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Work in progress report - Thoracic general

Polyhematoporphyrin-mediated photodynamic therapy and decortication in palliation of malignant pleural mesothelioma: a clinical pilot study[☆]

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Abstract

The aim of this study was to evaluate the additional effect of intraoperative photodynamic therapy (PDT) under hyperbaric oxygenation (HBO) when compared with decortication alone. From 1/1993 to 8/2002, palliation with decortication was done in 25 patients suffering from advanced malignant pleural mesothelioma. Fourteen patients received additional intraoperative PDT under HBO. The surgery and PDT/HBO was done 48 h after photosensitization with a polyhematoporphyrin, 2 mg/kg/BW using a diode laser delivering red light at 630 nm through a microlens. The light dose was calculated for 300 J with a distance of 1 cm from the tumor surface. At 6-month follow up local tumor control and survival showed a significant difference in both groups. Although the study only includes a small number of patients not allowing definite conclusions, it indicates that the additional PDT/HBO represents a safe and technically feasible approach in the palliative setting of advanced malignant mesothelioma of the pleura.

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1. Introduction

Because of the lack of sufficient treatments [1,2], malignant pleural mesothelioma has become a model disease for the development of adjunctive treatment modalities. The efficacy of photodynamic therapy as a treatment protocol of malignant pleural mesothelioma has been described and established in several clinical studies [3–6].

Photodynamic therapy 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 energy 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 photo-oxygenation reaction) the excited sensitizer itself initiates a free radical reaction.

Both types of reaction are associated with photodynamic therapy (PDT). Potentially, they cause an acute necrosis of tumor in the illuminated tumor region [7].

In vitro experiments, however, have shown that oxygen is a key component in PDT [8,9]. Under hyperbaric oxygenation (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. 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 et al. [8], use of HBO in PDT accelerates the photodynamic reaction 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 et al. [9] 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.

The rationale of this clinical trial was to study both the technical feasibility and the efficacy of combined decortication of the pleura and intraoperative PDT under HBO. Main

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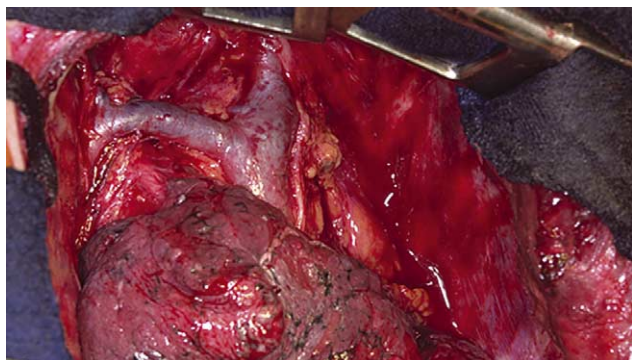


Fig. 1. Intraoperative view after tumorectomy/decortication and lymphadenectomy of the upper mediastinum and the paracaval region.

variables were considered as PDT associated side effects, morbidity/or mortality and survival time compared to debulking procedure alone.

2. Patients and methods

In a prospective non-randomized clinical trial from January 1993 to August 2002, tumorectomy/decortication was done in 25 patients (21 male, four female; mean age: 64.3 years, range: 54–79 years), suffering from advanced malignant mesothelioma of the pleura. Fourteen patients received additional intraoperative photodynamic therapy under HBO.

In case of palliation, decortication combined with additional intracavitary PDT of residual tumor tissue was offered to all patients. However, since additional intracavitary PDT represents an experimental treatment and the disadvantage of long lasting skin photosensitization (8–12 weeks) only 14 patients agreed additional PDT. Therefore, patient selection for additional PDT was done according signed informed consent.

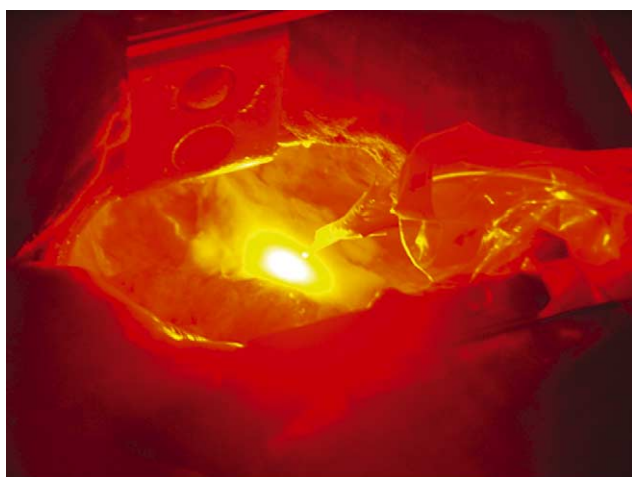


Fig. 2. Intraoperative PDT under HBO in a walk-in hyperbaric chamber.

