay identifies 37 mucosal HPV types. For this study, genotyping focused on 13 high-risk carcinogenic types: HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68.

2.8. Phase II study

Phase II evaluated the efficacy and safety of PDT using the RD (100 J/cm^2) established in phase I. The same TS dose (40 mg/m^2) and 664 nm laser were used. The treatment effect was classified as CR, PR, SD, or PD per the phase I criteria. Safety endpoints included adverse events and skin photosensitivity reactions as previously described.

2.9. Long-term follow-up

To evaluate long-term outcomes, patients were followed for more than 5 years. Gynecological outcomes included CIN recurrence and need for additional treatments. Obstetric outcomes included pregnancy rate, delivery mode, and incidence of preterm birth (<37 weeks). These outcomes were compared to historical controls who underwent standard conization therapy.

3. Results

3.1. Phase I: Laser dose escalation study

3.1.1. Patient characteristics

A total of nine subjects were enrolled in the phase I study following informed consent and confirmation of eligibility. All patients received photodynamic therapy (PDT) with talaporfin sodium (TS) administered intravenously at a dose of 40 mg/m^2. In all cases, distinct red TS-derived fluorescence was observed in cervical intraepithelial neoplasia (CIN) lesions adjacent or within squamo-columnar junction (SCJ) and transformation zone, in contrast, weak red fluorescence was observed in the surrounding normal squamous epithelium, during colposcopy under blue light excitation performed 4–6 hours after TS administration, suggesting the preferential accumulation of TS in the CIN lesions. Fluorescence microscopy of frozen biopsy specimens also verified TS localization within the cytoplasm of tumor cells throughout the entire thickness of CIN3 and within the cytoplasm of tumor cells in the basal two-thirds of tumor cells in CIN2, supporting the proof of concept (Fig. 1).

The laser irradiation energy densities evaluated were 50, 75, and 100 J/cm^2, with three patients assigned to each dose level. Baseline patient and lesion characteristics before PDT in the phase I study are summarized in Table 1-1. The median age was 39 years (mean, 37.0 years); four patients were married, and five were unmarried. Three patients had a history of pregnancy, and two had a history of childbirth. Histopathological diagnosis before treatment was CIN2 in four cases (44.4%) and CIN3 in five cases (55.6%). High-risk human papillomavirus (HR-HPV) infection was detected in eight of the nine patients.

3.1.2. Dose-limiting toxicity (DLT)

DLT outcomes are presented in Table 1-2. No DLTs were observed at any dose level, including the highest irradiation energy density of 100 J/cm^2 (step 3). Based on these findings, the recommended dose (RD) for phase II was determined to be 100 J/cm^2.

3.1.3. Safety

All nine patients were evaluated for safety. Adverse events with a potential causal relationship to TS or laser irradiation were recorded as treatment-related side effects. Photosensitivity test results were also assessed for all patients.

All nine patients (100%) experienced at least one treatment-related adverse event (Table 1-2). There were no serious adverse events. Non-serious adverse events included lower abdominal pain in all patients (100%), fever in four (44.4%), and increased ALT, decreased hemoglobin, and photosensitivity in one patient each (11.1%). Grade 2 adverse events included lower abdominal pain in two patients and fever in one. These symptoms resolved to Grade 1 within two days and recovered promptly.

