1. Purpose
The purpose of these safety guidelines is to promote the safety of patients, doctors and medical personnel performing photodynamic therapy (PDT) procedures for early superficial type cancers of the head and neck and in the field of otorhinolaryngology (ENT), through listing the requirements and conditions that need to be adhered to.

As of August, 2009, PDT procedures for ENT • head and neck disorders are not covered by the Japanese National Health Insurance system, and this indication is deemed to be still in the research stage. The guidelines are to be read as a reference.

2. Qualification and requirements of the medical facility where PDT is to be performed
In order to perform PDT for early stage superficial type cancers in the field of ENT • head and neck disorders, the facility must possess the necessary surgical tools, machinery and laser devices needed for PDT. The facility must be capable of light shielding and light management in the operating or treatment rooms where PDT will be performed, and is required to have medical doctors and medical personnel with ample knowledge of handling of the devices along with the knowledge of PDT and appropriate photosensitizers. It is desirable that the facility have supplementary diagnostic devices such as CT and MRI systems, ultrasonography and NBI endoscopic devices.

Such institutions would be those accredited by the Japan Society for Laser Surgery and Medicine 1) as an instructional or board-certified facility and/or accredited by the Otorhinolaryngological Society of Japan 2) as a designated training facility. It is desirable that these facilities also have a yearly treatment experience of over 100 cases of head and neck malignancies.

3. Adherence to the user’s manuals and appendices
All medical and paramedical personnel associated with the PDT procedure are required to have thoroughly read the appendices to the photosensitizers Photofrin injection 75 mg (Photofrin) and Laserphyrin 100 mg for injection (Laserphyrin); and to have read the user’s manuals for the laser devices (excimer laser PDT EDL-1 • PDT EDL-2, YAG-OPO Laser 1000 and the PD laser specific for Laserphyrin). The head of the medical facility must require the Laser Safety Officer (LSO) to understand and adhere to the content of the appendices and user’s manuals and the LSO must ensure that the user of the laser devices must understand and adhere to the content of the appendices and user’s manuals.

4. Superficial type early stage head and neck cancers indicated for PDT
Firstly, only patients who have understood that PDT for ENT, head and neck cancers has not yet been approved or covered by the Japanese National Health Insurance system and are still willing to be treated, are candidates for PDT. Conventional treatments of early stage head and neck cancers (superficial type) are surgical resection or radiation therapy, when the tumor invasion depth is limited and no lymph node metastasis is present. 3) Since in oral and pharyngeal cancers, surgery may result in permanent dysphagia or
dysarthria, while in laryngeal cancers surgery may result in permanent dysphonia or worse, aphony, some patients refuse surgery. The surgeon may hesitate in choosing surgery or radiation therapy as the means of treatment in cases where the patient’s general physical condition is poor and curative resection is difficult, or in cases that show traits distinctive to head and neck cancers where there are multiple lesions or where the lesion is superficial but widespread, and in extremely elderly patients or juvenile cases where radiation-induced cancers become a concern. Therefore PDT is a treatment that should be chosen when a curative resection or radiation therapy is possible but the sequelae are grave and substantial.

1) If curative resection or radiation therapy is possible, it should take precedence over other treatment methods.

2) Oral, pharyngeal cancers (superficial type) as indications for PDT are lesions less than 4 cm long, with no evidence of lymph node metastasis through diagnostic imagery, and are resectable, but lesions where resection will cause substantial sequelae. The preoperative staging of the lesion must be less than T2 according to the “General Rules for Clinical Studies on Head and Neck Cancers: 4th revised edition, October, 2005.”

3) Early stage laryngeal cancers as indications for PDT are glottis cancer limited to the glottis where there are no restrictions to the movement of the glottis and supraglottic cancer (superficial type) less than 2 cm along the major axis and where no evidence of lymph node metastasis is present, and where substantial dysphonia is expected when resected surgically. The lesion must be staged T1 or earlier according to the “General Rules for Clinical Studies on Head and Neck Cancers: 4th revised edition, October, 2005.” Details are noted within, and should be consulted.

5. Rules which should be observed to ensure safe PDT procedures

The rules which should be observed to ensure safe PDT procedures are listed below in accordance with the chronological order of the procedure.

