MODIFIED PHOTODYNAMIC THERAPY FOR GASTROINTESTINAL CANCERS

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Photodynamic therapy (PDT) is based on the theoretical principle: the specific low level laser light irradiation activates a photosensitizer which is selectively concentrated in rapidly proliferating tissues including malignant tumor cells, resulting in selective necrosis by the intracellular singlet oxygen from photochemical reaction. PDT using Photofrin® (porfimer sodium) with excimer-dye laser (EDL) was approved in Japan. Its indication for GI cancers was limited to superficial esophageal and early gastric cancer not indicated for other curative treatments. Meanwhile, endoscopic mucosal resection (EMR) is considered the first choice of treatment for intra-mucosal GI cancers. Thus PDT has been considered as one of the alternative treatments for GI cancers including recurrent cancer; however, its efficacy was relatively limited. Therefore, we have designed a new therapy called "Modified PDT". The major points of Modified PDT are as follows. 1. Irradiation of EDL is applied to the lesion not only 48 but also 72 hours after Photofrin® injection. 2. When the cancer is polypoid type, partial resection of the cancer is performed before irradiation. 3. Before the second irradiation, necrotic tissue covering the surface of the lesion is removed. Modified PDT was carried out on 20 patients (mean age 73 years). Complete response was achieved in 4 of 6 (66.7%) of superficial esophageal cancers, 9 of 10 (90%) of early gastric cancers, 1 of 3 (33.3%) of advanced gastric cancers and 1 rectal cancer. No serious complication occurred. Modified PDT may be considered an alternative therapy for GI cancers not indicated for EMR or surgery.

Key words: Modified photodynamic therapy (PDT), superficial esophageal cancer, early gastric cancer, rectal cancer

Photodynamic therapy (PDT) is a unique treatment for not only gastrointestinal (GI) cancers but also malignant tumors of other organs. This therapy is based on the theoretical principle: the specific low level laser light irradiation activates a photosensitizer which is selectively concentrated in rapidly proliferating tissues including malignant tumor cells, resulting in selective necrosis by the intracellular singlet oxygen from photochemical reaction. Dougherty et al. reported clinical applications of PDT using hematoporphyrin derivatives (HpD) as a photosensitizer for cutaneous or subcutaneous malignant tumors. The endoscopic application of PDT using HpD for upper GI cancers has been done in Japan since 1979. HpD was further modified to increase its localization in tumors and named Photofrin® (porfimer sodium). After developing a new designed pulsed excimer-dye laser (EDL) (Hamamatsu Photonics Inc., Hamamatsu, Japan) for PDT, Japanese government (at present, Ministry of Health, Labor and Welfare) approved PDT using Photofrin® (at present, Wyeth-Takeda, Tokyo, Japan) as a photosensi-
tizer in 1994. However, its indication for GI cancers was limited to superficial esophageal and early gastric cancer which was not indicated for surgical operation.

In almost the same period, endoscopic mucosal resection (EMR) has developed for curative treatment of intra-mucosal GI cancers (esophageal, gastric and colon)\(^{(4)}\), and it is considered the first choice of treatment in Japan. Thus PDT has been considered as one of the alternative treatments for GI cancers not indicated EMR including recurrent cancer; however, its efficacy was relatively limited. Therefore, we have designed a new therapy called "Modified PDT" to treat GI cancers not indicated for EMR or surgery.

**Procedures and Principles of PDT using Photofrin® in Japan**

Photofrin® (2mg per kg) is injected intravenously to the patient suffering from superficial esophageal and/or early gastric cancer. After injection of Photofrin®, it is cleared from most tissues in 40 to 72 hours but retained for longer periods in cancer cells, skin, and the reticuloendothelial system. Hence light application is usually scheduled at 40 to 50 hours after injection\(^{(5)}\). At that time, low level laser light of EDL (630nm, 4mj output, 40Hz) is irradiated to the target lesion including cancer through bare quartz fibers endoscopically. Total light doses of 60 to 100 J/cm\(^2\) are used for superficial esophageal cancer and early gastric cancer. Upon light exposure, the production of singlet oxygen and other reactive chemical radicals cause local non-thermal cellular damage, vascular thrombosis, and necrosis, which evolve over hours to several days\(^{(6)}\). Even if there is damage to healthy tissues, that is healed by regeneration. Therefore, the cancer and its surrounding healthy tissue can be treated without surgery. And treated areas are safely healed without risk of perforation and intense bleeding. On the other hand, cutaneous photosensitivity occurs in the patient because Photofrin® is retained for longer periods in skin. Thus avoidance of exposure to bright light or direct sunlight is needed for the patient for at least 30 days and often up to 90 days\(^{(5)}\).

