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Photodynamic therapy enhanced by hyperbaric oxygen in acute endoluminal palliation of malignant bronchial stenosis (Clinical pilot study in 40 patients)☆

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Abstract

Objectives: Photodynamic tumor therapy (PDT) is based upon a photochemical reaction that is limited by the availability of molecular oxygen in the target tissue. The use of hyperbaric oxygenation (HBO) increases the amount of oxygen available for the process may thereby enhance the efficacy of PDT. We proved in a prospective, non-randomized clinical pilot study the acute effects on malignant bronchial stenosis and the technical feasibility of combined PDT/HBO. **Methods**: Forty patients (29 males, 11 females, mean age: 64.3 years; range 39–82 years) with inoperable, advanced malignant bronchial tumor stenosis were studied prospectively. Photosensitization was carried out using a hematoporphyrin-derivative 2 mg/kg bw 48 h prior to PDT. The light dose was calculated as 300 J/cm fiber tip. The assessment of outcome 1 and 4 weeks after PDT/HBO was done by endoscopy, chest X-ray, spirometry, laboratory parameters, subjective report of dyspnea and Karnofsky performance status. **Results**: At 1 and 4 weeks after the treatment the patients felt a significant improvement of dyspnea and hemoptysis alongside with an objective subsiding of poststenotic pneumonia, though spirometric parameters revealed no significant difference. A significant reduction of tumor stenosis ($P < 0.05$) and an improvement of the Karnofsky performance status ($P < 0.05$) were documented 1 and 4 weeks after PDT/HBO. No therapy related complications were observed. **Conclusion**: Although the small number of patients does not allow to draw definitive conclusions, the results suggest that combined PDT/HBO represents a new, safe and technically feasible approach. It enables efficient and rapid reduction of the endoluminal tumor load and helps conditioning the patient for further treatment procedures. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Photodynamic therapy; Hyperbaric oxygenation; Malignant bronchial stenosis

1. Introduction

Advanced malignant bronchial tumor stenosis represent in case of tumor associated complication a challenge in any palliation treatment protocol. Most of these tumor stenosis are caused by lung cancer, which is the most common cancer among the male population in the western world. In Austria, approximately 3700 new cases are diagnosed and about the same number of patients die annually of this disease [1]. As the overall resection rate does not exceed 20%, about 80% of the patients suffering from lung cancer need palliation of tumor associated symptoms [2].

The aim of any palliation protocol in advanced malignant bronchogenic stenosis is a rapid reopening of the bronchial lumen thereby enhancing the quality of life and preventing tumor associated complications such as asphyxia, poststenotic pneumonia and arrosional bleeding.

Photodynamic tumor therapy (PDT) is based on the illumination of malignant tissue after selective accumulation of photosensitizers in tumor cells. Photosensitizing agents can absorb photons of appropriate wavelength and become excited to a triplet species. The photon is transferred to ground-state triplet oxygen producing the excited singlet oxygen (type II photo-oxygenation reaction). In the other type of photo-oxidative process (type I) the excited sensitizer itself initiates a free radical reaction. Both types of reaction are associated with PDT. Potentially, they cause an acute necrosis of tumor in the illuminated tumor region [3].

In vitro experiments, however, have shown that oxygen is

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Table 1
Clinical characteristics of 40 consecutive patients with advanced malignant bronchogenic stenosis treated by combined PDT/HBO

Male/female	$n = 29/n = 11$
Age: mean/range (years)	64.3/39–82
Adeno-/squamous cell-/large cell carcinoma	$n = 21$/n = 10/$n = 5$
Stage IIIA/IV	$n = 24/n = 12$
Bronchial metastesis	$n = 4$
Location: main bronchi/lobar bronchi	$n = 19/n = 21$
Karnofsky performance status:mean/range	70/50–80
Clinical signs: dyspnea/hemoptysis/ pneumonea	$n = 40/n = 12/n = 15$
Tumor stenosis: mean/range (mm)	3.4/0–6
Tumor stenosis: percentage-mean/range (%)	45/25–90
Tumor length: mean/range (cm)	1.9/1–4

a key component in PDT. There is decreased cell sensitivity to PDT in the presence of low oxygen. Furthermore, animal tumor models have demonstrated a decreased effect to PDT under hypoxemic conditions [4,5].

