Photodynamic therapy for malignant pleural mesothelioma
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INTRA-OPERATIVE PHOTODYNAMIC THERAPY AFTER PLEUROPNEUMONECTOMY IN PATIENTS WITH MALIGNANT PLEURAL MESOTHELIOMA: DOSE FINDING AND TOXICITY

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ABSTRACT

Objective: To determine the optimal administered dose of meta-tetrahydroxyphenylchlorin (mTHPC) for intraoperative Photodynamic Therapy (IPDT) in resected malignant pleural mesothelioma (MPM). The primary objective of this combination treatment was to improve local tumor control.

Design: Phase I/II dose escalation study.

Setting: Two Dutch cancer centers.

Patients: The study included 28 patients (2 women, 26 men), with pathologically confirmed MPM. Mean age was 57 (range 37-68), WHO performance score 0-1. Epithelial mesothelioma was found in 17, sarcomatous in 1 and mixed epithelial/sarcomatous in 10 patients.

Methods: Patients were injected with 0.075 (4 patients), 0.10 (19 patients) or 0.15 (5 patients) mg.kg⁻¹ mTHPC 4 or 6 days before surgery and IPDT. Complete surgical resection (pleuropneumonectomy) was followed by integral illumination with monochromatic light of 652 nm, (10 J.cm⁻², 6 Watt diode laser). Real time fluence rate measurements were performed using 4 isotropic detectors in the chest cavity to calculate the total light dose.

Results: Dose limiting toxicity was reached at the level of 0.15 mg.kg⁻¹ mTHPC. Three patients died in the perioperative period, one death was directly PDT related. Real time dosimetry identified 12 patients in whom additional illumination had to be given to the diaphragmatic sinuses, which were shielded during integral illumination. In 2 patients illumination was cancelled due to insufficient resectability of the tumor. Local tumor control, nine months after treatment, was achieved in 13 of the 26 patients treated with IPDT.

Conclusion: IPDT using mTHPC, combined with a pleuropneumonectomy, resulted in local control in 50% of treated cases. The considerable toxicity associated with the procedure, however, precludes its recommendation for widespread use. Stricter patient selection and improvements of PDT technique may reduce toxicity.

INTRODUCTION

Malignant mesothelioma (MM) is an uncommon disease, although the incidence has increased throughout the western world, during the last decades (1-3). In 1998 about 5000 deaths were attributed to this disease in Western Europe (3). MM develops long after asbestos exposure (20 to 50 yrs). Therefore, abundant use of asbestos in the sixties and to a lesser extent in the seventies, still leads to increasing numbers of newly diagnosed MM patients, which is predicted to rise until at least 2010. Neither surgery, radiotherapy nor chemotherapy have resulted in successful local control or sufficient response rates to influence survival significantly (4-7).

Numerous reports conclude that new treatment modalities or combinations must be investigated. One of the newer combined modality treatments available is the use of adjuvant intra-operative photodynamic therapy (IPDT) with second-generation photosensitizers. Ris et. al. were the first to use the very potent second-generation photosensitizer meta-tetrahydroxyphenylchlorin (mTHPC) for patients with pleural malignancies (8).
Recently we reported the feasibility of this approach in combination with integral chest illumination and real time light dosimetry (9). It was concluded that mTHPC mediated photodynamic therapy (PDT) offered advantages compared to the use of less potent sensitizers, since the light doses required are much lower and consequently the additional time for the IPDT was limited to < 1 hour. The integral illumination of the entire chest cavity with real time monitoring of the cumulative fluence also ensured uniform illumination and accurate estimation of the total fluence.

This feasibility study was continued as a phase I/II study on which we now report. The main objective of the treatment combination was to achieve local control. We report on the dose limiting toxicity, site of recurrence and long-term follow-up of 26 patients treated with surgery and IPDT.

MATERIALS AND METHODS

Patients

Patients with a histologically confirmed diagnosis of malignant pleural mesothelioma (MPM) were informed about the combination therapy, surgical resection and IPDT. Most of them were referred to one of the participating institutions for preoperative assessment. Extensive preoperative work-up was performed to select patients who were able to undergo an extrapleural pneumonectomy. The work-up consisted of a computerized tomography scan (CT), cardiologic analysis (including ultrasound), mediastinoscopy and thoracoscopy for optimal staging of the tumor.

