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Multimodal therapy of malignant pleural mesothelioma: is the replacement of radical surgery imminent?

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Abstract

OBJECTIVES: Malignant pleural mesothelioma (MPM) remains an aggressive thoracic malignancy associated with poor prognosis. There is no standard treatment regimen, and particularly, the impact of radical surgery remains controversial. The main goal of our retrospective single-centre study was to evaluate the surgical and non-surgical treatment modalities applied at our division regarding their effect on the patient's survival.

METHODS: During the last decade, 82 patients with histologically confirmed MPM were treated at our division. The complete clinical records of 61 patients were eligible for statistical evaluation.

RESULTS: There were 14 women (23%) and 47 men (77%) with a mean age of 63.7 years. Epitheloid subtype was found in 48 patients (78.7%), sarcomatoid in 3 (4.9%) and biphasic in 10 (16%). Surgery as the first treatment modality was performed in 44 patients (72.1%). Pleurectomy/decortication was done in 28 cases (45.9%), extended pleurectomy/decortication was performed in 13 (21.3%) and extrapleural pneumonectomy in 3 (4.9%). Additional intraoperative photodynamic therapy was administered in 20 patients, 34 underwent chemotherapy (55.7%) and 12 had radiotherapy (19.7%). Mean survival time for the collective was 18.3 months. Five-year survival was 17% in the epitheloid histology group, where patients treated with chemotherapy alone yielded a significant increase in survival ($P = 0.049$), and those with other subtypes survived for a maximum of 20.6 months.

CONCLUSIONS: Chemotherapy and pleurectomy/decortication can extend the survival time of patients with MPM remarkably. The adequate treatment options have to be tailored to the specific particular needs of each patient considering histological subtype, tumour stage and patient's individual functional assessment as well as comorbidity.

Keywords: Mesothelioma • Pleural disease • Palliative care • Thoracic surgery

INTRODUCTION

Malignant pleural mesothelioma (MPM) is a rare and aggressive thoracic malignancy associated with poor prognosis as well as increasing incidence within the last 20 years.

Up to this time, a standard treatment algorithm for MPM has not yet been developed, and in particular, the role of surgery still remains controversial. Several studies suggested that trimodality treatment might offer a chance to prolong overall survival [1]. Innovative treatment options such as immunotherapy, gene or targeting therapy offer an experimental molecular approach and are still the subjects of further investigations [2].

We have been applying a multimodal treatment regimen for MPM that is individualized according to oncological, functional and anatomical findings. It comprises Pleurectomy/Decortication (P/D) as well as extended P/D, Extrapleural Pneumonectomy (EPP) with or without supportive intracavitary photodynamic therapy (PDT), systemic chemotherapy, external beam radiotherapy (EBRT) and chemical pleurodesis.

The primary objective of our retrospective single-centre study was to evaluate the efficacy of this multimodal treatment regimen, focusing on the influence of the different treatment options on patient's' overall survival. The secondary objective was to evaluate the impact of gender, life style, tumour subtype and grading as well as further prognostic factors on survival.

MATERIALS AND METHODS

Within a time range of 10 years, between January 2000 and December 2009, the records of 61 patients suffering MPM who were referred to our department, were available for evaluation. The observation period finished in 2011. This retrospective analysis was approved by the Local Ethics Committee.

Tumour staging was done according to the recent TNM system of the International Mesothelioma Interest Group (IMIG). Diagnosis was based on histology and immunohistochemical analysis, achieved by diagnostic video-assisted thoracoscopy (VATS). In case of peritoneal mesothelioma, diagnostic laparoscopy was done. Functional evaluation of the patients included ECG, spiro-ergometry, body-plethysmography and cardiac ultrasound. The oncological staging consisted of computed tomography (CT-scan), positron emission tomography (PET-scan) and bone scan.

In case of suspicion of distant metastases, ultrasound of the abdomen or magnetic resonance imaging of the liver was done. Mediastinoscopy for N2 disease was not performed.

