8) Mimura S., Ito Y., Nagayo T. et al. : Cooperative clinical trial of photodynamic therapy with Photofrin II and excimer dye laser for early gastric cancer. Lasers Surg Med **19** : 168～172, 1996.
9) Hayata Y., Kato H., Huruse K., Kusunoki Y., Suzuki S., Mimura S. : Photodynamic therapy of 168 early stage cancers of the lung and oesophagus : a Japanese multi-centre study. Lasers Med Sci **11** : 255～259, 1996.
10) Mimura S., Otani T. and Okuda S. : Photodynamic therapy for superficial esophageal cancer using an excimer dye laser. Diagn Ther Endoscopy **1** : 99～105, 1994.
11) Mimura S, Narahara H, Otani T., Okuda S. : "Photodynamic therapy for early gastric cancer : its application for wider lesions," in 5th International Photodynamic Association Biennial Meeting, Denis A. Cortese, Editor, Proc. SPIE **2371**, 522～525, 1995.
12) Mimura S, Ichii M and Okuda S : Photodynamic therapy for early gastric cancer using excimer dye laser. Photodynamic Therapy and Biomedical Lasers, Spinelli P, Dal Fante M, Marchesini R Editors, 272～276, Elsevier Science Publishers BV, Amsterdam, 1992.
13) Narahara H., Mimura S., Otani T. and Okuda S. : "The application of photodynamic therapy for gastric cancer using Photofrin II and an excimer dye laser," in the 6th International Photodynamic Association Biennial Meeting at Melbourne in 1996.
14) Mimura S., Narahara H., Otani T. and Okuda S. : "A case report of advanced gastric cancer treated by photodynamic therapy using Photofrin II and an excimer dye laser," in 6th International Photodynamic Association Biennial Meeting at Melbourne in 1996.
15) Okunaka T., Kato H., Konaka C, Sakai H., Kawabe H. and Aizawa K. : A comparison between argon-dye excimer-dye laser for photodynamic effect in transplanted mouse tumor. Jpn J Cancer Res **83** : 226～231, 1992.
16) Takemura T, Umeuchi S, Nakajima S, Sakata I. : "Mechanism of photodynamic therapy (PDT) : investigation of sensitizer dose and light dose-rate effects," in the 5th International Photodynamic Association Biennial Meeting, Denis A. Cortese, Editor, Proc. SPIE **2371**, 351～354, 1995.

Photodynamic Therapy (PDT) for Early Stage Cervical Cancer

Tetsuya Muroya, Y. Suehiro, T. Kunugi, K. Umayahara, T. Akiya,
H. Iwabuchi, H. Sakunaga, M. Sakamoto, T. Sugishita and Y. Tenjin
Dept. of Gynecology, Sasaki Institute, Kyoundo Hospital, Tokyo.

INTRODUCTION

Recent awareness and increasing availability of cervical cancer examinations have increased the discovery rates of dysplasia and CIS. This has resulted in an increase in the number of patients and a lowering of the average age of patients. Among these patients, it is desirable to perform operations to preserve fertility in consideration of the quality of life of each patient.

As an operation that can preserve fertility, conventional conization by cold knife (Sturmdorf operation) has been employed, but recent laser therapy using high-power lasers such as CO_2 laser and YAG laser and Loop Electrosurgical Excision Procedure are frequently employed.

However, it should be noted that these treatments are sometimes accompanied by unexpected bleeding. Also, since the treatment causes pain, anesthesia is necessary in most cases. In addition, a large portion

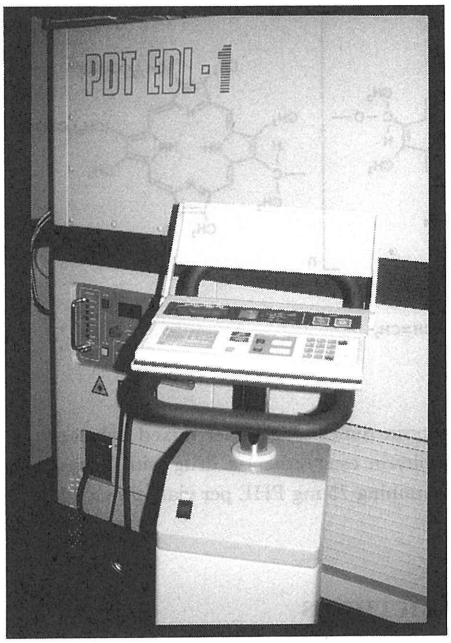


Fig. 1 Excimer Dye Laser (EDL)
The EDL is a low energy pulse laser, and its 630 mm wavelength dye laser is generated when rhodamine 640 pigment solution is irradiated by 308 mm ultraviolet rays generated by an XeCl Excimer laser. The laser wave length is 630～5 mm, width of pulse is 10±5 nsec, and pulse radiation energy is 4～5 mj/pulse maximum. Pulse repeated frequency is 40Hz in normal cases (interchangeable to 40, 60, and 80).

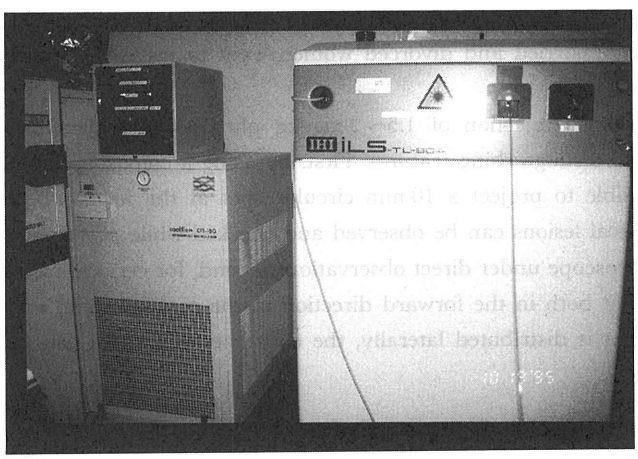


Fig. 2 YAG-OPO Laser
PDT laser in which an optic parametric oscillator (OPO), Q switch pulse YAG laser intensifier is installed. Laser wave is 620～670 nm, pulse width is 7±1nsec, pulse irradiation energy is 6 mj/pulse, and pulse repeated frequency is 50Hz.

of the cervical glands critical for reproduction tends to be lost during the operation.