Staging was based on the new criteria of the International Mesothelioma Interest Group (IMIG) (10). Other inclusion criteria were WHO < 2; age < 70 years; weight loss < 10% in the preceding month and a calculated postoperative FEV1 > 40% of predicted. The local ethical committees approved the study and patients were asked for a written informed consent. Twenty-five patients were treated in the Netherlands Cancer Institute and three were treated in the Daniel den Hoed Kliniek, using the same procedure and the same equipment.

Study design

Drug dose levels of mTHPC used were 0.075, 0.1 and 0.15 mg.kg⁻¹. In the phase I part of the study 4 patients were treated on each dose level, with surgical resection and illumination at 4 days after intravenous (i.v.) injection of mTHPC.

Significant perioperative morbidity and/or mortality was considered the dose limiting toxicity and the dose level below that was considered the maximum tolerable dose. An additional group was created at the level of the dose limiting toxicity (0.15 mg.kg⁻¹) with a longer drug light interval of 6 days, assuming that this would be less toxic than the same drug dose with illumination after 4 days. Once the maximum tolerable dose had been defined (0.1 mg.kg⁻¹ mTHPC with illumination at 4 days), this group was expanded with a further 15 patients as a phase II study.
Surgical procedure

The surgical and IPDT procedure used was described previously (9). In short: patients were intubated selectively by a double lumen endotracheal tube and placed in a lateral decubitus position. A postero-lateral thoracotomy was performed and previous entrance ports were excised. In selected cases a caviron ultrasound surgical aspirator (CUSA) was used to limit blood loss and to facilitate the resection of the tumor. The aim was to remove all macroscopic tumor. Small residues of < 5 mm tumor were accepted, if they could not be removed without disrupting the normal anatomic boundaries like diaphragm and pericardium, in order to avoid local tumor spread. Staples were used (TA 55, Autosuture) to close the bronchial stump and an ipsilateral mediastinal lymph node dissection was performed. After this procedure the IPDT was performed (see below), followed by closure of the thoracotomy and immediate detubation. The patients were monitored at the intensive care unit (ICU). Oxygen saturation was only measured for a few minutes every hour during the patients stay in the ICU, to avoid skin burn lesions induced by the light of the oxymeter. Digoxin was started the day before operation, oral anticoagulants were given postoperatively for a period of 3 months. After discharge from the ICU, patients stayed in the hospital until they were sufficiently recovered. Patients were monitored 6 times during the first year and three times per year thereafter with physical examination, standard laboratory tests, chest X-ray and CT scan of the thorax and upper abdomen.

Intraoperative PDT Procedure

According to the protocol doses of 0.075, 0.1 or 0.15 mg/kg of mTHPC (Foscan®, Scotia Pharmaceuticals Limited, Surrey, England) were administered to the patient 4 or 6 days before illumination. Twenty milligrams of the drug were dissolved in 5 ml of solvent, containing ethanol, polyethylene glycol and water. The solution was shaken vigorously for 5 minutes and this procedure was repeated once more after 1 hour before slow push i.v. administration (4 mg.ml−1). Patients were nursed in subdued light for two weeks. After the extrapleural pneumonectomy, the chest cavity was extensively inspected and bleeding lesions were coagulated. Isotropic light probes (Cardiofocus, West Yarmouth, MA, U.S.A) inserted in sterile transparent tubes (1-2 mm Vygon, Ecoun, France), were sutured on strategic sites in the cavity (apex, posterior diaphragmal sinus, pericardium or anterior chest wall and near the esophagus). These isotropic probes measure the fluence rate delivered to the tissue, including both direct incident and scattered light from the tissue (Fig 1). The isotropic probes were connected to photodiodes (Photop UDT-455, Graseby Electronics, Orlando FL, USA). These signals were transmitted to a Personal Computer for data recording and real time display. A transparent sterile plastic bag (Steri-Drape 3M) was placed in the cavity and filled with sterile saline at body temperature (2.5 – 4 liters) for better expansion of the diaphragm and mediastinal folds. The surgical wound was approximated and a spherical bulb fiber (3 mm diameter, Cardiofocus, West Yarmouth, MA, USA) was inserted in the center of the bag. Laser light of 652 nm was obtained from a 6 Watt diode laser (Applied Optronics, South Plainfield, USA). Integral illumination of the chest cavity was achieved by positioning the bulb fiber so that the isotropic detectors indicated comparable fluence rates. After integral illumination, the saline filled plastic bag was removed from the chest cavity. If one of the measured locations was insufficiently
Figure 1
Schematic set up of IPDT procedure. Cross-sectional and frontal view of situation after pleuropneumonectomy, with light emitting bulb fiber and 4 isotropic light detectors placed in their treatment positions.

