Photodynamic therapy for malignant pleural mesothelioma
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Citation for published version (APA):

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INTRODUCTION
AND OUTLINE OF THE THESIS
Malignant Mesothelioma

Malignant Mesothelioma (MM) is a neoplastic disease arising from the pleura, peritoneum or tunica vaginalis. The pleural localisation is by far the most frequent. Few mesotheliomas remain small and localised, most are characterised by a diffuse growth pattern.

History

MM is a relatively rare disease which was recognised only late in medical history as a distinct pathological entity (1). E. Wagner, who called it a “tubercle like lymphoma of the pleura”, was the first to publish a histopathological description of MM (2), although an unpublished report from Lieutaud in 1767 already mentioned two possible cases (3). In a literature review, Saccone and Coblenz identified 41 cases of possible MM in a total of approximately 46,000 autopsies and referred to the disease as “endothelioma” (4). After the second world war malignant mesothelioma became the generally accepted expression for this disease.

Etiology and epidemiology

In 1960 J.C. Wagner demonstrated the relationship between asbestos exposure and the development of malignant mesothelioma (5). Since this publication asbestos exposure is commonly accepted as a risk factor for this disease. In about 80% of all patients with MM, previous asbestos exposure is confirmed if patients are interviewed meticulously (1). Several occupational groups with an increased risk of asbestos exposure have been identified, such as workers in asbestos mines or manufactories, shipyards, and isolation and construction workers (6). The risk of exposure to asbestos fibres from car brake linings and clutch facings is also thought to be significant, although no increased risk of MM could be demonstrated in a recent meta-analysis (7). In the western world, many restrictive measures on the use of asbestos were enforced from the nineteen sixties onwards (8). Nevertheless, the incidence of MM is still expected to rise until approximately 2020, due to the long latency period between exposure and the first manifestation of this disease (20 to 50 years in most cases) (9,10,11). In several publications, authors warned that there could be a doubling of the incidence of MM by 2020 (10,11), due to the abundant use of asbestos between 1950 and 1980. Improvements in diagnostic techniques and registration policies may be other factors responsible for the increased documented incidence of this disease (8). Recent data from the Dutch Mesothelioma Registry, however, indicate that this could be an overestimate.

The degree of carcinogenicity, associated with various types of asbestos fibres varies. The risk is thought to be related to the length-diameter ratio, fibres with the highest ratio being the most carcinogenic (1). Users of serpentines like chrysotile (white asbestos) and anthophyllite have a significantly lower risk of developing malignant mesothelioma than those using amphiboles like crocidolite (blue asbestos) or tremolite (12). The exact role of chrysotile fibers in causing mesothelioma is still a matter of debate. The increased risk among chrysotile users may well be attributed to contamination with low concentrations of fibrous tremolite, which is a very common phenomenon (6,12).
Malignant pleural mesothelioma (MPM) without demonstrable exposure to asbestos has been described in inhabitants of the area of central Cappadocia in Turkey (13,14). In some villages of this region, more than 50% of cancer related deaths is caused by MM. The rocks and soils in these region contain the zeolite fiber erionite, which is highly carcinogenic. Other causative relations in non asbestos related MM have been suggested for tuberculosis, especially when treated with iatrogenic pneumothoraces (15), radiotherapy (16) and man made mineral fibres (MMMF's) like glass fibres (17).

Diagnosis

MM is characterised by an insidious onset of symptoms which are aspecific. The most common presenting symptoms in MPM are thoracic pain, breathlessness and cough. During the course of the disease most patients are confronted with loss of appetite weight loss and fever (8). At physical examination the affected side of the chest may be reduced in dimensions and signs of a pleural effusion are often found. Blood analyses are not helpful in establishing the diagnosis and demonstrate only the general impression of a malignant disease. Chest X-rays of patients with MPM show evidence of pleural fluid formation which is generally confirmed by CT scanning. Typical CT images in this disease show nodular thickening of the pleura and retraction of the affected side of the chest. A pathological diagnosis can be obtained by cytological investigation of pleural fluid (18), the vast majority of patients, however, require histological assessment of tissue samples for diagnosis. The most commonly used methods to obtain these tissue samples are transthoracic puncture (true cut), thoracoscopy or a small thoracotomy.