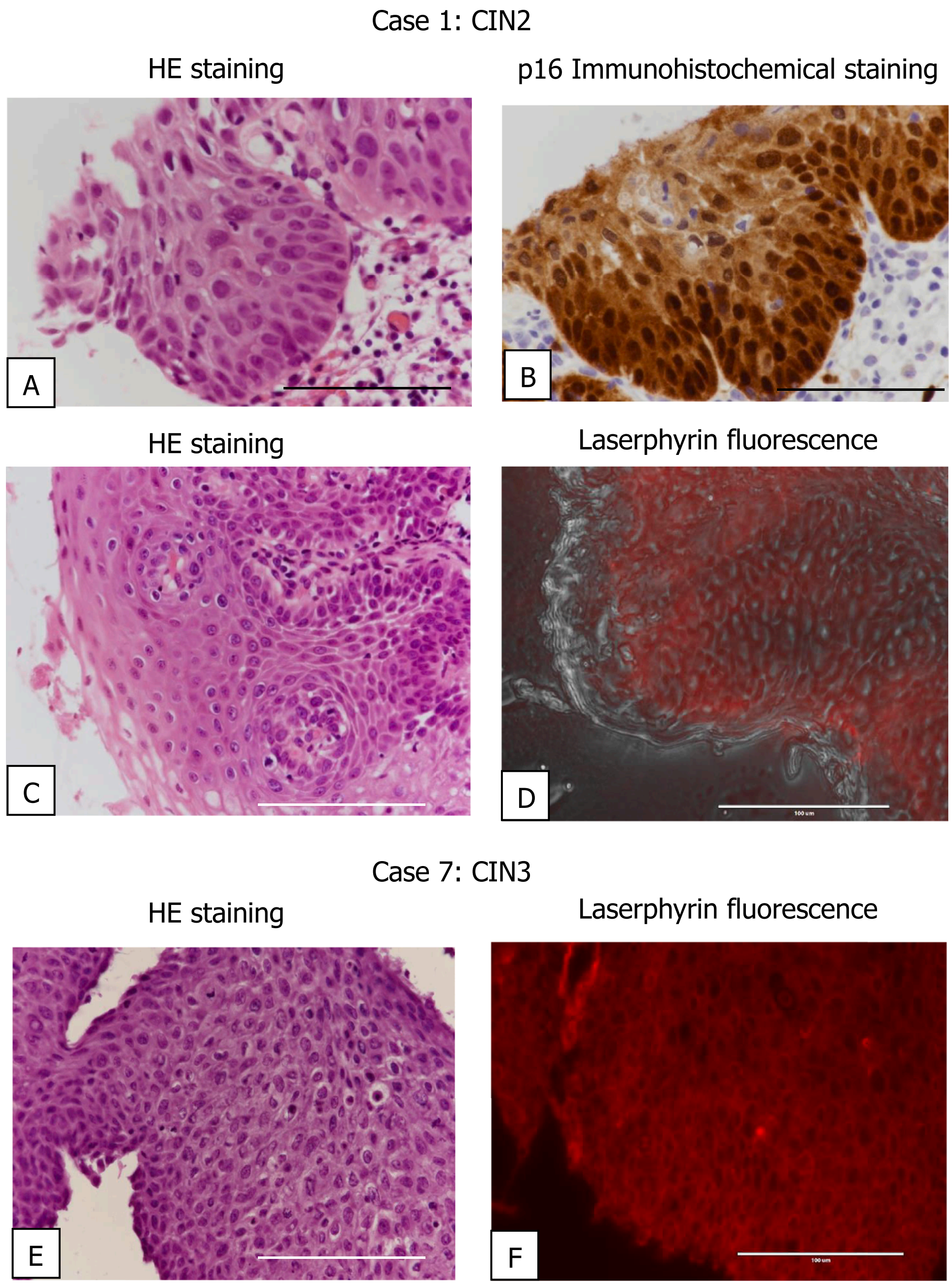

Fig. 1. Histological localization of Laserphyrin® to CIN lesion confirmed by Fluorescence Microscopy.
Representative histological and fluorescence images obtained 4 hours after intravenous administration of Laserphyrin® (talaporfin sodium) are shown. Tissue sections are oriented with the epithelial surface (vaginal side) on the left and the stromal side (uterine side) on the right.
Case 1 (CIN2):
(A) Hematoxylin and eosin (H&E) staining of cervical biopsy specimen (scale bar = 50 μm).
(B) Immunohistochemical staining for p16 performed on the serial section of (a), showing p16 expression in approximately half of the atypical epithelial cells (scale bar = 50 μm).
(C) Another H&E-stained section from the same CIN2 lesion (scale bar = 100 μm).
(D) Fluorescence microscopy image of the serial section of (c), demonstrating Laserphyrin®-derived red fluorescence predominantly localized to the basal two-thirds of the dysplastic epithelium, indicating preferential drug accumulation in CIN2 lesions (scale bar = 100 μm).
Case 7 (CIN3):
(E) H&E staining of cervical biopsy specimen showing CIN3 (scale bar = 100 μm).
(F) Fluorescence microscopy image of the serial section of (e), showing Laserphyrin®-derived fluorescence distributed throughout the full thickness of the neoplastic epithelium, consistent with extensive intratumoral drug accumulation (scale bar = 100 μm).
These findings demonstrate preferential intratumoral accumulation of Laserphyrin® in CIN lesions, with fluorescence distribution varying according to dysplasia grade, supporting the pharmacological rationale and proof of concept for Laserphyrin-based photodynamic therapy (L-PDT).

Table 1-1
Baseline patient and lesion characteristics before L-PDT in the phase I study.

Phase I Step I	50J/cm2	Age (y)	Marriage	Pregnancy	Parity	Cytology	Histology	HPV genotype
No.1		29	married	0	0	ASC-H, moderate dysplasia	**CIN2 (moderate)**	**35**
No.2		41	single	1	0	HSIL, CIS	**CIN3 (severe)**	**52**
No.3		42	single	0	0	HSIL, moderate dysplasia	**CIN2 (moderate)**	**16**
Phase I Step II	**75J/cm2**							
No.4		31	married	1	1	HSIL, severe dysplasia	**CIN3 (severe)**	negative
No.5		35	single	0	0	HSIL, CIS	**CIN3 (severe)**	**33**
No.6		35	s–>m	0	0	HSIL, moderate dysplasia	**CIN2 (moderate)**	**58**
Phase I Step III	**100J/cm2**							
No.7		39	married	2	1	HSIL, severe dysplasia	**CIN3 (severe)**	**16**
No.8		41	married	0	0	HSIL, moderate dysplasia	**CIN3 (severe)**	**51**
No.9		40	s–>m	0	0	HSIL, severe dysplasia	**CIN2 (moderate)**	**52**

Baseline patient and lesion characteristics before L-PDT in Phase I study.
As laser irradiation dose escalation phase I study, three cases for step I, II and III were irradiated at 50, 75 and 100 J/cm2, respectively.
Abbreviations: Pregnancy: Pregnancy times before PDT; Parity: Delivery times before PDT; HPV: human papillomavirus;
ASC-H: Atypical Squamous Cells cannot exclude HSIL; HSIL: High-grade squamous intraepithelial lesion;
HSIL, CIS: HSIL estimating Carcinoma in situ; CIN2: Cervical Intraepithelial Neoplasia grade 2; CIN3: Cervical Intraepithelial Neoplasia grade 3;
moderate: Moderate dysplasia; severe: Severe dysplasia.

Table 1-2
Hematological and non-hematological toxicity in the phase I study.

Phase I	Step I (50J/cm2), n = 3				Step II (75J/cm2), n = 3				Step III (100J/cm2), n = 3				Total (any grade, %)
	Grade				Grade				Grade				
	1	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	
Hemoglobin decrease	0	0	0	0	0	0	0	0	**1**	0	0	0	**1 (11%)**
White blood cell decreased	0	0	0	0	0	0	0	0	0	0	0	0	
Neutrophil count decreased	0	0	0	0	0	0	0	0	0	0	0	0	
Platelet count decreased	0	0	0	0	0	0	0	0	0	0	0	0	
Fever	**1**	0	0	0	**1**	**1**	0	0	**1**	0	0	0	**4 (44%)**
Abdominal pain	**3**	0	0	0	**2**	**1**	0	0	**2**	**1**	0	0	**9 (100%)**
Anorexia	0	0	0	0	0	0	0	0	0	0	0	0	
Nausea	0	0	0	0	0	0	0	0	0	0	0	0	
ALT increase	**1**	0	0	0	0	0	0	0	0	0	0	0	**1 (11%)**
Photosensitivity	0	0	0	0	0	0	0	0	**1**	0	0	0	**1 (11%)**

No Dose-Limiting Toxicities were observed in any steps of the phase I study
The main side effects were lower abdominal pain during Laser irradiation in G1-2 and fever within one week after PDT in G1-2 level
In the phase I study, photosensitivity in G1 level was observed in only 1 of 9 cases (11%).

Photosensitivity reactions by skin test resolved within 7 days in six patients (66.7%) and within 14 days in the remaining three. No patients exhibited a reaction score of 3 (severe erythema or edema).

3.1.4. Efficacy

Representative colposcopic findings before and after PDT treatment using TS for CIN3 cases are presented in the Fig. 2. Colposcopic findings suggestive of CIN3, such as W2 and P1, observed before PDT treatment, disappeared 1 week after PDT treatment, and the surface of the lesion became necrotic. After 2 weeks, the lesion peeled off and showed true erosion, and after 3 months, the true erosion had repaired and the findings of CIN3 had completely disappeared.

Therapeutic outcomes and HR-HPV status post-treatment for each patient are shown in Table 1-3. All nine patients achieved complete response (CR). Among the eight HR-HPV-positive patients, all tested negative following PDT.