**Materials and Methods**

**Patients**

Between November 2002 and September 2005, Modified PDT was carried out on 20 patients (mean age 73 years, range 55 to 87) suffering from GI cancers (6 superficial esophageal, 10 early gastric, 3 advanced gastric and 1 rectal) who were not indicated for surgical operation or EMR. Written informed consent was obtained from all patients.

**Methods of Modified PDT**

The major points of Modified PDT are as follows.
1. Irradiation of EDL (630nm, 4mj output, 60-80Hz) is applied to the cancerous lesion and its surrounding mucosa not only 48 (Day 1) but also 72 hours (Day 2) after Photofrin® (2mg per kg) injection. Target light dose is 60-100 J/cm\(^2\).
2. When the cancer is polypoid type, partial resection of the cancer is performed before irradiation.
3. Before the second irradiation on Day 2, necrotic tissue covering the surface of the cancerous lesion is removed by biopsy forceps. Target light dose of the second irradiation is less than 60 J/cm\(^2\).

According to the shape and/or location of the cancerous lesion, cylindrical type of quartz fiber was applied for contact laser irradiation. For the treatment of superficial esophageal cancer, transparent food was used to obtain precise laser irradiation\(^{(7)}\).

Admission period of Modified PDT patient was set at 2 weeks and avoidance of exposure to bright light or direct sunlight was demanded for the patient for at least 4 weeks after discharge.

**Evaluation of Efficacy**

Follow-up endoscopic examinations were carried out at 1 week, 3 months (M) and 6M after irradiations of EDL. Evaluation of the efficacy of Modified PDT was performed at the 3M follow-up period. Complete response (CR) was defined as: there was no evidence of residual and/or recurrent cancer cells by endoscopic observation and biopsy. Partial response (PR) was defined as: there was some evidence of residual and/or recurrent cancer. No change (NC) was defined as: there was no response for cancers by Modified PDT or rapid growth of recurrent cancer the same as the cancerous lesion before treatment.

**Results**

The efficacy results of Modified PDT for GI cancers are shown in Table 1.

In 6 esophageal cancer patients, 5 of them were squamous cell carcinoma histologically including two recurrent patients after chemoradiotherapy. There were 7 squamous cell carcinoma lesions and 6 of them (85.7%) disappeared completely by single course of Modified PDT. The other esophageal cancer patient
had 3 adenocarcinomas arising from Barrett’s esophagus including 2 polypoid lesions. One flat lesion disappeared completely and 2 polypoid lesions decreased by single course of Modified PDT. Finally, 4 of 6 patients (66.7%) with superficial esophageal cancers were considered CR.

In 10 early gastric cancer patients, 3 were recurrent after EMR. There were 13 adenocarcinoma lesions including 4 poorly differentiated type and 11 of them (84.6%) disappeared completely by single course of Modified PDT. Finally, 4 of 6 patients (66.7%) with superficial esophageal cancers were considered CR.

In 10 early gastric cancer patients, 3 were recurrent after EMR. There were 13 adenocarcinoma lesions including 4 poorly differentiated type and 11 of them (84.6%) disappeared completely by single course of Modified PDT. Finally, 4 of 6 patients (66.7%) with superficial esophageal cancers were considered CR.

Concerning rectal cancer patient, there was a polypoid lesion recurrent after EMR in the lower portion of rectum. Several times of piecemeal polypectomy were performed before Modified PDT, and the cancerous lesion disappeared completely after 30 M follow-up period. This patient was considered CR.

No patient died of recurrent GI cancers during 10 to 44M follow-up period. Slight sunburn in the face and/or the limbs occurred in 4 patients (20%) but they recovered. No serious side effect occurred.