Pathology

After malignant transformation, mesothelial cells form small nodules and pleural thickenings. In the majority of patients with MPM the tumour originates from the parietal pleura. Unfortunately, by the time of diagnosis tumour cells have often affected the opposite visceral pleura and invaded the lobar fissures. Pleural thickenings have a tendency to coalesce, especially in the diaphragmal sinus, finally resulting in encasement of the lung. MM is characterised by 2 histological subtypes, often both recognised in one patient. In a review of a large series of patients it was reported that 50% of the patients had epithelial, 16% had sarcomatous and 34% had mixed epithelial and sarcomatous mesothelioma (19). The distinction between MM and other malignant or non malignant disease is often difficult. MM may mimic adenocarcinoma histopathologically (especially in cases when the epithelial form is considered). Histochemical and immuno-histochemical staining methods can provide strong evidence in the differentiation between MM and adenocarcinoma, although no combination of staining patterns can produce a definite diagnosis (20). Positivity for PAS, CAM 5.2, Vimentin, HBME-1 and negative staining with DPAS, CEA and Ber-EP 4 strongly suggest MM, while the opposite indicates adenocarcinoma (21,22). Another problem in establishing the diagnosis of mesothelioma is formation of desmoplastic areas, which are characterised by a paucity of cells surrounded by collagenous tissue. Desmoplasia is suggestive for fibrous pleurisy, but if factors like chest wall invasion of neoplastic spindle cells and evidence of necrotic or sarcomatoid degeneration are recognised, the diagnosis MM is most likely (23).
Table 1. IMIG staging system for malignant pleural mesothelioma.

<table>
<thead>
<tr>
<th>T = tumour</th>
<th>N = lymph nodes</th>
<th>M = Distant metastase</th>
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</thead>
<tbody>
<tr>
<td><strong>T1</strong></td>
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<td></td>
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<tr>
<td>T1a</td>
<td>Tumour limited to the ipsilateral parietal including mediastinal and diaphragmatic pleura. No involvement of the visceral pleura.</td>
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<tr>
<td>T1b</td>
<td>Tumour involving the ipsilateral parietal including mediastinal and diaphragmatic pleura. Scattered foci of tumour also involving the visceral pleura.</td>
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<td><strong>T2</strong></td>
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<tr>
<td>T2</td>
<td>Tumour involving each of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic and visceral pleura) with at least one of the following features:</td>
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<td></td>
<td>• Involvement of diaphragmatic muscle.</td>
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<tr>
<td></td>
<td>• Confluent visceral pleural tumour (including fissures), or extension of tumour from visceral pleura into the underlying pulmonary parenchyma.</td>
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<tr>
<td><strong>T3</strong></td>
<td></td>
<td></td>
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<tr>
<td>T3</td>
<td>Describes locally advanced but potentially resectable tumour. Tumour involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic and visceral pleura) with at least one of the following features:</td>
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<tr>
<td></td>
<td>• Involvement of the endo thoracic fascia.</td>
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<td></td>
<td>• Extension into the mediastinal fat.</td>
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<td></td>
<td>• Solitary, completely resectable focus of tumour extending into the soft tissues of the chest wall.</td>
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<td></td>
<td>• Nontransmural involvement of the pericardium.</td>
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<tr>
<td><strong>T4</strong></td>
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<tr>
<td>T4</td>
<td>Describes locally advanced technically unresectable tumour. Tumour involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic and visceral) with at least one of the following features:</td>
<td></td>
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<tr>
<td></td>
<td>• Diffuse extension or multifocal masses of tumour in the chest wall, with or without associated rib destruction.</td>
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<td></td>
<td>• Direct transdiaphragmatic extension of tumour to the peritoneum.</td>
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<td></td>
<td>• Direct extension of tumour to the contralateral pleura.</td>
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<tr>
<td></td>
<td>• Direct extension of tumour to one or more mediastinal organs.</td>
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<tr>
<td></td>
<td>• Direct extension of tumour into the spine.</td>
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<tr>
<td></td>
<td>• Tumour extending through the internal surface of the pericardium with or without a pericardial effusion; or tumour involving the myocardium.</td>
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</table>