2.1. Diagnostic work-up

All patients suffered from dyspnea and chest pain caused by direct tumor expansion and pleural effusion associated to the tumor. Twenty-one patients had a history of asbestos exposure and 18 patients were heavy cigarette smokers. In presence of a tentative diagnosis made after initial radiological work-up including conventional chest roentgenograms and computed tomography (CT)-scan of the thorax. Video-assisted diagnostic thoracoscopy (VATS) with pleural biopsy, confirming the diagnosis in all patients. Ipsilateral mediastinal lymphnode biopsy during the VATS procedure was done if technically feasible. Clinical staging revealed UICC III ($T_2 n = 15$; $T_3 n = 10$; $N_1 n = 7$; $N_2 n = 18$).

Histological examination revealed 14 epithelial, nine biphasic and two sarcomatous subtypes.

After establishing the definitive diagnosis CT scan of the abdomen and bone-scan completed the staging procedure. Additional positron emission tomography (PET) scan was done in six patients.

2.2. Surgery

In 25 patients, debulking and decortication was done through a posterolateral thoracotomy. All gross disease (up to 1200 g) was removed, leaving as little residual tumor as possible and mediastinal lymph nodes were sampled routinely (Fig. 1). In two cases subtotal pericardiectomy followed by synthetic mesh reconstruction was done.

In 14 cases, the treatment was completed with intraoperative photodynamic therapy enhanced by hyperbaric oxygenation applied to all residual tumor surfaces (Fig. 2).

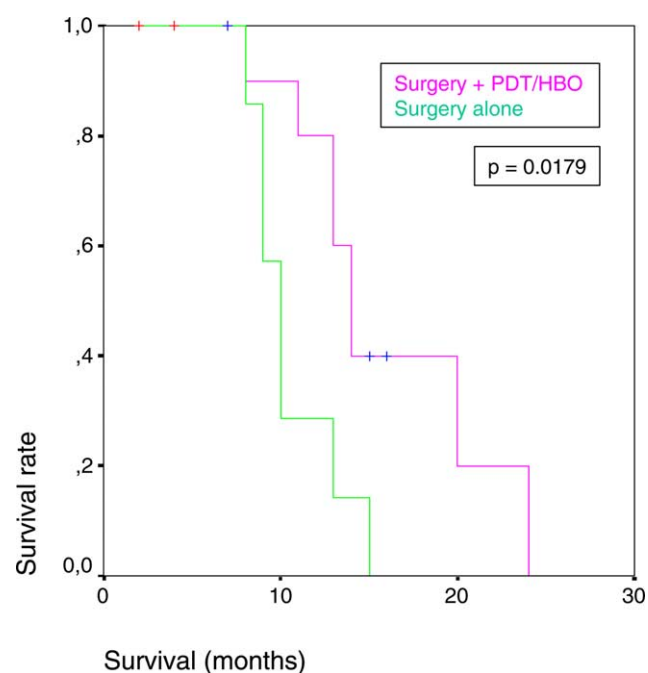


Fig. 3. Kaplan–Meier survival distribution.

Pathological staging confirmed UICC stage III in all patients.

2.3. Intraoperative photodynamic therapy (PDT) under hyperbaric oxygenation (HBO)

In order to achieve an optimum effect of the photosensitizer the operation was scheduled 48 h after intravenous application of 2 mg/kg BW of a polyhematoporphyrin (Photosan-3, Seehof Laboratory, Wesselburenkoog, Germany).

The operation was done in a hyperbaric chamber fully equipped as an operating theatre. After finishing decortication and lymphadenectomy, PDT was done by one surgeon, under hyperbaric oxygenation (100% oxygen, 2ATA pressure). Transcutaneous pO₂-levels were used as an indirect indicator of the oxygen load. They rose from 59 to 77 mmHg (mean: 68 mmHg) under normobaric conditions to 500–750 mmHg (mean: 580 mmHg) tcpO₂-levels under 2 ata [10,11].

After a steady state of transcutaneous pO₂ had been reached, PDT/HBO was started. Using a diode laser system (Ceramoptec®, Bonn, Germany) delivering red light at 630 nm through a microlens (PhotoDynamicTherapy®, Vienna, Austria), the light dose at the tumor surface was calculated as 300 J with a distance of 1 cm from the tumor surface. Illumination of the tumor area was done cm² per cm² of tumor surface using a microlens that was moved stepwise along a flexible sterile plastic grid.

Depending on the topography and extent of the tumor area, the delivery time ranged from 40–60 min (median time: 50 min).

2.4. Follow-up

Follow-up investigations were scheduled 3, 6 and 12 months after combined surgical resection ± intraoperative PDT/HBO comprising CT-scans of the thorax and abdomen and assessment of changes in the quality of life, by using the Karnofsky index.

Table 1
Six-month follow-up

	PDT/surgery (n = 14)	Surgery (n = 11)	
Local tumor regrowth	n = 4	n = 8	P = <0.05
KPS	95 (90–100)	92 (85–100)	n.s.
Decrease of dyspnea	n = 14	n = 11	n.s.
Decrease of pain	n = 11	n = 7	n.s.
FVC1	1.61 (1.1–2.4)	1.71 (1.1–2.3)	n.s.