**Case 1, 62 year-old man, recurrent esophageal squamous cell cancer after chemoradiotherapy**

In August, 1999, endoscopic examination revealed squamous cell carcinoma in the middle portion of the esophagus (Fig. 1). Chemoradiotherapy was carried out because he was not indicated for surgery by liver cirrhosis. Squamous cell carcinoma recurred in the same portion of esophagus 3 years after chemoradiotherapy (Fig. 2). EMR was not indicated for the recurrent cancer because endoscopic ultrasonography estimated it submucosal invasion. Thus Modified PDT was performed in May, 2003. Forty-eight hours after injection of Photofrin® (2mg per kg), EDL was irradiated at a dose of 100 J/cm² via endoscopy attached transparent food on its tip. Seventy-two hours after Photofrin injection, irradiation of EDL at a dose of 60 J/cm² was added. One week after Modified PDT, endoscopy

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**Table. 1: Efficacy results of Modified PDT for GI cancers**

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>n</th>
<th>CR (%)</th>
<th>PR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophageal</td>
<td>6</td>
<td>4 (66.7)</td>
<td>2 (33.3)</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>10</td>
<td>9 (90.0)</td>
<td>1 (10.0)</td>
</tr>
<tr>
<td>Gastric cancer (advanced)</td>
<td>3</td>
<td>1 (33.3)</td>
<td>2 (66.7)</td>
</tr>
<tr>
<td>Rectal cancer*</td>
<td>1</td>
<td>1 (100)</td>
<td>–</td>
</tr>
</tbody>
</table>

* Not indicated for surgical operation or EMR.

(Follow-up period: 10 to 44 months.)
revealed a large laser ulcer coated with whitish necrotic tissue but no cancerous lesion remained by biopsy (Fig. 3). Three months after Modified PDT, laser ulcer healed completely and no cancerous lesion remained by biopsy (Fig. 4). There was no recurrence or metastasis until his death of cerebral hemorrhage 24 months after Modified PDT.

Case 2, 88 year-old woman, recurrent gastric cancer after EMR

In 2000, EMR was carried out for early gastric cancer; however it resulted in incomplete resection and the cancer recurred. She was followed up by endoscopy because she was not indicated for surgery by cerebral infarction and her advanced age. However, the recurrent cancerous lesion gradually enlarged and her anemia was progressive, therefore Modified PDT was carried out in January, 2003. Endoscopic examination before Modified PDT revealed superficial elevated cancerous lesion located in the anterior side of the middle portion of stomach (Fig. 5). The lesion was estimated submucosal invasion by endoscopic ultrasonography. Forty-eight hours after injection of Photofrin® (2mg per kg), EDL was irradiated at a dose of 80 J/cm² via endoscopy using cylindrical type of quartz fiber for contact laser irradiation. Seventy-two hours after Photofrin injection, irradiation of EDL at a dose of 80 J/cm² was added after removal of necrotic tissue (Fig. 6).

Fig. 3: Endoscopic image at 1 week after Modified PDT
A large laser ulcer coated with whitish necrotic tissue was seen but no cancerous lesion remained.

Fig. 4: Endoscopic image using iodine dye stain at 3 M after Modified PDT
Laser ulcer had healed completely and no cancerous lesion remained.

Fig. 5: Endoscopic image before Modified PDT in November, 2002
Superficial elevated cancerous lesion was located in the anterior side of the middle portion of stomach.

Fig. 6: Endoscopic image during irradiation of EDL on Day 2.
Fig. 7: Endoscopic image at 1 week after Modified PDT
A large laser ulcer coated with whitish necrotic tissue was seen but no cancerous lesion remained.

Fig. 8: Endoscopic image at 3M after Modified PDT
Laser ulcer had healed completely and no cancerous lesion remained.

6) One week after Modified PDT, endoscopy revealed a large laser ulcer coated with whitish necrotic tissue but no cancerous lesion remained by biopsy (Fig. 7). Three months after Modified PDT, laser ulcer healed completely and no cancerous lesion remained by biopsy (Fig. 8). There was no recurrence or metastasis 36 months after Modified PDT.