**Nx**  | Regional lymph nodes cannot be assessed. |
**N0**  | No regional lymph node metastase. |
**N1**  | Metastases in the ipsilateral bronchopulmonary or hilar lymph nodes. |
**N2**  | Metastases in the subcarinal or the ipsilateral mediastinal lymph nodes including the ipsilateral internal thoracic nodes. |
**N3**  | Metastases in the contralateral mediastinal, contralateral internal thoracic, ipsilateral, or contralateral supraclavicular lymph nodes. |
**Mx**  | Presence of distant metastases cannot be assessed. |
**M0**  | No distant metastase. |
**M1**  | Distant metastases present. |

**Stage I**

| 1a | T1a, N0, M0 |
| 1b | T1b, N0, M0 |

**Stage II**

| T2, N0, M0 |

**Stage III**

| Any T3, M0 |
| Any N1, M0 |
| Any N2, M0 |

**Stage IV**

| Any T4, N3 or M1 |
Mechanisms by which mesothelial cells undergo malignant transformation are largely unknown. Chromosomal deletions and loss of heterozygosity have been reported for many chromosomal regions such as 1p, 3p, 6q, 9p, 13q and 22q (24), but, a specific recurrent event, as has been found for some other malignancies, has not yet been identified (20). Much attention has been paid to the role of SV-40 large antigen (Tag). SV-40 related alterations in cell cycle control have been shown to be synergistic with carcinogenic effects of asbestos (25). It is suggested that Tag may inactivate tumour suppressor genes like p53. However, p53 mutations or deletions were only demonstrable in a minority of patients with MM (26). Possibly the most consistent genetic alteration in malignant transformed mesothelial cells in MM is the expression of the Wilms’ tumour susceptibility gene (WT-1) (27). The exact role in the control of cell growth of WT-1 is still unclear, since mutations in this tumour suppressor gene are seldom demonstrated in MM tissue (28).

The definition of tumour specific antigens in MM has been difficult, and very little is known about potential target antigens for immunotherapy (29). A variety of growth factors, such as platelet derived growth factor (PDGF) A and B and transforming growth factor-b have been demonstrated both in human and murine mesothelioma cell lines (29). The strongest evidence for a tumorigenic effect was found for PDGF-A, which induced transformation of nonmalignant mesothelial cells when transfected in a nude mouse model (30).

Staging

In 1976, Butchart was the first to propose a staging system for MPM which soon became widely accepted (31). This system was based on 4 different clinical stages and was practical to use. The need for more accurate stratification of patients for clinical trials subsequently stimulated several investigators to design more refined staging systems, although none of these achieved widescale acceptance. Moreover, data demonstrating that lymph node involvement occurred more frequently than was previously thought, emphasised the necessity of an adequate TNM based system (32), as proposed by the International Mesothelioma Interest Group (IMIG) in 1995 (33) (Table 1). This staging system separates patients according to their survival probabilities (34). A distinction is made between stage 1A and 1B based on a study of Boutin et.al., investigating the value of careful staging by thoracoscopy (35). In their report a clear difference was demonstrated for survival of patients with involvement confined to the parietal pleura versus patients with evidence of spread to the visceral pleura. The 4 stages of the IMIG system are characterised by separating tumours which are resectable (stage I and II), potentially resectable (III) and technically unresectable (IV). This system is now widely accepted, although there are still some disadvantages. Accurate staging is based on surgical procedures, like thoracoscopy and thoracotomy. However, many patients present with obvious widespread, or even metastatic, disease or are in poor general condition. For these patients extensive surgical procedures are not reasonable and they are therefore excluded from proper staging.
Table 2. Independent prognostic factors in malignant mesothelioma, according to multivariate analyses (derived from Edwards et al 2000).