Most patients want to preserve their fertility. We also perform PDT in high risk patients, elderly patients, and those who refuse surgery. The technique required for PDT is relatively simple, and it can be performed without anesthesia, since it causes no pain or bleeding.

The excimer dye laser (EDL) type of low-power pulsed laser (Fig. 1), has a considerably higher degree of tissue penetration than the argon dye laser (ADL). Also, PDT using the EDL can manage glandular involvement of CIN, and its ability to selectively destroy malignant cells with little effect on normal tissues is noteworthy. Beginning in 1995, we have used a YAG-OPO laser (Fig. 2) with a variable laser wavelength for PDT.

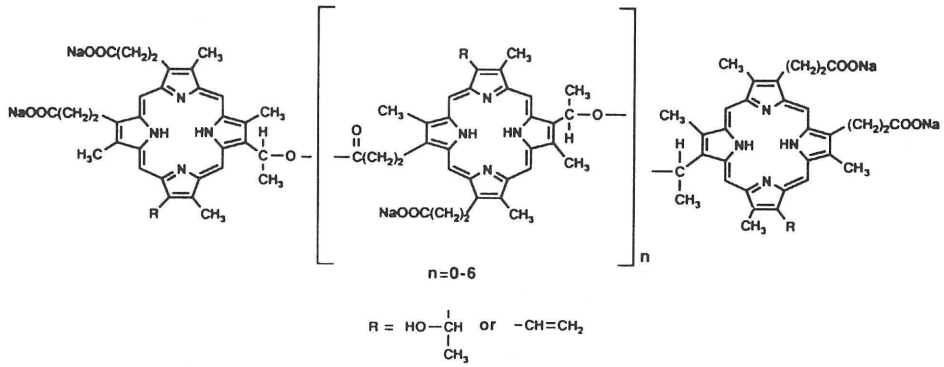


Fig. 3 Porfimer Sodium (PHE)
Tumor affinity photosensitive substance : Porphyrin dimer to octomer mixed substance. Main component is dimer DHE (dihematoporphyrin ester/ether) a drug with a freeze-dried powder consistency with dark red color containing 75 mg PHE per vial (provided by Lederle (Japan), Ltd.).

MATERIALS AND METHODS

PDT was performed on 87 patients during the period from October 1989 through October 1996 (Tables 1 and 2). Except for 16 patients who refused surgery and 1 elderly patient, 70 out of 87 PDT patients wanted to preserve fertility. Many unmarried and divorced women want to preserve fertility (Table 3).

PDT is performed 48 hours after intravenous injection of 1.5～2 mg/kg photosensitizer porfimer sodium (PHE) (Fig. 3). Our method has two distinguishing features. First, by using a colposcope with an optical path for a laser beam, it is possible to project a 10 mm circular spot at the focus where observation is made. With this method, cervical lesions can be observed and checked while performing stable and precise photoradiation via the colposcope under direct observation. Second, for cervical canal treatment, our cervical probe can deliver light both in the forward direction in the cervical canal and circumferentially. Since 70% of the laser light is distributed laterally, the entire cervical canal can be photoradiated.

[1] Colposcope irradiation (spot irradiation)

1. Lesions located in the uterine cervix should be photoradiated at an energy intensity rate of 100 J/cm^2 per spot. The authors use an Olympus laser colposcope (Olympus Opticial Co. Ltd., Tokyo, Japan) under direct observation (Fig 4). The laser irradiation scope provides a 10 mm circular spot at the focus where observation is made. Compared to conventional radiation using cut fibers, more stable and precise photoradiation is now possible.

2. Large amounts of viscous secretions are produced following photoradiation. They should be removed by using swabs or a 1 cc syringe for cervical aspiration as necessary.

3. For large lesions, overlapping spot irradiation, resembling the Olympic ring logo, should be performed.

4. Lesions on uneven surfaces or areas difficult to approach frontally, such as the cervical canal, should be irradiated in all directions by carefully adjusting the vaginal speculum and changing the laser angle. If there is glandular involvement, irradiation needs to be as thorough as possible.

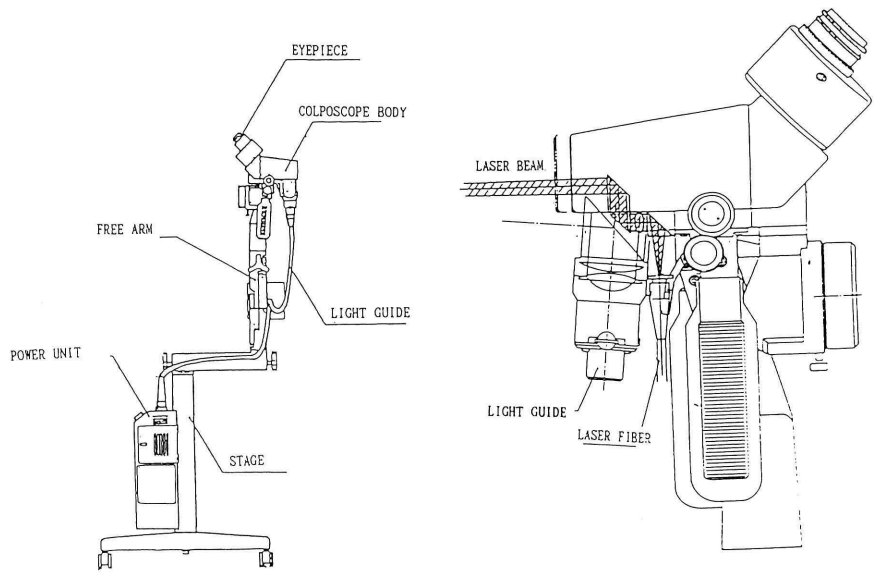


Fig. 4 Colposcope for Laser Therapy
The Olympus Laser Colposcope features an optical path for the laser and allows cervical lesions to be examined during photoradiation. With this method it is possible to show a 10 mm circular spot at the focus where observation is made. This results in stable and precise photoradiation.