The rationale of this clinical trial was to prove the technical feasibility and to study the acute effect of PDT under hyperbaric oxygenation (HBO) regarding relief of poststenotic symptoms in case of 40 malignant bronchogenic stenosis.

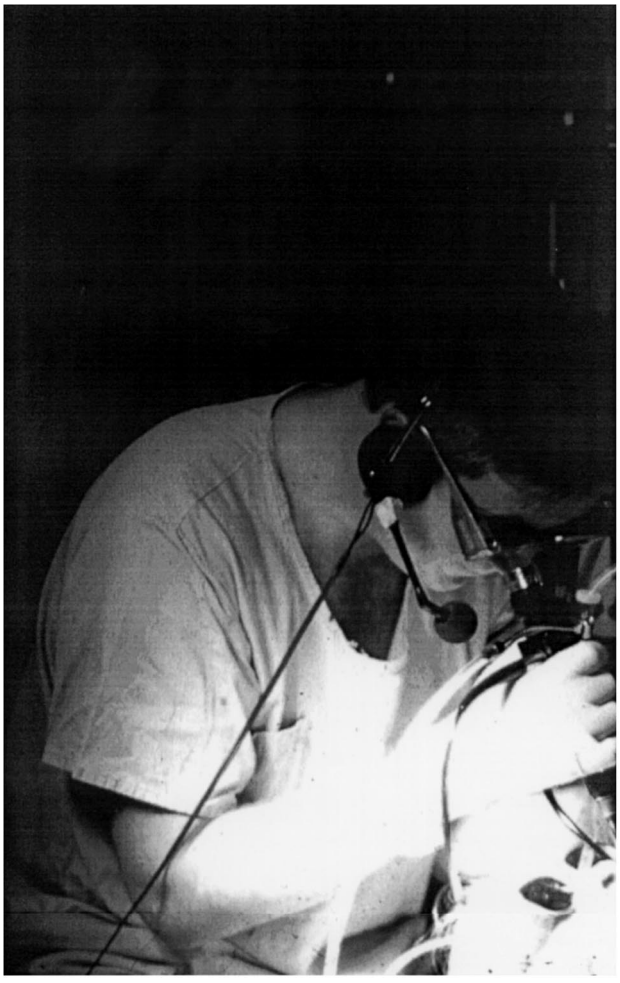

Fig. 1. Combined PDT/HBO (walk-in, drive-in hyperbaric chamber).

2. Materials and methods

In a prospective non-randomized clinical trial from February 1997 to July 2000, 40 patients with bronchial stenosis due to endoluminal growth of malignant tissue (Table 1), who were not eligible for resection treatment due to poor performance status and functional and/or anatomical or oncological inoperability underwent PDT under HBO.

The protocol was approved by the Institutional Ethical Committee of the Medical Faculty at the University of Graz and informed written consent was obtained from each patient.

2.1. PDT under hyperbaric oxygenation

Forty-eight hours after intravenous administration of 2 mg/kg bw of a hematoporphyrin derivative (Photosan-3, Seehof Laboratory, Wesselburenkoog, Germany) bronchoscopically guided PDT/HBO was performed under general anesthesia and routine cardiorespiratory monitoring [6].

Through the endotracheal tube the fibrescope was introduced and the laser application system, using a balloon-catheter (PhotoDynamicTherapy®, Vienna, Austria) was inserted through the biopsy channel close to the surface of the histologically proven tumor. In case of tumor stenosis preventing passage by the endoscope, interstitial therapy was done guiding the fiber endoscopically.