Based on the results of the patient's functional evaluation and on the oncological staging, the further therapeutic approach was decided by the multidisciplinary tumour board. Patients with epitheloid histological subtype of MPM and IMIG stage I or II were presented for surgery at the earliest possible date. Adjuvant treatment such as intraoperative PDT or chemo- and/or radiotherapy, respectively, was equally scheduled by the tumour board.

Patients unfit or oncologically ineligible for surgery were offered pleurodesis, chemo- and/or radiotherapy.

Corresponding to the intrathoracic tumourous involvement, the following surgical techniques were applied individually in those patients who were presented for surgery. Those different surgical approaches were performed and described according to the recommendations for uniform definitions of surgical techniques for MPM of the International Association for the Study of Lung Cancer International Staging Committee and the IMIG [3].

Pleurectomy/decortication and extended pleurectomy/decortication

Pleurectomy/decortication (P/D) was done through a postero-lateral thoracotomy and therefore included the resection of the parietal and visceral pleura without ipsilateral diaphragm or pericardial resection.

P/D was termed 'Extended P/D' when the ipsilateral diaphragm and/or the pericardium had to be resected due to tumourous involvement. Pericardium and diaphragm were reconstructed using prosthetic patches (Gore-Tex PRECLUDE® Pericardial membrane; W.L. Gore & Associates, Inc, Flagstaff, AZ 86004; USA).

Regardless of the type of P/D used, all visible tumourous disease was removed sparing the underlying lung in order to obtain macroscopic tumour clearance ('cyto-reductive surgery'). Mediastinal lymph node dissection was done in our series routinely. The preferred way of performing that complete mediastinal lymphadenectomy was the same as we did in cases of surgery for non-small-cell lung cancer. We tried to dissect at least three different levels of mediastinal lymph nodes.

The main goal of both surgical approaches was to remove as much tumour as possible, enabling re-expansion of the trapped lung and prevention of further tumour-related pleural effusion.

Therefore, P/D was performed in cases of epitheloid MPM with tumourous involvement of the pleura without gross infiltration of the lung parenchyma or mediastinal structures. Extended P/D was considered in cases of epitheloid MPM with tumourous involvement of the parietal and the visceral pleura as well as tumourous infiltration of the ipsilateral diaphragm and the pericardium.

Extrapleural pneumonectomy

EPP included en bloc resection of the parietal and the visceral pleura with the ipsilateral lung (pleuro-pneumonectomy) as well as resection of the ipsilateral diaphragm and pericardium performed through a postero-lateral thoracotomy. Pericardium and diaphragm were reconstructed using prosthetic patches (Gore-Tex PRECLUDE® Pericardial membrane; W.L. Gore & Associates, Inc, Flagstaff, AZ 86004; USA). Complete mediastinal lymphadenectomy was done in the same manner as we did in case of (extended) P/D.

EPP was considered in cases of epitheloid MPM with additional gross tumourous infiltration of the lung as well as the mediastinal and pleural surfaces.

Additional intraoperative photodynamic therapy

Intracavitary PDT was performed during surgery after preceding EPP, D/P or extended D/P before the chest was closed in order to improve local tumour control at the resected intrathoracic surfaces. The mechanism of PDT, a non-thermal laser technique, is based on monochromatic illumination of malignant tissue after selective accumulation of photosensitizer in tumour cells resulting in local tumour necrosis. Therefore, the requirements for PDT are a photosensitizing drug, laser light of a wavelength appropriate to the sensitizer and the presence of molecular oxygen that has shown to be crucial for the photochemical reaction. The detailed mechanism of the function is described elsewhere [4].

Unlike radiotherapeutic or chemotherapeutic measures, the method is not limited by cumulative doses. Forty-eight hours before PDT, 2 mg/kg bodyweight of the photosensitizer, a haematoporphyrine derivative (Photofrin®75, Houdon, France) was administered intravenously.

