The role of photodynamic therapy (PDT) in inoperable oesophageal cancer

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Abstract

Objective: To evaluate the role of PDT in palliation of patients with inoperable oesophageal cancer and to identify subgroups in which this role is of particular significance. Methods: Sixty-five patients (37 male, 28 female) aged 42–89 (mean 65.6) with advanced and inoperable oesophageal cancer were the subjects of this study. Inoperability was due to advanced stage of the disease in 61 and because of general condition in 4. Fifty-eight (89%) had previous treatments, other than PDT. All patients had dysphagia of whom 20 could not swallow fluid. Pre-PDT clinical, radiological and endoscopic examinations were carried out. Performance status (PS) and clinical staging was assessed. PDT protocol consisted of: intravenous injection of 2 mg/kg; photofrin (or equivalent polyhaematoporphyrin) followed 24–72 h later by endoscopic illumination using 630 nm laser light. Main outcome measurements: (1) Relief of dysphagia generally and specifically in those with cervical and post-cricoid carcinoma who were previously treated by external beam radiotherapy (EBR) (n = 6) and those with previous intubation or stent (n = 9); (2) Survival. Results: There was no PDT related mortality. Three patients (4.6%) developed a mild skin photosensitivity reaction. Dysphagia was relieved in all patients. The mean and median survival of the 58 patients who have died was 7.7 and 6 months respectively. Seven patients are alive from 2–30 months (mean 16). Survival was not significantly influenced by tumour histology, location in the oesophagus, severity of dysphagia on admission, or by previous therapy. Survival was significantly influenced by Performance Status prior to treatment (P = 0.03 log rank, for PS ≤ 2 vs. PS = 3), and most significantly by the stage of the disease (P = 0.0001 log rank, for Stage III vs. Stage IV). Conclusions: (1) PDT is safe and effective for palliation of dysphagia in inoperable oesophageal cancer. This is particularly important in post-cricoid and cervical oesophageal cancer previously treated by other methods and for patients with recurrent malignant obstruction who previously had intubation or stent placement. (2) Survival is influenced by better PS (≤ 2) and in those with disease Stage III rather than patients in Stage IV. This study has not been able to determine the influence of complete tumour staging on survival because, apart from four patients, all others were Stages III and IV cancer. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Photodynamic therapy; Oesophageal cancer

1. Introduction

At presentation between 40–50% of patients with oesophageal cancer are deemed surgically unresectable and, of those resected, no more than 15–20% have chance of cure of their disease or long survival [1,2]. Clearly, therefore, for the majority, the mainstay of treatment is palliation of symptoms which, for all practical purposes, means the relief of dysphagia. For this, bypass surgery, external beam radiotherapy (EBR), brachytherapy, chemotherapy, indwelling tube and stent placement, or a combination of these, have been advocated [3–7]. More recently, endoscopic photoradiation has been used to relieve malignant obstruction of the oesophagus. In this regard, the beneficial effect of neodymium aluminium garnet (NdYAG) laser has been reported extensively and has become a well-established therapeutic method [8–10].

In an initial pilot study [11] we demonstrated the safety and efficacy of PDT in palliation of dysphagia in oesophageal cancer. The aim of the present paper is to review and analyse the results of our total and updated experience in endoscopic PDT for inoperable oesophageal cancer and to
discuss its place within the spectra of available methods for this condition. We also attempt to identify a subset of patients for whom such a therapy is of particular importance.

2. Patients and methods

From January 1992 to December 1998, 65 consecutive patients with inoperable oesophageal cancer entered into a prospective study. Inoperability in 61 patients was because of the advanced stage of the tumour and in four due to poor general condition.

The main criteria for entry into the study were:

- patients of either sex and any age with advanced and/or inoperable oesophageal cancer;
- biopsy proven malignant endoluminal lesions, irrespective of location or histology of the tumour;
- dysphagia of any grade — Grade 1 being dysphagia to solid food (meat and fish), Grade 2 and 3 dysphagia to semi-solid food and puree, respectively, and Grade 4 total dysphagia [12];
- WHO performance status (PS) ≤ 3 (Table 1).

Most patients (n = 58, 89%) in the series had been diagnosed as having advanced unresectable cancer and had been treated elsewhere by other methods prior to referral to us. The remaining seven patients were considered as inoperable because of their general condition in four and due to the extent of the disease in three. Work-up at our centre consisted of full clinical, laboratory, radiological and endoscopic investigations.

On admission to the study, patients were examined clinically and recording was made of their symptoms, notably the grade of dysphagia, performance status using the WHO scale and previous treatment. Every patient had chest radiography, CT of the thorax and upper abdomen, a barium swallow contrast study and oesophagoscopy with biopsy. From these investigations, clinical staging and extent and location of tumour within the oesophagus were determined using UICC (Union International Contre Cancer) TNM classification [13]. Only patients with intraluminally visible and histologically proven cancer were considered for endoscopic PDT.

