**M.Pazurek, E.Małecka-Panas**

# PHOTODYNAMIC THERAPY - USEFULNESS IN THE PALLIATIVE TREATMENT OF CERVICAL ESOPHAGEAL CANCER

*Department of Digestive Tract Diseases Medical University of Lodz, Poland*

**Abstract**

Esophageal carcinoma is one of the most common cancers in the world and has an increasing incidence in Western civilization and poor prognosis. In most cases palliative treatment is the only kind of therapy, which can be applied.

In the Department of Digestive Tract Diseases, Medical University, Lodz, Poland we have used PDT in two cases of palliative therapy of advanced esophageal cancer in cervical location of esophagus.

We find PDT very promising, minimally invasive, safe and easy technique to perform for esophageal cancer of cervical localization.

**Key words:** photodynamic therapy, palliative treatment, esophageal cancer

**Introduction**

Esophageal carcinoma is one of the commonest cancers in the world and has an increasing incidence in Western civilization.[1].

There are many risk factors for esophageal carcinogenesis including cigarette smoking, alcohol and coffee drinking and Barrett's esophagus [8]. Kaneko at al. suggested that consumption of alcohol and/or cigarettes may act as a promotor for progression from low grade dysplasia to high grade dysplasia [16].

Esophageal cancer has a poor prognosis. Five years survival is reached only in 10% of patients. The present standard of care is surgery, associated with disappointing survival rates [1].

The diagnosis in clinical practice is often reached only in advanced stage [2,3]. Less than the half of patients are amenable to curative treatment because of locally advanced or metastatic disease [8]. In these cases palliative treatment is the only kind of therapy, which can be applied.

Palliation is often required for symptoms, such as dysphagia, gastrointestinal bleeding, aspiration caused by tracheoesophageal fistula, nausea and vomiting secondary to gastric outlet obstruction, and malnutrition [8].

Photodynamic therapy (PDT) is the non-thermal ablative technique accepted in palliative treatment of esophageal cancer. It is based on photosensitivity followed by light application of the appropriate wavelength to initiate the photo- oxidative reaction that results in tumor cell death and necrosis [23].

**Materials, Methods and Result**

In the Department of Digestive Tract Diseases, Medical University, Lodz, Poland we have used PDT in two cases of palliative therapy of advanced esophageal cancer.

First case.

White woman 45 years old, presented with dysphagia grade 4. She has been smoking 20 cigarettes per day for 25 years. The dysphagia onset was 10 months and pharyngeal pain 6 months before admission. Her weight loss was 15 kilograms during six months (BMI–18,3). Blood cell count (Hgb-13,4g/dl, Ht-42,4%, E-4150000/ul) and plasma GOT, GPT, protein, urea, creatinine were within normal ranges.

Upper G.I. endoscopy revealed severe stenosis in upper part of esophagus at 2 cm below upper esophageal sphincter (UES) not allowing further inserting of the endoscope. Only guide wire could be introduced through this stenosis. X-ray showed esophagus lumen of only 2 mm width. In X-ray, the stenosis extended 6,5 cm distally from 2 cm below UES. Pathology revealed squamous cell carcinoma of esophagus.

CT scan showed the widening of esophageal wall and enlarged mediastinal lymph nodes.

There was no neoplasmatic infiltration in local blood vessels and the broncho-esophageal fistula was excluded. The patient was not fit for radical surgical operation.

Our decision to use PDT was based on above mentioned conditions as well as the cervical localization of stenosis, minimally invasive characteristics of this procedure, not complicated technique and similar survival time compared to other palliative therapies. This technique is also well accepted by the patients.

Photofrin of 2 mg/kg b.m. was given intravenously. After 48 hours from Photofrin administration at upper G.I. endoscopy, we illuminated two 2,5 cm long segments of esophagus (length of laser fiber) with laser beam of 630 nm wavelength using 350 J energy in 720 seconds time to each segment. The patient was located in dark room after Photofrin administration. The irradiation was superficial.

Laser DIOMED 630 PDT (2W) produced by DIOMED Limited (Great Britain) was used in this case. We did not use any means for the stabilization of light fiber position.

During second endoscopy after next 48 hours we removed all necrotic tissues and repeated illumination procedure.

We have observed normal esophageal lumen width. Dysphagia score improved from 4 to 2 grade. Removal of necrotic tissues was also performed during next endoscopy 7 days later. This effect lasted for three months. At this time, the esophageal stenosis recurred and was of the same extent as before PDT procedure. We then repeated illuminating laser procedure, obtaining normal esophageal lumen width, which was shown in upper G.I. endoscopy performed after the next two days. As before, the dysphagia score diminished from 4 to 2 grade.

Unfortunately, after another three months, stenosis relapse was seen, which did not permit the insertion of the guide wire into esophagus. The patient was scheduled for surgical gastrostomy.

We observed hyperthermia, muscle, bone pain and edema of thyroid gland pain after Photofrin administration. No skin burn was observed. Life time was 7 months.

Second case.

White 67 years old woman has complained of dysphagia for six months. Her weight loss was 10 kilograms during that time (BMI-24,2). Dysphagia grade 4 was observed during hospitalization. In laboratory examination mild anemia (Hgb-11,7g/dl, Hct-33%, E-3760000/ul) and normal values of GOT, GTP, protein, urea, creatinine were found.

In upper G.I. endoscopy concentric stenosis was found 17 cm below incisor line. The stenosis in cervical part of esophagus extended 11,5 cm distally from 2 cm below UES on X-ray pictures. The lumen of stenotic segment was

1-2 mm wide. Squamous cell carcinoma was found in histopathologic examination. The neoplasmatic infiltration and enlarged mediastinal lymph nodes were also seen on CT scans.

