Combined photodynamic therapy and hyperbaric oxygenation in carcinoma of the esophagus and the esophago-gastric junction

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Abstract

Objectives: The photochemical reaction of photodynamic therapy (PDT) depends on the presence of molecular oxygen. Due to anoxic regions in tumor tissue and vascular shutdown during PDT the efficiency is limited. Therefore, the use of hyperbaric oxygen which increases the oxygen in tumor tissue, as well as the amount of singlet oxygen, may enhance the efficiency of PDT.

Patients and methods: After diagnostic work-up, photosensitization was carried out with a hematoporphyrin-derivate 2 mg/kg BW 48 h prior to PDT. The light dose was calculated as 300 J/cm fiber tip. Thirty-one patients were treated by PDT alone and 44 patients received PDT under hyperbaric oxygen at a level of two absolute atmospheric pressure.

Results: Improvement regarding stenosis-diameter could be obtained in both treatment arms with no significant difference ($P = 0.82$). The dysphagia-score and tumor-length also decreased in both groups and showed a significant difference in favour of the PDT/HBO-group ($P = 0.0064$ and $P = 0.0002$, respectively). The median overall survival for the PDT-group was 7 months and for the PDT/HBO-group 12 months ($P = 0.0098$). Conclusion: According to this prospective non-randomized study, combined PDT/HBO represents a new approach in the treatment of esophageal and cardia cancer which appears to have enhanced the efficiency of PDT.

Keywords: Photodynamic therapy; Hyperbaric oxygenation; Esophageal carcinoma; Cardia carcinoma

1. Introduction

Photodynamic therapy (PDT) for the treatment of advanced esophageal cancer has been approved in the USA, Finland and UK. However, in other countries, it is still an experimental treatment and its role in clinical practice has not yet been established. The use of PDT to treat malignant tumors is based on the adaptation of three components [1]: light, a photosensitizing drug and oxygen. Due to differences in vascular supply and lymphatic clearance from tumors and the retention of the photosensitizing drug by tumor cells, the photosensitizer is selectively retained in the tumor cells and interstitial tissue of the tumor. After 48–72 h there is a greater concentration of the photosensitizer in the tumor than in the adjacent normal tissue. The photosensitizer will absorb light energy and produces singlet oxygen, which then destroys the tumor [2]. However, the photochemical reaction depends on the presence of molecular oxygen. Experimental studies have shown that hypoxic cells are less affected by porphyrins and light [3–5]. Depending on the vascular supply of the tumor tissue, there are regions with various degrees of hypoxia. In addition, as oxygen is consumed during PDT, too high fluence rates of the exposure light will lead to oxygen depletion. On the other hand, too low fluence rates need a long exposure time and lead to vascular shutdown which also causes hypoxia of the tumor tissue [2]. Therefore, the presence of molecular oxygen in tumor tissue is crucial for the effectiveness of PDT. The use of hyperbaric oxygen to increase the availability of oxygen in hypoxic tissue is well known. Experimental studies by Dong and Jirsa [6,7]; documented the enhanced effect of hyperbaric oxygen combined with PDT.

In a prospective non randomized study we assessed the use of PDT under HBO, compared with PDT under normobaric conditions, in patients with advanced esophageal carcinoma.
2. Patients and methods

From January 1996 to January 1999, 75 patients with advanced esophageal carcinoma who were not eligible for resection treatment were treated by PDT. All patients were selected for endoluminal treatment rather than resection treatment due to significant co-morbidity i.e. ischemic heart disease, chronic pulmonary obstructive disease, liver- and/or renal malfunction and/or distant metastasis. In 44 of these patients, PDT was performed under hyperbaric oxygen conditions at a level of 2 absolute atmospheric pressure (ATA).

The Institutional Ethical Committee of the Medical School at the University of Graz had no objections to the protocol. Informed written consent was obtained from each patient. A prospective randomization of the patients was not possible due to the variable availability of the hyperbaric chamber. However, the patients were selected in two treatment arms (Tables 1 and 2) independent from the stage of disease, localization, histology, age, sex, dysphagia and Karnovsky performance status (KPS). The only selecting factor was the availability of hyperbaric oxygenation 48 h after photosensitization as the determined time for PDT.