The patient was transferred into the multiplace hyperbaric chamber and hyperbaric oxygenation (100% oxygen, 2 ATA pressure) (Fig. 1) was initiated under continuing cardiorespiratory monitoring and recording of the transcutaneous pO2-levels as an indirect indicator of the oxygen load. After a steady state of transcutaneous pO2 had been reached, PDT was started. Transcutaneous steady-state oxygen pressure levels ($tcpO_2$) of 500–750 mmHg under 2 ATA HBO versus $tcpO_2$-levels of 60–75 mmHg under normobaric conditions were found [7].

We used a pumped Cooper vapor dye laser (Laserscope, Surgical Systems, Gwent, UK) delivering red light at 630 nm through a fiber with a radial diffuser (2 cm radial light-diffusing cylinder, PhotoDynamicTherapy®, Vienna, Austria). The light dose was calculated for 300 J/cm fiber tip. Depending on the topography and length of the tumor, single or multiple placements of the diffuser were necessary.

Following PDT, debulking of post-therapeutic tumor necroses was done endoscopically after 3 and 7 days, respectively, removing necrotic tumor fragments by forceps or by mere suction.

2.2. Follow-up

Follow-up investigations were scheduled at 1 and 4

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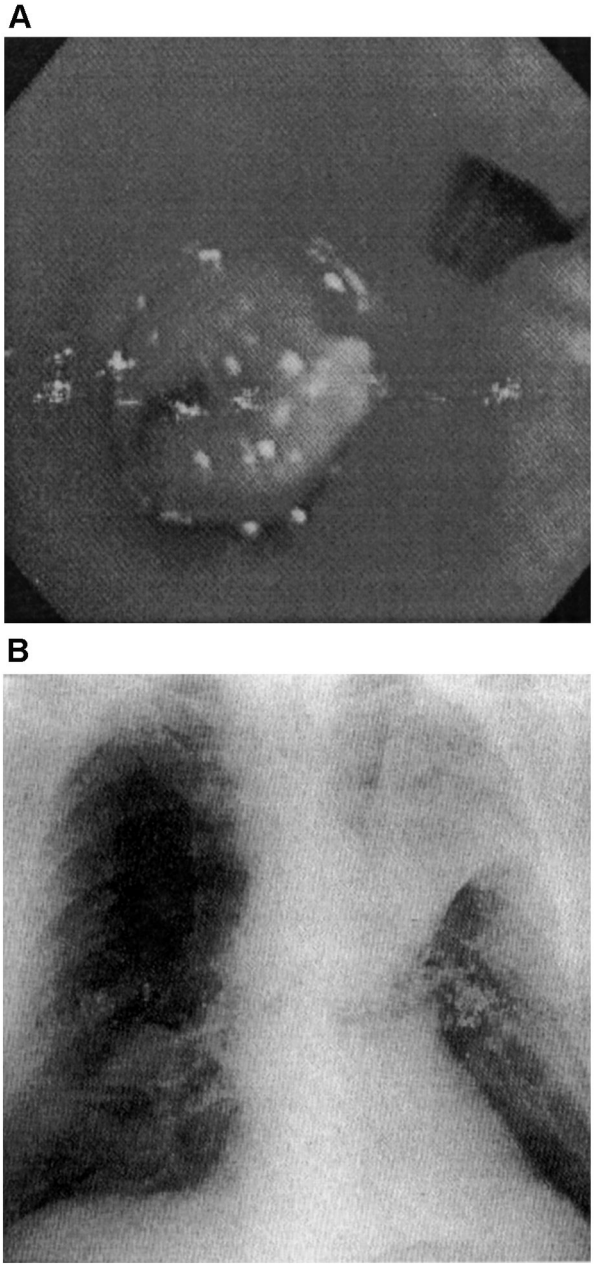

Fig. 2. (A,B) Chest X-ray and endoscopic view of a malignant stenosis of the left lower lobe.

weeks after combined PDT/HBO. The acute effects on tumor stenosis were assessed by bronchoscopy, chest roentgenograms, spirometry, and subjective relief of dyspnea and hemoptysis, as well as by evaluation of the Karnofsky performance status.