2.1. Protocol of treatment

The protocol of oesophagoscopic PDT has been previously reported [11]. Briefly, this consisted of:

- information to patients about PDT, its principles, possible skin photosensitivity reaction and general discussion about the treatment;
- intravenous administration of 2 mg/kg body weight of photofrin (or equivalent polyhaematoporphyrin (PHP) 24–72 h prior to illumination. This was carried out in the outpatient clinic where counselling was also provided and informed consent obtained;
- illumination of the tumour with 630 nm light produced by a copper vapour pumped-dye laser system (Oxford Lasers CU15, DL30) and delivered via a 400-μm-core optical fibre with a 2-cm diffusing end. A total dose of 200 J/cm of the tumour length is normally delivered;
- one or more site illumination was carried out according to topography and extent of the tumour. The choice of method of illumination, either interstitial or intraluminal, depended on the information recorded at pre-treatment assessment endoscopy relating to extent of tumour and its endoluminal component (Fig. 1a,b).

For interstitial illumination the optical fibre was introduced through the biopsy channel of the oesophagoscope and the cylindrical diffusing end section placed directly into the tumour under vision. For intraluminal illumination the optical fibre was placed first within the previously described applicator [11] and then positioned in the lumen of that part of the oesophagus involved circumferentially by tumour. The diffuser was first placed into the most distal 2 cm of the involved oesophagus. The applicator was then withdrawn 2 cm at a time for illumination of the more proximal parts until the whole extent of the tumour was treated.

Both types of placement were necessary in 60 cases. Two patients with early carcinoma and three others with tumour...
circumferentially involving the lumen of the oesophagus had intraluminal placement only.

All treatments were undertaken under general anaesthesia as day cases. One to two hours after treatment patients were examined and, providing their condition was satisfactory, they were given fluid to drink and discharged 2–3 h after PDT. They were instructed to continue at home with a fluid diet and after 24–48 h attempt meals of increasing consistency. Patients with bulky tumours were brought back for a second illumination 5–7 days after the first treatment. All cases were followed up as outpatients 4–6 weeks later when they were examined and arrangement was made for repeat endoscopy 6–8 weeks after the initial treatment. In patients with recurrence of dysphagia and malignant stricture repeat PDT or alternative treatment was undertaken as appropriate. Every patient was followed up until death.

2.2. Measurement of the outcome

The results were assessed using the following parameters:

- patient satisfaction to treatment;
- change in dysphagia grade at 6–8 weeks after treatment;
- weight gain/loss at follow-up;
- endoscopic aspect and pathological response to treatment 6–8 weeks after PDT and, thereafter, at intervals until patients death. Partial response (PR) was defined as macroscopic absence and/or considerable (> 50%) reduction in the size of tumour. Complete response (CR) was macroscopic absence of tumour in the oesophageal lumen and negative histology of biopsy samples;
- survival with the influence of location, histology, stage of tumour and patient performance status on admission.

2.3. Statistics

Survival curves have been generated using Kaplan–Meier analysis for the total population of patients. Survival for patients whose PS was ≤ 2 vs. those with PS = 3 and patients with Stage III cancer versus Stage IV were compared using the log-rank test. Pre- and post-treatment dysphagia grades were compared using the chi-squared test.

3. Results

There were 37 male and 28 female patients in the series, aged between 42 and 89 years (mean 65.6 years), 58 (89%) of whom had previous treatments, other than PDT, for palliation of dysphagia prior to referral. Forty-six patients (71%) had more than one previous treatment modality. Nine patients had pre-PDT radiotherapy and indwelling oesophageal tube or stent and their referral was because of tumour growth above, below or within the tube or stent. Every patient in the series was symptomatic on admission. All (100%) had dysphagia of various degrees; 20 were totally dysphagic. Sixty-one patients had lost 6 kg or more of their body weight and 20 patients had haematemesis. Location, histology and stage of tumours are shown in Table 2. The total number of treatments was 110 (1.6 treatments per patient).

There was no procedure or treatment-related mortality nor was there any morbidity. Three patients (4.6%) developed mild skin photosensitivity reaction in the form of erythema and slight oedema of hands and face. This subsided within 2–3 days of treatment with topical steroid. Six patients needed dilation of their post-PDT stricture and three of these had to have placement of celestine tube due to extrinsic oesophageal obstruction by glands.