Diagnostic work-up and clinical staging were done by means of barium esophagogram, esophago-gastroscopy, bronchoscopy, computed tomography scans of the chest and abdomen, abdominal ultrasonography and bone scan. Unfortunately, endoscopic ultrasound as the most reliable method for staging and post-interventional follow-up, was not available during the study period. Functional inoperability was confirmed by ECG, spirometry, blood gas analysis and cardiac ultrasonography. At the time of admission, all patients complained about dysphagia of semisolid diet (level 2) and liquids (level 3) within the last 3 months. Seven patients complained about aphagia (level 4) and were not able to handle their saliva. Weight loss of at least 5 kg within the last 2 months, as well as insufficient nutrition was evident in most patients.

Prior to PDT, dilatation (Savary–Gillard device) and retrograde Nd-YAG laser disobliteration became necessary in 15 cases due to severe stenosis only passable for the 3.2 mm endoscope (six in the PDT/HBO group and nine in the PDT group). A flexible guide-wire was passed through the endoscope and careful dilatation to at least 9 mm was done. The 7 mm bronchoscope was now passed over the guidewire and retrograde Nd-YAG laser disobliteration was performed to facilitate further endoluminal PDT or PDT/HBO as the main step in tumoricidal treatment. Perforation was excluded by esophagogram using water-soluble contrast medium.

All patients received 2 mg/kg BW [8,9] of a hematoporphyrine derivate (Seehof Laboratory, Wesselsburenkoog, Germany), administered intravenously. skin protection was done by using a camouflage (Covermark® FARMECO, Milan, Italy) for 2 weeks. For a further 10 weeks a sun-blocker was used. In case of repetitive PDT several months later, a second injection of the hematoporphyrine derivate, 2 mg/kg BW, was done. PDT was carried out 48 h after sensitization, using a fiber with a 1 cm tip radial light diffusing cylinder (Photo Dynamic Therapy® HgesmbH, 1190 Vienna, Austria), which was inserted through the biopsy channel of the endoscope. However, for all treatments several placements of the light diffusing cylinder became necessary depending on the length of the tumor. Due to the risk of perforation in case of interstitial therapy the light-diffuser was closely applied to the tumor surface. Unfortunately, a light distributor as described for non-bulky tumors [10] providing a homogeneous light distribution was not available during the study period. The light dose was calculated as 300 J/cm [8,9]. Light at 630 nm was applied with a KTP-Nd-YAG Laser having a DYE-box (Laserscope™ Surgical Systems, Gwent, UK) [2]. Wavelength and light dose at the tip of the light diffuser (length: 1 cm) were controlled before and after PDT. In 44 patients, PDT was done under hyperbaric oxygen at a level of 2 ATA in the walk-in hyperbaric chamber of the university hospital of Graz (Waagner Biro® AG, Graz, Austria). Oxygen was applied with the Scuba-valve (Oxidem 2000®, Dräger, USA). Transcutaneous pO₂-levels of 500–750 mmHg (TCM™3, Radiometer Medical A/S, Copenhagen, Denmark) under hyperbaric oxygen at a level of 2 ATA, compared with tcpO₂ levels of 60–75 mmHg under normobaric conditions could be measured [11]. Prior to HBO, all patients had an ear, nose and throat (ENT) check-up. Despite i.v. anesthesia under hyperbaric conditions and