The acute effect (Figs. 2 and 3) on tumor stenosis was determined by comparing the pre- and posttherapeutic increase of luminal diameter measured at the point of maximum constriction. All luminal diameters were confirmed by easy passage of graduated bronchoscopes of known diameter (3.2, 5, 6, 7 mm) and/or easy passage of balloon catheters of known diameter (8–12 mm). The minimum lumen of the treated bronchial region was recorded at each endoscopy.

Radiological signs of poststenotic pneumonia and laboratory parameters corresponding to inflammatory processes (white blood cell count, C-reactive protein, fibrinogen) were recorded at each follow-up.

2.3. Statistical analysis

For statistical comparison of numeric parameters, the Wilcoxon test for paired observations was used. All data are presented as mean values ± SEM. $P < 0.05$ was considered as the level of significance.

3. Results (Table 2)

The clinical signs of dyspnea, hemoptysis and poststenotic pneumonia showed a significant improvement at 1 and 4 week follow up ($P < 0.05$).

An improvement of dyspnea after 1 week was reported in 80% (32/40) of the patients. The relief of dyspnea was reported as substantial in 20/40, as slight to moderate in 12/40 and no change could be observed in 8/40. Four weeks after PDT/HBO an improvement of dyspnea could be achieved in 97% (39/40) of the patients. The relief of symptoms was reported as substantial in 27/40, in 11 as slight to moderate and as nil in two patients. However, pulmonary function parameters (FVC/FVC1) before treatment, 1 and 4 weeks after PDT/HBO did not show any statistically significant differences ($P > 0.05$).

In 7 out of 15 patients initially admitted due to inflammatory infiltration the clinical and radiological signs of poststenotic pneumonia improved 1 week after PDT/HBO. After 4 weeks 11 out of 15 patients improved. The initial symptom of hemoptysis in 12 patients subsided in 10/12 cases at 1 and 4-week follow up.

At the time of admission the Karnofsky performance status showed a mean of 70; range: 50–80. One and 4 weeks after PDT/HBO a significant improvement ($P < 0.05$) with a mean of 80 and 85, respectively, could be achieved.

One week after PDT/HBO there was a significant overall decrease of tumor stenosis from a mean of 3.4 to 7.0 mm (range: 0–6 mm and 4–11 mm, respectively; $P < 0.05$). Four weeks after PDT/HBO the mean decrease of tumor stenosis was mean: 8 mm; range: 5–13 mm. After 4 weeks, the overall percentage of free lumen was 84% of normal.

3.1. Survival

Six patients are still alive with a median survival of 11.6 months (range: 1–32 months). Three of the patients who survived had brachyradiotherapy, in two of them radiation was completed with external beam irradiation. The patient had three cycles of chemotherapy.

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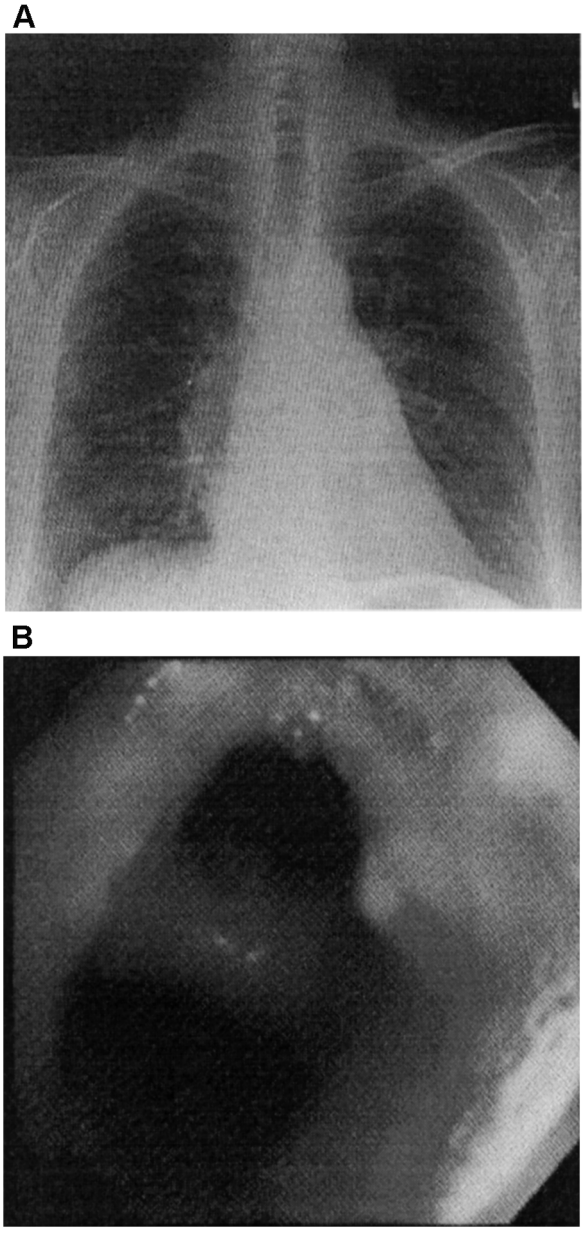

