1. Purpose
Photodynamic therapy (PDT) is a conservative treatment modality using the combination of a photosensitizer possessing high tumor affinity and irradiation with laser or light energy at a low intensity which enables selective destruction of cancerous or dysplastic cells while preserving the uterus. The purpose of these safety guidelines is to list the requirements that need to be strictly adhered to, in order to ensure the safety of the patient, doctor and medical personnel in the course of the PDT procedure for early stage cancer and dysplasia of the uterine cervix.

2. Requirements of the medical facility for performing PDT
In order to perform PDT for early stage cervical cancer and dysplasia, the medical facility must possess adequate hardware and machinery including laser or light devices delivering light energy at an appropriate wavelength and colposcopes, along with medical personnel who are well trained and capable of operating the hardware and devices and who have a thorough knowledge of the photosensitizer being used for the PDT procedure.

Prior to the PDT procedure, a definitive colposcopic, cytologic and histopathologic diagnosis must be made.

Such a medical facility would be a facility where a gynecological specialist certified by the Japan Society of Obstetrics and Gynecology works full time and is also a facility officially accredited by the Japan Society for Laser Surgery and Medicine as either an instructional or certified facility.

3. Doctors and medical personnel who are performing PDT must have thoroughly read and comprehended the attached documents and instructions for both the photosensitizer, Photofrin Injection 75 mg and the laser devices specific for Photofrin such as the excimer dye laser device PDT EDL-1, PDT EDL-2 and YAG-OPO Laser 1000.

The medical facility must keep these documents and instructions at the site of the PDT procedure and have them available at all times.

The head of the medical facility is required to ensure that the facility’s Laser Safety Officer (LSO) adheres to the content of the instructions regarding the specific device and its environment while the LSO is required to ensure that the users of the laser device adhere to the content of the instructions for its safe and effective use.

If and when a complication due to medication or malfunction of the laser device occurs, a report on the nature of the complication and or malfunction must immediately be sent to the pharmaceutical company, laser manufacturer and, if warranted, to the appropriate regulatory authorities.
4. Satisfactory results for PDT as a uterine preserving treatment have been reported. 1-7) PDT is introduced as a treatment method where the results are comparable to conventional cervical conization using the cold knife, surgical lasers and Loop Electrosurgical Excision Procedure (LEEP).

The indications for PDT in early stage cervical cancer or dysplasia are when colposcopic, cytologic and histopathological findings are all consistent with cervical dysplasia or carcinoma in situ (Stage 0, cervical cancer), or micro-invasive cancer (Stage Ia1). Patients with such cancers or dysplasia, and who also request fertility preserving treatment, or are patients complicated by being at high risk for conventional surgery, or are elderly qualify as candidates, in addition to those who refuse conventional surgery. 7)

PDT may also be employed when colposcopic findings show no sign of invasion, while cytology and biopsy specimens show micro-invasion not exceeding Stage Ia1. 8) Recently there are reports that PDT is effective for residual lesions following conization. 6-7)

5. Considerations for the safe performance of PDT

For the safe performance of PDT, rules that should be observed are listed below in chronologic order of the course of treatment.

1) Pre-treatment examination

Patients diagnosed as having cervical dysplasia or early stage cervical cancer as previously noted, based on smear cytology, colposcopy and colposcopic biopsy are indicated for PDT. From colposcopic findings, lesions limited to the vaginal portion of the cervix are defined as type I. Lesions that involve the endocervix but have visible upper margins are defined as type II. Lesions deep into the endocervix with UCF findings are categorized as type III. PDT of type III lesions is basically contraindicated since laser irradiation of the lesion will essentially be of a blind nature.

Aside from findings of the lesion itself, blood laboratory tests including peripheral blood count, blood chemistry, blood coagulation and screening for viral infection should be performed. Attention should be paid especially to hepatic function since drugs used in PDT are mostly metabolized by the liver and excreted through the biliary tract.

While early stage cervical cancers, especially those earlier than Stage Ia1, are not known to metastasize to other organs or to lymph nodes, radiologic exams such as chest X-rays and CTs should however be performed to confirm this and to rule out the chance of double cancers of other organs. MRIs, PET/CT may be performed if necessary.

2) Inspection of the hardware and devices prior to PDT

The laser hardware must be both visually and functionally inspected prior to the injection of the photosensitizer. If at the time of power check, the laser output is unusually low, all connections from the laser mainframe to the probe need to be examined and the tip of the probe should be checked for any contamination and the output power should be checked again.

The laser probe is disposable and the probe should be changed periodically. Spare probes must be prepared at all times since the probe may be damaged during the PDT procedure.