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<tr>
<th>Table 1</th>
<th>Clinical characteristics of 31 consecutive patients treated by PDT</th>
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<tr>
<td>Male/female</td>
<td>( n = 28/n = 3 )</td>
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<tr>
<td>Mean age/range (years)</td>
<td>67/47–85</td>
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<tr>
<td>Squamous cell/adenocarcinoma</td>
<td>( n = 18/n = 13 )</td>
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<tr>
<td>Localization (distal/middle/proximal-third)</td>
<td>( n = 22/n = 7/n = 2 )</td>
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<tr>
<td>Stage III/IV</td>
<td>( n = 24/n = 7 )</td>
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<tr>
<td>Dysphagia-score (level 2/level 3/level 4)</td>
<td>( n = 7/n = 15/n = 9 )</td>
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<tr>
<td>Karnovsky performance status (&lt;80/&gt;80)</td>
<td>( n = 2/n = 9 )</td>
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<tr>
<td>Tumor length (mean/range) (cm)</td>
<td>6.3/4–10</td>
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<td>Stenosis diameter (mean/range) (mm)</td>
<td>7.8/4–12</td>
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<td>PDT sessions (mean/range)</td>
<td>1.1/1–3</td>
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<tr>
<th>Table 2</th>
<th>Clinical characteristics of 44 consecutive patients treated by combined PDT/HBO</th>
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<tr>
<td>Male/female</td>
<td>( n = 32/n = 12 )</td>
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<tr>
<td>Mean age/range (years)</td>
<td>67.5/46–87</td>
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<tr>
<td>Squamous cell/adenocarcinoma</td>
<td>( n = 22/n = 22 )</td>
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<tr>
<td>Localization (distal/middle/proximal-third)</td>
<td>( n = 28/n = 10/n = 6 )</td>
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<tr>
<td>Stage III/IV</td>
<td>( n = 35/n = 9 )</td>
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<tr>
<td>Dysphagia-score (level 2/level 3/level 4)</td>
<td>( n = 16/n = 22/n = 6 )</td>
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<tr>
<td>Karnovsky-performance status (&lt;80/&gt;80)</td>
<td>( n = 2/n = 42 )</td>
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<tr>
<td>Tumor length (mean/range) (cm)</td>
<td>6.3/4–14</td>
</tr>
<tr>
<td>Stenosis diameter (mean/range) (mm)</td>
<td>9.0/4–12</td>
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<tr>
<td>PDT sessions (mean/range)</td>
<td>1.2/1–3</td>
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the impossibility of active pressure compensation by the patients, paracentesis was not done prior to HBO due to the low risk of developing a barotrauma of the ear, at a level of 2 ATA.

Each treatment was done under short-term intravenous anesthesia (Propofol 1% Zeneca®, Vienna, Austria) with endotracheal intubation and spontaneous breathing using a scuba-valve (Oxidem 2000®, Dräger, USA), combined with topical anesthesia (Xylocain 1%, Fieberbrunn, Austria). The monitoring consisted of ECG, non-invasive continuous blood pressure control and tcpO2 (TCM™3, Radiometer Medical A/S, Copenhagen, Denmark).

Two to 3 days after PDT, endoscopy was repeated and necrotic tissue, was removed mechanically if necessary. The depth of tumor necrosis was determined by the postdebridement increase in the luminal diameter measured at the point of maximum constriction. All luminal diameters were confirmed by noting the easy passage of graduated bronchoscopes (3.2, 5, 6 and 7 mm) and esophago-gastroscopes (9, 11.6 and 14 mm) of known diameter and/or the easy passage of Savary–Gillard dilatators of known diameter. The patients then underwent repetitive endoscopy, first after 1 month and then once every 3 months (Figs. 1 and 2). The stage of disease, Karnofsky performance status (KPS), dysphagia-score, diet and complications were recorded at each follow-up control to assess the outcome. Biopsy samples, tumor length and minimal opening diameter were recorded at each endoscopy. Computed tomography scan of the chest was performed every 6 months. Survival time was analyzed after informed consent was obtained.

2.1. Statistical analysis

Statistical analysis of qualitative variables was done by Fishers exact test in case of dichotomous variables (two times two tables), and by Kruskal–Wallis test for ordered categories (i.e. dysphagia score, KPS). The changes in stenosis and tumor length were analyzed by Mann–Whitney tests. Survival rates were assessed by the Kaplan–Meier product limit method and compared log-rank test. Proportional hazards regression was done in addition to identify potential outcome predictors. Except for the Kruskal–Wallis test, that was done using the exact algorithm of StatXact 4.01 (Cytel Software Corporation, Cambridge, MA), NCSS 2000 (NCSS Statistical Software, Kaysville, UT) was used for statistical analysis. A two-sided probability of 0.05 was considered as significant.

3. Results

Statistical analysis for qualitative variables showed no significant difference as to sex ($P = 0.08$), histology ($P = 0.64$), TNM-stage ($T: P = 0.10$, $N: P = 1.00$, $M: P = 1.00$), dysphagia ($P = 0.99$) and KPS ($P = 0.07$) between both groups before entering the treatment schedule.