3.2. Phase II study

3.2.1. Patient characteristics

Thirty-four patients were enrolled in the phase II study following informed consent and eligibility screening. All received PDT with TS. Baseline patient and lesion characteristics data before PDT in the phase II study are shown in Tables 2-1. The median age was 32 years (mean, 32.1 years); 13 patients were married and 21 were unmarried. Eight patients had a history of pregnancy, but none had delivered. All patients (100%) were diagnosed with CIN3. HR-HPV infection was detected in 32 patients (94.1%) before treatment.

3.2.2. Efficacy

Treatment responses and post-treatment HR-HPV results are presented in Tables 2-3. CR was achieved in 33 of 34 cases (97.1%), and one patient (2.9%) remained a partial response (PR) at 6 months after PDT. Among two PR cases at 3 months after PDT, one achieved CR at the 6-month follow-up. The other PR case had residual cervical lesions at 6 months despite apparent response at 3 months.

Among the 32 HR-HPV-positive patients before treatment, only 8 remained positive at 3 months post-PDT, and 26 out of 34 tested were negative. Of those 8, three became negative at 6 months. Persistent HR-HPV infection was observed in two cases, including one PR case.

3.2.3. Safety

All 34 patients were included in the safety analysis. No deaths or serious adverse events occurred. Adverse events with a potential causal relationship to TS are detailed in Tables 2-2 and 2-3

All patients (100%) experienced at least one adverse event. Non-serious events included lower abdominal pain (100%), fever (50.0%), increased ALT (11.8%), decreased hemoglobin (8.8%), cervicitis (5.9%), increased ALP (5.9%), photosensitivity (5.9%), and eczema (5.9%). Grade 2 events included lower abdominal pain (n=6), cervicitis (n=2), fever (n=3), and increased ALT (n=1). All resolved promptly with appropriate management. Cervicitis resolved within 7 days with

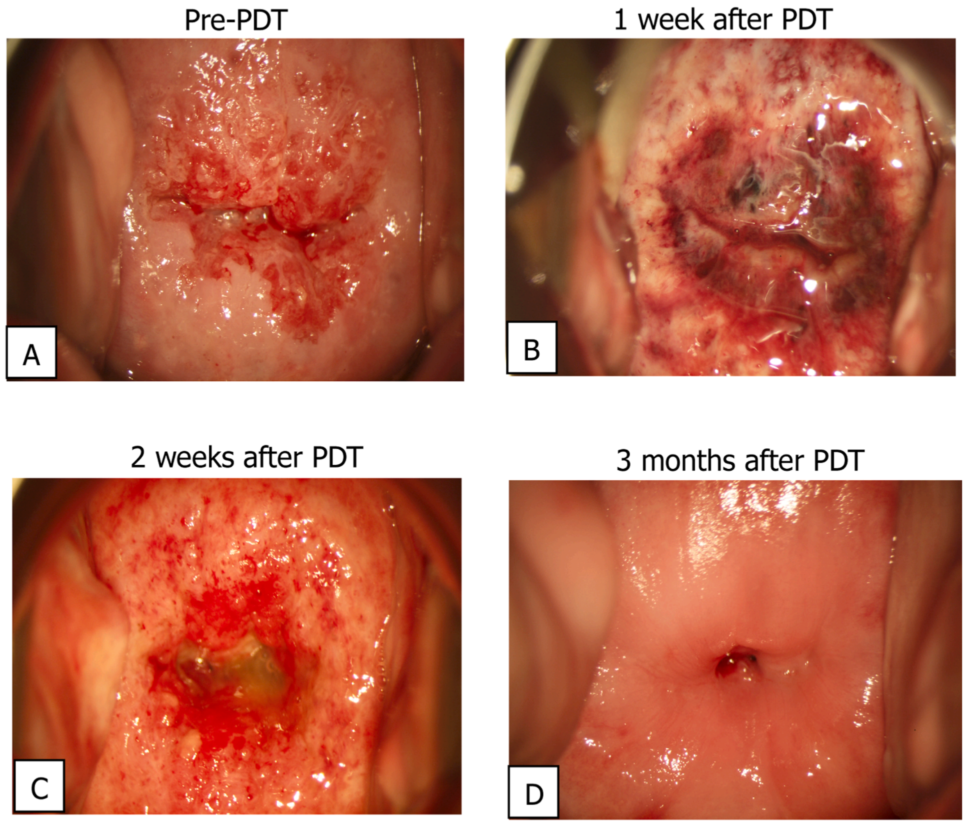

Fig. 2. Colposcopic findings before and after L-PDT in a representative CIN3 case (Case 4).
These photographs show serial colposcopic findings in a patient with CIN3 at baseline (pre-L-PDT), 1 week, 2 weeks, and 3 months after L-PDT.
A. The pre-treatment image shows dense acetowhite epithelium indicating the presence of CIN3.
B. One week after PDT, superficial necrosis of the dysplastic lesion was observed.
C. Two weeks after PDT, whole layers of the dysplastic lesion peeled off, showing true erosion of the uterine cervix.
D. At 3 months after PDT, abnormal colposcopic findings, including dense acetowhite epithelium, had disappeared completely.

antibiotic treatment, and elevated ALT normalized within 21 days.

Photosensitivity reactions by skin test resolved by day 7 in 26 patients (76.5%) and by day 14 in 7 of the remaining 8 patients. No cases exhibited score 2 or 3 reactions.

3.3. Summary of phase I/II study

The phase I/II clinical study demonstrated the safety and efficacy of L-PDT using a diode laser and talaporfin sodium. The main adverse events with a potential causal relationship to TS were lower abdominal pain and fever, primarily of Grade 1 or 2 severity. Photosensitivity (Grade 1) within two weeks occurred in only 2 of 43 patients. Histological disappearance of CIN2/3 was achieved in 41 of 43 patients (95.3%) at 3 months and in 42 of 43 (97.7%) at 6 months post-treatment. These results suggest that L-PDT has a favorable safety profile, particularly regarding photosensitivity, compared to P-PDT, and demonstrates strong therapeutic potential. (Table 3)

3.4. Gynecological and obstetrical outcomes

No recurrences were observed among the 42 patients who achieved CR during a median follow-up period of 66.4 months (range: 6.5~97.9months), resulting in a recurrence rate of 0%. Regarding fertility outcomes post-PDT, 20 patients gave birth to 27 healthy infants, including three preterm deliveries at 30, 33, and 36 weeks. Only one case (delivery at 33 weeks) was thought to be attributable to cervical factors, but this case also did not have cervical incompetence as the patient delivered at term 2 years later. Excluding cesarean sections due to umbilical cord entrapment or placenta previa, the preterm birth rate related to cervical factor was low (1/27; 3.7%) (Table 5).