illuminated, one or two of the isotropic detectors were moved to the vicinity of this location and additional illumination was subsequently given by a handheld microlense or spherical diffuser. The total fluence delivered to the tissues was aimed at 10 J.cm$^2$. Before and after the procedure all isotropic detectors were checked for their performance and calibrated for
Intraoperative Photodynamic Therapy

measurements in saline (correction of the refractory index induced by the saline). For further details on calibration see Marijnissen and Star (11).

RESULTS

From January 1996 till December 1999, 28 patients entered this study. Four patients on whom we previously reported were included in this study (9). Patient characteristics, major complications and duration of hospital stay are shown for the three different mTHPC dose groups in Tables 1 and 2. All patients had a negative mediastinoscopy and had no contra-indications for the combined procedure. In two patients, who had already been injected with mTHPC, large quantities of tumor reamained even after extensive diaphragmal or pericardial resections. IPDT was not performed in these patients because the risk of damage due to direct illumination of adjacent organs was considered to outweigh any possible improvement in local control.

The average time required for light delivery was 27 minutes (range 16 – 54 minutes). In 14 of the 26 illuminated patients, the integral illumination was uneventful and a uniform total fluence of 10 J.cm$^{-2}$ could be delivered to the entire cavity.

Additional illumination was required in 12 patients because of a relative protrusion of the diaphragm and consequent shielding of the diaphragmal sinus. Examples of an optimal illumination and one in which additional illumination of the diaphragmal sinus was required are shown in Fig. 2 A and B. In these figures the total fluence is shown as a function of the illumination time. In the patient represented in Fig. 2B, additional illumination was selectively aimed at the diaphragmal sinus between the eighth and sixteenth minute of the illumination period. The mean total fluences per patient varied between 9.2 and 12.9 J.cm$^{-2}$. Details of light dosimetry are shown in Table 3.

Post-operative treatment mortality

The first serious adverse event resulting in death occurred in a 69 year old man injected with 0.15 mg.kg$^{-1}$ mTHPC 4 days before operation. A large fibrotic tumor mass hampered complete tumor resection. Hypotension developed due to blood loss and the patient was transfused with 15 units of packed red blood cells. The light delivery was uneventful. On the first day after surgery a myocardial infarction was diagnosed. The patient died on day 6 postoperatively, despite extensive supportive measures. At post mortem examination severe generalized vascular atherosclerosis was observed as well as a large anterior myocardial infarction. Necrotic tumor nests were found in the dorsal sinuses without viable tumor cells, indicating that PDT had been effective.

The second lethality was a 56 year old man with a right sided pleural mesothelioma, who died 13 days after treatment (0.15 mg.kg$^{-1}$ mTHPC / 6 days interval). Surgery and IPDT passed without obvious problems. Left sided pleural fluid (exsudate) was drained seven days after treatment. Eleven days after operation a sudden deterioration of his clinical condition occurred. Bronchoscopy revealed a right bronchopleural fistula. A rethoracotomy was proposed but refused by the patient. He died on day 12 after treatment. At autopsy the bronchopleural fistula was confirmed with diffuse inflammation and extensive formation of debris in the right chest cavity. Culture from this cavity showed Klebsiella pneumonia and several Streptococcal species.
The third lethality was in a patient treated with 0.1 mg.kg$^{-1}$ mTHPC / 4 days before illumination. In this case the illumination was not performed strictly according to the protocol. This was due to an abnormal geometry of the left chest cavity. One isotropic detector was placed in the apex of the cavity and three probes were placed on and around the diaphragm. This resulted in an overdose in the region of the esophagus and the heart. The patient developed an esophageal fistula after 7 days, which was corrected with placement of an omentum flap and the construction of a Clagget thoracotomy. On day 12, a bleeding occurred in the chest cavity. In this patient no anticoagulant therapy was given. Despite intensive supportive treatment the patient died. Postmortem examination revealed diffuse bleeding from multiple sites and necrosis in the margins of the esophageal fistula. Typical PDT induced necrosis was observed in the epicardium reaching into the myocardium without coronary artery occlusion.