<table>
<thead>
<tr>
<th>First author/Year of publication</th>
<th>N</th>
<th>age</th>
<th>gender</th>
<th>chest pain</th>
<th>weight loss</th>
<th>PS</th>
<th>pathology</th>
<th>platelet count</th>
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<tr>
<td>Chabinian, 1982</td>
<td>69</td>
<td>+</td>
<td>-</td>
<td></td>
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<td>+</td>
<td></td>
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<tr>
<td>Samson, 1987</td>
<td>76</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Alberts, 1988</td>
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<td></td>
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<td>-</td>
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<td>Antman, 1988</td>
<td>180</td>
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<tr>
<td>Chailleux, 1988</td>
<td>167</td>
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<td>Spiritas, 1988</td>
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<tr>
<td>Ruffie, 1989</td>
<td>332</td>
<td>+</td>
<td>-</td>
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<td>+</td>
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<tr>
<td>Tammilehto, 1992</td>
<td>98</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Boutin, 1993</td>
<td>188</td>
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<td>De Panger, 1993</td>
<td>80</td>
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<td>Manzini</td>
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<tr>
<td>Fusco, 1993</td>
<td>113</td>
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<tr>
<td>Curran, 1998</td>
<td>204</td>
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<td>+</td>
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<td>+</td>
<td>+</td>
<td></td>
<td>-</td>
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<tr>
<td>Herndon, 1998</td>
<td>337</td>
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<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Pass, 1998</td>
<td>48</td>
<td>+</td>
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<td>+</td>
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<tr>
<td>Edwards, 2000</td>
<td>101</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
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<td>-</td>
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</table>
Prognostic factors

In addition to tumour staging, other factors such as age, cell type and performance score may provide important information about expected survival in patients with MM (36). The most consistent prognostic factors identified in 15 studies are summarised in Table 2. Biologic markers like microvessel density (22), proliferation index (37), syndecan 1 (38), Simian-virus 40 (39) and K-Ras expression (40) have also been suggested to bear prognostic significance, although none of these has yet been confirmed as independent prognostic factor and their clinical significance is unclear.

Therapy

Survival figures after treatment of MM are still disappointing. Monotherapy with surgery, radiotherapy or chemotherapy can only achieve long term control for a very small number of patients (1). Different combinations of treatment are under investigation, but no combination has consistently proven to be superior to supportive care alone. Median survival after diagnosis of MM is always between 9 and 14 months in large series, independent of any possible treatment (including supportive care only).

Surgery

Surgical intervention can be used for palliative reasons or as a curative option in highly selected cases (1). During a pleurectomy the thickened pleura is stripped from the lung in an attempt to relieve symptoms which are related to entrapment of the lung or to pleural effusion. A pleurectomy should be considered as a purely palliative procedure.

Pleuropneumonectomy is an en bloc resection of the parietal pleura and the lung which, in cases of MM, is combined with resection of the tumour. Performed by experienced surgeons, perioperative mortality of this procedure is less than 10%, but serious side effects, including empyema, bronchopleural fistula and arrhythmia, occur in about 25% of cases. Pleuropneumonectomy only can result in median survivals of up to 21 months for selected patient groups (8). Most pleuropneumonectomies leave microscopic disease, whereby patients suffer from a local recurrence within a short period after operation.

