Photodynamic therapy (PDT) in Barrett’s esophagus with dysplasia or early cancer

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Abstract

Objective: Esophagectomy is the standard treatment for high-grade dysplasia (HGD) and intramucosal adenocarcinoma (IMC) arising within Barrett’s esophagus. Results of photodynamic therapy (PDT) were retrospectively studied to evaluate the effectiveness of PDT in ablating HGD and/or IMC complicating Barrett’s esophagus.

Methods: Thirty-one patients unfit for or refusing esophagectomy (male: 20, mean age: 73.4 ± 9.3 years) underwent Porfimer sodium PDT ablation of their HGD (15 patients), HGD plus IMC (10 patients) or submucosal/limited T2 adenocarcinoma (6 patients). The mean Barrett’s length was 5.8 ± 2.2 cm. Pre-PDT endoscopic mucosal resection or Nd:YAG laser ablation of mucosal nodularity within Barrett’s segment was offered in six patients.

Results: The main PDT complications were esophagitis (16.1%), photoreactions (12.9%) and stricture requiring dilatation (6.25%). The median post-PDT follow-up was 14 months. The long-term results were (a) for HGD/IMC: initial complete response (endoscopic and histologic absence of HGD—IMC) to PDT was observed in 80.95% of patients, partial response (no endoscopic abnormality, residual IMC—HGD on biopsy) in 9.52%, no response in 9.52% (the recurrence rate after an initial complete response was 17.64%) and (b) for T1b/limited T2 tumors: two patients died from cancer after 24 and 46 months, no evidence of tumor was found in two patients after 12 and 19 months and tumor recurrence was seen in two after 15 and 17 months. The mean survival was 22.1 ± 12.3 months.

Conclusions: PDT is effective in ablating HGD/IMC complicating Barrett’s esophagus in the majority of cases, while it also seems to be quite effective in treating T1b/limited T2 carcinomas.

Keywords: Barrett’s esophagus; High-grade dysplasia; Intramucosal esophageal adenocarcinoma; Porfimer sodium; Photodynamic therapy; Endoscopic ablative techniques

1. Introduction

Barrett’s esophagus is the most frequent predisposing condition for the development of esophageal adenocarcinoma, by increasing the risk of developing adenocarcinoma by about 40 times when compared to the general population [1–4]. Dysplastic changes in Barrett’s metaplastic epithelium will appear in a subset of patients (20%) and will lead to esophageal cancer through the sequence: Barrett’s epithelium—low-grade dysplasia (LGD)—high-grade dysplasia (HGD)—adenocarcinoma [3].

Currently, the standard treatment for Barrett’s esophagus complicated with HGD of the mucosa is early invasive cancer [5–7]. However, all patients are not fit for esophagectomy and alternative minimally invasive endoscopic mucosal ablative therapies have been developed, such as photodynamic therapy (PDT), neodymium—yttrium—aluminum—garnet (Nd:YAG) laser thermal photoablation, multipolar electrocoagulation, argon plasma coagulation (APC), endoscopic mucosal resection (EMR) and some combination of the previously mentioned therapies [2,8].

Photodynamic therapy with Porfimer sodium (Photofrin®), Sinclair Pharmaceuticals Ltd, Borough Rd., Godalming, Surrey, UK has recently (2003) been approved in UK by the National Institute for Clinical Excellence and in USA by the FDA for the destruction of pre-cancerous esophageal lesions in people who do not undergo esophagectomy. The results of PDT using Porfimer sodium for Barrett’s esophagus with HGD and early Barrett’s adenocarcinoma were studied in biopsies until the development of early invasive cancer [5–7].
order to evaluate the effectiveness of Porfimer sodium PDT in a population of patients unfit for esophagectomy or refusing the operation.

2. Patients and methods

2.1. Patients

Thirty-one patients (20 male, 11 female), who were referred for PDT for their Barrett’s esophagus complicated with HGD and/or early esophageal adenocarcinoma between 1/1998 and 12/2004 (7 years), were included in the retrospective study. The mean age of patients was 73.45 ± 9.38 years (range: 53—85 years, age > 80 years: 9 patients). The condition to be treated was HGD in 15 patients, HGD and intramucosal adenocarcinoma in 10 patients and T1b or limited T2 adenocarcinoma in 6.

