SAFETY GUIDELINES FOR PERFORMING PHOTODYNAMIC THERAPY (PDT) ON DIGESTIVE TRACT

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1. Purpose

The purpose of these Guidelines is to ensure and secure the safety of all those concerned (the patient, medical and paramedical personnel) in PDT procedures PDT for digestive tract lesions (superficial esophageal cancers, early stage superficial gastric cancers, and so on) by listing rules and stipulations that need to be observed.

As of July, 2005 the only PDT for digestive tract insured by the Japanese health system is PDT with Photofrin injection and irradiation with the excimer laser or the YAG-OPO laser. The procedure is restricted to superficial esophageal cancers and early stage superficial gastric cancers. PDT for any other digestive tract lesion is still in its investigative stage and will be noted at the of these Guidelines for reference purposes.

2. Qualification and requirements of the doctor performing PDT, and the facility where PDT is to be performed

1) Qualifications and requirements of the facility

The facility must have a complete set of all hardware including endoscopes and other laser light managing devices and employ personnel with ample knowledge on handling of the devices along with the knowledge of PDT and appropriate photosensitizers. The facility is required to have qualified medical doctors fulfilling the qualifications and requirements for medical doctors, listed below.

It is better that the facility has a CT scanning device and ultrasonographic devices for assisting diagnosis.

Facilities maintaining the status of Board Certified Facility or Board Certified Instructional Facility from the Japan Society of Laser Surgery (¹) and Medicine or the status of Board Certified Facility from the Japan Gastroenterological Endoscopy Society (²) are adequate.

2) Qualifications and requirements of the medical doctor

It is better that the attending surgeon performing the PDT procedure be a member of the Japan Society of Laser Surgery (¹) and Medicine or the status of Board Certified Facility from the Japan Gastroenterological Endoscopy Society (²) are adequate.
3. Adherence to the user's manuals and appendices and the safe keeping and management thereof.

All medical and paramedical personnel associated with the PDT procedure are required to have thoroughly read the manual and user's guide which come with the laser hardware (excimer dye laser PDT EDL-1, PDT EDL-2, YAG-OPO Laser 1000) and the medication (photofrin). The facility must keep the manual and user's guide in a safe location, ensure that it is constantly updated by the manufacturer, and have it available for reading at all times. The head of the medical facility must require the Laser Safety Manager (LSM) who is in charge of the manual and user's guide to ensure that all users adhere to the contents of the material. In the case of malfunction of the hardware or if any complications occur which are evidently due to such malfunction, the LSM is required to report the event as an ‘adverse incident' to the manufacturer and distributor, the facility management, and to the appropriate government agencies if necessary using the correct forms.

4. Superficial esophageal cancers and early stage superficial gastric cancers indicated for PDT

The first choice of treatment for superficial esophageal cancers where the tumor depth is limited to the mucous membrane layer and where there are no signs of lymph node metastasis, is endoscopic mucosal resection (EMR). (3) Since surgical removable of the esophagus is extremely invasive and associated with high morbidity, there may be cases where the patient does not wish to be operated on, or where the patient’s general condition does not allow surgery and in these instances, EMR may be performed even though the tumor has spread to the submucosal layer. Also for esophageal squamous cell carcinoma, chemoradiation therapy is known to be efficacious. Therefore PDT for esophageal cancer is strictly limited to cases where complete resection by EMR is impossible and also where surgery and chemoradiation are contraindicated.

The first choice of treatment for superficial early stage gastric cancers less than 2 cm in diameter, is EMR. (4,5) For any superficial early stage gastric cancers divergent from this type, surgery is indicated. Therefore PDT is limited to cases where both EMR and surgery is either contraindicated or difficult.

1) If and when complete resection by EMR is possible, it should take precedence over PDT.

2) Superficial esophageal cancers suitable for treatment with PDT are tumors which have spread to less than 1/3 to 1/2 of the circumference and whose size is less than 2 cm x 2 cm and can be captured in a single visual field of the endoscope. The tumor must be diagnosed as non-resectable with EMR, its invasion depth limited to the submucosal layer and showing no evidence of lymph node metastasis.

3) Early stage superficial gastric cancers for which PDT is appropriate are those listed below, which have been diagnosed as non-resectable with EMR and show no signs of lymph node metastasis.
   a) Tumors without ulceration, the length of the longer axis are 1 to 3 cm and whose invasion depth is limited to the submucosal layer.
   b) Tumors with ulceration the length of the longer axis is less than 2 cm and whose invasion depth is limited to the submucosal layer.