Pleuropneumonectomy is no longer considered useful anymore as a single modality treatment. Investigators have incorporated this intervention in a combination of treatment procedures. Promising results were reported for the combination of surgery, chemotherapy (cyclofosfamide, doxorubicin and cisplatin) and external radiotherapy (median dose of 30 Gy to the hemithorax) in 183 patients (41). This intensive schedule resulted in a 2 year survival rate of 38% (excluding 7 patients who died in the perioperative period). Other experimental techniques used in combination with tumour resections are immunotherapy, gene therapy and photodynamic therapy (42).

Radiotherapy

External radiotherapy has proven ineffective in prolonging survival in MM, although tumour regression has been documented (43). Even for adequate palliation without long term control, a total dose of at least 50 Gy is required, which is associated with considerable toxicity in
adjacent vital organs such as the lung, spinal cord, heart, and oesophagus. Radiation therapy may be effective in combination with surgery, but this combination should still be considered experimental (41). Probably the most widely used indication for radiotherapy in MM is the prophylactic treatment of transthoracic tracts resulting from thoracoscopies or diagnostic punctures. Effective prevention of tumour cell seeding in these tracts can be achieved with a dosage of 3 x 7 Gy (44).

Chemotherapy

Although many single agents and combinations of cytotoxic agents have been tested in MM, chemotherapy should still not be advocated outside experimental protocols. Many chemotherapeutic agents have been tested in phase II trials, but a consistent response rate of more than 20% has not been achieved for any single drug or combination of drugs. (45,46). Unconfirmed response rates of 25 to 47% (47,48) illustrate the problem of different criteria by which responses are defined. Whether standard World Health Organisation (WHO) criteria should be used for MM is still a matter of debate, since these criteria were not defined for evaluating tumours growing superficially. Evaluation of morphologic changes after treatment in MM should probably be performed with alternative criteria but such criteria have not yet been properly defined. Nevertheless, many investigators have attempted to use substitutes for the WHO criteria, such as minimal tumour regression or resolution of pleural fluid. The use of alternative response criteria has led to different conclusions regarding treatment outcome. For instance the reported response rate of 47% for a combination of cisplatin and gemcitabine using alternative criteria was reduced to 18% when formal WHO criteria were used for tumour response measurement (49).

Photodynamic Therapy

History

During the last two decades photodynamic therapy (PDT) has been introduced as a new anti-cancer treatment. Raab first discovered the process of photodynamic therapy in 1900 (50), when he observed that paramecia placed in a dye solution died when they were exposed to light. It then took more than 60 years before Lipson (1961) identified haematoporphyrin (51) as a compound which specifically induced fluorescence in mammary carcinoma. Further analyses of this drug by Dougherty and Kessel led to the so called "first generation clinical photosensitiser" (52). Di-haematoporphyrinether (DHE) consisted of mono-, di- and oligomers of the porphyrin molecule and initially it was unclear which of these porphyrins was responsible for the photochemical reactions. The current commercially available compound photofrin is an enriched fraction of these porphyrins. The long lasting skin photosensitivity and impurity of the drug were the most important stimuli for further development of alternative photosensitising agents.

Introduction

The basic principle of PDT is illumination of a photosensitiser with light of a suitable wavelength to excite it from its ground state to its excited singlet state. From this excited state the photosensitiser either decays back to its ground state (emitting light in the form of fluorescence) or undergoes electron spin conversion to its triplet state. The
triplet state sensitiser can react with biological substrates, by proton or electron transfer, leading to the formation of radicals and radical ions which interact with oxygen to form oxidised products (type I reaction) (53). An alternative pathway leads to the formation of singlet oxygen (\(\text{O}_2^*\)); this occurs when the triplet state sensitiser directly transfers its energy to molecular oxygen (type II reaction) (54) (Figure 1). PDT toxicity is mainly related to the effects of singlet oxygen. Toxic products of both type I and II photochemical reactions are highly reactive, with short half-lives. Selectivity in the effect of PDT between neoplastic and normal tissue was originally thought to be related to preferential uptake in malignant tissue (55,56). However, for many photosensitisers including mTHPC, damage related to vascular mediated mechanisms may be more important than direct cell phototoxicity (57,58). Oxygen is a prerequisite for both types of photochemical reactions (type I and II), without a sufficient supply of oxygen PDT will not result in the desired tissue damage (53,54). An inherent problem of PDT in relation to its oxygen supply is that oxygen is consumed during the photochemical reaction and supply is increasingly disturbed by vascular injury (59). This vascular injury may even become irreversible once intraluminal fibrin emboli form.