Discussion

PDT, a treatment now being used in patients with various types of cancers including GI tract, uses a combination of photosensitizer (a drug that is activated by light) and non-thermal low power laser light. Neither the photosensitizer nor the laser light alone can destroy the cancer cells; they must be used in combination.

The first endoscopic application of PDT for upper GI cancers was started in Japan (2). At that time, HpD as a photosensitizer and an argon-dye laser were used for patients with superficial and non-superficial esophageal cancer and with early gastric cancer. Hayata et al. concluded that PDT using HpD should be employed primarily in inoperable early-stage cancer, to reduce the extent of resection, or to make previously inoperable cases to operable because of the difficulty in early stage diagnosis and in determining all cases of lymph node involvement (2).

According to the recent remarkable development of endoscopic and other imaging technologies, gastroenterologists have regarded that superficial esophageal and early gastric cancers were not rare cases especially in Japan. The majority of esophageal cancer is squamous cell carcinoma and gastric cancer is very common in Japanese people. On the other hand, more than half of esophageal cancer is adenocarcinoma arising from Barrett’s esophagus and gastric cancer is extremely rare in Western white people. Under these circumstances, development of endoscopic PDT for GI cancers has been quite different in Japan and Western countries.

In 1995, Food and Drug Administration (FDA) of USA approved PDT using Photofrin® with diode laser (Diomed PDT laser system) for palliation of patients with completely or partially obstructing esophageal cancer (not only squamous cell carcinoma but also adenocarcinoma) after multicenter randomized trial (8). In 2003, FDA approved PDT using Photofrin® for the ablation of high-grade dysplasia associated with Barrett’s esophagus in patients who do not undergo esophagostomy, Canada and Europe also approved it in 2004. The other indication of PDT using Photofrin® approved by FDA is reduction of endo-bronchial obstruction in patients with nonsmall cell lung cancer who are not candidates for surgery or radiotherapy (5).

In Japan, Ministry of Health and Welfare approved PDT using Photofrin® for the patients with early-stage cancers of proximal lung (bronchial), esophageal, gastric, uterine cervix and with dysplasia of uterine cervix who are not indicated for surgery or other curative treatment including EMR. For the purpose of curative treatment for early stage cancers, EDL was developed. EDL enables irradiation of a pulsed laser with extremely high peak power in comparison with argon dye laser. Mimura et al. reported the cooperative clinical trial of PDT using Photofrin® with EDL on 27 patients.
with early gastric cancer. Complete responses (CR) were obtained in 88% of 24 assessable patients and the response rate was 100%. CR was observed in all cases of lesions of superficial depressed type without ulceration and/or with tumor diameter less than 2 cm. Regarding complications, mild cutaneous reaction and photosensitivity were seen and lasted several weeks. The efficacy of PDT using Photofrin® with EDL is satisfying; however, superficial depressed type gastric cancers without ulceration and/or with tumor diameter less than 2 cm are considered the indication for EMR.

In 2004, PDT using a new photosensitizer named Laserphyrin® (mono-L-aspartyl chlorin e6, Meiji Seika, Tokyo, Japan) with a new designed diode laser (PD laser, Panasonic, Tokyo, Japan) was approved only for early lung cancer.

Under these conditions, we have designed a new therapy called "Modified PDT" to treat GI cancers not indicated for EMR or surgery. In spite of small number of patients, Modified PDT was remarkably effective for early stage of esophageal and gastric cancer in this study. This new method may be considered as curative therapy for early stage of GI cancers when the patients are not candidates for surgery or other curative therapy including EMR. Recently, Modified PDT was evaluated as salvage treatment for local failures after definitive chemoradiotherapy for esophageal cancer. In combination with other treatment modalities, Modified PDT might be more valuable not only for early but also for advanced stages of GI cancers.

**Conclusion**

Modified PDT is remarkably effective and useful in the treatment of GI cancers which are not indicated for EMR or surgical operation. This technique may be considered an alternative therapy for not only esophageal but also gastric cancer, and even rectal cancer.

**Acknowledgement**

The authors wish to express their thanks to Dr. Michimaro Ejiri and Dr. Yoji Ishii (Nozatomon Clinic, Himeji, Japan) for their help and advice.

**References**


