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Clinical outcome of photodynamic therapy in esophageal squamous cell carcinoma

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ABSTRACT

The aim of this study was to evaluate the feasibility and safety of photodynamic therapy (PDT) as a curative treatment option or as palliative therapy for esophageal squamous cell carcinoma.

Medical records of patients who received PDT for esophageal squamous cell carcinoma, including carcinoma in situ, were reviewed retrospectively. Survival analysis was performed using the Kaplan–Meier method.

A total of 31 cases were treated with PDT between 2003 and 2013. Treatment was for palliative purposes in 11 cases (35.5%) and for therapeutic purposes in 20 cases (64.5%). We achieved 15 cases (48.4%) of complete remission and 16 (51.6%) cases of partial remission during the follow-up period. There were 6 fatalities, 5 of which were related to disease progression. Complications, including benign strictures, occurred in 11 cases (35.5%) but there was only 1 complication-related death. Recurrence occurred in 2 patients with complete remission. Overall survival was 31.9 months for patients with complete remission and 28.2 months for those with partial remission. Disease-free survival of patients with complete remission was 21.9 months.

Our data suggest that photodynamic therapy is a reasonable palliative treatment option with acceptable complication rates for esophageal cancer and could be performed for therapeutic purposes in cases of early esophageal cancer.

1. Introduction

Photodynamic therapy (PDT) is an endoscopic procedure involving selective uptake of a photosensitizer by proliferative, especially malignant, cells that allows targeted cytotoxic effects when light of a specific wavelength is applied. PDT requires 3 components: a tumor-specific photosensitizer, oxygen, and a light source [1]. Separately, none of these are harmful, but the combination of these three components initiates a serial photochemical reaction that rapidly causes significant cytotoxicity.

The first step of PDT is administration of the photosensitizer, which usually has a tetrapyrrole structure. Subsequent irradiation with light of an appropriate wavelength corresponding to the absorption band of the photosensitizers results in the generation of singlet oxygen and induces cell death via 3 phenomena: apoptosis, necrosis, and autophagy [2,3].

The first clinical use of PDT was in 1978 for patients with metastatic skin cancers [4]. Since then, photodynamic therapy has become increasingly applied in anticancer therapy. It appears to be a reasonable option for the treatment of malignant and premalignant non-melanoma skin lesions, and also for Barrett's esophagus and unresectable cholangiocarcinoma [1,5].

PDT is very attractive therapeutic modality that has many advantages. It is a minimally invasive technique with few deleterious effects on normal tissue. It has negligible systemic effects and can be applied in combination with other therapeutic modalities. It has also been reported to yield a survival benefit and an improvement in quality of life.

Clinical applications of PDT for esophageal cancer have been reported in high-grade dysplasia and Barrett's esophagus, for early

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esophageal cancer in inoperable patients, and in palliative treatment for obstructive lesions.

Although PDT was approved by the Food and Drug Administration as a drug-device almost 2 decades ago [1], it remains underutilized clinically and its full effectiveness has not yet been fully elucidated, especially for therapeutic purpose in early esophageal cancer. In this study we analyzed the results of 31 sessions of PDT for esophageal cancer in order to gain insight into its indications in this disease entity.

2. Patients and methods

Medical records of patients with esophageal cancer who underwent photodynamic therapy in our institute between 2003 and 2013 were reviewed retrospectively. Candidates for PDT were selected as follows: (1) patients with early esophageal cancers who could not receive surgery because of comorbidities or who refused surgery; (2) patients with recurrent cancer or unresectable tumor requiring palliative surgery; (3) patients requiring emergency alleviation of severe pain or obstruction.

All patients underwent routine laboratory blood tests and careful physical examination. Enhanced chest computed tomography (CT) and positron-emission tomography CT were performed for cancer evaluation and detection of metastasis. Endoscopic examination including endoscopic ultrasound (EUS) was essential for the assessment of staging and pathology.