**Figure 1**: Type I and type II reactions

\[
\begin{align*}
\text{Type I:} & \quad \text{Absorption of light to give singlet state} \\
\text{Type II:} & \quad \text{Energy transfer to give singlet oxygen}
\end{align*}
\]

Second generation photosensitizers.

Many review articles have addressed the issue of the requirements which should be fulfilled by an ideal photosensitiser (60,61,62). An important characteristic is its selective destruction of malignant tissue, independent of the mechanism responsible for this selectivity (differences in biodistribution or preferential injury to blood vessels feeding this tumour). Another issue is the light absorption profile of the sensitiser. Ideally the absorption spectrum of a photosensitiser should contain a peak with a wavelength above 650 nm. At these wavelengths light penetration of 5 – 10 mm can be achieved in tissues without too much absorption by other chromophores in the tissue itself or in blood.
Photosensitisers with a high yield of singlet oxygen could also be expected to have greater efficacy and sensitisers inducing shorter periods of skin photosensitivity would make PDT a much more practical treatment option. Second generation sensitisers like phthalocyanine (63,64), chlorines (65,66) and the purpurins (67) have been developed with these considerations in mind. One of the most widely used second generation sensitisers is meta-tetrahydroxyphenylchlorin (mTHPC) (figure 2). This sensitiser has advantages over photofrin in that it is chemically pure and has a major absorption peak in the near infra-red part of the light spectrum at 652 nanometers (68) (Figure 3). The absorption coefficient is also high at this wavelength (22,400 l.mol.\(^{-1}\). cm\(^{-1}\)). These properties result in a clinically relevant PDT effect in tissue with a penetration depth between 5 and 10 mm (69). High energy absorption with efficient production of high concentrations of singlet oxygen are accomplished in a short period of time (minutes). It has also been shown that skin phototoxicity, after commonly used drug doses, is reduced to 2 to 3 weeks for this drug, while patients who are injected with photofrin have to avoid light exposure for 6 weeks (70).

Figure 2. Chemical structure of mTHPC
Indications for the use of photodynamic therapy.

The first patients in whom PDT was applied had large tumours and the intended effect was merely tumour debulking. These included patients with obstructing tumours of the tracheobronchial tree and the upper digestive tract (71,72). Although some relief of symptoms, and impressive tumour regression could be achieved, long standing palliation was rare and survival was not improved (73). At the same time alternative techniques for desobstruction of these organ systems were further developed (74). PDT was subsequently tested for the treatment of small localised tumours, where adequate light penetration could be achieved throughout the tumour. Many types of superficial tumours (and premalignant dysplasias) in the oral cavity, oesophagus, bronchial tree, bladder and skin have now successfully been treated by some kind of PDT (75, 76, 77,78,79). One advantage of PDT compared with surgical excision of small tumours is that PDT heals mainly by regeneration rather than scarring. This is associated with good functional and cosmetic outcome, which is especially important in patients with head and neck cancer, who may have been previously treated with other modalities like surgery and radiotherapy. Moreover PDT can be repeated as many times as indicated without detrimental effects related to cumulative toxicity. Developments in the field of light delivery and dosimetry have greatly improved our ability to adequately illuminate tumours in a wide variety of sites (80). Real time light dosimetry allows much better control of the delivered light dose and should improve the balance between tumour control and normal tissue damage (81). PDT can also be used as an adjuvant treatment in combination with surgery for more widespread malignancies. (see malignant mesothelioma and photodynamic therapy).