There was no neoplasmatic infiltration in local blood vessels and the broncho-esophageal fistula was excluded. The patient was not fit for radical surgical operation.

We decide to use PDT, as in first case due to cervical localization of stenosis, minimally invasive character of this procedure, not complicated technique and similar survival time compared to other palliative therapies.

Photofrin in the dose 2 mg/kg b.m. was used intravenously. The procedure of laser illumination was the same as in the first case.

Laser DIOMED 630 PDT (2W) produced by DIOMED Limited (Great Britain) was also used.

In this case only the slight esophageal lumen widening was obtained. It enabled us to perform the dilation with through-the-scope baloon dilators.

In this case hyperthermia, muscle and bone pain as well as the exacerbation of glaucoma, probably caused due to prolonged stay in the dark, after PDT procedure was observed. Dysphagia score improvement was not significant. Survival time was only 2 weeks probably caused by essential disease.

We think that longer extension of neoplasmatic infiltration and too short active part of laser fiber was the main reason of the failure of PDT in this case.

**Discussion**

Nowadays there are several effective palliation therapies available in oesophageal cancer, such as expandable metal stents, high dose rate (HDR) brachytherapy, photodynamic therapy (PDT), Nd:YAG laserotherapy, radiotherapy, systemic and local chemotherapy [4,9-14].

Brachytherapy in single dose gives slow improvement of dysphagia, but better long term results than metal stent placement [36]. Similar slow improvement of dysphagia is being observed after external beam radiation [19,20]. Hyperfractionated radiotherapy may be more effective to palliate dysphagia than external beam radiation [21]. Concurrent chemoradiation gave longer survival time than chemotherapy, but was associated with more frequent complications [20]. Nd:YAG laser ablation compared with stent placement appears to better palliation of dysphagia, with lower morbidity for tumors less than 5 cm in length [24].

Photodynamic therapy (PDT) is a minimally invasive treatment in malignant disease [15]. The use of photosensitizing chemicals to produce cytoxicity began in the early nineties; however reports on the use of PDT for esophageal cancer first appeared in early eighties [27]. PDT involves in situ photo-activation of photosensitizing drugs by light at appropriate wavelength, generating highly active and short live – oxygen derived species. The reactive oxygen products have low diffusion capacities, and resultant tissue damage begins at the level of the plasma and organelle membranes, especially the mitochondria, the primary site of localization of photosensitizer. Vasoactive and inflammatory mediators are released, resulting in vascular stasis, haemorrhage and eventually, direct and anoxic tumor cell death. The level of singlet oxygen required for cell death is lower for neoplastic tissue than for normal tissue and, following PDT, nonmalignant tissue regenerates its normal architecture (mucosa, submucosa, and so forth) and strength [28,29].

PDT seems to offer advantages in several situation and subgroups. PDT is less operator dependent and technically easier for an endoscopist to perform compared with Nd:YAG laser thermal ablation. For PDT, a diffusing fiber is placed in the area of malignant stenosis, and low powered laser irradiation is carried out to large areas of tumor simultaneously. Much more manipulation with endoscope is required for standard Nd:YAG laser treatment. [30].

PDT is relatively comfortable procedure for the patients compared with Nd:YAG laser therapy. Nd:YAG is more difficult to carry out in lightly sedated patients. PDT showed trends for better tumor response than Nd:YAG therapy in tumors longer than 10 cm, located in narrow upper third and in the angulated lower third of the esophagus, and in patients who had previous treatment failures or cancer recurrence after primary therapy [30].

Luketich observed 77 patients who underwent PDT for oesophageal cancer. The mean dysphagia score at 4 weeks in 90,8 % patients improved from 3,2 to 1,9 points. PDT adequately controlled bleeding in all six patients. The overall mean dysphagia - free interval was 80,3 days. The 30-day mortality rate was 3,9% (n=3), one was caused by esophageal perforation [31].

In Moghissi study on 102 patients with oesophageal cancer, post PDT complications included photosensitivity skin reaction (sunburn) in 5 patients and esophageal stricture in 8 patients. Mean survival time in advanced carcinoma was 9.5 months. Dysphagia grade improvement has also been observed [17].

In another study on the same subject, there was no PDT related mortality. It was safe and effective for palliation of dysphagia in inoperable oesophageal cancer. The authors emphasized, that PDT is particularly useful in post-cricoid and cervical oesophageal cancer previously treated by other methods and in patients with recurrent malignant obstruction who previously underwent intubation or stent placement [32].

Lightdale CJ et al. reported more frequent complete or partial response (based on luminal diameter) after 1 month treatment in PDT group (32%) versus Nd:YAG group (20%). Complete tumor response was achieved in nine cases (8,2%) after PDT and in two (1,9%) after Nd:YAG [30]. Trends for improved responses for PDT were seen in tumors located in the upper and lower third of the esophagus. Mild or moderate toxicities were more frequent after PDT, with the sunburn occurring in 19% of patients treated with PDT. Adverse event required aborting of laser therapy in 3% of patients treated with PDT versus 19% of those treated with Nd:YAG laser. Perforation occurred in 1% of patients treated with PDT compared with 7% treated with Nd:YAG laser [23,30].

Better life quality and longer duration of response after PDT then after Nd:YAG was confirmed by Heier at al. [34].

Small risk of esophageal perforation after PDT, is due to the depth of tumor necrosis, which is limited to 5 mm [33].

It was only our first experiences in PDT therapy in our Department. We find PDT very promising, minimally invasive, safe and easy technique to perform for esophageal cancer of cervical localization.

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Pazurek Marek MD
e-mail – marekpaz@wp.pl, marekpaz@o2.pl