Post-operative morbidity

The mean hospital stay was 28 days, ranging from 18 to 61 (Table 2). The majority of patients (23, 82%) had one or more postoperative complications varying from pain in the surgical scar to diaphragmatic rupture or myocardial infarction. Congestive heart failure and atrial fibrillation were the most frequent side effects. Empyema occurred in 4 patients, 3 to 6 months after the procedure. One of these patients had only been resected and not treated with IPDT. Complications occurred more frequently in the group treated with the highest drug dose. In some cases complications, such as excessive intrathoracic fluid accumulation, could be attributed to the IPDT. In others, complications such as atrial fibrillation might have been elicited by the pleuropneumonectomy. In the majority of cases it was difficult to attribute complications specifically to either modality. However, no further patients were enrolled in the 0.15 mg.kg$^{-1}$ dose group after the second fatality. The 0.1 mg.kg$^{-1}$ group was subsequently expanded.

One of the two female patients (0.1 mg.kg$^{-1}$) had two major complications. She suffered from a diaphragmatic rupture with displacement of the stomach into the chest cavity on day 14 after treatment; this required surgical intervention. Tissue samples taken during rethoracotomy showed a very thin muscle layer without evidence of PDT induced necrosis. This patient subsequently developed a cardiac tamponade on day 14 during anti-coagulant therapy. A pericardial drain was inserted. The hemorrhagic effusion revealed no malignant cells. This patient recovered successfully.

Another patient (0.15 mg.kg$^{-1}$ mTHPC / 4 days) suffered from a per-operative myocardial infarction and subsequent spinal cord infarction due to hypotension caused by severe blood loss. The tumor had grown into the subclavian artery wall and into the myocardium. A vascular prosthesis had to be inserted in the resected subclavian artery. This patient was discharged on day 60 to a rehabilitation center. Skin phototoxicity was not a significant clinical problem in our study and no sun light induced skin toxicity was observed. Skin burn effects were most frequently seen in the 0.15 mg.kg$^{-1}$ group (2/5). This was induced by the theater lights despite covering of the wound edges with green surgical drapes.
Table 1 Patient characteristics

<table>
<thead>
<tr>
<th>mTHPC dose (mg.kg⁻¹)</th>
<th>0.075 (n = 4)</th>
<th>0.1 (n = 19)</th>
<th>0.15 (n = 5)</th>
<th>All groups (n = 28)</th>
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<tr>
<td>Mean age, yr</td>
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<td>56</td>
<td>62</td>
<td>57</td>
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<tr>
<td>Range, yr</td>
<td>46-62</td>
<td>37-66</td>
<td>55-68</td>
<td>37-68</td>
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<td>Right sided disease, #</td>
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<td>19</td>
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<td></td>
<td></td>
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<tr>
<td>Epithelial</td>
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<td>12</td>
<td>3</td>
<td>17</td>
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<tr>
<td>Sarcomatous</td>
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<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Mixed</td>
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<td>7</td>
<td>1</td>
<td>10</td>
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<tr>
<td>Stage, #</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>II</td>
<td>1</td>
<td>4</td>
<td>0</td>
<td>5</td>
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<tr>
<td>III</td>
<td>1</td>
<td>8</td>
<td>1</td>
<td>10</td>
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<tr>
<td>IV</td>
<td>2</td>
<td>5</td>
<td>2</td>
<td>9</td>
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</table>

Table 2 Major complications, (#)

<table>
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<tr>
<th>mTHPC dose (mg.kg⁻¹)</th>
<th>0.075 (n = 4)</th>
<th>0.1 (n = 19)</th>
<th>0.15 (n = 5)</th>
<th>All groups (n = 28)</th>
</tr>
</thead>
<tbody>
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<td>diaphragmal rupture</td>
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<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>empyema</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>perforation esophagus</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>bleeding stump pulm.artery</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>fluid retention</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>mucus impaction</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>depression</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>wound infection</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>7</td>
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<tr>
<td>spinal cord injury</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Perioperative death</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Mean hospital stay, days</td>
<td>20</td>
<td>26</td>
<td>57</td>
<td>28</td>
</tr>
</tbody>
</table>

The patient group receiving 0.15 mg.kg⁻¹ with a 4 day illumination interval was closed prematurely after 3 patients had been entered. One death occurred and one patient suffered severe toxicity. An additional two patients were illuminated at 6 days after 0.15 mg.kg⁻¹ mTHPC but, when one of these patients also died, this drug dose level was abandoned.
Figure 2