4) The endoscopic diagnosis criteria and endoscopic findings of superficial esophageal cancers and early stage superficial gastric cancers are listed in detail in the 9th edition of the Japanese Classification of Esophageal Cancer (revised February, 1999) (6) and in the 13th edition of the Japanese Classification of Gastric Cancer (revised September, 1999) (7) respectively.

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 according following the chronicity of the procedure.

1) Pre-PDT examinations
   Check and confirm that the indications listed in the user’s manual are in concordance with the endoscopic findings which were observed according to the endoscopic diagnosis criteria for superficial esophageal cancers and early stage superficial gastric cancers, as previously mentioned. Histologic
evaluation of the tumor type is mandatory while ultrasonographic endoscope evaluation of the tumor invasion depth is desirable.

Peripheral blood counts, blood chemistry, blood coagulation and examination for any infectious diseases should be performed as in all endoscopic procedures. 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 other metastasis by chest and abdominal X-ray imagery, 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 power check of the laser output at the laser emission tip and system calibration according to the manufacturer’s instructions, 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 any staining. Perform the power check again and if output is still low, check and contemplate gas or dye exchange (in the case of the use of an excimer dye laser).

A new probe should always use for the 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. Care must be taken so that no extravasation occurs. The dosage of Photofrin 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 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 illumination be kept between 100 and 300 lx.

Foods 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 peristalsis, respiration and heartbeats should take into account, in order to evenly distribute laser light to the lesion and care should be taken to minimize laser irradiation of normal tissue.

In regular cases, the amount of laser light indicated is listed below

Superficial esophageal cancer: Energy Density of 60-150 J/cm²

Early stage superficial gastric cancer: Energy Density of 60-200 J/cm²

Equation to calculate irradiation time

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\text{Irradiation time (secs)} = \frac{\text{Energy Density (J/cm}^2\text{) x Irradiation area (cm}^2\text{)}}{\text{Laser tip output (mJ/pulse) x Repetition Rate (Hz) x 1/1000}}
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(2) In an event where something irregular occurs adversely affecting patient’s condition, make sure that the endoscope is removed from the patient only after the laser irradiation is terminated by pressing the “stop” button (in such case, the laser hardware has memory of the laser irradiation time and hence the procedure may be resumed by pressing the “start” button, as originally planned, after the recovery of the patient).

(3) When, during the PDT procedure, a malfunction of the laser hardware such as aberrant laser output occurs, first abort the procedure by stopping the emission of the laser. Record all pertinent parameters, and then remove the probe from the endoscope and inspect the laser hardware. After inspection, the procedure is resumed by pressing the “start” button if the pertinent parameters are memorized by the hardware (if the parameters are lost from memory, re-calculate the irradiation time and total energy and re-start the proce-
dure).

(4) If sedatives are required during the PDT procedure, the patient should be monitored by a pulse-oxymeter. If there is any concern on fluctuation of the blood pressure of the patient, 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 that of normal atmospheric level and no higher.

(5) After the PDT procedure

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

(6) Management of photosensitivity and exposure to sunlight

Immediately following the injection of Photofrin, the patient must avoid all exposure to sunlight for at least 30 days. After 30 days a challenge test for photosensitivity must be performed. If the patient tests negative for photosensitivity, then the patient may resume normal daily activities, but the patient should be advised to avoid direct exposure to sunlight exposure 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, as early as 2 weeks, is possible. These patients must have a full understanding of photosensitivity, and have knowledge on what measures to take in case of a deleterious incident.

(7) Informed consent

Written consent forms signed by the patient and family members are required after they have been fully informed regarding the therapeutic effect, risks and complications associated with the procedure.

6. Rules and stipulations for the distributors and manufacturers of the PDT related drugs and laser hardware.

1) Obligation of the distributors to offer complete information of 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 the institutions, medical and paramedical personnel through the user's manuals and appendices, for the proper and safe usage of the drugs and devices. They must hold technical courses, such as showing actual video footage of PDT procedures, at meetings and congresses of relevant academic and 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 surgical devices” appendix to “Concerning 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 and Welfare, dated April 22nd, 1980. The content concerning checking and maintenance of laser devices must include: (a) daily pre-operative checks involving both visual and operational checks; (b) intra-procedure checking (checking while the device is actually being used); and (c) postoperative checks at the end of the day, including checks to be performed on the day after the procedure, and cleaning up.