3) Preparation and administration of the photosensitizer

In the case of Photofrin, a single vial (75 mg) is dissolved in 30 ml of 5% glucose solution resulting in a concentration of 2.5 mg per ml. Photofrin is a strongly colored substance. Mixing and stirring of the Photofrin solution should be extensive and care should be taken to make sure all of the Photofrin has dissolved. The Photofrin solution is injected into the patient intravenously. The total amount of Photofrin administered must be 2 mg/kg body weight of the patient. The amount of Photofrin administration should be checked and confirmed by multiple medical personnel.

4) Light shielding management following sensitizer administration (in order to avoid a hyperphotosensitive reaction)

The medications used in PDT are photosensitizing substances. In order to avoid hyperphotosensitive reactions, patients must avoid direct sunlight exposure by using light shielding curtains and maintain themselves in a luminescence controlled environment. The luminescence of the room should be controlled to a level between 100 to 300 lx, in the case of Photofrin.

The patients must be informed and given written and oral instructions regarding their post-procedural condition and abstain from ingesting large
amounts of the following: chlorella- or chameleon plant-derived supplements, vegetables such as celery and other foodstuff which may aggravate hyperphotosensitivity. The patients must be aware of their condition and must keep with them a copy of the above instructions when leaving the medical facility.

An example of light shielding and light management

Following photosensitizer administration, photosensitivity is the highest during the first week. Any skin exposure to strong light will cause hypersensitive reactions such as irritation, redness and edema of the exposed area. Room luminescence must be controlled using a lux meter, and luminescence above the bed should be as follows.

The luminescence immediately prior to administration of the photosensitizer until the 4th post-administration day should be controlled to less than 10 lx. From the 5th post-administration day the luminescence should be less than 30 lx and the patient is allowed to watch television. From the 6th day, less than 60 lx; the 11th day less than 100 lx; 15th day, less than 150 lx; 19th day less than 200 lx and from the 22nd day light shielding and limitation are no longer necessary and the patient can be discharged from the hospital after sunset.

During the duration of hospitalization, the patient is required to protect herself with sun screens while staying in her room. If the patient leaves the room, attire such as sunglasses, headwear, gloves, socks, scarfs and long sleeved shirts are required to avoid unnecessary exposure to light.

Following discharge from the hospital, the patient must be instructed to be careful of exposing herself to daylight on sunny days and to avoid direct exposure to the sun for prolonged periods of time during the first couple of months. Sunbathing at the beach or elsewhere should be avoided for roughly 6 months.

5) Precautions during the PDT procedure

① During the PDT procedure, the patient, doctors and medical personnel are required to wear protective goggles, and the laser must be used in accordance with the manufacturer’s instructions and any other instructions from the LSO.

② Exposed areas of the patient should be kept to a minimum; all areas not pertinent to the PDT procedure must be draped or dressed.

③ The external genitalia should also be hidden with damp gauze dressings in order to avoid any accidental damage due to exposure to laser energy.

④ If and when a malfunction of the laser device is suspected and a power check is warranted, first and foremost the power to the laser device must be turned off and laser emission suspended. After shutting down the laser device, record all parameters such as the duration of laser emission, and only after confirmation that no accidental access to laser energy is possible can the laser device be inspected. After the inspection is completed and the procedure is to be restarted, if the laser emission data before the suspension were recorded by the laser device, simply continue the procedure. If the record is lost, the parameters and dosage must be recalculated before laser emission can be recommenced.

6) Method of the actual PDT procedure

Inject Photofrin intravenously, in the concentration and preparation previously noted, at an amount of 2 mg/kg bodyweight of the patient. After 48 hours where the Photofrin concentration difference between tumor and normal cells is at the greatest, a low output, the target lesion is irradiated with a pulsed excimer dye laser at a wavelength of 630 nm. The lasers devices to be used are the PDT EDL-1・PDT EDL-2 and the YAG-OPO Laser 1000.

① Colposcopic laser emission (spot laser emission)

Colposcopic laser emission is performed using a colposcope incorporating the distal output device of the laser. Direct visualization of the cervical lesion is possible with the colposcope and simultaneous laser emission at an energy density of 100 J/cm² per spot is performed. The shape of the laser output at the focused visual field of the colposcope is a circle with a diameter of 10 mm. Compared to conventional cut end optical fibers, a more uniform and precise treatment is possible. To ensure that no part of the lesion is left untreated, the irradiated spots should overlap each other in a fashion similar to the Olympic logo.