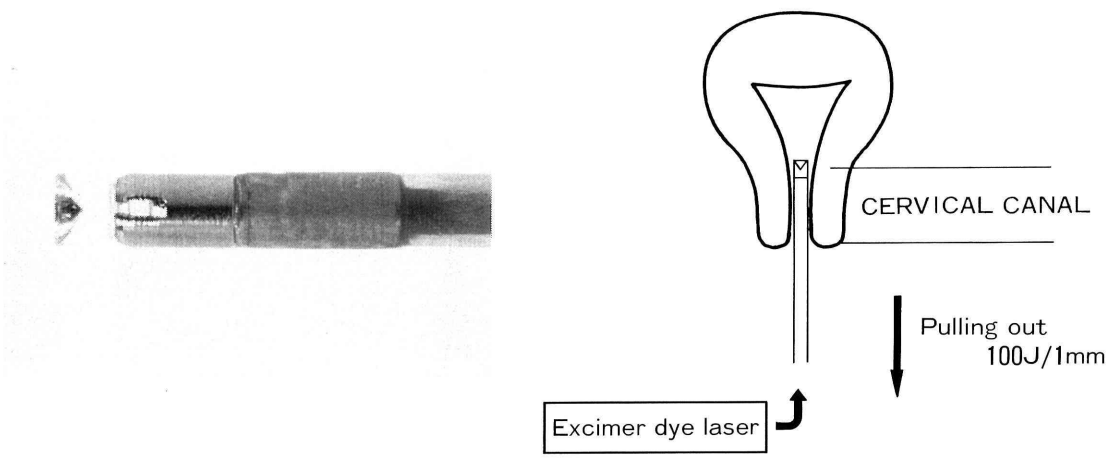


Fig. 5 Cervical Probe
This probe was developed to administer PDT in the cervical canal, i.e., endocervix. A special sapphire chip or ceramic chip is mounted on the tip of the cut fiber.

[2] Cervical canal irradiation (Cervical probe)

1. For cervical canal treatment, a cervical probe with the function to administer photoradiation to the entire cervical canal (Fig. 5) and manipulator (Olympus) are used to irradiate at 100 J/cm^2. The cervical probe was developed for endocervical lesions. A special sapphire tip or ceramic tip is attached

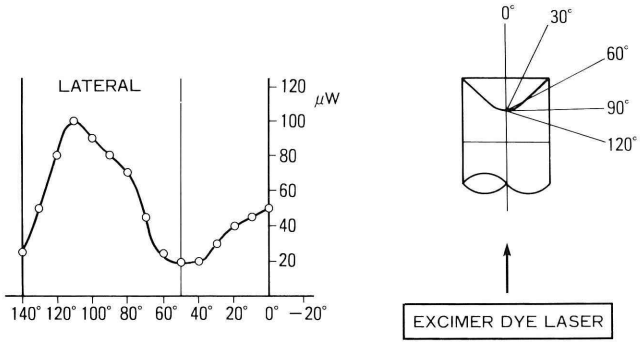


Fig. 6 Laser Power Distribution of the Cervical Probe
It can administer photoradiation in a forward direction on the cervical canal side walls : 70% of the laser light is scattered to the side walls and 30% of the laser light forward. Thus, all of the cervical canal can be radiated.

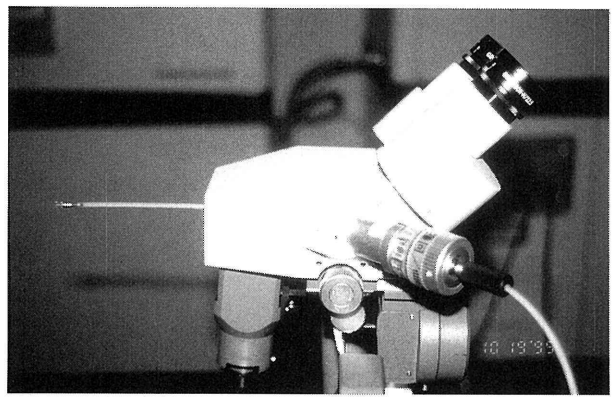


Fig. 7 Cervical Probe Manipulator

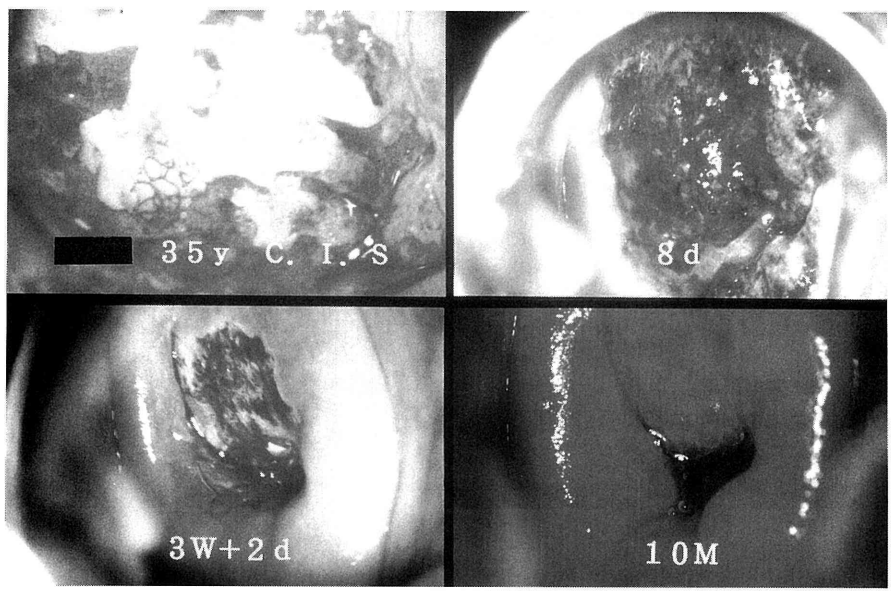


Fig. 8 Colposcopic findings : Case 1.