2.5. Statistical workup

The Chi-square test was used to compare paired values as well as the Kaplan–Meier survival table and log-rank test.

3. Results

At 6-month follow-up, dyspnea, pain, Kanofsky performance status, FVC1 and tumor regrowth was checked (Table 1).

Comparison of CT scans 1 and 6 months post operative documented focal regrowth of the tumor in eight/11 cases of the non-PDT group. However, in the PDT group tumor regrowth was detected in four/14 cases.

3.1. Survival (Fig. 3)

In the non-PDT group nine patients died from their disease due to local tumor progression and distant metastases. Two patients are still alive 6 and 8 months from the date of operation.

In the PDT group 10/14 patients died from their disease, due to local tumor progression and/or distant metastases. Four patients are still alive from the date of operation at 6, 7, 12 and 18 months, respectively, postoperatively.

3.2. Complications

There were no major intra- or postoperative complications. The mean stay at the intensive care unit was 3 days (range from 1 to 7 days) and the mean estimated blood loss was 640 ml (range from 300 to 2400 ml). Sixteen patients required blood transfusions to maintain a hemoglobin of at least 12 g/l. Two patients needed mechanical respiratory support for more than 24 h (40 and 46 h). Air leaks could be observed in 21 patients, however, these closed spontaneously within 3–6 days.

The patients were discharged from hospital between days 9 and 20 (mean 14 days).

In two cases with additional PDT a superficial dehiscence of the thoracotomy wound was present which, however, closed spontaneously under outpatient wound care. In one patient, re-admission, 4 weeks after discharge due to empyema became necessary. He could be successfully managed by open window thoracostomy.

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 photosensitivity in two patients who had neglected the instructions to avoid sunlight after PDT and use a sun blocker for at least 12 weeks [10]. A single episode of fever up to 39 °C in the afternoon after the PDT-procedure was observed in four patients. None of these effects required specific treatment.

4. Discussion

Debulking and decortication are frequently used as palliative treatment in case of advanced malignant pleural mesothelioma. Local recurrences are almost unavoidable, as surrounding structures and the diffuse character of the tumor preclude an actually radical resection. Because of the low chemosensitivity of mesothelioma, and the difficulty of radiotherapy to include all areas, the additive use of radio- and/or chemotherapy conveys little benefit [1,2].

Several reports suggested that malignant mesothelioma of the pleura responds to PDT [3–6], an attractive antitumor treatment characterized by high potential for selectivity, destroying tumor tissue along the path of monochromatic light, while sparing adjacent healthy structures. Therefore it might be reasonable to use it in addition to debulking and/or pleuropneumectomy to improve local control of the tumor. However, as mentioned in several reports [5,6], the esophagus and bronchial stump should be protected to prevent fistula formation.

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 wavelength and energy. In this energetic state, they react directly through a free radical mechanism, or indirectly via molecular oxygen which undergoes a spin-state transition to reactive singlet oxygen. The depth of penetration of monochromatic light – about 5–7 mm – limits the active range of the cytotoxic effect. Both pathways yield potentially cytotoxic compounds, although the singlet oxygen process is thought to be predominant in PDT [12,13] and oxygen has been shown to be fuelling the polyhematoporphyrin based photodynamic action in vitro [14]. Considering the interactions of photosensitizer, 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 [15]. Therefore the use of HBO in this concept increased the oxygen tension from below 75 mmHg of up to 750 mmHg.

Side effects of HBO may affect the central nervous system and the lung but they subside spontaneously and are very rarely seen at pressures below 2 ATA and exposure times less than 90 min. Accordingly, we did not observe them in our patients.

From the technical point of view, combined surgical treatment followed by PDT and HBO did not include any problems provided the laser light generator was positioned outside the hyperbaric chamber with only the fiber being exposed to the hyperbaric atmosphere.

We did not observe any complications specifically related to intraoperative PDT and HBO.

Because of the residual tumor in case of tumor debulking in advanced malignant mesothelioma, PDT represents a safe additional tool in tumor reduction.

Even radical and aggressive surgical procedures could not serve the purpose of oncological success, associated by severe morbidity and mortality.

Therefore PDT seems to be an additional option in palliative surgery of malignant mesothelioma to achieve respectable results and clinical outcome in consideration of low morbidity and treatment associated complications.

The statistically significant survival benefit as well as the longer interval of tumor recurrence in patients receiving additional PDT/HBO are explicable due to: (a) the treatment of non-resected involved parts of the thoracic cavity, i.e. the phrenic nerve, the pericardium, the diaphragm, the hilus and the lung; and (b) the treatment of the mediastinum after systematic lymphadenectomy.

In conclusion, the poor prognosis of advanced malignant mesothelioma of the pleura necessitates new treatment protocols.

PDT represents a highly selective tumoricidal tool, whereby oxygen seems to be one of the keys to improve this additive therapy.

Although the study only includes a small number of patients not allowing definite conclusions, it indicates that the additional PDT under HBO represents a safe and technically feasible approach in the palliative setting of advanced malignant mesothelioma of the pleura.

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