Improvement regarding dysphagia could be obtained and at least a semi-solid diet at least was possible in all patients after PDT (Fig. 1) or PDT/HBO (Fig. 2). None of the patients needed further hospitalization for nutritional support. Hospitalization in both groups was 3–9 days (median: 4.9 days). At the 3-month follow-up or last follow-up in case of earlier death, the dysphagia score could be lowered by one level in eight cases and two levels in 23 cases in the PDT-group, and by one level in nine cases, two levels in 33 cases and three levels in two cases in the PDT/HBO-group. Kruskal–Wallis test showed a significant difference in favour of the PDT/HBO-goup ($P = 0.0064$). After 3 months, the stenosis decreased in both treatment
arms without any significant difference between the two treatment arms \((P = 0.82;\ \text{Mann–Whitney test})\). In the PDT-group, the median decrease of stenosis was 6 mm (range: 3–8 mm) and in the PDT/HBO-group 6 mm (range: 3–10 mm). The tumor-length also decreased in both treatment arms and showed a significant difference in favour of the PDT/HBO-group \((P = 0.0002;\ \text{Mann–Whitney test})\). In the PDT-group, the median decrease of tumor-length was 2 cm (range: 0–4 cm) and in the PDT/HBO-group 3 cm (range: 1–5 cm).

No recurrence of dysphagia was observed within 3 months after the first PDT or PDT/HBO. Due to bulky tumors in all cases with the ensuing impossibility to eradicate the tumor completely, no patient was re-admitted with post PDT stricture.

3.1. Survival analysis

Kaplan–Meier statistics showed a median overall survival for the PDT group compared to the PDT/HBO group of 7 and 12 months, respectively. The 12-month survival rate for PDT versus PDT/HBO is 25, and 52%.

The Log-rank test showed a difference in survival in favour of the PDT/HBO group, \(P = 0.0098\) (Fig. 3), compared to the PDT group.

Proportional hazards regression revealed KPS \((P = 0.0000)\), PDT with additional HBO \((P = 0.0046)\) and M-stage \((P = 0.0635)\) as independent prognostic factors regarding survival time.

3.2. Complications

No major post-interventional complications related to PDT, HBO and photosensitization of the skin could be observed. No barotrauma of the ear or lung and no sunburn occurred. Minor complications like post-interventional odynophagia (six after PDT and eight after PDT/HBO), fever up to 39°C in the afternoon of the interventional day (one after PDT and three after PDT/HBO) and chest pain for 1 or 2 days (four after PDT and seven after PDT/HBO) \([12]\) could be observed. The 30-day mortality rate was 0%.

Complications not related to the treatment occurred due to alcohol abuse in two patients, delirium tremens in two and additional pneumonia in one case.

Due to tumor progression, we found six esophagotracheal fistulas \([13]\), in two cases after PDT, 5 and 17 months, and in four cases after PDT/HBO, 4, 7, 14 and 24 months, respectively. Interestingly, all patients with this severe tumor related complication had a T\(_4\)-stage, except one patient in the T\(_3\)-stage at the time of admission, developed esophagotracheal fistula 24 months later. All esophagotracheal fistulas could be treated by intubation, using self-expandable coated stents (Microvasive® Boston Scientific Corporation, Watertown, MA). Additional tracheotomy in two cases due to massive intratracheal tumor growth and dyspnoe became necessary. Stenting and tracheotomy was done without any complication in these patients.

One patient with T\(_4\) N\(_1\) M\(_1\) stage at the time of admission, developed spontaneous perforation of the esophagus carcinoma with esophago-mediastino-pleural fistula and consecutive pleural empyema, 5 months after PDT/HBO. Despite esophageal exclusion, feeding gastrostomy and chest tube drainage, the patient died 1 day later.

4. Discussion

The poor prognosis of patients with advanced esophageal carcinoma is well known and reported in literature \([14]\). Local palliation with the aim to improve swallowing, short hospitalization, low complication rate, increase of KPS and quality of life, as well as economic aspects, especially in patients with a short life expectancy, are the goals of treatment of patients with advanced cancer of the cardia and the esophagus. PDT in the palliation of esophageal tumors as reported in literature \([8,15,16]\) is now a more and more accepted method and is used depending on its availability. However, there are some economic arguments against the use of PDT, especially in patients with a short life expectancy \([17]\).