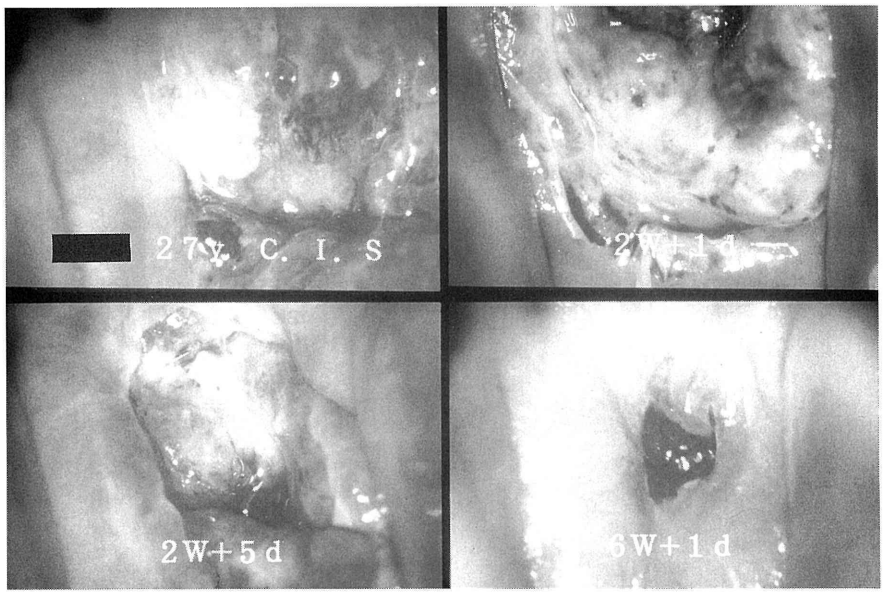


Fig. 9 Colposcopic findings : Case 2.

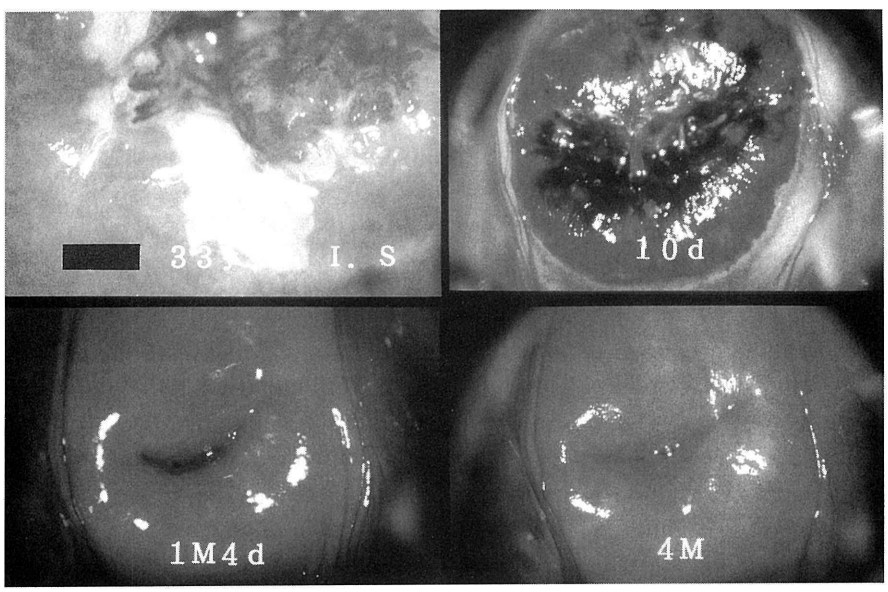


Fig. 10 Colposcopic findings : Case 3.

to the tip of the cut fiber. This allows photoradiation both forward and laterally in the cervical canal : 70% of the laser light is scattered to the side walls, 30% of the laser light forward. Thus, the entire cervical canal can be photoradiated (Fig. 6).

After confirming the lesion inside the cervical canal with a hysteroscope, the cervical probe should be inserted to the required depth. Photoradiation should be repeated as the inserted fiber is withdrawn from the cervical canal in 1 mm increments until it emerges from the external uterine orifice.

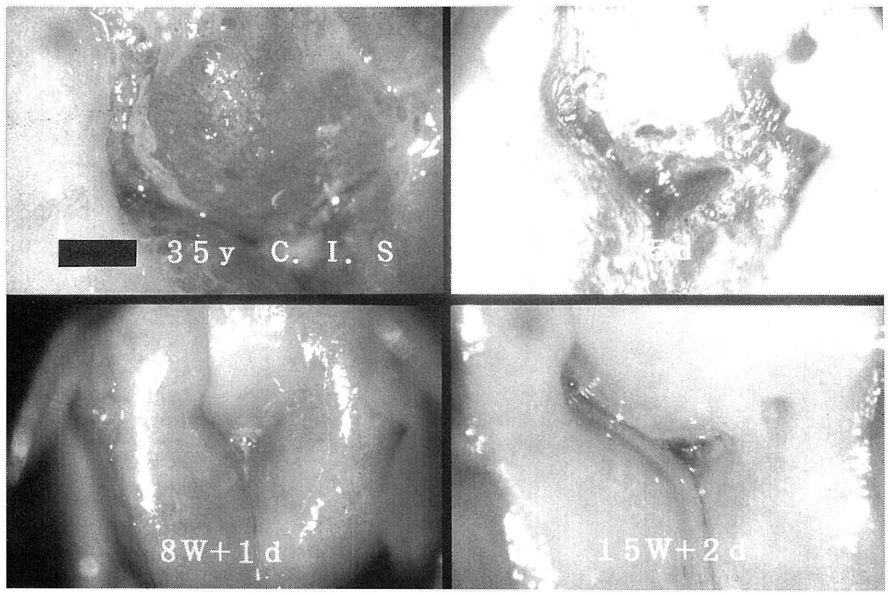


Fig. 11 Colposcopic findings : Case 4.

Previously, the operator needed to mark the position where the cervical probe was originally inserted in order to withdraw it in 1 mm increments. However, the new cervical probe manipulator installed in the colposcope can be moved 0.5 mm with half a revolution of the control knob and 1 mm with one complete revolution (Fig. 7).

〔3〕 PATIENT CARE AFTER PHE INJECTION

Patients become extremely sensitive to sunshine for about a week after PHE injection. When exposed to strong light, the exposed skin reddens and may develop hyperesthesia and edema. Therefore, the patient's room brightness should be measured by a lux meter and the following rules observed :

Before the intravenous injection and for 4 days after the PHE injection the light level of the patient's room should be 5 lux. From the fifth day after PHE injection, the illumination level should be increased to 15 lux, and patients can be allowed to watch television. On the 8 th, 11 th, 16 th and 19 th day after PHE injection, the illumination level is increased to 30, 60, 80 and 100 lux respectively.