② Laser irradiation of the endocervix

A specialized laser probe, the Cervical Probe, is used for the laser irradiation of the endocervix. This probe is specialized in that it can deliver laser energy to the whole circumference laterally by dispersing 70% of the laser light laterally and 30% in a forwards direction. Treatment of an endocervical lesion utilizes the same laser energy density of 100 J/cm². The endocervical lesion must be assessed by hysteroscopy prior
to the PDT procedure. The Cervical Probe is inserted within the cervical canal to a pre-determined depth (usually 25 mm). The lateral circumference is irradiated with laser energy, and then the probe is retracted 1 mm at a time. Laser irradiation, with retraction in 1 mm increments is continued until the probe exits the external uterine orifice. A Cervical Probe Manipulator can be used for precise 1 mm retraction per one circumferential laser irradiation.

7) Post-PDT
Cervical mucus produced during or following PDT may solidify and obstruct the uterine orifice. The patient must be examined on the first post-operative day and any necrotic tissue and hardened mucus around the cervix must be removed. If this step is not followed, the patient may contract cervicitis lead to a febrile condition. Following the first examination mucus discharge will occur spontaneously, but the post-operative course is known to be better when the patient is treated 2 to 3 days later. Periodic observations of the lesion under the colposcope are necessary along with smear tests. At the 3rd post-operative month and later when warranted, a histopathological examination must be performed to assess the efficacy of the PDT procedure.

8) Management during the light shielding period
Following the administration of the photosensitizing agent, hyperphotosensitivity tests are required as noted in the instructions which come with the photosensitizing agent. In the case of Photofrin, the test should be performed at one month post-administration. When patients go outdoors, they must wear sunglasses and protect exposed skin with hats, gloves and long sleeved shirts.

9) Informed consent
After patients have received a thorough grounding regarding the treatment procedure, side effects and possible complications, they must sign a form of written consent to undergo the procedure. Pretreatment sun tanning is known to reduce the rate of hyperphotosensitivity. Patients should therefore be encouraged to get a suntan while waiting for the PDT procedure.

10) Rules and stipulations for the distributors and manufacturers of PDT related drugs and laser hardware

① Obligation of the distributors to offer complete information on the products through user’s manuals and appendices.

All distributors and manufacturers of drugs and laser hardware associated with PDT must provide ample and sufficient information to institutions, medical and paramedical personnel through the user’s manual and appendices to ensure the proper and safe usage of the drugs and laser devices. This may be done through technical seminars showing actual video footage of PDT procedures, either independently or at meetings and congresses of relevant medical societies with the cooperation of those societies. They are required to disseminate information for the safe and effective treatment with PDT.

The content and information that are required in the user’s manual are dictated in the “Instructions for the use of laser devices”, release no. 524 Notice from the Division Head of the Evaluation and Licensing Division, Pharmaceutical Affairs Bureau of the Japanese Ministry of Health Labour and Welfare, dated April 22nd, 1980. The content concerning checking and maintenance of laser devices must include: (a) daily preoperative checks involving both visual and operational checks; (b) intraprocedural checking (checking while the device is actually being used); and (c) postoperative checks to be performed at the end of the day, including checks to be performed on the day after the procedure, and cleaning up.

② Written confirmation of delivery of the laser devices

③ Items requiring written confirmation upon the delivery of the laser device

Upon the delivery of the laser device, the distributor and the medical facility must sign and seal a written confirmation concerning the items listed below, abiding by Appendix 2 of “Rules and Regulations of the Manufacturer and Distributor” from the business communications of the Division of Medical Device Development, Pharmaceutical Affairs Bureau of the Japanese Ministry of Health, Labour and Welfare, dated August 6th, 1991. Two copies of this written confirmation must be made, each party keeping a single copy.

Subjects requiring confirmation upon deliv-
ery of the laser device

(a) That laser safety officers (LSOs, chief and deputy, at least 2 people) are assigned and present.

(b) That a registered users’ list has been made

(c) That the planned users of the device are surgeons who are board certified by the Japan Society of Obstetrics and Gynecology and the Japan Society for Laser Surgery and Medicine, and that the LSO has the right to appoint the user of the device.

(d) That the user is technically qualified and has attended courses for handling of the drug and laser device, laser safety management, risk and danger prevention.

(e) That the laser device is key controlled, and that the safe keeping of the key has been determined by the LSO.

(f) That appropriate protective goggles for the wavelength of the laser device are supplied.

(g) That a protective earth terminal is made available.

References


8: Guidelines for the treatment of uterine cervical cancer (Edited by the Japan Society of Gynecological Oncology, Published by Kanehara Shuppan, Tokyo, 2011) in print