It should be emphasized that PDT provides the clinician with another modality which should be appropriately included in the overall management of the patient along with other modalities like dilatation, Nd-YAG laser disobliteration, irradiation and chemotherapy. The guiding principle is that PDT is more localized and selective than some other treatments but cannot be expected to entirely eliminate large, bulky tumor, especially outside the lumen or in lymph nodes. However, the main advantage of PDT compared to other treatment options i.e. radio and chemotherapy, stenting and laser disobliteration are the short hospitalization, low morbidity and mortality as well as the possibility to repeat the treatment depending on the patients symptoms of dysphagia.
Photodynamic therapy involves the interaction of photosensitizers, light and oxygen. Sensitizers in a low energy state are initially excited by absorption of light. In this energetic state, it can react directly through a free radical mechanism or indirectly via molecular oxygen which undergoes a spin-state transition to reactive singlet oxygen. Both pathways yield potentially cytotoxic compounds, although the singlet oxygen process is thought to be predominant in PDT [18]. Oxygen has been shown to be crucial for hematoporphyrin-derivate photodynamic action in vitro [19], consistent with the hypothesis that singlet oxygen is the mediator of photodynamic cytotoxicity.

According to the experimental studies by Dong et al. [7], the addition of HBO in PDT accelerates the photodynamic reaction processes by raising the transmission efficiency of light energy, increasing the quantum amount of oxygen and extending the effective distance radius of oxygen. The animal model by, Jirsa Jr. et al. [6], showed the influence of HBO and PDT in tumor bearing nude mice. They concluded that the combination of HBO and PDT improve the efficiency of PDT by increasing the depth of tumor cell damage, and/or by reducing doses of sensitzers. Another important phenomenon was found by Wieman et al. [20]. They showed that PDT induces reduced blood flow and causes a shutdown of tumor vessels resulting in hypoxia with decreased oxygen tension.

Based on these reported experimental studies by Dong, Jirsa and Wieman [6,7,20], the use of hyperbaric oxygen in this special field of cancer treatment could be the key to gain high levels of molecular oxygen in tumor tissue to increase the amount of oxygen as the main cytotoxic product.

Lambertson et al. [22] determined that, in a typical tissue, the arteriovenous oxygen difference rises to 350 mmHg when 100% oxygen is breathed at 3 ATA. If the blood flow to the tissues is reduced by a half, the corresponding values of capillary pO2 will be 288 and 50 mmHg. Of course, the oxygen requirement of different tissues varies. Another factor is the vasoconstricting effect of HBO, which reduces the blood flow. However, effective cellular oxygenation can be accomplished at very low rates of blood flow when arterial pO2 is very high. Furthermore, HBO improves the elasticity of the red blood cells and reduces platelet aggregation. This, combined with the ability of plasma to carry dissolved oxygen to areas where red blood cells cannot reach, has a beneficial effect on the oxygenation of many hypoxic tissues. However, general effects of HBO in human patients, result in a decrease in cardiac output, due to bradycardia, rather than a reduction of stroke volume. Blood pressure remains essentially unchanged. Blood flow to most organs falls in correspondence to the decrease of cardiac output except on the right and the left ventricles of the heart. There is no impairment in function of any of these organs because the elevated pO2 more than compensates for the reduction in blood flow. Vasoconstriction may be viewed as a regulatory mechanism to protect the healthy organs from exposure to excessive pO2. A very important phenomenon in this concept is that the vasoconstrictor response does not take place in hypoxic tissues [23].

The aims of local palliation determined by a decreased dysphagia score and tumor-length, as well as increased quality of life could be obtained in both treatment arms. However, dysphagia-score and the tumor-length showed a significant difference in favour of the PDT/HBO group (P = 0.0064 and P = 0.0002, respectively). These findings can be explained by the rising transmission efficiency of light energy which resulted in an increased destruction of tumor cells as described by Dong and Jirsa [6,7]. The significant difference in survival, in favour of combined HBO/PDT (P = 0.0098) is very difficult to interpret, since many questions are impossible to answer in a non-randomized study. However, the results of the proportional hazards regression analysis suggest at least a contribution of additional HBO to the better survival in the PDT/HBO group.