From the 22nd day after PHE injection, restrictions on brightness are removed and on the 24th day after PHE injection, the patient may leave the hospital after sunset.

Patients use make-up cream that reduces ultraviolet light, and sunscreen cream, even with reduced room brightness. When going out of the room, sunglasses, a hood, gloves, socks, scarf, and long sleeves should be worn to prevent exposure to light.

After being discharged, patients are instructed to avoid direct sunshine for prolonged periods of time for up to 2 months after PHE injection. Caution should be observed when going outside at times when ultraviolet light is stronger and when there is much sunshine. They are also instructed to avoid such activities as swimming outdoors for about 6 months after the PHE injection.

〔4〕 EVALUATION OF EFFECTIVENESS OF PDT

Two months after PDT, patients are checked by cytological, colposcopic, and histological findings, and are divided into the following four categories :

Complete response (CR) : All lesions are completely cured in terms of cytological, colposcopic, and histological findings.

Partial response (PR) : Almost all lesions are cured, but the cytological, colposcopic, and histological findings suggest that some lesions are not yet cured.

No change (NC) : Most lesions are not cured, and cytological, colposcopic, and histological findings before and after PDT are almost the same.

Progressive disease (PD) : Among cytological, colposcopic, and histological findings, one or more category of findings became worse than before PDT.

〔5〕 CLASSIFICATION BY COLPOSCOPIC FINDINGS

PDT cases are classified into three categories according to location of the lesions in the uterine cervix, but III was excluded. Type I : the second S-C junction is visible. Type II : the second S-C junction is not visible. Type III : unclassifiable colposcopic findings. As a rule, Type III cases were excluded from PDT because the photoradiation would have had to be performed in a blind manner.

RESULTS

PDT was performed on 87 patients (60 CIS and 25 dysplasia, 1 squamous cell carcinoma, microinvasion (stage Ia) and 1 CIS+endocervical adenocarcinoma, microinvasion). Among these, there were 84 CR (96.6%), only one NC, and two PR with very limited residual lesions. (Tables 1 & 2)

Among Type I, all except one were CR and one 79-year-old Type III CIS case was also CR. Both Type II cases had limited residual lesions.

In one case where there was a strong suspicion of invasive carcinoma, after the patient had a normal delivery a semi-total hysterectomy was performed. In another case, a residual lesion was evident at the end of the cervical canal after PDT, but CR was obtained by another PDT. The last of the NC and PR cases was severe dyslasia and is now under observation.

The first PDT was performed about 7 years ago and there has been no report of relapse. Among 87 cases, 10 became pregnant after PDT (2 for the second time), and 7 had deliveries (6 normal deliveries and 1 cesarean section). Currently, 3 are pregnant.

Side effects

Side effects of PDT are similar to symptoms of sunburn such as reddened skin due to sensitivity to sunlight. However, only 8 cases among 87 required treatment, and they improved the following day after applying steroid ointment. In some cases, there was some skin irritation on exposure to sun in the summer. Applying calomine lotion relieved the symptoms.

In patients who kept to the rules about avoiding sunlight, there were no side effects. No abnormal findings related to use of PHE were recognized in the blood or urine. Also, there was no stricture or abnormal secretion in the cervical canal due to laser irradiation.

DISCUSSION

PDT's primary limitation is sensitivity to sunlight. In order to prevent sunburn the patient must be kept

Table 1-1 Case Results of PDT

No.	Age	Pathological diagnosis	Type	Date of PDT	Reason for PDT	PHE (mg/body) (mg/kg)	Total energy (Joule)	Response	Pregnancy/ delivery
1	39	CIS	Type II	19 Oct. 89	Refusal	101 (2.0)	1,466	CR	
2	27	CIS	Type I	27 Nov. 89	Fertility	118 (2.0)	1,041	CR	18 Aug. 92 ♂ 16 April 96 ♂
3	48	Moderate Dysplasia	Type I	8 Dec. 89	Refusal	94 (2.0)	1,269	CR	
4	35	CIS	Type I	9 Feb. 90	Fertility	119 (2.0)	1,013	CR	TAH
5	27	Mild Dysplasia	Type I	16 Mar. 90	Fertility	100 (2.0)	646	CR	14 Aug. 96 ♀
6	38	CIS	Type I	6 Apr. 90	Refusal	89 (2.0)	1,729	CR	
7	32	CIS	Type I	20 Apr. 90	Fertility	103 (2.0)	2,095	CR	
8	79	CIS	Type III	23 Aug. 90	Age	79 (2.0)	741	CR	
9	31	Moderate Dysplasia	Type I	21 Sep. 90	Fertility	95 (2.0)	1,236	CR	
10	35	CIS	Type I	4 Oct. 90	Refusal	106 (2.0)	1,510	CR	
11	33	CIS	Type I	25 Oct. 90	Fertility	131 (2.0)	1,160	CR	
12	27	CIS	Type II	15 Nov. 90	Fertility	98 (2.0)	2,306	NC	14 Oct. 91 ♂
13	26	Moderate Dysplasia	Type I	30 Nov. 90	Fertility	97 (2.0)	1,067	CR	
14	30	CIS	Type I	19 Jan. 91	Fertility	97 (2.0)	1,025	CR	18 Jun. 92 ♂ 5 Feb. 95
15	48	Severe Dysplasia	Type II	24 Jan. 91	Refusal	115 (2.0)	1,571	CR	TAH
16	46	Severe Dysplasia	Type I	7 Feb. 91	Refusal	91 (2.0)	1,504	CR	