1) Pre-PDT examinations
Check and confirm the diagnosis according to the criteria listed in the previously noted “General Rules for Clinical Studies on Head and Neck Cancers.” Biopsies are required to assess the histological type of the lesion, and endoscopic ultrasonographic evaluation of the tumor invasion depth is desirable.

Peripheral blood counts, blood chemistry, assessment of blood coagulation and examination for any infectious diseases should be performed. Since drugs used in the PDT procedure are excreted through the biliary system, close attention must be paid to hepatic function.

Confirm that there are no signs of lymph node or distant metastasis by chest and abdominal X-ray, ultrasonography and/or CT imaging.

2) Examination of the hardware prior to PDT
Preoperative examination of the hardware (visual examination, full scale operational check) including verification of the laser output power at the laser emission tip and system calibration according to the manufacturer’s instruction, must be performed prior to the infusion of the photosensitizer. If the tests reveal that the laser output at the emitting tip is extremely low, check all connections between the hardware, fiber and probe for poor connection and for the presence of any marks or foreign bodies on the coupling surfaces. After carrying out this process, perform the power check again and if the output is still low, check and examine the gas or dye exchange (in the case where an excimer or dye laser is to be used).

A new probe should always be used for each procedure and since intraprocedural damage to the probe resulting in decreased output of laser light is a possibility, a spare probe must be available at all times.

3) Preparation and infusion of the photosensitizer
In the case of Photofrin, 1 vial (75 mg) should be dissolved in 30 ml of 5% glucose solution creating a preparation of 2.5 mg/ml solution of Photofrin. Caution is advised to not create any bubbles or foaming of the solution and to make sure that the solution is well mixed and that no solute is left undissolved.

The preparation is infused slowly intravenously at a dose of 2 mg/kg for Photofrin and 40 mg/m² for Laserphyrin. Care must be taken so that no extravasation occurs. The dosage of the photosensitizer must be checked and re-checked by multiple medical personnel.
4) Management of the patient after infusion
(in order to avoid side effects due to photosensitivity)
Since the drugs used for PDT are photosensitizers, the patient must avoid exposure to direct sunlight and must be placed in a room with adequate shading curtains where the illumination of the room is well controlled. In the case of Photofrin, it is dictated that the luminance be kept between 100 and 300 lx.

Food and supplements containing chlorella, Houttuynia cordata and celery are known to increase photosensitivity. The patient must be informed through written materials of such precautions and be given information and guidance concerning activities outdoors. The patient must keep these materials at hand at all times.

5) The PDT procedure
(1) Precautions concerning laser light emission
During the procedure the patient, doctor and medical personnel are required to wear adequate protective goggles. Laser irradiation must be performed according to the user’s manual. Movements such as respiration and swallowing should be taken into account, in order to evenly distribute laser light to the lesion and care should be taken to minimize laser irradiation of normal tissue. If possible, the procedure should be performed under general anesthesia.

(2) Adverse event during treatment
In the event where something irregular occurs adversely affecting the patient’s condition, remove the probe only after the laser irradiation is terminated by pressing the “stop” button (in such case, the laser hardware retains the laser irradiation time in its memory, and hence the procedure may be resumed by pressing the “start” button, as originally planned, after the patient has recovered).

(3) Malfunction of the laser hardware
If a malfunction of the laser hardware, such as aberrant laser output, occurs during the PDT procedure, first abort the procedure by stopping the emission of the laser. Record all pertinent parameters, and then remove the probe and inspect the laser hardware. After the inspection and provided the malfunction has been rectified, the procedure may be resumed by pressing the “start” button if the pertinent parameters have been retained in the system hardware. In the event that the parameters are lost from memory, re-calculate the irradiation time and total energy and re-start the procedure.

4) Use of sedatives during a procedure
If sedatives are required during the PDT procedure, the patient should be monitored by a pulse-oxymeter. If there is any concern regarding fluctuation of the patient’s blood pressure, monitoring with an automated sphygmomanometer is advised. One must be careful with the pulse-oxymeter, since there are reports of skin damage caused by prolonged application of the device. When oxygen is administered to the patient during the PDT procedure, the oxygen level should be maintained at normal atmospheric level and no higher.