It is evident that presented study protocol (photosensitizer 2 mg/kg BW, light dose 300 J/cm fiber and HBO at a level of 2 ATA) was associated with a very low complication rate and a mortality rate of 0%. Although any therapeutic application of hyperbaric oxygenation is intrinsically associated with the potential for producing mild to severe toxic effects, the appropriate use of hyperoxia is one of the safest therapeutic procedures available in modern medicine [21–23]. This study shows that the use of combined PDT/HBO involves minimal technical difficulties. All technical devices used, such as endoscopes, light applicators, monitors and perfusion-pumps functioned properly under hyperbaric conditions.

Considering the fistula formation in this study it is difficult to distinguish between tumor and treatment related complications, especially if these occur several months after treatment. Nevertheless, we believe that there is an initial connection between treatment and the fistula incidence in our study. As risk factors for the development of esophago-tracheal fistulas, T4-stage and tumor localization in the proximal third of the esophagus were evident in our patients. Therefore, one should be cautious about performing PDT or PDT/HBO in patients with T4 carcinoma and signs of tracheo-bronchial tumor involvement at staging bronchoscopy.

Although the presented study only includes a small number of patients which does not allow to draw definite conclusions, it indicates that combined PDT/HBO represents a new, safe and feasible approach in the treatment of advanced esophageal carcinoma and can enhance the efficiency of PDT.

References


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hyperbaric oxygen combined with photodynamic therapy for oxygen (singlet oxygen) is required to fatally injure the cell.

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Appendix A. Editorial Comment

Over a century ago Oscar Raab, a student working in the laboratory of Professor von Tappeiner, discovered that an administered aniline dye was toxic to paramecia only in the presence of light. von Tappeiner examined many other substances including chlorophyll and called the phenomenon ‘photodynamische Erscheinung’. He demonstrated that a photosensitiser, light and molecular oxygen were vital for the effect [1]. He also suggested that tumours could be treated and some early clinical results were reported in 1905.

Photodynamic therapy is a very exciting method for the local treatment of cancer. The particular involvement of oxygen in the process is of profound importance and interest. Oxygen in biological systems remains a paradox since, although necessary for life it is also highly reactive and potentially toxic and lethal. The generation of reactive oxygen species is an initiator of apoptosis and is responsible for the photo-destructive effect. Eukaryotic cells have developed mechanisms to survive in the combustible oxygen rich environnement. This may have occurred following the endosymbiosis of mitochondria which contain many oxygen quenchers [2,3]. A certain concentration of toxic oxygen (singlet oxygen) is required to fatally injure the cell.

The approach reported in this issue by Maier et al. using hyperbaric oxygen combined with photodynamic therapy for the palliation of advanced oesophageal cancer, is a rational
and interesting approach. They report an improved dysphagia score and median survival in those patients treated with combined therapy of photodynamic therapy and hyperbaric oxygen. Unfortunately there is no clear quantitative data to indicate the depth of necrosis induced by either therapy. This data is important since the authors report the worrying incidence of tracheo-oesophageal fistulation in patients with T4 tumours even though the illumination in their cases appears not to have been interstitial. This contrasts with a recently published study [4] in which there were no cases of oesophago-airway fistula. Previous studies have indicated that, using haematoporphyrin derivative as a photosensitiser and various light doses, up to 6 mm of necrosis is possible in the oesophagus. [5] This depth of necrosis may be safe provided the tumour is not penetrating the full thickness of the oesophagus, since healing can occur safely. The authors rightly conclude that both photodynamic therapy with or without hyperbaric oxygen should be used very judiciously when there is a T4 tumour or involvement of adjacent organs, in particular the trachea or the bronchi. An interesting approach could be to combine hyperbaric oxygen with endogenous photodynamic therapy using 5 aminolaevulinic acid, since the depth of necrosis is limited to a maximum of 2 mm [6]. A large and important randomised comparison (236 patients) of NdYAG laser therapy with photodynamic therapy (PDT) showed that both were equally effective. The
improvement in dysphagia and endoscopic tumour response was equal between the two groups (PDT: 110 patients, NdYAG therapy: 108 patients). PDT was associated with temporary photosensitivity but was easier to perform and associated with less perforations (PDT: 1%, thermal laser: 7%). [7]. The use of photodynamic therapy with the requirement for a photosensitiser and expensive lasers can be difficult to justify. The benefits of adding hyperbaric oxygen, further complicating the technique, are unlikely to become widely adopted.

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