2) Items requiring written confirmation upon the delivery of the laser device.

Upon 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 communication of the Division of Medical Device Development, Pharmaceutical Affairs Bureau of the Japanese Ministry of Health 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 delivery of the laser device

(1) That laser safety managers (LSMs, chief and deputy, at least 2 people) are assigned and present.

(2) That a registered users’ list has been made.

(3) That the manager 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.

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

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

References and URLs

1: Japan Society of Laser Surgery and Medicine <http://www.jslsm.com/>


(Edited by Japan Esophageal Society, Published by Kanehara Shuppan, Japan)

4: Treatment Guidelines for Gastric Cancer. 2nd edition.
<http://www.jgca.jp/guideline/index.html>

5: Treatment Guidelines for Gastric Cancer, for Medical Doctors, revised April, 2004, 2nd edition.
(Edited by the Japan Gastric Cancer Association, Published by Kanehara Shuppan, Japan)

6: 9th edition of the Japanese Classification of Esophageal Cancer, revised February, 1999 (Edited by Japan Esophageal Society, Published by Kanehara Shuppan, Japan)

7: 13th edition of the Japanese Classification of Gastric Cancer revised September, 1999 (Edited by the Japan Gastric Cancer Association, Published by Kanehara Shuppan, Japan)

< Reference Notes >

1. Contrivances for laser irradiation during PDT

   The images generated by generally used electronic fiberoscopes during laser irradiation tend to be disrupted. In order to avoid this, an extracorporeal video camera is attached to the fibroscope and the procedure is watched on a video monitor. If a safety filter or film, with a major cut-off at the wavelength of 630nm (13), is taped to the video lens, a much sharper image can be gained. For esophageal lesions, oblique view endoscopes, and for gastric lesions side view endoscopes best fit the purpose.

   (13) In some cases of both esophageal and gastric lesions where direct view endoscopes are used for lesions that are tangent relative to the visual field, a transparent hood attached to the tip of the endoscope may be useful for laser irradiation. For PDT of esophageal cancer lesions, iodine staining is useful in delineating the circumference of the lesion while for PDT for gastric cancer lesions, spraying of indigocarmine makes the lesion more visible and such marking of the lesion prior to laser irradiation should be performed. (15) In general, the lesion and the area 5 mm circumscribing the lesion are irradiated with the laser. (16) If the area of the lesion is extensive or the lesion is deep in the submucosal layer, repeated laser irradiation at 48 hours and 72 hours after the infusion of Photofrin is recommended. This is using the characteristics of Photofrin where the difference in the tissue concentration level of Photofrin between cancer cells and normal tissue is at the greatest at this respective times. (17)

2. Extending the indications for superficial esophageal cancers and early stage superficial gastric cancers.
Recent advances and development surrounding EMR has led to the expansion of indications for EMR. Surgery has become safer than before, even for the elderly. However, there are still cases where a gross deterioration of the quality of life (QOL) of the patient can be anticipated following surgery, and in cases where PDT may be curative, PDT may be chosen and performed but only after the consent of the patient and family members. PDT may be chosen in cases for those who refuse surgery, even after a thorough explanation, and at the same time have lesions contraindicating EMR, such as submucosal invasion of the lesion. For such cases, PDT following chemotherapy, EMR or polypectomy is more effective and recommended.

In general, it is thought that PDT is strongly indicated for remnant tumors or local recurrences following EMR of esophageal and gastric cancers. Efficacy of PDT of remnant esophageal cancer after chemoradiation has also been reported. (14,18)

3. Extending the indication of PDT beyond superficial esophageal cancers and early stage superficial gastric cancers.

There are reports depicting the efficacy of PDT with Photofrin for treatment of digestive tract lesions other than superficial esophageal cancers and early stage superficial gastric cancers. However, from the fact that PDT of such lesions have not yet been approved by the Japanese Social Healthcare System and that the number of patients in the reports are still limited, one should take into account that such indications of PDT are still in the clinical trial stage. Only in cases where there are no other treatment methods, and only when the patient strongly asserts their desire to undergo PDT should the attending physician thoroughly inform the patient of the benefits and risks associated with the procedure, and should refer the patient to physicians and to facilities which have experience of the procedure. Before any treatment commences, the issue should be discussed and approved by the Ethics Committee of that facility.