Fig. 3. (A,B) At 4-week follow up: complete recanalisation and ventilation of the left lower lobe as shown in Fig. 2A,B.

34 patients died from their disease. Thirty-two due to distant metastasis and two due to severe intrabronchial hemorrhage, 2 and 13 months after PDT/HBO, respectively. The median survival of those patients who died was 10.7 months; range: 2–27 months.

3.2. Complications

No major complications related to either to photosensitization, to PDT or to HBO were observed during or after the intervention. Side-effects included mild skin photosensensitivity in two patients who had neglected the instructions to avoid sunlight after PDT and use a sun-blocker for at least 12 weeks. A single episode of fever up to 39°C in the afternoon after the PDT-procedure ($n = 14$) and mild chest pain corresponding to the treated area for 1 or 2 days ($n = 19$). None of these effects required specific treatment.

4. Discussion

The poor prognosis of patients with advanced, nonresectable lung cancer or malignant bronchogenic stenosis is a well known fact [8]. A quick reopening of airway stenosis at a low rate of collateral damage and side-effects, resulting in a reduction of the need for hospital stay and an increased quality of life is vital in these patients. Conventional laser desobliteration always results in thermal damage of the surrounding mucosa, stenting is seldom practicable beyond the level of the main or intermediate bronchi and the application of endoluminal brachytherapy is limited to about 20 Gy due to the cumulative dose to the mucosa.

PDT has become a widely accepted method in the palliation of malignant bronchogenic stenosis and is currently performed dependent on its availability [9–13].

PDT can be included into any local or systemic treatment protocol along with other modalities like Nd-Yag laser desobliteration, brachytherapy, external beam radiation, chemotherapy and stenting. The guiding principles are that PDT is more selective than other methods of treatment and that it can, in theory, be applied repetitively without a limitation of the cumulative dosage. However, PDT cannot be expected to eliminate bulky tumor outside the lumen or in lymph nodes i.e. beyond the reach of the laser beam.

PDT involves the interaction of photosensitizers, light and oxygen. Sensitizers, originally in a low energy state, are excited to a maximum by absorption of monochromatic light of appropriate wave length and energy. In this energetic state, they react directly through a free radical mechan-

Table 2
Results at 1- and 4-week follow up after combined PDT/HBO

Clinical signs	1-week (improvement)	4-week (improvement)	*P* level
Dyspnea	80% (32/40)	97% (39/40)	$P < 0.05$
Poststenotic pneumonea	46% (7/15)	73% (11/15)	$P < 0.05$
Hemoptysis	83% (10/12)	83% (10/12)	$P < 0.05$
Spirometry (FVC/FVC1) (L)	2.14/1.36	2.27/1.48	n.s.
Karnofsky mean (range)	80 (70–90)	85 (70–100)	$P < 0.05$
Tumor stenosis mean (range) (mm)	7 (4–11)	8 (5–13)	$P < 0.05$

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ism, 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 [14] and oxygen has been shown to be fuelling the hematoporphyrin-derivative based photodynamic action in vitro [15].