6) After the PDT procedure
After the PDT procedure, adequate measures must be taken such as the administration of analgesics for pain relief, administration of anti-ulcer agent to treat the ulcer created by the laser irradiation. Periodic endoscopic and histologic examinations and imaging are required for the follow up of the lesion.

7) Management of photosensitivity and exposure to sunlight
Immediately following the injection of the photosensitizer, the patient must avoid all exposure to sunlight and have a challenge test for photosensitivity at 1 month post-injection for Photofrin and at 2 weeks post-injection for Laserphyrin. If the patient tests negative for photosensitivity, than the patient may resume normal daily activities, but the patient should be advised to avoid direct exposure to sunlight for a further period of time. If the patient tests positive for photosensitivity, the patient must remain under management until the patient tests negative. For those patients who can manage shielding themselves from exposure to light at home, early discharge from the hospital is possible. These patients must have a full understanding of photosensitivity, and have knowledge on what measures to take in case a deleterious incident should occur.

8) Informed consent
Written consent forms signed by the patient and family members are required after both patient and family have been fully informed of the therapeutic effect, risks and complications associated with the procedure.
6. The handling and management of PDT related drugs and laser devices

1) Appendices and user’s manuals
All distributors and manufacturers of drugs and laser hardware associated with PDT must provide ample and sufficient information to the institutions, medical and paramedical personnel through the user’s manuals and appendices. The user’s manuals and appendices of the laser device contain material dictated by “Instructions for the use of laser surgical 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:

(i) A daily pre-operative check involving visual and operational checks
(ii) Intra-procedural checking (checking while the device is actually being used)
(iii) A postoperative check at the end of the day, including checks to be performed on the day after the procedure and cleaning up

2) 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.

3) Subjects requiring confirmation upon delivery of the laser device
(1) That laser safety officers (LSOs, chief and deputy, at least 2 people) are assigned and present.
(2) That a registered users’ list has been made.
(3) That the LSO has the right to appoint the user of the device.
(4) 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.
(5) That the laser device is key controlled, and that the safe keeping of the key has been determined by the LSO.
(6) That appropriate protective goggles for the wavelength of the laser device are supplied.
(7) That a protective earth terminal is made available.

<Reference Notes>

1. Contrivances for laser irradiation during PDT
The images generated by generally used electronic fiberscopes during laser irradiation tend to be disrupted. In order to avoid this, an extracorporeal video camera is attached to the fiberscope and the procedure is watched on a video monitor. If a safety filter or film, with a major cut-off at the 630 nm for Photofrin PDT and at 664 nm for Laserphyrin PDT, is taped to the video lens, a much sharper image can be obtained. In cases of PDT for the larynx, rigid fixed laryngoscopic observation and laser irradiation under the microscope may be useful.

In PDT for oro-pharyngeal cancers, iodine staining of the lesion should be performed for further visualization of the lesion. In general, the lesion and the area 5 mm circumscribing the lesion are irradiated with the laser.

2. Extending the indication of PDT for ENT • head and neck disorders
Surgical treatment and radiotherapy are established treatment methods for early stage head and neck cancers. Surgery can be performed safely even in elderly patients. However, when extreme deterioration of the patient’s QOL due to surgery is expected and when PDT is deemed to be curative, PDT may be a better choice if the patient has been thoroughly informed regarding the procedure. PDT may be selected if a patient, who has been fully informed and notified of his/her condition and prognosis, still refuses conventional surgery or radiotherapy.

Although PDT for ENT • head and neck disorders has not yet been approved or covered by Japanese National Health Insurance system, the treatment record of PDT for superficial type early head and neck cancers is favorably comparable to conventional surgical and radiation treatment.