(1) Prevention of cancer in Barrett’s esophagus

In Western countries where the incidence of esophageal adenocarcinoma is high due to high incidence of reflux esophagitis and Barrett’s esophagus, PDT for Barrett’s esophagus is performed from the standpoint of preventive medicine. (19) Presently, in Japan the incidence of Barrett’s esophagus-based adenocarcinomas is low and hence there are no facilities which have clinically attempted PDT for the condition. However, this is a possibility for future consideration.

(2) Advanced esophageal cancers

In Western countries, PDT procedures are performed for inoperable, chemoradiotherapy-resistant advanced esophageal cancers. Such treatment is approved in these countries and PDT is routinely performed as a palliative measure. (20)

(3) Advanced gastric cancers

Treatment of advanced gastric cancers with PDT alone is only performed as a palliative measure to alleviate stenosis, for hemostasis and for debulking of tumor mass. For polypoid tumors whose invasion is limited to the layer of muscularis propria, polypectomy or EMR followed by PDT, there are cases reported where local control of the tumor has been achieved. (17)

(4) Advanced biliary tract cancers

There are reports that PDT and stent placement for inoperable biliary tract cancers have increased the longevity and prognosis in certain patients (21). There are a number of institutions that are contemplating performing the procedure in Japan (22).

(5) Rectal cancer

There are reports that PDT is effective in certain cancers of the lower rectum, located at positions where no danger of perforation is present. (23)

(6) Others

While clinical trials of PDT for pharyngeal, duodenal, intestinal and colonic lesions are being attempted, the safety and treatment efficacy remain to be established.

4. Complications of PDT other than photosensitivity

So far in Japan, only a single case has been reported of post-operative hemorrhage following PDT for early stage superficial gastric cancer. To date there are no reports on any serious complications such as perforation.

For PDT of esophageal lesions using a direct view endoscope without using a transparent hood, the lesion presents at a tangent angle relative to the visual field. This and movements due to peristalsis and cardiac movement causes laser irradiation of large non-lesional areas. In cases of post-EMR or post-chemoradiotherapy, such laser irradiation may cause mediastinitis or stricture of the esophagus, and care must be taken. One must keep in mind that PDT for extended indications is more suscepti-
ble to complications such as stenosis and perforation.

5. Laser hardware used for PDT
   When performing PDT using Photofrin as the photosensitizer, a laser device emitting laser light at the wavelength of 630 nm is required. The first laser device approved by Japan’s social health care service was the excimer-dye laser. Recently, PDT using Photofrin and the YAG-OPO laser has also been approved due to similar treatment efficacy. In most Western countries, smaller and less expensive diode lasers are used for PDT with Photofrin, but such a combination has not yet been approved in Japan. If photosensitizers other than Photofrin are to be used, laser devices emitting laser light of the wavelength appropriate for the respective agents are required.

6. PDT using agents other than Photofrin
   There are other agents besides Photofrin that are fit for PDT. For some agents the safety and efficacy have already been proven. However, the use of those agents in PDT for gastrointestinal lesions has not been approved, and from the fact that the numbers of patients in the reports are still limited, one should take into account that such sensitizers are still in the clinical trial stage. Only in cases where there are no other treatment methods, and only when the patient strongly asserts their desire to undergo PDT, should the attending physician thoroughly inform the patient of the benefits and risks associated with the procedure, and should refer the patient to physicians and to facilities which have experience of the procedure. Before any treatment commences, the issue should be discussed and approved by the Ethics Committee of that facility.

   (1) Laserphyrin (mono-L-aspartyl chlorine e6)
       PDT for early stage lung cancer using intravenous infusion of 100 mg of this agent in combination with a specific diode laser (PD laser) has already been approved. Comparable treatment efficacy with PDT using Photofrin for gastrointestinal lesions is anticipated and shorter periods of irradiation with laser energy are strongly awaited in the field of PDT for gastrointestinal lesions.

   (2) 5-ALA (aminolevulinic acid)
       This agent is used mostly in Western countries for the treatment and prevention of Barrett’s esophageal adenocarcinomas. This agent is highly acknowledged for its use in fluorescence diagnostics but use as an agent for PDT is limited to relatively superficial lesions. The hepatic toxicity of this agent should be considered when it is used.

   (3) Foscan (mTHPC)
       This is new photosensitizing agent that has been approved in Western countries. Therapeutic benefits for even deeply invasive lesions have been shown.

References