17	29	CIS	Type II	18 Apr. 91	Fertility	112(2.0)	2,481	CR	
18	30	CIS	Type I	13 Jun. 91	Fertility	154(2.0)	1,347	CR	
19	33	CIS	Type I	18 Jul. 91	Fertility	112(2.0)	2,357	CR	
20	23	CIS	Type I	1 Aug. 91	Fertility	107(2.0)	1,242	CR	
21	29	CIS	Type II	12 Dec. 91	Fertility	128(2.0)	1,190	CR	
22	38	Moderate Dysplasia	Type I	19 Dec. 91	Fertility	140(2.0)	1,010	CR	27 Apr. 93 ♀
23	26	CIS	Type II	23 Jan. 92	Fertility	88(2.0)	833	CR	21 May 95 ♂
24	42	Severe Dysplasia	Type I	30 Jan. 92	Refusal	95(2.0)	494	CR	
25	26	CIS	Type II	9 Jul. 92	Fertility	90(2.0)	939	CR	14 Oct. 94 ♂
26	43	Severe Dysplasia	Type I	16 Jul. 92	Refusal	75(1.5)	1,518	CR	
27	48	Severe Dysplasia	Type I	23 Jul. 92	Refusal	78(1.8)	772	CR	
28	32	Severe Dysplasia	Type I	10 Sep. 92	Fertility	84(1.5)	1,012	CR	
29	39	CIS	Type II	24 Sep. 92	Fertility	80(1.5)	1,030	CR	
30	41	Severe Dysplasia	Type I	15 Oct. 92	Fertility	79(1.5)	701	CR	
31	24	CIS	Type I	5 Nov. 92	Fertility	95(1.8)	1,347	CR	
32	27	CIS	Type I	19 Nov. 92	Fertility	67(1.5)	1,125	CR	
33	30	CIS	Type II	18 Jan. 93	Fertility	75(1.8)	1,765	CR	
34	29	Severe Dysplasia	Type II	22 Apr. 93	Fertility	90(1.5)	861	CR	

Fertility : Fertility preservation Refusal : Surgery refused Age : Advanced age

Table 1-2 Case Results of PDT

No.	Age	Pathological diagnosis	Type	Date of PDT	Reason for PDT	PHE (mg/body) (mg/kg)	Total energy (Joule)	Response	Pregnancy/ delivery
35	38	CIS	Type II	30 Apr. 93	Fertility	75(1.5)	782	CR	
36	26	Severe Dysplasia	Type II	20 May. 93	Fertility	100(1.5)	851	CR	
37	37	CIS	Type II	27 May. 93	Fertility	87(1.8)	1,403	CR	
38	24	CIS	Type I	28 May. 93	Fertility	90(1.8)	1,738	CR	
39	40	Severe Dysplasia	Type I	15 Jul. 93	Fertility	75(1.5)	1,264	CR	
40	35	CIS	Type I	2 Oct. 93	Fertility	69(1.5)	2,080	CR	
41	32	Severe Dysplasia	Type II	14 Oct. 93	Fertility	71(1.8)	1,098	CR	
42	34	CIS	Type I	21 Oct. 93	Fertility	69(1.5)	1,099	CR	
43	26	CIS	Type I	18 Nov. 93	Fertility	62(1.8)	1,040	CR	
44	37	CIS	Type II	27 Jan. 94	Fertility	81(1.5)	1,079	CR	
45	41	Severe Dysplasia	Type I	27 Jan. 94	Fertility	91(1.8)	1,238	CR	
46	39	CIS	Type II	3 Feb. 94	Refusal	87(1.8)	1,069	CR	
47	39	CIS	Type II	20 Apr. 94	Refusal	92(1.5)	815	CR	
48	28	CIS	Type II	2 Jun. 94	Fertility	75(1.8)	1,925	CR	
49	34	CIS	Type II	22 Jul. 94	Fertility	72(1.8)	1,903	CR	
50	34	CIS	Type I	11 Aug. 94	Fertility	75(1.5)	861	CR	
51	29	CIS	Type I	9 Dec. 94	Fertility	67(1.5)	958	CR	

52	42	CIS	Type II	16 Dec. 94 27 Apr. 95	Refusal	75(1.8) 95(2.0)	2,371 1,411	PR CR	
53	46	CIS	Type I	27 Jan. 95	Refusal	82(1.8)	1,677	CR	
54	31	CIS	Type I	3 Feb. 95	Fertility	76(1.8)	1,424	CR	
55	32	CIS	Type I	10 Aug. 95	Fertility	90(2.0)	1,194	CR	
56	47	CIS	Type II	25 Aug. 95	Refusal	127(2.0)	1,117	CR	
57	33	CIS	Type I	19 Oct. 95	Fertility	90(2.0)	1,109	CR	Preg.
58	35	CIS	Type I	16 Nov. 95	Fertility	128(2.0)	1,006	CR	
59	28	CIS	Type I	1 Dec. 95	Fertility	91(2.0)	1,859	CR	
60	41	CIS	Type I	7 Dec. 95	Fertility	106(2.0)	816	CR	
61	35	CIS	Type I	14 Dec. 95	Fertility	88(2.0)	950	CR	
62	37	CIS	Type I	1 Jan. 96	Fertility	139(1.8)	2,641	CR	
63	35	CIS	Type I	25 Jan. 96	Fertility	97(1.8)	3,919	CR	
64	36	CIS	Type I	1 Feb. 96	Fertility	99(2.0)	671	CR	
65	27	CIS	Type II	15 Feb. 96	Fertility	131(2.0)	863	CR	Preg.
66	35	CIS	Type II	22 Feb. 96	Fertility	101(2.0)	1,147	CR	
67	49	Severe Dysplasia	Type I	29 Feb. 96	Refusal	90(2.0)	2,719	PR	
68	30	Severe Dysplasia	Type I	14 Mar. 96	Fertility	105(1.8)	1,236	CR	
69	33	CIS	Type II	21 Mar. 96	Fertility	108(2.0)	4,291	CR	
70	35	CIS	Type I	21 Mar. 96	Fertility	99(2.0)	2,485	CR	