PDT consists of two stages: administration of photodynamic therapy and irradiation with light of an appropriate wavelength. The administrated dose of photosensitizer was 2 mg/kg. After a waiting period of 24–48 h after the administration of photosensitizer via an intravenous route, the patients underwent endoscopic tumor ablation with a light diffusion catheter (Xcell PDT Balloon with Fiber Optic Diffuser, Cook Endoscopy, Winston-Salem, NC, USA) using a tunable laser (Diomed® 630 PDT Laser System, Diomed, Ltd., Cambridge, UK).

Although various kinds of photosensitizers were used, in most cases we used Photofrin (Pinnacle Biologics, Bannockburn, IL, USA). Other options were chosen if Photofrin caused any adverse reactions. Patients were given 200–400 J per session, with treatment duration of 500–700 s.

Patients underwent assessment by endoscopy 2 days after the first treatment. Mechanical debridement of necrotic tissue was performed if necessary. Dilatation of the esophageal lumen to prevent or eliminate stenosis and additional laser irradiation was also performed if necessary.

All patients were recommended to avoid sunlight for 4 to 6 weeks after the final PDT. If the patient had no complaints they were given soft food beginning. Follow-up endoscopy was performed at 1, 3, and 6 months after the first PDT. Chest CT was also performed 6 months after PDT.

Treatment results were categorized into 3 groups: complete remission (CR), defined as no evidence of disease on follow-up chest CT or endoscopy 6 months after PDT; partial remission (PR), in which tumor regressed or was still observed in the tumor bed or there was regrowth after remission; or no response, defined as up to 50% of the tumor remaining or an increase in tumor size after PDT.

We evaluated treatment response in each case. Local recurrence was defined as emergence of tumor regrowth after complete or partial remission on follow-up endoscopy or chest CT. Survival and complication rates were calculated using Kaplan–Meier survival analysis. SPSS 20.0 (IBM, New York, NY, USA) was used for statistical analysis.

3. Results

3.1. Patient characteristics

A total of 31 cases were analyzed. 2 were female, and the rest were male. The median follow-up period was 26.0 months. Average age at the time of treatment was 65.1 (±9.71) years. PDT was performed 26 times (83.9%) for primary lesions and 5 times (16.1%) for recurrent lesions. Information on patients is summarized in Table 1, and the treatment modalities that patients received before PDT are categorized in Table 2.

3.2. Treatment results

CR was achieved in 15 (48.4%) of the 31 cases. One patient could have reached CR after 4 sessions of PDT. Two patients in the CR group had recurrences during the entire follow-up period. No patients in the CR group died during the follow-up period.

PR was observed in 16 (51.6%) cases. Two of these patients should have received surgery because of residual tumor. Six patients with PR died during the follow-up period (19.4%): 4 from cancer progression, 1 from PDT complications, and the other from aspiration pneumonia.

The overall complication rate was 35.5% (11 cases). The most common complication was benign stricture, which occurred in 6 cases (19.4%). Two of these patients needed stent insertion for their stricture. One patient died as a result of esophageal perforation after PDT, which was the only complication-related death.

Local recurrence was observed in 9 patients (29.0%). Among the PR cases, there were 7 cases of recurrence, defined as regrowth of tumor in follow-up examination. Of those 7 patients, 4 died of cancer progression. For treatment of recurrence, 2 patients received surgery and 6 received recurrent PDT.

Two of the patients with CR showed recurrence, but none died of cancer progression. One patient received endoscopic mucosal resection (EMR) and other received radiation therapy for treatment of recurrence (Table 3).

Table 1
Patient characteristics.

Variables	Frequency	%
Age (years)	65.1 ± 9.71	
Median follow-up periods (months)	26.0 (1.6–105.4)	
Gender		
Male	29	93.5
Female	2	6.5
Cancer status		
CIS	7	22.6
T1	15	48.4
T2	0	0.0
T3	1	3.2
T4	1	3.2
Unknown	2	6.5
Recurred	5	16.1
Cancer location		
Upper	6	19.4
Mid	11	35.5
Lower	14	45.2
Treatment purpose		
Therapeutic	20	64.5
Palliative	11	35.5
Emergency	0	0.0

CIS = carcinoma in situ.