4. Discussion

Photodynamic therapy (PDT) has gained increasing attention as a minimally invasive therapeutic modality for cervical intraepithelial neoplasia (CIN), especially in the context of fertility preservation and reduced procedural morbidity. PDT utilizes tumor-selective photosensitizers activated by light of a specific wavelength to produce reactive oxygen species, primarily singlet oxygen, that induce selective cytotoxicity in dysplastic and neoplastic tissues. This mechanism not only spares the surrounding normal cervical epithelium but also preserves stromal and anatomical integrity, making PDT a particularly attractive option for women of reproductive age.

Historically, porfimer sodium (Photofrin®), a first-generation photosensitizer, has been used in PDT for CIN and early-stage cervical cancer in Japan. However, the widespread adoption of porfimer sodium-based PDT (P-PDT) has been limited due to significant drawbacks such as prolonged photosensitivity necessitating up to four weeks of post-treatment light avoidance and the need for large, costly laser systems [11]. In contrast, talaporfin sodium (Laserphyrin®), a second-generation photosensitizer, offers a more favorable pharmacokinetic profile with a shorter half-life and light-shielding requirement of approximately two weeks [18]. Additionally, talaporfin sodium is compatible with compact, diode laser systems, improving accessibility and ease of use in clinical settings [17,19].

In Japan, porfimer sodium (Photofrin®)-based photodynamic therapy has been established as the standard PDT regimen for cervical intraepithelial neoplasia. While direct comparison between different

Table 1-3
The efficacy and prognosis of PDT in the phase I study.

Phase I Step I	50J/cm2	Colposcopic irradiation	Cervical irradiation	Total irradiation dose	Response of PDT	HR-HPV genotype 3M after PDT	HR-HPV genotype 6M after PDT	HR-HPV genotype 12M after PDT	Oncologic outcome	Obstetric outcome	Duration (days)
No.1		φ20mm, 6 spots, 300J	10mm, 2 times, 100J	400J	**CR**	negative	negative	**18** (new)	NED	1G1P	2618
No.2		φ20mm, 10 spots, 500J	10mm, 2 times, 100J	600J	**CR**	negative	negative	negative	NED	0G0P	2206
No.3		φ20mm, 9 spots, 450J	10mm, 2 times, 100J	550J	**CR**	negative	negative	negative	NED	0G0P	2192
Phase I Step II	**75J/cm2**										
No.4		φ20mm, 11 spots, 825J	10mm, 2 times, 150J	975J	**CR**	negative	NT	negative	NED	0G0P	639
No.5		φ20mm, 8 spots, 600J	10mm, 2 times, 150J	750J	**CR**	negative	negative	negative	NED	0G0P	2606
No.6		φ20mm, 7 spots, 525J	10mm, 2 times, 150J	675J	**CR**	negative	negative	negative	NED	1G1P	1822
Phase I Step III	**100J/cm2**										
No.7		φ20mm, 7 spots, 700J	10mm, 2 times, 200J	900J	**CR**	negative	negative	negative	NED	1G1P	1825
No.8		φ20mm, 6 spots, 600J	10mm, 2 times, 200J	800J	**CR**	negative	negative	negative	NED	1G0P	2938
No.9		φ20mm, 6 spots, 600J	10mm, 2 times, 200J	800J	**CR**	negative	negative	negative	NED	2G1P	2316

All nine cases of Phase I study showed histological CR and HR-HPV negative after L-PDT
Abbreviations: CR: Complete response; HR-HPV genotype 3M after PDT: high-risk human papillomavirus genotype 3 months after PDT; NT: Not Tested; NED: No Evidence of Disease
Obstetric outcome: number of pregnancy and deliveries abbreviated as _G_P; Duration: observation period (days) after PDT

PDT regimens is limited by heterogeneity in study design, photosensitizers, and evaluation time points, Laserphyrin®-based PDT may be positioned as a next-generation or complementary approach to Photofrin-based PDT. In particular, the shorter duration and lesser severity of skin photosensitivity and the ability to perform photodynamic fluorescence diagnosis immediately prior to treatment represent potential practical advantages.

In our phase I/II study, we evaluated the safety, efficacy, oncologic and reproductive outcomes of L-PDT using talaporfin sodium in patients with CIN. The complete response (CR) rate reached 95% (95% confidence interval: 89.1-100%) at three months and increased to 98% (95% confidence interval: 93.2-100%) by six months. These response rates are consistent with those reported in previous PDT studies (Table 6), although cross-study comparisons must be interpreted with caution because of differences in study design, patient populations, and treatment protocols. For example, Istomin et al. reported a CR rate of 93% in 112 cases of CIN2–3 treated with Photolon, a photosensitizer similar in structure and mechanism to talaporfin sodium [15]. Likewise, Mizuno et al. observed a 70% CR rate using 5-aminolevulinic acid (5-ALA) PDT in 51 patients with CIN [20]. While 5-ALA is less associated with systemic photosensitivity, its hydrophilic nature limits cellular membrane and interstitial tissue penetration, which may partially explain the lower response rates. 5-ALA itself is a prodrug that is metabolically converted intracellularly to protoporphyrin IX (PpIX), which acts as the actual photosensitizer, and its diffusion characteristics differ from those of chlorin-based agents such as talaporfin sodium. Thus, talaporfin sodium, with its deeper therapeutic penetration at 664 nm and favorable tumor affinity, may provide consistent treatment responses, although these observations are based on indirect comparisons and should be interpreted cautiously [21]. When compared with the negative margin rate of 84.8% after conization for CIN3 reported by Mikami et al., the lower limit of the 95% confidence interval (93.2%) for the CR rate with L-PDT exceeded this benchmark, suggesting potential superiority to conization. However, this comparison is indirect and does not allow a definitive conclusion regarding superiority over conization [22].

Recent evidence (2023–2025) further contextualizes our findings and supports the role of PDT as a uterus-preserving treatment option for HSIL/CIN2–3. A multicenter retrospective cohort and matched case–control analyses from China comparing hematoporphyrin monomethyl ether (HMME, HiPorfin) -based photodynamic therapy with LEEP reported comparable lesion regression and HPV eradication, with fewer adverse events after PDT and no excess recurrence during follow-up (Scientific Reports 2024) [30,31]. Two comparative studies of topical 5-aminolevulinic acid (5-ALA)-mediated PDT versus LEEP—one in the Photodiagnosis Photodyn Ther. 2024 and another in Pharmaceutics 2024—demonstrated similar effectiveness for histologic regression and HPV clearance, with a more favorable side-effect profile for PDT, underscoring the fertility-sparing potential of non-excisional therapy [23,32]. Long-term follow-up after ALA-PDT (median 43.5 months) showed durable CR (95.8%) and high HPV clearance (83.6%) with minimal complications (Photodiagnosis Photodynamic Therapy 2024) [33]. Taken together with our L-PDT outcomes, these data suggest that standardized PDT protocols—especially those addressing endocervical involvement—can achieve oncologic control comparable to excision while preserving cervical integrity.