Overall satisfaction to treatment was expressed by every patient. There was improvement in patients swallowing and fall in dysphagia grade 6–8 weeks after treatment, which is shown in Table 3. A chi-squared test on this data indicated a high degree of significance (P < 0.0001). This improvement was, however, matched with weight gain in only 17 patients (26%). Indeed five patients in grade IV continued to lose weight despite relief of dysphagia. On the whole, there was no change in the performance status of patients at 6–8 weeks following treatment.

3.1. Survival

Fifty-eight patients (89%) have died from their disease. The mean and median survival in these was 7.7 ± 0.8 and 6 ± 0.7 months, respectively. Seven patients (11%) are alive from 2–30 months (mean 16). Survival was not significantly affected by tumour histology or location, severity of dysphagia, or the type of treatment prior to PDT. It was influenced (P = 0.03 log rank) by better Performance Status (PS ≤ 2 vs. PS = 3) on admission to treatment. Only four patients (6%) had tumour Stage I and II, three of whom are alive between 8 and 30 months. The other patient died at 18 months, reportedly from unrelated causes. The survival of

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**Table 2**

<table>
<thead>
<tr>
<th>Location</th>
<th>Number (%)</th>
<th>Histology (no.)</th>
<th>Stage of tumour (no.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Adeno Squamous</td>
<td>Adeno/squamous</td>
</tr>
<tr>
<td>Cervical oesophagus</td>
<td>6 (10)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Mid-thoracic oesophagus</td>
<td>26 (40)</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>Lower thoracic oesophagus</td>
<td>33 (50)</td>
<td>24</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>65</td>
<td>41</td>
<td>19</td>
</tr>
</tbody>
</table>

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Survival curves have been generated using Kaplan–Meier analysis for the total population of patients. Survival for patients whose PS was ≤ 2 vs. those with PS = 3 and patients with Stage III cancer versus Stage IV were compared using the log-rank test. Pre- and post-treatment dysphagia grades were compared using the chi-squared test.
these four patients was better than in the 61 patients with disease Stage III and IV, although this small number does not allow statistical analysis. However, the survival difference between Stage III and Stage IV patients was highly significant ($P < 0.0001$ log rank). Median survival of patients with Stage III tumour was 8.0 (±0.7) months, compared to 3.0 (±0.5) for those with Stage IV. Fig. 2a shows the survival curve of all patients in the series. Fig. 2b demonstrates the curves for patients with tumours of different stage. Fig. 2c presents survival of those with PS ≤ 2 and PS = 3.

Pathologically all patients responded to treatment: partial response (PR) in 61 patients with advanced disease and complete response (CR) in four patients with Stage I and Stage II tumours.

4. Discussion

The use of PDT in cancer treatment is based on the principle of photosensitization of the tumour with a chemical followed, after an interval, by exposure to a specific wavelength laser light. The interaction between the photosensitiser and the light, in the presence of oxygen, exerts a cytotoxic effect leading to necrosis of the tumour. The application of the principle of employing photo chemicals for treatment of malignant tumours of the oesophagus entails intravenous administration to the patient followed by endoscopic illumination of the tumour mass by laser light of an appropriate wavelength delivered through the oesophagoscope. We have employed photofrin, which is the most commonly used drug, whose absorption band is within the red light spectrum at 630 nm.

Since its introduction into the therapeutic arena, the tendency of some investigators has been to use PDT in patients with early superficial tumours, to the exclusion of advanced cases [14]. Others have employed it in all inoperable cancers [15,16]. Whilst acknowledging that PDT in early cases has a high chance of total eradication and ‘cure’ of the disease we have been particularly looking at the role of PDT in inoperable and/or advanced stage tumours. This decision arose from the fact that in the western world, in the absence of screening, at presentation no more than 7–10% of cases are at an early stage [1,17]. Also, surgical resection in such early cancer is attended by over 70% long survival (5 years) amounting to cure of the disease [17]. At the present stage of PDT development it is reasonable to principally target patients with inoperable or advanced stage cancer though one should not lose site of the fact that, oncologically, the best results are obtained in early stage tumours.

Our experience indicates that in endoscopic PDT some technical aspects have important therapeutic relevance:

- in patients with extensive tumours both interstitial and intraluminal illumination is needed. This is because often one part of the tumour projects more prominently into the oesophageal lumen, requiring interstitial illumination, whereas the other parts might involve the lumen circumferentially requiring intraluminal exposure to light;
- to achieve complete necrosis in a bulky tumour two separate, consecutive sessions of endoscopic illumination are needed, the second one being carried out 5–7 days after the first. In this session the lumen of the oesophagus is also cleaned of necrotic debris;
- a small percentage of patients will develop stricture as
we have seen in our series. In some instances the stricture is non-malignant but requires dilatation. Also, as the tumour continues to invade the oesophageal wall, lymph nodes and surrounding structures, some patients will develop extrinsic compression of the lumen requiring intubation. For these patients we have used Celestin tubes since, in all such cases in this series, the obstruction was in the mid and lower oesophagus extending down for a considerable distance or even to the stomach.