Twenty-six out of the 31 included in the study group patients (83.87%) were unfit for major surgery (esophagectomy) because of comorbidities, while the remaining five patients refused surgery as their treatment option and PDT was offered as the alternative to surgery treatment. The decision to proceed with PDT was taken within a multi-disciplinary oncological upper gastrointestinal team in the majority of cases.

2.2. Pre-treatment surveillance

All the patients included in the study were under continuous endoscopic surveillance prior to their referral for their Barrett’s esophagus. Four-quadrant biopsies every 2 cm were taken from their whole Barrett’s esophagus length at 6—12 months intervals. Three patients were asymptomatic and 26 patients suffered from trivial or mild reflux symptoms. Severe reflux symptoms associated with a long-standing hiatal hernia were present in one patient and dysphagia in another one.

The median time of endoscopic surveillance from the initial detection of Barrett’s segment until the detection of HGD or early adenocarcinoma was 24 months (variance: 0—180 months). Two experienced pathologists confirmed the diagnosis of HGD. The Barrett’s segment extended to a mean of 5.86 ± 2.28 cm (variance: 3—11 cm) above the gastro-esophageal junction (GOJ), while a hiatal hernia was present in 10 patients and T1b or limited T2 adenocarcinoma in 6.

2.3. PDT protocol

In all the PDT candidates, the photosensitizer Porfimer sodium (Photofrin®) was injected 24 h before the application of laser light in a dose of 2 mg/kg of body weight. Surface photolitigation with red laser light at 630 nm wavelength was applied in their whole Barrett’s segment, 24 h after the photosensitizer injection. Laser light was applied via a 25 or 30 mm length cylindrical diffuser that was inserted through the working channel of a flexible esophagoscope and it was appropriately positioned along the Barrett’s segment to be treated. The laser power was set at 0.4—0.5 W when HGD was the target of the treatment and at 1.0—1.2 W when early esophageal adenocarcinoma was the target of the treatment, for deeper light penetration. The laser light application time was 500 s in each application, while more than one applications were offered in nine patients to treat the whole Barrett’s segment. Two applications were needed in seven patients and three applications in two patients. All the patients were maintained on proton pump inhibitors after their PDT treatment.

PDT treatment was given under general anesthesia in 26 patients and under sedation in 5 patients, who were unable to tolerate even a short-time general anesthesia.

2.4. Post-PDT follow-up

Every patient had check esophagoscopy 2—4 months after PDT treatment. The intervals of post-PDT surveillance endoscopies varied from 3 to 6 months according to the initial post-treatment assessment.

The results were assessed on the basis of mortality and morbidity of the procedure, patient’s satisfaction to treatment, changes in Barrett’s segment, necessity for additional PDT or other treatment and long-term survival. The response of Barrett’s segment to PDT treatment was defined as: (a) Complete response: macroscopic and pathologic absence of pre-neoplastic or neoplastic changes; (b) Partial response: no macroscopic evidence of tumor within Barrett’s segment, while biopsies revealed residual HGD and/or IMC; and (c) No response: macroscopic evidence of residual tumor or tumor progression. All the necessary information was collected from the patient’s notes and after communication with the referring consultant or the primary care doctor responsible for each patient.

3. Results

3.1. Mortality—morbidity

Mortality of the procedures was nil. All patients were sent home within 6 h after the procedure or the day after.