Indications for PDT applications in non-malignant disease which are in current clinical use are age related macular degeneration, atherosclerosis and rheumatoid arthritis.

![Figure 3. Absorption spectrum of Photofrin and mTHPC in relation to transmittance in human tissue](image-url)
Malignant mesothelioma and Photodynamic therapy.

One of the possible adjuncts to surgery in MPM is photodynamic therapy (PDT). PDT should be able to destroy nests of tumour cells left behind in the chest wall after tumour resection.

Two studies concerning combination therapy with surgery and Photofrin mediated PDT were published in 1994. In the Roswell Park study 23 patients were entered, some of them were treated with a pleuropneumonectomy others with a pleurectomy (82). Median survival for patients with limited disease extension was 36 months (83). However, median survival for the whole group was only 15 months and 3 patients who died of treatment related causes were excluded from analysis. Twelve patients had serious complications during the postoperative period: infections (n=6), prolonged ventilatory support (n=4), cardiac arrhythmia (n=4), bronchopleural fistula (n=3), chylothorax (n=1), haematotherax (n=1), superior vena cava syndrome (n=1) and rupture of the spleen (n=1).

In a phase I study from the Bethesda group 40 patients with MM were operated and treated with PDT (84). Extent of resection was dictated by the bulk of disease. This resulted in some pleurolobectomies and in the majority of patients in a pleurectomy or a pleuropneumonectomy. The illumination procedure was performed with real time dosimetry using flat photodiodes. The median survival for the whole series was 10 months, without perioperative mortality. Complications were seen in 15 patients: supraventricular arrhythmia (n=1), congestive heart failure (n=2), perforation of a gastric ulcer (n=1) and poor healing of the thoracotomy wound (n=1).

This phase I study was followed by a phase III study from the same group (85). In this study 63 patients were randomised to receive intraoperative PDT or no PDT. After surgery with or without PDT, patients were treated with immuno-chemotherapy using cisplatin, interferon and tamoxifen. PDT was applied according to the same protocol described for the phase I study. There was no difference between the PDT and the no PDT group in incidence or severity of complications. Median disease free survival (PDT 8.5, no PDT 7.7 months) and survival (PDT 14.1, no PDT 14.4 months) were not significantly different.

The first study using mTHPC as photosensitiser was reported in 1996 by H.B. Ris et al. (86). PDT was performed in 8 patients using 0.3 mg.kg\(^{-1}\) mTHPC and an incident light dose of 10 J.cm\(^{-2}\), without real time light dosimetry. Postoperative morbidity consisted of a colonic perforation (n=1), a bronchopleural fistula (n=1) and aspiration pneumonia (n=1). Several patients succumbed due to causes related to distant manifestations of MM, which may indicate that local control was achieved in those patients.

mTHPC mediated PDT could potentially improve the effectiveness of adjuvant PDT after surgery in MM patients compared with photofrin. mTHPC has a higher singlet oxygen yield and light of the wavelength used for activation (652 nm) penetrates deeper into tissues than the 630 nm light used to activate Photofrin. The more efficient photosensitiser in combination with high power diode lasers, means that effective illumination can be accomplished in shorter periods of time. Decreased illumination times are more practical and may improve patient outcome because the total operation time is shorter. PDT protocols could also be improved by the use of isotropic light detectors and online real time light dosimetry to monitor the cumulative light dose at tissue surfaces, including contributions of scattered light (87).

Several aspects of mTHPC mediated PDT in MM are not sufficiently well characterised. The influence of drug dose, drug-light interval, fluence rate, total light dose...
and tumour tissue oxygenation levels in relation to PDT efficacy need further clarification. In addition, the question of normal tissue toxicity is of paramount importance for large volume PDT, such as for treatment of MM, where damage to normal organs could have a fatal outcome. Myocardial infarction and oesophageal perforation are examples of these potentially fatal complications.