Another crucial parameter in evaluating the success of CIN therapy is human papillomavirus (HPV) clearance, given the well-established etiological role of high-risk HPV (HR-HPV) in cervical dysplasia and progression to malignancy. Our study demonstrated total HR-HPV clearance in 80.0% (original HR-HPV clearance in 92.5%) of pre-PDT HR-HPV-positive patients at 3 months and in 85.0% (original HR-HPV clearance in 95.0%) at 12 months post-treatment (Table 4). These results are promising, particularly when compared with the HPV clearance rates reported in previous PDT studies. Istomin et al. noted HR-HPV clearance in 53% of cases treated with Photolon [15], while Mizuno et al. observed a rate of 79.4% using 5-ALA PDT [20]. A retrospective

Table 2-1
Baseline patient and lesion characteristics before L-PDT in the phase II study.

Phase II 100J/cm2	Age (y)	Marriage	Pregnancy	Parity	Cytology	Histology	HPVgenotype
No.1	24	s–>m	0	0	HSIL, severe	**CIN3 (severe)**	**16**
No.2	30	single	1	0	HSIL, CIS~MIC	**CIN3 (severe)**	**58**
No.3	31	single	0	0	HSIL, moderate	**CIN3 (severe)**	**16,18**
No.4	34	married	0	0	HSIL, severe	**CIN3 (severe)**	**58**,66
No.5	41	single	1	0	HSIL, CIS	**CIN3 (severe)**	**18**
No.6	30	s–>m	0	0	HSIL, severe	**CIN3 (severe)**	**16**, 51
No.7	28	s–>m	0	0	HSIL, severe	**CIN3 (severe)**	**18**
No.8	33	s–>m	2	0	HSIL, severe	**CIN3 (severe)**	**16,31,52**
No.9	25	single	0	0	HSIL, severe	**CIN3 (severe)**	**16**
No.10	33	married	0	0	HSIL, CIS	**CIN3 (severe)**	**58**
No.11	25	single	0	0	HSIL, severe	**CIN3 (severe)**	**16**
No.12	37	single	0	0	HSIL, CIS	**CIN3 (CIS)**	**31**
No.13	36	married	0	0	HSIL, severe	**CIN3 (severe)**	**58**
No.14	30	married	0	0	HSIL, severe	**CIN3 (CIS)**	negative
No.15	36	married	0	0	HSIL, severe	**CIN3 (CIS)**	**16,52**
No.16	32	single	0	0	HSIL, severe	**CIN3 (severe)**	**31**
No.17	30	married	0	0	HSIL, severe	**CIN3 (severe)**	**58**
No.18	32	married	0	0	HSIL, severe	**CIN3 (severe)**	negative
No.19	36	s–>m	0	0	HSIL, severe	**CIN3 (severe)**	**52**
No.20	37	married	1	0	HSIL, moderate	**CIN3 (severe)**	**52**
No.21	30	s–>m	0	0	HSIL, severe	**CIN3 (severe)**	56, 66
No.22	37	s–>m	0	0	HSIL, severe	**CIN3 (severe)**	**16**, 66
No.23	28	single	0	0	HSIL, severe	**CIN3 (severe)**	**16**
No.24	34	s–>m	1	0	HSIL, moderate	**CIN3 (severe)**	**16**
No.25	37	married	1	0	HSIL, severe	**CIN3 (severe)**	**16**
No.26	35	married	1	0	HSIL, CIS	**CIN3**	**18**
No.27	25	single	0	0	HSIL, severe	**CIN3 (severe)**	**52**
No.28	34	single	0	0	HSIL, moderate	**CIN3 (severe)**	**52**
No.29	30	single	0	0	ASC-H, severe	**CIN3 (severe)**	**16, 52**
No.30	32	married	0	0	HSIL, severe	**CIN3 (severe)**	**16**
No.31	25	single	0	0	HSIL, severe	**CIN3 (severe)**	**16**
No.32	37	married	0	0	HSIL, CIS	**CIN3 (CIS)**	**52**
No.33	43	married	2	0	HSIL, moderate	**CIN3 (severe)**	**52**
No.34	24	s–>m	0	0	HSIL, severe	**CIN3 (severe)**	**16**, 66

Abbreviations: Pregnancy: Pregnancy times before PDT; Parity: Delivery times before PDT;
HPV: human papillomavirus; ASC-H: Atypical Squamous Cells cannot exclude HSIL;
HSIL: High-grade squamous intraepithelial lesion;
CIN3: Cervical Intraepithelial Neoplasia grade 3; severe: Severe dysplasia; moderate: Moderate dysplasia;
CIS: Carcinoma in situ; MIC: Microinvasive carcinoma.

Table 2-2
Hematological and non-hematological toxicity in the phase II study.

Phase II	(100J/cm2), n = 34				Total (any grade, %)
	Grade				
	1	**2**	**3**	**4**	
Anemia	**3**	0	0	0	**3 (8.8%)**
White blood cell decreased	0	0	0	0	
Neutrophil count decreased	0	0	0	0	
Platelet count decreased	0	0	0	0	
Fever	**14**	**3**	0	0	**17 (50%)**
Abdominal pain	**28**	**6**	0	0	**34 (100%)**
Anorexia	0	0	0	0	
Nausea	0	0	0	0	
ALT increased	**3**	**1**	0	0	**4 (11.8%)**
ALP increased	**2**	**0**	0	0	**2 (5.9%)**
Cerivicitis	**0**	**2**	0	0	**2 (5.9%)**
Photosensitivity	**2**	0	0	0	**2 (5.9%)**
Eczema	**2**	0	0	0	**2 (5.9%)**

The main side effects were lower abdominal pain in G1-2 level during Laser irradiation
and fever in G1-2 within one week after PDT. In the phase II study, photosensitivity in
G1 level was observed in only 2 of 34 cases (6%).

comparison by Wang et al. between 5-ALA PDT and loop electrosurgical excision procedure (LEEP) in patients with high-grade squamous intraepithelial lesions (HSIL) revealed HPV clearance rates of 81.0% with PDT versus 62.0% with LEEP, along with a significantly lower incidence of adverse events in the PDT group [23].