Recently PDT studies of second generation photosen-
sitzers such as Laserphyrin have been reported.\textsuperscript{13, 14) The reduction in photosensitive reactions has allowed shorter duration of hospitalization and even same-day surgery.\textsuperscript{15) The selective accumulation of Laserphyrin in the cancerous lesions and photobleaching of the treated area following laser irradiation have been reported, further validating the indications for PDT.\textsuperscript{16, 17)}

There are other disorders of the head and neck, apart from early stage head and neck cancers, for which PDT has been reported to be effective as listed below. If no other treatment method is available or suitable for the patient, and if the patient strongly requests to be treated with PDT, the patient should be fully informed of the procedure and the PDT should be performed at an approved facility, and at the hands of a surgeon well experienced in PDT. Prior to such PDT, the procedure must be approved by the medical ethics committee of the medical facility.

1) \textbf{Pre-cancerous lesions}

   Application of PDT for leukoplakia, severe dysplastic epithelium of the oro-pharynx has been proven to be beneficial and effective.

2) \textbf{Advanced head and neck cancers}

   In Western countries, PDT for cancer is considered a pillar of the cancer treatment stratagem where not only early stage cancers are treated, but also unresectable advanced cancers are treated for volume reduction. Many favorable results have been reported for the use of PDT in these indications.

3) \textbf{Application of PDT as one of multidisciplinary treatments for cancer}

   Application of PDT for advanced cancers as a mode of multidisciplinary treatment is anticipated. There are cases of elevated or deeply invading cancers where PDT following local mucosectomy for volume reduction may lead to local healing.

4) \textbf{PDT for remnant tumor following surgical resection and recurrent lesions}

   PDT is considered to be indicated for remnant tumors and recurrences. There are reports of PDT being effective for recurrences following chemotherapy and radiotherapy.\textsuperscript{18)}

5) \textbf{Oral cancer}

   Presently, application of PDT for oral cancers is being considered. There are reports such as a study of 15 cases of PDT where PDT was extremely effective in 13 cases (86.7 \%) and effective in 2 cases (13.3 \%),\textsuperscript{19) and a study reporting on the curative rate according to tumor invasion depth.\textsuperscript{20) Therefore oral cancers can be considered as a good indication for PDT.

6) \textbf{Lingual cancer and salivary gland cancers}

   Basic studies with cultured cells and animal models are presently being considered.\textsuperscript{21-23)}

3. \textbf{Complications of PDT other than photosensitivity}

There have been reports of only 4 cases of dysphonia following PDT for early stage head and neck cancers (superficial type). No other severe complication has been reported. As for PDT for lesions of the larynx, post-operative dyspnea was problematic, requiring repeated daily laryngoscopic lavage and removable of debris by suction. During the earlier period, prophylactic tracheotomies were performed but after the proper irradiation levels were determined, it became unnecessary. Cases where lesions were previously treated or where excessive laser treatment has been performed, the tissue responses were severe causing necrosis of normal mucous membrane tissue followed by webbing and stricture of the larynx, and resulting in a severe case of dysphonia. A case was reported where PDT for a T3 oral cancer caused extensive erosions and ulceration of the oral cavity and tube feeding was required. Another case of excessive irradiation of the gingiva resulting in bone exposure due to periosteal necrosis has been reported. As for systemic complication, there was a report of hepatic dysfunction following PDT which became evident at a blood chemistry examination following the procedure, but no causal relationship to PDT was found.

PDT for head and neck cancers following chemoradiation therapy is known to cause stenosis of the pharynx and larynx, and PDT procedures should be undertaken with caution. PDT for advanced cancers, or of those exceeding the recommended indications, is prone to complications such as perforations and stenoses, and special attention must be paid.
1: Japan Society of Laser Surgery and Medicine <http://www.jslsm.com/>  
2: Criteria for the accreditation as an instructional institution by the Oto-Rhino-Laryngological Society of Japan  
3: Clinical Practice Guidelines for Head and Neck Cancers, 2009 edition (Edited by Japan Society for Head and Neck Cancer, Published by Kanehara Shuppan, Japan)  
4: General Rules for Clinical Studies on Head and Neck Cancers: 4th revised edition, October, 2005 (Edited by Japan Society for Head and Neck Cancer, Published by Kanehara Shuppan, Japan)  
5: Japan Industrial Standards: JIS C6802: 1997 (Safety Standards for Laser Products)  
6: Safety Guidelines for the Clinical Application of Medical Lasers 1988. (Japan Society of Laser Surgery and Medicine, Japanese Society of Medical Instrumentation)  