PDT in the setting of adjuvant treatment after surgery in MPM has proven to be associated with a high incidence of serious side effects. Therefore only patients with good prognosis, who might reasonably be expected to benefit from an aggressive approach should be offered this combined modality treatment. Performance status should be considered a pivotal criteria in the decision to treat, because it is one of the most important prognostic factors in MM. Since both surgery and PDT are local treatments, the combination should be aimed at improving local control. This implies that only patients with localised disease should be treated and patients with more widespread or even metastatic disease have to be excluded from such treatment protocols.
REFERENCES

46. Baas P. Chemotherapy for malignant mesothelioma. Lung Cancer 2001; 34: Suppl 1, S12-14
The aim of this thesis is to investigate the value of photodynamic therapy (PDT) in combination with surgery for patients with malignant pleural mesothelioma. Basic mechanisms of PDT effects in tumours were studied in mice and normal tissue damage was investigated in a minipig and a rat model. Patient selection for treatment with intra-operative PDT was assessed by analysing prognostic factors and mediastinal lymph node involvement.

In chapter II the efficacy of mTHPC mediated PDT was investigated in relation to sensitizer dose, drug-light interval, fluence rate and total light dose. PDT response was assessed by means of tumour growth delay and cure of a human mesothelioma xenograft (H-MESO1) grown in nude mice. In addition the effect of carbogen and nicotinamide on tumour oxygenation and PDT response were studied.

In chapter III oxygen depletion before, during and after PDT using mTHPC was measured using polarographic needle histography. The extent of PDT induced hypoxia was also visualised by immunohistochemistry using the hypoxic marker EF3. Changes in extent of hypoxia during and after PDT were measured in cryostat sections of murine RIF1 tumours and H-MESO1 xenografts and results were compared with polarographic needle results for tumour pO₂.

In chapter IV PDT induced thoracic normal tissue damage was studied in minipigs and Sprague Dawley rats. The influence of drug dose, drug-light interval, and total light dose were studied and normal tissue damage was assessed histologically.

In chapter V prognostic variables were assessed in 51 patients with malignant mesothelioma (MM). Univariate and multivariate regression analyses were carried out for factors already known to bear prognostic importance. Serum levels of two cytokeratin markers, Cyfra 21-1 and Tissue Polypeptide Antigen (TPA), were also estimated and analysed for their additional value in predicting survival of patients with MM.

In chapter VI the value of Computer Tomography (CT) scanning and cervical mediastinoscopy (CM) were compared with final histopathological findings at thoracotomy or at CM. Both investigations were incorporated in the preoperative work up before combination treatment with surgery and mTHPC mediated PDT. Diagnostic performance was assessed for mediastinal lymph nodes accessible for CM.

In chapter VII PDT as an adjunct to surgery was studied in 28 patients with malignant pleural mesothelioma (MPM). The optimal mTHPC dose was selected in relation to toxicity and duration of local tumour control. Light dosimetry was performed on 4 positions in the chest cavity with the possibility to adjust the fluence rate during illumination.

In chapter VIII a summary of the studies in chapter II to VII is given together with a general discussion.
chapter 1

RIF1 tumour during illumination with laser light of 652 nm and simultaneous tumour oxygen measurement with the Eppendorf polarographic needle, chapter III

SD rat with open chest cavity illuminated with laser light of 652 nm and left lung gently pushed aside, chapter IV
A transparent plastic bag is filled with NaCl 0.9% at body temperature for better expansion of the diaphragm and mediastinal folds, Chapter VII

Diode laser and dosimetry device used for illumination and real time light dosimetry on 4 intrathoracic positions. Fluence rate (left column) and total light dose (right column) are displayed on a personal computer, chapter VII