Two examples of the light dosimetry measurements. Total light Dose is shown as a function of time for 4 different locations of the inner chest cavity. In Figure 2A the recorded fluence was nearly similar for all locations. In Figure 2B the recorded fluence in the dorsal diaphragmal was insufficient, this location was then additional illuminated with a microlens.
Site of recurrence

During follow up, three types of recurrences could be identified: local, in the surgical scar and distant. Recurrence was established in twenty patients. There were 8 local-, 4 scar- and 8 distant failures (Table 4). Local control at 9 months was achieved in 13 of the 26 patients treated with surgery and IPDT.

Disease free survival and survival

The median follow-up of the patients was 31 months (range 9 – 53) Actuarial disease free survival and survival are shown in Figure 3 for the 26 patients treated with surgery plus IPDT. Median disease free survival after surgery and IPDT was 9 months, survival 10 months. These data for all patients were comparable with the results in the 0.1 mg.kg−1 group alone with 7 and 10 months disease free and overall survival respectively.

![Figure 3](image)

Kaplan Meier curves for disease free survival and survival of the 26 patients treated with surgery and IPDT
Table 3 Light dosimetry of 26 patients treated with IPDT

<table>
<thead>
<tr>
<th></th>
<th>(n = 3)</th>
<th>(n = 18)</th>
<th>(n = 5)</th>
<th>(n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>3</td>
<td>18</td>
<td>5</td>
<td>26</td>
</tr>
<tr>
<td>Lowest light dose, J.cm²</td>
<td>9</td>
<td>7</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Highest light dose, J.cm²</td>
<td>10.8</td>
<td>15.6</td>
<td>14.8</td>
<td>15.6</td>
</tr>
<tr>
<td>Mean light dose, J.cm²</td>
<td>10.1</td>
<td>12.9</td>
<td>12.1</td>
<td>11.5</td>
</tr>
<tr>
<td>Number of boosts</td>
<td>1</td>
<td>10</td>
<td>1</td>
<td>12</td>
</tr>
</tbody>
</table>

DISCUSSION

Treatment for MPM is still unsuccessful, in terms of cure and survival. Several investigators have tried to improve local control by incorporating surgery in their treatment strategy. Multimodality therapy with chemotherapy, radiotherapy, or both, after tumor resection have been advocated (5). However, these combination therapies have not managed to achieve local control in the majority of patients (12). PDT might have a role to play in increasing local control, since it has proven to be successful in the treatment of superficial malignancies. Enthusiasm following initial promising results on the use of PDT in MPM (8,13,14) have been somewhat tempered by a randomized study of Pass et al, published in 1997 (15). He observed no advantage of the addition of Photofrin mediated IPDT to a regime of surgery and immunochemotherapy in a total of 25 patients. Median survival did not exceed 14 months in this study, which does not compare favorably with current alternative treatment options. Probably the most optimistic phase II results were from the recently published study of Moskal (16). He reported that several long-term survivors were observed after the combination of surgery and PDT with Photofrin. However, patients who died perioperatively (3 of 40 treated) were excluded from analysis in this study.

Table 4 Site of recurrence of 26 patients treated with IPDT

<table>
<thead>
<tr>
<th>mTHPC dose (mg.kg⁻¹)</th>
<th>0.075 (n = 3)</th>
<th>0.1 (n = 18)</th>
<th>0.15 (n = 5)</th>
<th>All groups (n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence, #</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Local</td>
<td>1</td>
<td>6</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>surgical scar</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>distant*</td>
<td>1</td>
<td>7</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>none</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Perioperative death</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

* lymph node (n = 2), liver (n = 2), contralateral lung, abdominal and skeleton.
In our study we have tried to optimize one of the treatment parameters, drug dose, using a new delivery procedure for IPDT in patients with MPM. It is nearly impossible to analyze all PDT factors (drug dose, light dose and drug light interval) adequately in one study. We focussed on varying drug dose, with both light dose and drug light interval fixed. The differences in extent of the surgical procedure also significantly influenced the final results and toxicity. Despite careful pre-operative screening, some patients proved to have an irresectable tumor during the surgical procedure. In three patients with extensive resections of tumor invading vasculature or the chest wall, IPDT was given according to the protocol. These patients had significant per and post-operative complications as mentioned above. Such patients should probably be excluded therefore from IPDT and more stringent attempts should be made to identify patients with irresectable tumor preoperatively. MRI (17-19), 3-dimensional tumor volume estimation (20) and standardized uptake values of FDG PET scanning (21-22) may improve selection of patients for surgical based therapy.