Fertility : Fertility preservation Refusal : Surgery refused Age : Advanced age

Table 1-3 Case Results of PDT

No.	Age	Pathological diagnosis	Type	Date of PDT	Reason for PDT	PHE (mg/body) (mg/kg)	Total energy (Joule)	Response	Pregnancy/ delivery
71	37	CIS	Type II	28 Mar. 96	Fertility	91 (2.0)	1,254	CR	Preg.
72	33	CIS	Type I	4 Apr. 96	Fertility	113 (2.0)	1,333	CR	
73	34	CIS	Type I	25 Apr. 96	Fertility	88 (2.0)	1,059	CR	
74	37	CIS	Type I	13 Jun. 96	Fertility	97 (1.9)	1,964	CR	
75	30	Severe Dysplasia	Type I	4 Jul. 96	Fertility	75 (1.4)	988	CR	
76	33	CIS	Type I	25 Jul. 96	Fertility	99 (2.0)	1,127	CR	
77	25	Severe Dysplasia	Type I	26 Jul. 96	Fertility	111 (2.0)	887	CR	
78	35	CIS	Type II	8 Aug. 96	Fertility	87 (1.8)	1,246	CR	
79	31	CIS	Type I	8 Aug. 96	Fertility	84 (1.8)	2,503	CR	
80	60	CIS	Type III	22 Aug. 96	Refusal	102 (2.0)	1,392	CR	
81	24	Severe Dysplasia	Type I	5 Sep. 96	Fertility	80 (1.5)	894	CR	
82	35	CIS	Type I	12 Sep. 96	Fertility	90 (1.8)	1,028	CR	
83	35	CIS	Type I	19 Sep. 96	Fertility	84 (1.8)	1,058	CR	
84	37	CIS+ EC-Ad-Ca I a	Type II	3 Oct. 96	Fertility	112 (2.0)	1,576	CR	
85	27	CIS	Type I	17 Oct. 96	Fertility	91 (1.8)	988	CR	
86	36	Severe Dysplasia	Type I	24 Oct. 96	Fertility	75 (1.5)	930	CR	
87	32	S.C.C. I a	Type II	31 Oct. 96	Fertility	105 (2.0)	1,365	CR	

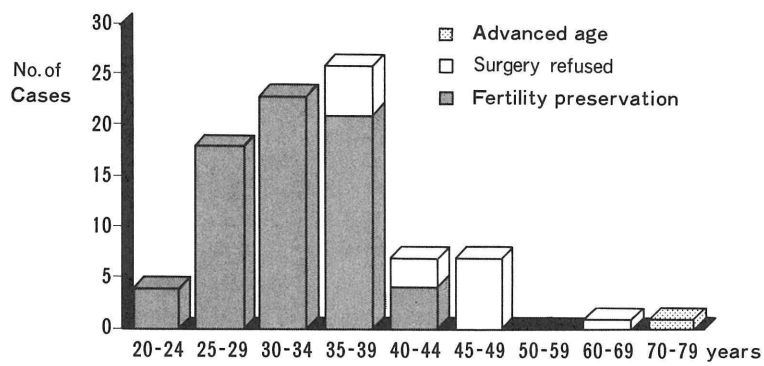
Table 1-4 Case Results of PDT YAG-OPO LASER

No.	Age	Pathological diagnosis	Type	Date of PDT	Reason for PDT	PHE (mg/kg)	Total energy (Joule)	Response	Pregnancy
1	32	CIS	Type I	10 Aug. 95	Fertility	2.0	1,163	CR	
2	47	CIS	Type II	24 Aug. 95	Refusal	2.0	1,069	CR	
3	33	Severe Dysplasia	Type I	19 Oct. 95	Fertility	2.0	1,109	CR	+
4	35	CIS	Type I	16 Nov. 95	Fertility	2.0	1,006	CR	
5	28	CIS	Type I	1 Dec. 95	Fertility	2.0	1,859	CR	
6	41	Severe Dysplasia	Type I	7 Dec. 95	Fertility	2.0	816	CR	
7	35	CIS	Type I	14 Dec. 95	Fertility	2.0	950	CR	
8	27	CIS	Type II	15 Feb. 96	Fertility	2.0	863	CR	+
9	33	CIS	Type II	21 Mar. 96	Fertility	2.0	4,291	CR	
10	35	CIS	Type I	21 Mar. 96	Fertility	2.0	2,485	CR	
11	37	CIS	Type II	28 Mar. 96	Fertility	2.0	1,254	CR	+
12	33	CIS	Type I	4 Apr. 96	Fertility	2.0	1,333	CR	

Table 2 Summary of the Results of PDT

CASES	CIS 62 +1			DYSPLASIA 25		
PHE	2.0 mg/kg	1.8 mg/kg	1.5 mg/kg	2.0 mg/kg	1.8 mg/kg	1.5 mg/kg
	34 +1	19	9	12	4	9
TYPE	I II III	I II	I II	I II	I II	I II
	19 13+1 2	12 7	5 4	11 1	3 1	7 2
CR	19 12+1 2	12 6	5 4	11 1	2 1	7 2
PR	0 0 0	0 1	0 0	0 0	1 0	0 0
NC	0 1 0	0 0	0 0	0 0	0 0	0 0
	CR 60+1/62+1		(96.8%)	CR 24/25		(96.0%)
	TYPE I 36/36		(100%)	TYPE I 20/21		(95.2%)
	TYPE II 22+1/24+1		(91.7%)	TYPE II 4/4		(100%)
	TYPE III 2/2		(100%)			
	PR 1/62+1(TYPE II)		(1.6%)	PR 1/25		(4.0%)
	NC 1/62+1(TYPE II)		(1.6%)			
	CR		84+1/87+1(96.6%)			
	PR		2/87+1(2.3%)			
	NC		1/87+1(1.1%)			

Table 3 Age and Reason for PDT



in the shade, resulting in a longer period of hospitalization.

We perform PDT in relatively younger patients who want to remain fertile. Since young patients are sensitive about skin blemishes resulting from sunburn, we need to minimize the side effects from sunburn sensitivity. Recently, since the effectiveness of PDT has become recognized, various other sensitizing agents have been developed. Such sensitizers as ATX-S10 and NPe6, are both chlorine derivatives, with absorption bands located at longer wavelengths in which high tissue penetration is possible. These derivatives are rapidly discharged from the body. If the sensitizer could be excreted rapidly after the intravenous injection, a long period of shading from light would be unnecessary.

The PHE we use can cause side effects from sunlight sensitivity up to four weeks after the intravenous injection if the patient is exposed to significant amounts of sunlight. Patients who went skiing three months after PHE injection had no significant side effects.