From a safety standpoint, our trial confirmed that L-PDT is well tolerated. The most common adverse events were transient lower abdominal pain and low-grade fever, classified as Grade 1–2 according to CTCAE v4.0. Importantly, only two cases of mild photosensitivity reactions were observed within two weeks, both resolving without intervention. These findings affirm that L-PDT offers a safer profile compared to P-PDT, which has been associated with more frequent and longer-lasting phototoxic reactions [24]. The relatively short duration of light shielding required for talaporfin sodium enhances patient compliance and overall treatment satisfaction.

One of the primary advantages of L-PDT over excisional procedures such as conization or LEEP lies in its preservation of cervical structure and reproductive function. Surgical excision has been associated with increased risks of adverse obstetric outcomes, including cervical insufficiency, preterm birth, and second-trimester miscarriage [25]. A meta-analysis by Arbyn et al. reported a 3.7% recurrence rate in CIN2+ cases with negative margins following conization, along with significantly elevated risks of preterm delivery and low birth weight infants [26]. In contrast, our study observed no recurrence requiring intervention among the 42 patients who achieved CR, over a median follow-up period of 66.4 months (range: 196–2938 days). Only one patient with a partial response underwent conization 3.5 years post-L-PDT, which confirmed residual CIN3 in the endocervical canal deeper than 1.5 cm depth. The resulting recurrence rate of 0% appears favorable compared with the 1.4% recurrence rate (7 of 511 cases) reported for P-PDT by Sakamoto et al. and may support the long-term oncologic efficacy of

Table 2-3
The efficacy and prognosis of PDT in the phase II study.

Phase II	100J/ cm2	Colposcopic irradiation	Cervical irradiation	Total irradiation dose	Response of PDT	HR-HPV genotype 3M after PDT	HR-HPV genotype 6M after PDT	HR-HPV genotype 12M after PDT	Oncologic outcome	Obstetric outcome	Duration (days)
No.1		φ20mm, 6 spots, 600J	10mm, 2 times, 200J	800J	**CR**	negative	negative	negative	NED	2G2P	2603
No.2		φ20mm, 6 spots, 600J	10mm, 2 times, 200J	800J	**CR**	negative	negative	negative	NED	2G2P	2554
No.3		φ20mm, 6 spots, 600J	10mm, 2 times, 200J	800J	**CR**	negative	negative	negative	NED	1G1P	2094
No.4		φ20mm, 6 spots, 600J	10mm, 2 times, 200J	800J	**CR**	negative	negative	negative	NED	0G0P	2690
No.5		φ20mm, 6 spots, 600J	10mm, 2 times, 200J	800J	**PR**	**18**	**18**	**18**	Cone	0G0P	1261
No.6		φ20mm, 5 spots, 500J	10mm, 2 times, 200J	700J	**CR**	negative	**52** (new)	**52** (new)	NED	1G1P	2198
No.7		φ20mm, 5 spots, 500J	10mm, 2 times, 200J	700J	**CR**	negative	negative	negative	NED	2G2P	1906
No.8		φ20mm, 5 spots, 500J	10mm, 2 times, 200J	700J	**CR**	negative	negative	negative	NED	2G2P	2641
No.9		φ20mm, 5 spots, 500J	10mm, 2 times, 200J	700J	**CR**	negative	negative	negative	NED	0G0P	727
No.10		φ20mm, 6 spots, 600J	10mm, 2 times, 200J	800J	**CR**	negative	negative	negative	NED	0G0P	557
No.11		φ20mm, 6 spots, 600J	10mm, 2 times, 200J	800J	**CR**	**16**	negative	**52** (new)	NED	2G0P	2569
No.12		φ20mm, 5 spots, 500J	10mm, 2 times, 200J	700J	**CR**	negative	negative	negative	NED	0G0P	1825
No.13		φ20mm, 5 spots, 500J	10mm, 2 times, 200J	700J	**CR**	negative	negative	negative	NED	2G2P	727
No.14		φ20mm, 5 spots, 500J	10mm, 2 times, 200J	700J	**CR**	negative	negative	negative	NED	1G0P	2543
No.15		φ20mm, 5 spots, 500J	10mm, 2 times, 200J	700J	**CR**	negative	negative	negative	NED	0G0P	453
No.16		φ20mm, 5 spots, 500J	10mm, 2 times, 200J	700J	**CR**	negative	negative	negative	NED	0G0P	1818
No.17		φ20mm, 5 spots, 500J	10mm, 2 times, 200J	700J	**CR**	**52**,68 (new)	**52** (new)	negative	NED	1G1P	2148
No.18		φ20mm, 5 spots, 500J	10mm, 2 times, 200J	700J	**PR->CR**	negative	negative	negative	NED	1G1P	2356
No.19		φ20mm, 5 spots, 500J	10mm, 2 times, 200J	700J	**CR**	negative	negative	negative	NED	2G1P	1906
No.20		φ20mm, 5 spots, 375J	10mm, 2 times, 150J	525J	**CR**	51,68 (new)	51,68 (new)	negative	NED	2G1P	1881
No.21		φ20mm, 5 spots, 500J	10mm, 2 times, 200J	700J	**CR**	negative	56	negative	NED	1G1P	1864
No.22		φ20mm, 5 spots, 500J	10mm, 2 times, 200J	700J	**CR**	**58** (new)	**58** (new)	**58** (new)	NED	0G0P	2270
No.23		φ20mm, 5 spots, 500J	10mm, 2 times, 200J	700J	**CR**	**58** (new)	negative	negative	NED	0G0P	1013
No.24		φ20mm, 5 spots, 500J	10mm, 2 times, 200J	700J	**CR**	negative	negative	negative	NED	0G0P	2191
No.25		φ20mm, 5 spots, 500J	10mm, 2 times, 200J	700J	**CR**	negative	negative	negative	NED	2G2P	1993
No.26		φ20mm, 5 spots, 500J	10mm, 2 times, 200J	700J	**CR**	negative	negative	negative	NED	0G0P	2364
No.27		φ20mm, 5 spots, 500J	10mm, 2 times, 200J	700J	**CR**	negative	negative	negative	NED	0G0P	2197
No.28		φ20mm, 4 spots, 400J	10mm, 2 times, 200J	600J	**CR**	negative	negative	negative	NED	0G0P	1829
No.29		φ20mm, 5 spots, 500J	10mm, 2 times, 200J	700J	**CR**	negative	negative	NT	NED	0G0P	196
No.30		φ20mm, 5 spots, 500J	10mm, 2 times, 200J	700J	**CR**	negative	negative	negative	NED	2G2P	1822
No.31		φ20mm, 5 spots, 500J	10mm, 2 times, 200J	700J	**CR**	**58** (new)	negative	negative	NED	2G2P	2240
No.32		φ20mm, 5 spots, 500J	10mm, 2 times, 200J	700J	**CR**	negative	negative	negative	NED	0G0P	1346
No.33		φ20mm, 5 spots, 500J	10mm, 2 times, 200J	700J	**CR**	negative	negative	negative	NED	1G1P	1910
No.34		φ20mm, 5 spots, 500J	10mm, 2 times, 200J	700J	**CR**	66	**16**, 66	**16**	NED	2G1P	1819

In the phase II study, case No. 5, who had endocervical fibroid polyp and CIN3 lesions in both ectocervix and endocervix, had residual lesion only in the deep endocervix 6 months after PDT, resulting in PR as response to L-PDT.