The observed complications of PDT are presented in Table 1. The most common complications were esophagitis (16.12%) and mild skin photoreactions (12.90%). The observed temporary dysphagia due to post-PDT esophagitis had settled down within 1 month after PDT in three patients, while it had led to stricture formation in one patient, 3 weeks after PDT treatment. This stricture responded well to dilatation with Maloney bougies. One patient had a late...
3.2. Changes in Barrett’s segment

Endoscopic changes observed during first post-PDT endoscopy in the treated Barrett’s segment

<table>
<thead>
<tr>
<th>Endoscopic changes</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barrett’s esophagus with HGD (15 patients)</td>
<td></td>
</tr>
<tr>
<td>Residual Barrett’s mucosa (tongues or islands)</td>
<td>10</td>
</tr>
<tr>
<td>Complete re-epithelization of the treated area</td>
<td>5</td>
</tr>
<tr>
<td>Limited healing scar</td>
<td>2</td>
</tr>
<tr>
<td>Barrett’s esophagus with HGD and IMC (10 patients)</td>
<td></td>
</tr>
<tr>
<td>Residual Barrett’s mucosa (tongues or islands)</td>
<td>10</td>
</tr>
<tr>
<td>Benign stricture</td>
<td>2</td>
</tr>
<tr>
<td>Increase in the shoulder of intraluminal lesion</td>
<td>1</td>
</tr>
<tr>
<td>T1b and limited T2 tumors (6 patients)</td>
<td></td>
</tr>
<tr>
<td>Tumor progression</td>
<td>1</td>
</tr>
<tr>
<td>Persistent residual tumor</td>
<td>3</td>
</tr>
<tr>
<td>None evidence of tumor</td>
<td>2</td>
</tr>
</tbody>
</table>

(3 months post-PDT) stricture formation, presenting with dysphagia that needed balloon dilatation. The stricture formation was related to the higher laser power set-up (1.0—1.2 W). The need for specific treatment was limited in two patients, requiring esophageal dilatation (6.45%). The results of dilatation were excellent.

3.2. Changes in Barrett’s segment

Endoscopic changes in Barrett’s segment, which were observed during the first post-PDT endoscopy, are presented in Table 2.

3.3. Repeat PDT—additional endoscopic treatment

Forty PDT sessions were applied in 31 patients. Five patients underwent two PDT sessions and two patients had three PDT sessions. The need for a second or a third PDT was:

- Recurrence of HGD 9 months after the first PDT session in one patient, permanently reversed by a second PDT.
- Partial response to the initial PDT in two patients.
- Invasive adenocarcinoma arising from the background of HGD in one patient, detected 6 months after the initial PDT treatment.
- Residual or persistent adenocarcinoma in three patients

EMR of a superficial (intramucosal) esophageal adenocarcinoma was performed prior to any PDT treatment in three patients. Nd:YAG laser treatment was applied before any PDT treatment in three patients, to destroy areas with mucosal nodularity suspicious for adenocarcinoma. One patient, who had a suspicious 4 mm nodule within his Barrett’s segment, underwent an EMR of the nodule because no changes in the nodule appearance were found at check endoscopy, despite the reversion of HGD. Histology results of the resected lesion proved a benign esophageal lesion (neurofibroma). Another patient had Nd:YAG laser ablation of a malignant 10 mm nodule close to GOJ that was appeared and diagnosed for the first time at check endoscopy performed 18 months after PDT for Barrett’s esophagus with HGD. Complete response was documented at 6 and 12 months after the initial PDT in the previously mentioned patient.

3.4. Long-term results

Post-PDT follow-up for all patients varied from 4 to 70 months (median: 14 months).

3.4.1. HGD and/or IMC

In four patients, the follow-up period was limited to 4 months and the only finding to be reported was that of neo-epithelization of their Barrett’s esophagus, with some small residual areas of columnar epithelium. The median time of post-PDT surveillance for the rest 21 patients was 14 months (range: 6—70 months). Synoptic long-term results of PDT in these 21 patients are presented in Table 3.

Persistent or recurrent disease was located within 2 cm distance from the GOJ. In one patient the recurrence site was the site of a previous EMR, where complete resection of the lesion was documented at biopsy.

Buried glands under the neo-squamous epithelium were found in five patients (20%) during their post-PDT surveillance biopsies.