Considering the fact that over the past 40 years many methods have been used to relieve dysphagia in patients with malignant obstruction of the oesophagus, one may justifiably debate the rationale of introducing yet another treatment to the existing arsenal. This debate should, however, be undertaken with the acknowledgement that none of the hitherto available methods are applicable to all patients or every cancer in different oesophageal locations. Also, of all the available methods, only radiotherapy and chemotherapy have specific action on cancer but both inflict collateral damage. PDT may be used in addition to other available methods for palliation. It is a target oriented mode of therapy and, ideally, one should be able to tailor the most appropriate treatment method to suit individual patient requirement. This can be achieved if there is a range of compatible treatment methods available.

Our study shows that PDT is capable of relieving dysphagia. Significantly, none of our patients died in total dysphagia which cannot be said to be the case in some alternative methods of palliation used in oesophageal cancer. The question may justifiably be asked whether endoscopic PDT in inoperable or advanced oesophageal cancer can fulfil any role that other methods cannot. Our experience suggests the answer to be affirmative. Firstly, in early stage cancer in patients who either refuse operation or cannot have major surgery on the grounds of poor general condition, PDT has the potential of cure and inflicts none of the general or collateral injuries afforded by chemo/radiotherapy. Only two patients in this series had clinical Stage I cancer, both are alive with no evidence of recurrence at 10 and 30 months, respectively. Secondly, two subsets of patients in our series have demonstrated the role of PDT in patients with advanced disease. These subsets should be highlighted and deserve further analysis in the future:

1. Nine patients in this series had EBR and oesophageal intubation or stent to overcome luminal malignant obstruction before their referral to us for PDT due to overgrowth of tumour proximal or distal to the tube or through the wall of some stents. Using PDT we were able to palliate these patients very satisfactorily with the prosthesis in situ. We believe PDT has a unique place in this situation since, apart from piecemeal biopsy forceps removal of the overgrowth, no other option but PDT can be safely used for disobliteration. Obviously thermal (NdYAG) laser cannot be employed because of high temperature and the risk of fire or thermal damage in contact with the prosthesis. This has also been pointed out by other authors [18].

2. The second subset concerns those patients with post cricoid and cervical oesophageal cancer who have had previous radiotherapy (and some chemotherapy). When tumour in these patients recurs, therapeutic options for palliation become a challenging problem. Experience indicates that, in many such cases, proximity to the larynx prohibits the use of a prosthesis to relieve obstruction and that intubation is not attended by good functional results because of food inhalation. Even without aspiration, such intubation may result in respiratory difficulties through extrinsic compression of the upper airway by tube/stent. Six of our patients (see Table 2) had post-cricoid and upper cervical oesophageal cancer recurrence following EBR. All six benefited fully from PDT and could achieve swallowing until their death.

5. Conclusions

This study confirms that PDT is a safe and an effective method of treatment for advanced and/or inoperable oesophageal cancer. It is capable of palliation of dysphagia in cases with extensive intraluminal cancer. In those with less advanced and earlier stage of the disease (Stage I) it has the potential to promote long term survival benefit.

The current importance of PDT within the spectrum of therapeutic modalities is:

- for patients with extensive unresectable tumour who have had placement of tube/stent with overgrowth of tumour causing malignant obstruction of the prosthesis;
- for patients with inoperable post-cricoid or high cervical oesophageal cancer;
- for those with early stage cancer who are judged to be unsuitable for major resectional surgery by reasons of poor general condition. In such patients long survival/cure can be expected.

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References

Appendix A. Conference discussion

Dr D. Watson (Norwich, UK): What did you do before the photodynamic therapy in the patients who had stents in place, did you leave them in place or did you remove them before your treatment? In the patients that had stents placed before they were referred to you for photodynamic therapy, what did you do with those stents, did you remove them before you gave them PDT?

Prof. Moghissi: I left them because the tumor had grown either above or within. After treatment the stent became patent.

Mr. J. Dussek (London, UK): If you have a totally occluded esophagus at cricoid level, or subcricoid, can you get through that with your therapy or do you have to get a wire through first?

Prof. Moghissi: Because you are inserting the diffusing end of the fiber, in the tumor, you don’t need to dilate. In fact, one can have as little as 1-mm hole and place the diffuser fiber into it, because PDT is not a thermal laser.

Mr Dussek: You still need a lumen, you say, even a pinhole?

Prof. Moghissi: In my experience there has never been a case where I could not actually find the lumen, because you can always probe a bit with the finest bougie.