Abbreviations: CR: Complete response; HR-HPV genotype 3M after PDT: high-risk human papillomavirus genotype 3 months after PDT; NT:Not Tested; NED: No Evidence of Disease;
Obstetric outcome: number of pregnancy and deliveries abbreviated as _G_P; Duration: observation period (days) after PDT.

Table 3
Efficacy of the Phase I/II study on the L-PDT for CIN2-3.

Time after PDT	3 months	6 months
Complete Response Rate	41/43 (95.3%)	42/43 (97.7%)

Complete Responses (CR), showing histological disappearance of CIN2-3, were observed in 41/43, 42/43 cases (95, 98%) at 3 and 6 months after L-PDT, respectively, demonstrating efficacy similar to that of P-PDT.

Table 4
HR-HPV clearance after L-PDT in the Phase I/II study.

Time after PDT	Pre-PDT	3 Months	6 Months	12 Months
HPV genotyped cases	43	43	42	42
Total HR-HPV Cases (%)	40 (93.0%)	8 (18.6%)	7 (16.7%)	6 (14.3%)
Total HR-HPV Clearance		**80.0%**	**82.5%**	**85.0%**
Original HR-HPV Cases (%)	40 (93.0%)	3 (7.0%)	3 (7.1%)	2 (4.8%)
Original HR-HPV Clearance		**92.5%**	**92.5%**	**95.0%**

The clearance rates of original HR-HPV genotypes that caused CIN2-3 before L-PDT
were 92.5, 92.5, 95.0 percent after 3, 6, 12 months, suggesting a different efficacy in
eradicating HR-HPV after L-PDT.
Abbreviations: HR-HPV, high-risk human papillomavirus

Table 5
Gynecologic and obstetric outcomes of the Phase I/II study on the L-PDT for CIN2-3.

Observation period	Range 6.5~97.9 (Median 66.4) months
Recurrence rate	0/42 CR (0.0%)
Premature vaginal delivery rate	1/27 (3.7%)

In 42 cases in which CR was determined 3 to 6 months after LPDT treatment, no recurrence was observed during the observation period (range: 6.5~97.9 months;
median 66.4 months). (Recurrence rate: 0%).
Excluding cesarean sections due to umbilical cord entrapment or placenta previa, the
premature vaginal delivery rate due to a short cervix was low at 1/27 = 3.7%.

L-PDT [10]. However, the differences in study design and follow-up duration limit direct comparison.

The preservation of fertility and favorable obstetric outcomes are particularly compelling. Of the 31 patients in our study who expressed a desire to conceive, 23 successfully became pregnant, resulting in 34 pregnancies and 27 live births. The preterm birth rate among these deliveries was 3.7% (95% confidence interval: 0–10.8%), which appeared lower than the 25% reported in patients following conization procedures [27]. However, this comparison is indirect and should be interpreted with caution. This suggests that L-PDT not only avoids anatomical distortion of the cervix but also maintains its functional integrity including cervical mucin production. These findings are consistent with the results of Choi et al., who demonstrated successful pregnancy and delivery following PDT for CIN, with no increase in preterm delivery rates compared to untreated controls [28].

In terms of technological considerations, L-PDT offers logistical advantages due to the compact nature of the diode laser systems and the ease of outpatient administration. Unlike laser conization or cold knife procedures, L-PDT does not require general anesthesia, minimizing hospitalization and associated healthcare costs. Furthermore, since L-PDT can be repeated without cumulative tissue damage, it may serve as an alternative for patients with recurrent lesions or incomplete response to initial treatment, avoiding repeated excisions which exacerbate cervical shortening and obstetric complications. A cost-effectiveness analysis by Soergel et al. in Germany comparing conisation and HAL-based photodynamic therapy for CIN revealed that, when accounting for treatment efficacy, re-treatment rates, and added costs from perinatal morbidity due to conisation, the total cost per conisation was approximately €2,046, whereas PDT was about €1,558, supporting the economic advantage of PDT over conisation in this context [29].

Recent advances in basic research provide further mechanistic rationale for the clinical application of L-PDT. In particular, the role of ATP-binding cassette (ABC) transporters such as ABCG2 has been elucidated as a key determinant of photosensitizer efflux and treatment resistance in PDT [34,35]. Experimental models have demonstrated that inhibition or modulation of these transporters enhances intracellular retention of photosensitizers, thereby increasing PDT efficacy [36]. Screening studies further suggest that several clinically used photosensitizers differ in their susceptibility to ABC transporter efflux; notably, talaporfin sodium is not a substrate of ABCG2, P-gp, or MRP1 in vitro [37]. Moreover, the emergence of drug-delivery systems (DDS), including nanoparticle-based carriers and liposomal formulations, has improved tumor selectivity and bioavailability of photosensitizers, reducing off-target toxicity [38–40]. Integration of L-PDT with such DDS platforms or transporter modulators may potentiate therapeutic outcomes in refractory cases and broaden the future clinical utility of PDT in gynecologic oncology.

Despite these encouraging results, several limitations must be acknowledged. The current study, while prospective, was not randomized and had a relatively limited sample size. Additionally, histopathologic confirmation of residual disease post-treatment was limited to cases with cytologic or colposcopic abnormalities, which may underdetect microscopic persistence. Nevertheless, the consistency of our findings with published data supports the reproducibility of L-PDT outcomes. Ongoing multicenter trials are expected to further validate these findings and expand the clinical utility of L-PDT in routine gynecologic practice.