3.4.2. Early Barrett’s adenocarcinoma (T1b or limited T2)

The mean follow-up time for the six patients until today is 22.16 ± 12.35 months. One patient had no endoscopic evidence of tumor 12 months after PDT treatment. Two out of the six patients with an early esophageal adenocarcinoma died during the follow-up period, after 24 and 46 months, respectively. The first patient died from cancer, while the second patient had three PDT sessions during the 46 months follow-up, until death from unrelated causes. One patient had tumor recurrence 17 months after the initial treatment and he underwent a second PDT for his recurrent tumor. Two patients had persistent adenocarcinoma, but they were alive 15 and 19 months after the initial treatment (the second one after two PDT treatments).

Table 3

<table>
<thead>
<tr>
<th>Response to PDT treatment</th>
<th>Number of patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial complete response</td>
<td>17/21</td>
<td>80.95</td>
</tr>
<tr>
<td>Recurrent HGD (permanently reversed by a second PDT) and adenocarcinoma development a after initial complete response</td>
<td>3/17</td>
<td>17.64</td>
</tr>
<tr>
<td>Partial response b</td>
<td>2/21</td>
<td>9.52</td>
</tr>
<tr>
<td>No response</td>
<td>2/21</td>
<td>9.52</td>
</tr>
<tr>
<td>Permanent complete response</td>
<td>15/21</td>
<td>71.42</td>
</tr>
<tr>
<td>Adenocarcinoma development</td>
<td>4/21</td>
<td>19.04</td>
</tr>
</tbody>
</table>

a Two patients who developed adenocarcinoma (18 and 15 months after treatment), had a previous complete response 12 and 6 months after their first PDT, respectively.

b Significant tumor recurrence was found 15 months after a second PDT in the first patient, that was further treated with APC and finally with dilatation and stenting. He survived 32 months after the diagnosis. The second patient developed invasive cancer 15 months after the diagnosis. He underwent two repeat PDT sessions with partial response also and he died from esophageal cancer 17 months after the initial treatment.
3.5. Patient’s satisfaction to treatment

The immediate post-PDT quality of swallowing was excellent in all patients that underwent an uncomplicated with stricture or esophagitis procedure. After the subsidence of esophagitis, within one month after PDT, good quality of swallowing was also reported from this subgroup of patients. The two patients who underwent esophageal dilatation for post-PDT stricture are free of symptoms for a long period. Even patients with partial response to treatment had a very good quality of swallowing.

4. Discussion

PDT is a minimally invasive treatment method that involves in situ photoactivation of a photosensitizing drug by an appropriate light at specific wavelength. The interaction of the two components in the presence of oxygen generates through a photodynamic reaction highly active and short-lived derived cytotoxic species, such as singlet oxygen and free radicals. These cytotoxic species induct direct oxidative damage of cellular organelles (cellular toxicity) and of the microvasculature (vascular toxicity) which promotes necrosis of the treated tissue [9]. In the case of endoluminal esophageal pre-malignant or malignant lesions, PDT is carried out as a two-phase procedure, in the first of which the photosensitizing agent is administered. Time is then allowed for the agent to be absorbed and retained preferentially, with a higher dose in the lesion compared with normal tissue. In the second phase, the pre-sensitized tissue is exposed to the specific wavelength of light. Two methods of illumination are used according to the volume of tissue to be targeted by the light exposure: (a) interstitial, in which the light applicator is inserted into the mass of the target tissue, usually cancer and (b) surface or intraluminal, where, as name implies, illumination is carried out to affect the surface of the lesion [9].

Adenocarcinoma has been found in 38–50% of patients who underwent esophagectomy for HGD complicating Barrett’s esophagus, which was not detected at pre-operative surveillance endoscopic biopsies [10,11]. The main problem when deciding on how to treat HGD and IMC is that, carcinoma extending beyond the mucosa may coexist at the same time and even with the more strict protocol of endoscopic surveillance, a small foci of invasive carcinoma can be missed. For this reason, all these conditions should be considered together when deciding to offer treatment and the desirable depth of penetration should be deeper than the mucosal depth. Porfimer sodium PDT has a penetration depth of 3–4 mm in contrast to ALA PDT, where the depth of penetration is less than 2 mm [12,13]. Ackroyd et al. [14], in a series of 100 specimens of Barrett’s mucosa, reported that the depth of Barrett’s mucosa never exceeded 0.6 mm and subsequently deeper penetration is not required to eradicate HGD. Despite the reported higher stricture formation with Porfimer sodium PDT and balloon photolllumination (28%), photofrin is considered at the moment superior photosensitizer for treating HGD and/or IMC [13,15] Post-PDT strictures can be a problem, but strictures are usually successfully managed with dilatation. In the present series, the stricture formation was low (6.45%) and dilatation of the stricture resulted in a long-term symptom-free period. High rates of stricture formation (30%) reported in other series, may also be related to the technique used to apply the laser light (through windowed esophageal centering balloons) [11]. Photoreactions complicating Porfimer sodium PDT were limited to a small percentage (12.90% in the present study). Less photoreactions are expected if the candidate for PDT patient is well informed about the length of photosensitizing period and the risk arising from exposure to bright natural or artificial light during this period.