Until recently, MPM was thought to be primarily a local disease (23). If this is true, successful local control should significantly improve survival. However, autopsy reviews have indicated that over 50% of patients with MPM develop distant metastases (24,25) and Sugarbaker also demonstrated the prognostic importance of local (mediastinal) lymph node involvement (26). We have routinely incorporated a mediastinoscopy in the preoperative assessment of our patients, in order to exclude those with mediastinal lymph node metastases. Rusch showed that one quarter of mediastinal lymph nodes in MPM were not accessible to cervical mediastinoscopy (27).

In comparison with non small cell lung cancer, a relatively large number of MPM cases have nodal disease confined to areas such as peridiaphragmatic or internal mammary chains. Improvements in local control should therefore be integrated with effective systemic therapy to obtain a better prognosis for this disease in general.

The phase I part of our study demonstrated that a dose of 0.1 mg.kg\\(^{-1}\\) mTHPC given 4 days before illumination is the maximal tolerable dose. The IPDT could be given in a short period of time, which is one of the advantages of a potent photosensitizer such as mTHPC. The treatment did however still lead to considerable morbidity. Analysis of the toxicities in this study is complicated by the multimodality approach. Pleuropneumonectomy alone leads to significant toxicity, with about 10–15% mortality (28), which is comparable to that seen in the present combined modality study. Right-sided resections carry the greatest surgical risk and the majority of our patients (19 of 28) had right-sided disease. This might have influenced the results in a negative way. Large surface PDT alone would also be expected to be associated with significant toxicity. In our study the perforation of the esophagus was clearly related to the IPDT procedure. This fatal complication illustrates the importance of light dosimetry on more than one location. Temeck and Pass (29) reported this complication as a dose limiting factor in Photofrin mediated IPDT in two MM patients. With respect to the IPDT induced cardiac damage, a side study was initiated measuring T-troponin levels and performing cardiac examinations during and after operation. No significant myocardial damage was observed in 5 patients treated with 0.1 mg.kg\\(^{-1}\\) mTHPC 4 days before illumination (30), when the illumination procedure was performed in a standard way.

Our study has addressed the influence of sensitizer dose on IPDT related toxicity. With the exception of two patients treated 6 days after injection of mTHPC, the drug light interval was kept constant at 4 days and only limited variations in total fluence were allowed. These choices were based on reports in the literature and our own
experience (31,32). The light delivery system used in this study is now thoroughly tested and is, in our opinion, an important improvement for the application of PDT in general. Other investigators have used photodiode light detectors which measure only incident light fluence and not scattered and reflected light (13). Such detectors clearly give an underestimation of the total fluence delivered to the tissue surface (33). The use of only four detectors placed on strategic sites in the chest cavity and a single spherical bulb fiber placed in the center of a fluid filled transparent bag in the chest cavity allowed adequate integral illumination of the entire cavity in most cases. In view of the patient who was overdosed with light, we stress that it remains critical that detectors are placed with care and kept in their position during the full procedure.

Some sites, like the diaphragm, can be shielded from the light but they are easily detected by this system of real time dosimetry. Additional illumination can be performed with the isotropic bulb or lens fiber after completing the integral treatment. A possible disadvantage of our system is the pressure on surrounding tissue induced by the fluid filled bag. Pressure against malignant and normal tissue could perhaps reduce PDT efficacy, due to decreased tissue perfusion accompanied by decreased oxygenation (34,35).

In conclusion, combination of extensive surgical resection and IPDT was too toxic to be advocated as a widespread treatment option for patients with MPM. The use of intraoperative dosimetry devices is considered a prerequisite. Further studies should be performed with more limited surgical resections. Light doses of 10 J.cm$^{-2}$ at 4 days after administration of 0.1 mg.kg$^{-1}$ mTHPC resulted in significant toxicity in this patient group. Local control, however, could be achieved in half of the treated patients. Improvements in terms of clinical usefulness can be expected from stricter patient selection and PDT related technical improvements, e.g. specific illumination devices for treatment of the diaphragmal gutter.

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