In the initial group of 25, we administered 2.0 mg/kg of PHE. In the second group of 25 we reduced the amount of PHE to 1.5～1.8 mg/kg and compared the results of the two groups. With sufficient

photoradiation, results are good, and compared to the results in the former group, patients given 1.5～1.8 mg/kg had less sunlight sensitivity, allowing shorter hospitalization.

CIS can be treated by total hysterectomy, but for younger patients who want to preserve fertility and also to accommodate high risk elderly patients, PDT is a breakthrough treatment in terms of preserving the patient's quality of life. Both during and after the operation there is no bleeding and it can be performed without anesthesia since it causes no pain.

Regarding the healing ratio, CR was obtained in 96.6% after PDT. Among 87 cases, 10 patients became pregnant after the therapy and 7 gave birth, while the remaining 3 are still pregnant. Therefore, PDT is considered to have no negative effect on pregnancy and delivery.

One NC case was considered to be invasive cancer. Emphasis should be placed on the importance of diagnosis before treatment (especially evaluation of glandular involvement) and evaluation after PDT in order to consider the possibility of relapse. In our series of cases there were no relapses. Special attention must be given to the cervical canal and uneven surfaces where light might be blocked to ensure that those areas are also sufficiently photoradiated from all possible directions. Examination for residual lesions should be performed carefully.

PDT is performed for early lung, stomach, and esophageal carcinoma, as well as for malignant brain tumors. Apart from malignant tumors, the vascular shut-down effect of PDT is employed in the field of ophthalmology, diabetic retinopathy and senile macular degeneration caused by intraocular neovascular, which results in blindness.

Also, for tumors in parrenchymal organs such as liver tumors, research in acoustic chemotherapy with selective anti-tumoral activation using ultrasonic irradiation is being conducted. Progress is also being made in research for artherosclerosis, with PDT using a vascular catheter. All have proven effective in animal experiments. Various other sensitizers have been developed including ATS-S10, a chlorine derivative, with high specificity for malignant tumors and a longer absorption wavelength enabling deeper tissue penetration. NPe6 is discharged rapidly from the body, and ATX-70, Ga complex-free base porphyrin derivatives, which are used as the active substance for acoustic chemotherapy, are other sensitizers. Other photosensitizers include Pheophorbide-a (Phde-a) the raw material of which is chlorophyll which becomes active by photosynthesis of plants, ATN-10 and ATN-4T which are related to contrast media for radiologic diagnosis, KU2280 a sensitizer for malignant cell cumulative x-rays, and KADTF have been utilized.

To meet the needs of the various new types of sensitizers, new laser equipment has also been developed. The YAG-OPO laser with a tunable wavelength has been used in clinical trials for PDT. Smaller new diode lasers are also ready for clinical trials.

It is important to establish effective therapy by adopting better photoradiation methods and photosensitizers, with light. It is also necessary to optimize sensitizer doses to minimize the hospitalization and period of avoidance of sunlight.

CONCLUSION

Since it involves no bleeding or pain, has relatively simple technical requirements, and does not need anesthesia, we consider PDT to be the best therapy for treating CIN while preserving fertility.

REFERENCES

1) Tenjin, Y. Sugishita, T. : Basic Research for fertility preservation through PDT by Excimer Dye Laser. J. Obstetrical and Gynecological Therapy. Vol. **57**(4), 420～425, 1988.

2) Sakamoto, M. Muroya, T. Sugishita, T. Tenjin, Y. et al. : PDT's application to CIS of the uterine cervix and dysplasia. J. The Japan Society for Laser Medicine. Vol. **10**(3), 195～198, 1989.
3) Tenjin, Y. Sakunaga, H. Muroya, T. Sugishita, T. : Excimer Dye Laser Therapy for early cervical cancer and precervical cancer lesion of the uterine cervix. J. Obstetrical and Gynecological Therapy. Vol. **61**(5), 987～992, 1990.
4) Tenjin, Y. Sakunaga, H. Muroya, T. Sugishita, T. et al. : Research for the most appropriate irradiation for cervical cancer through PDT by Excimer Dye Laser. Development and clinical application of colposcope for laser therapy and cervical canal probe. Obstetrical and Gynecological Practice. Vol. **39**(13) : 1963～1967, 1990.
5) Muroya, T. Sakunaga, H. Sakamoto, M. Sugishita, T. Tenjin, Y. et al. : Clinical tests for type III patients of PDT for the early cervical cancer and pre-cervical cancer lesions by PHE (Porfimer Sodium) and Eximer Dye Laser (PDT EDL-1). Oncology & Chemotherapy. Vol. **8**(3) : 302～307, 1992.
6) Muroya, T. Sakunaga, M. Sugishita, T. Tenjin, Y. et al. : Fertility preservation treatment for early cervical cancer and dysplasia by PDT (Photodynamic Therapy). Oncology & Chemotherapy. Vol. **9**(1) : 21～32, 1993.
7) Muroya, T. Sakunaga, H. Sakamoto, M. Sugishita, T. Tenjin, Y. et al. : Photodynamic Therapy (PDT) clinical trials. From the viewpoint of colposcopic, cytological, hysteroscopical changes. J. The Japan Society for Laser Medicine. Vol. **15**(1) : 41～52, 1994.
8) Sakunaga, H. Muroya, T. Sugishita, T. Tenjin, Y. et al. : Present state and perspective of function preservation therapy. Oncology & Chemotherapy. Vol. **10**(4) : 1～4, 1994.
9) Muroya, T. Suehiro, Y. Umayahara, K. Akiya, T. Iwabuchi, H. Sakunaga, H. Sakamoto, M. Sugishita, T. Tenjin, Y. : Photodynamic Therapy for early cervical cancer. Cancer & Chemotherapy. Vol. **23**(1) : 47～56, 1996.
10) Muroya, T. Suehiro, Y. Umayahara, K. Akiya, T. Iwabuchi, H. Sakunaga, H. Sakamoto, M. Sugishita, T. Tenjin, Y. : Uterus Preservation Operation for CIN. PDT's Clinical Trial Results. J. Japan Society for Obstetrical and Gynecological Surgery. Obstetrical and Gynecological Surgery. No. **7** : 27～38, 1996.