Considering the interactions of photosensitizers, light and oxygen, with singlet oxygen as the final common mediator of photodynamic cytotoxicity, an enhanced tumoricidal effect may be achieved by increasing the amount of oxygen available for the photochemical reaction. This concept is of crucial importance, as PDT by itself induces reduced blood flow and causes a shutdown of tumor vessels resulting in hypoxia with decreased oxygen tension [16].

The use of HBO in this particular field of cancer treatment could be the key to obtain high levels of molecular oxygen in tumor tissue in order to increase cytotoxicity. According to the experimental studies by Dong [4], use 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 its radius of effective distance. In an experimental animal model, Jirsa [5] studied the influence of HBO and PDT in tumor-bearing nude mice. They concluded that combining HBO and PDT improves the efficiency of PDT by increasing the depth of tumor cell damage, and/or by reducing the doses of sensitizers.

Under HBO oxygen physically dissolves in all fluid components of the body, resulting in the fact, that oxygenation is no longer dependent on the presence of red blood cells. Lambertson et al. [17] determined that the arteriovenous oxygen difference rises to 350 mmHg when 100% oxygen is respirated at 3 ATA in a typical tissue. Even if the blood flow to the tissues is reduced by a half, the corresponding values of capillary pO_2 will be 288 mmHg and 50 mmHg.

In spite of vasoconstriction and a bradycardia-induced reduction of the stroke volume which have been known as physiological side-effects of HBO, oxygenation is pushed to high levels of up to 1000–2000 paO_2 at 2 or 3 atmospheres, respectively. In this context, HBO-induced vasoconstriction may be viewed as a regulatory mechanism to protect the healthy organs from exposure to excessive pO_2. A very important phenomenon in this concept is that the vasoconstrictor response does not take place in hypoxic tissues [18, 19]. Transcutaneous paO_2 in our patients was lower than to be expected but it is a well known fact, that the oxygen pressure recorded at the transcutaneous electrode tends to be lower than the true arterial pO_2 due to the oxygen consumption of the skin itself [7].

Side-effects of HBO may affect the central nervous system and the lung but they are easily reversible and are very rarely seen at pressures below 2 ATA and exposure times less than 90 min and we did not see any of them in our patients.

From the technical point of view, combined PDT and HBO did not include any problems provided the laser light generator was positioned outside the hyperbaric chamber with only the fiber being led into the hyperbaric atmosphere.

The aim of the study was, to assess the acute tumoricidal effects of PDT under HBO. As there were no preexisting guidelines concerning both the required laser energy, and the photosensitizer dose or the intensity of HBO, we decided for a moderate therapeutic pressure of 2 ATA at 'conventional' sensitizer and light doses. The fact, that we observed local tumor necrosis at the very end of the PDT/HBO session illustrates the high potential of the treatment. Frank necroses developed in each case and could be easily removed during control bronchoscopies. The reopening of the airway was quickly effectuated. In this study, a statistically significant PDT-induced reduction of tumor stenosis and enhancement of performance status, followed by an increased quality of life could be observed. Airway stenosis itself was no reason for hospitalization in the later course of the patients.

Theoretically, the effect of PDT could cause severe pulmonary hemorrhage due to rapid tumor destruction. There was, however, a long interval (7 weeks and 13 months) between PDT in the two patients in whom fatal bleeding occurred. Moreover, additional endoluminal treatment (in both cases endoluminal brachytherapy using a total treatment dose of 15 Gy/Ir 192) could have contributed to tissue damage.

Dougherty et al. [20] reported skin photosensitivity in 25–35% of the patients treated with PDT. HBO does not seem to increase the rate of photosensitivity, with only 2 out of 40 patients experiencing mild skin photosensitivity after neglecting the instructions to avoid sunlight.

Although the study only includes a small number of patients not allowing definite conclusions, it indicates that PDT under HBO represents a new, safe and technically feasible approach in the treatment of advanced malignant bronchogenic stenosis.

It enables efficient and rapid reduction of the endoluminal tumor load and helps conditioning the patient for further treatment procedures.

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