A disadvantage of PDT in treating dysplastic Barrett’s epithelium and IMC is considered to be the persistence of intestinal columnar mucosa beneath the neo-squamous epithelium. In the present series the incidence of buried glands was found at post-PDT biopsies to be 20%. However, in a well conducted series by Ban et al. [15], buried intestinal columnar epithelium was found in 51.1% of patients after PDT treatment, much higher than the reported incidence in the present series and in the series by Overholt et al. [10] (20% and 4.9%, respectively). More interesting is the finding that foci of dysplasia and carcinoma buried beneath squamous epithelium were found in 36.4% of patients with buried glands in the series by Ban et al. [15] In the larger published series until today by Overholt et al. [10] 3 out of 80 patients with HGD who underwent PDT (3.75%) developed subsquamous cancer. According to these findings, all patients treated with PDT should undergo intensive endoscopic surveillance, with multiple biopsies, after treatment.

In the present series, PDT ablation of HGD/IMC was effective in 71.42% of patients, where a long-term follow-up was available. Recurrence of HGD or adenocarcinoma development after a good initial response to PDT was observed in 17.64% of patients. Our results are close to that of Overholt et al. [10], where the success rate for PDT in ablating HGD was 77.5%. An important finding of the study is that, recurrences or resistant to PDT disease were located very close (<2 cm) to GOJ. A possible explanation could be the difficulty to properly apply laser light in this area. The proximal GOJ area is most affected by bile reflux and inflammation of the mucosa frequently occurs, causing thickening of the mucosa. Inflammation could alter the distribution of photosensitizer and the depth of light distribution.

Other endoscopic minimally invasive ablative techniques for Barrett’s HGD/IMC such as Nd:YAG laser, APC, electrocoagulation, EMR have also been developed as alternative to surgery techniques with good results [2]. In the previously mentioned ablative techniques, the pre-cancerous or early cancerous lesion needs to be first macroscopically detected and ablation should be targeted to the detected areas. The advantages of PDT are the selective targeting of malignant tissue, the lack of interaction between PDT and systemic forms of cancer therapies and the minimal intervention followed by relatively low morbidity and toxicity [9,16]. Nd:YAG laser has been used to ablate residual Barrett’s mucosa after PDT, detected by Lugol’s iodine, with good results [10]. Indeed, any suspicious nodularity should be ablated by Nd:YAG laser or resected by EMR before the application of PDT and the subsequent development of esophagitis. Maish and DeMeester [17] even suggests that
EMR should be used as a staging tool in patients with early esophageal cancer. The possible scarring and stricture formation after PDT may affect the endoscopic view of the previously suspicious for IMC nodularity, as well as the visualization of EUS. We have to note that in the present series, the site of a previous EMR for IMC, was the site of a late adenocarcinoma development in one patient.

In conclusion, the results of the present study support the value of Porfimer sodium PDT as a sufficient ablative technique in the majority of patients with HGD/IMC complicating Barrett’s esophagus, who do not undergo surgery. Porfimer sodium PDT is a safe ablative technique, where the only complication that needs further intervention is the development of esophageal stricture. Residual Barrett’s mucosa and buried glands beneath the neo-squamous epithelium still remain a problem of the technique, while resistant to PDT lesions are mainly located close to GOJ.

References