5. Conclusions

To our knowledge, this is the first prospective Phase I/II clinical trial evaluating Laserphyrin®-based PDT for CIN. This phase I/II clinical study demonstrates that photodynamic therapy with talaporfin sodium (Laserphyrin®) and a diode laser achieves high complete response and HPV clearance rates, while maintaining favorable reproductive outcomes and an excellent safety profile. Because L-PDT is non-excisional, it preserves cervical anatomy and may reduce obstetric risks, while also offering advantages such as a shorter and less severe photosensitivity period than P-PDT, supporting its role as a promising next-generation fertility-sparing treatment for CIN2/3. These findings provide a foundation for multicenter trials and may help to position L-PDT as a clinically useful non-excisional option for appropriately selected patients.

Authors' contribution

The authors' contributions to this work are listed below. As principal investigator, Sakamoto M. conceived the study, developed the methodology, performed the study, and reviewed and edited the manuscript. Okamoto A. supervised the study. Sakamoto M, Tanaka T, Umayahara K, Matsuoka K, Hirose S, Hirata M, Fujiwara A, and Takeda S recruited patients for this study. Iwaya K performed cytological and pathological

Table 6
Reference table of representative PDT studies for CIN, especially HSIL.
This table provides a reference summary of representative photodynamic therapy (PDT) studies for CIN, especially HSIL.
Direct comparison among studies should be interpreted with caution because of differences in drugs (photosensitizers or their prodrugs) used for PDT, study design, endpoints, evaluation time points, and follow-up duration.

Drugs used for PDT	Study	Study design PDT type and Cohort	Patient population	CR Rate	HR-HPV Clearance	Comparison	Adverse Events (most frequent)	Follow-up duration
Porfimer sodium (Photofrin®)	9) Muroya et al. Diagn Ther Endosc 1999	Non-controlled observational study Photofrin-PDT for dysplasia, CIS, MIC	n = 131 31 dysplasia, 95 CIS, 4 MIC, 1 VIN	127/131, 96.9% at 2-4 months	No mention	None	Photosensitivity	> 6 months, up to 10 years
Porfimer sodium (Photofrin®)	16) Yamaguchi et al. Oncology 2005	Non-controlled observational study Photofrin-PDT for CIN	n = 105 CIN1+CIN2+CIN3	94/105, 90% at 3 months	52/69, 75% at 3 months	None	Photosensitivity	Median 21.2 months
Chlorin e6 derivative (Photolon®)	15) Istomin et al. PDPDT 2010	Single arm, prospective study Photolon-PDT for HSIL	n = 112 CIN2+CIN3	104/112, 93% at 3 months	47/88, 53.4% at 3 months	None	Mild photosensitivity	12 months, up to 4 years
Talaporfin sodium (Laserphyrin®)	Sakamoto et al. Current study	Single arm, prospective study Lasephyrin-PDT for HSIL	n = 43 CIN2+CIN3	41/43, 95% at 3 mo 42/43, 98% at 6 mo	37/40, 93% at 3 mo 38/40, 95% at 6 mo	None	Transient lower abdominal pain	Median 66.4 months
Hematoporphyrin monomethyl ether (HMME; Hiporfin®)	31) Liu et al. Sci Rep 2024	Retrospective cohort study Hiporfin-PDT vs LEEP for HSIL	n = 104 HSIL, PDT (n = 52) vs HSIL, LEEP (n = 52)	51/52, 98.1% PDT vs 51/52, 98.1% LEEP at 3-6 months, p = 0.508	40/52, 76.9% PDT vs 36/52, 69.2% LEEP at 3-6 months, p = 1.000	LEEP	Photosensitivity with PDT Bleeding with LEEP	Mean 25.4 months
5-aminolevulinic acid (prodrug of PpIX)	20) Mizuno et al. PDPDT 2020	Single arm, prospective study ALA-PDT for CIN	n = 51 CIN1, CIN2, CIN3	36/51, 70.6% at 3 months	79% in CR patients at 3 months	None	Transient vaginal discharge without photosensitivity	Median 37 months
5-aminolevulinic acid (prodrug of PpIX)	32) Wang et al. Pharmaceutics 2024	Retrospective cohort study ALA-PDT vs LEEP for HSIL	n = 92 HSIL, PDT (n = 42) vs HSIL, LEEP (n = 50)	37/42, 88.1% PDT vs 35/50, 70.0% LEEP at 6 months, $p < 0.05$	34/42, 81.0% PDT vs 31/50, 62.0% LEEP at 6 months, $p<0.05$	LEEP	Vaginal discharge with PDT; Bleeding with LEEP	6 months, up to 10 years
5-aminolevulinic acid (prodrug of PpIX)	Qian et al. Front Oncol 2024	Retrospective observational study ALA-PDT for HSIL	n = 40 CIN2+CIN3	26/40, 65% at 3 mo 33/40, 82.5% at 12 mo	27/40, 67.5% at 3 months	None	No severe AEs	12 months, up to 4 years

Abbreviations: CIN, Cervical Intraepithelial Neoplasia; HSIL, High-grade Squamous Intraepithelial Neoplasia, CIS, Carcinoma in situ; MIC, Microinvasive carcinoma; VIN, Vulvar Intraepithelial Neoplasia; PDT, Photodynamic therapy; LEEP, Loop Electrosurgical Excision Procedure CR Rate, Complete Response rate; HR-HPV, High-Risk Human Papillomavirus; mo, months; ALA, 5-aminolevulinic acid; PpIX, protoporphyrin IX.
5-aminolevulinic acid (5-ALA) is a prodrug that is metabolically converted to PpIX, which acts as the actual photosensitizer.

diagnosis of the CIN cases.

Ethical approval and consent to participate

The Ethics committee of Sasaki Foundation approved this study design prior to patient recruitment on March 3rd, 2016, written informed consent was obtained all patients enrolled, and the study was also performed in accordance with the Declaration of Helsinki.

Consent for publication

This article contains some images, but identification of individual patients is not possible. All patients signed informed consent forms prior to participation in the clinical trial.

Data availability

The datasets generated during and analyzed during the current study are on file with our institution according to the protocol and are not publicly available.

CRediT authorship contribution statement

Masaru Sakamoto: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Shuji Takeda:** Resources. **Arisa Fujiwara:** Resources. **Momo Hirata:** Resources. **Sou Hirose:** Resources. **Kazuko Matsuoka:** Resources. **Kenji Umayahara:** Resources, Project administration. **Keiichi Iwaya:** Methodology, Investigation. **Tadao Tanaka:** Supervision, Resources. **Aikou Okamoto:** Supervision.

Declaration of competing interest

All the authors have no conflicts of interest to declare. This study received financial support from the Clinical Research Fund of the Sasaki Foundation Kyoundo Hospital.

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