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 residual tumour surface was calculated as 300 J. Illumination of the resected tumour area was done step-by-step, moving the microlens stepwise along a flexible sterile plastic grid applied very close to the intrathoracic surfaces.

Depending on the topography and the extent of the tumour-resected illuminated area, the delivery time took up to at least 90 min.

External beam radiotherapy

A dose of 40–50 Gy electron beam (2 Gy/day 5 days a week; mean 45 Gy) was applied to the affected hemithorax. EBRT was done as an adjuvant therapeutic option after surgery following P/D or EPP. However, in patients not eligible for surgery due to oncological or functional reasons as well as in case of non-epitheloid subtype, EBRT was administered following pleurodesis and/or systemic chemotherapy.

Systemic chemotherapy

Three cycles of systemic chemotherapy using Cisplatinum and Pemetrexed with substitution of folic acid and vitamin B12 were

offered as adjuvant therapy following P/D, first-line treatment instead of surgery in patients with non-epitheloid subtype or in those patients who were not eligible for surgery.

Pleurodesis

Pleurodesis for palliation was done in patients with recurrent malignant pleural effusion ineligible for surgery or in case of non-epitheloid subtype.

Prior to pleurodesis, a drain was inserted during diagnostic VATS and the effusion was evacuated. If the lung did not re-expand initially, suction drainage was continued for a maximum of 7 days to improve re-expansion.

Pleurodesis was done by careful application of a mixture of talcum and 50-ml doxycyclin-hydrochloride through a chest tube and subsequent clamping of the drainage for 6 h.

Statistical analysis

The following software packages were used: (a) SPSS 18 SPSS Inc, Chicago, IL, (b) StatXact 5.0 Cytel Corp, Boston, MA, and (c) nQuery 5.0, Statistical Solutions, Cork, Ireland.

Statistical tests were considered significant for P values <0.05. Percentages as presented in cross tabulations were analysed with Pearson's chi-square test using the exact option in SPSS or Fisher's exact test depending on the expectation values.

Continuous data were analysed with two-sample t-tests after checking for normality of the data and equality of the variances or Wilcoxon tests otherwise. Survival was calculated by the Kaplan–Meier life table method, and groups were compared by the Mantel–Haeszel log rank test.

The effect on survival was tested for the raw data set and also after adjustment for the main prognostic variables using the propensity score method.

RESULTS

We treated 14 women (23%) and 47 men (77%) with a mean age of 63.7 (range: 34–82) years. In 39 cases (63.9%), MPM was localized on the right, and in 22 (36.1%), on the left side.

At the time of admission, 60 patients (98.4%) had moderate to severe dyspnoea due to malignant effusion. Fifty-nine patients (96.7%) had ipsilateral thoracic pain. Five patients (8.2%) were admitted for pneumothorax. Shrinking of the affected hemithorax was found in 5 cases (8.2%).

A history of asbestos exposure was reported in only 25 patients (41.7%). In 37 cases (63.8%), daily consumption of alcohol was recorded, and 13 patients were smokers (22.4%). In the majority of cases, the patients were in a slightly reduced general condition. Comorbidity involved predominantly chronic obstructive pulmonary disease (19 cases [31.7%]) and coronary heart disease (11 patients [18%]).

MPM of the pleura was found in 59 cases (96.7%), whereas mesothelioma was localized in the peritoneum in 1 case. Two patients had mesothelioma of both pleura and peritoneum.

In 23 (41.8%) of 60 patients with malignant effusion, mesothelioma cells were found in the pleural fluid. Histological diagnosis was established by VATS in 55 (90.2%) and by laparoscopy in 3 patients (4.9%). Epitheloid subtype was detected in 48 (78.7%), sarcomatoid subtype in 3 (4.9%) and biphasic subtype in 10 patients (16%). G1 was found in 39%, G2 in 50% and G3 in 11%. Patients with G1 had significantly higher median survival than those with G2 or G3 (P = 0.019; Fig. 1).

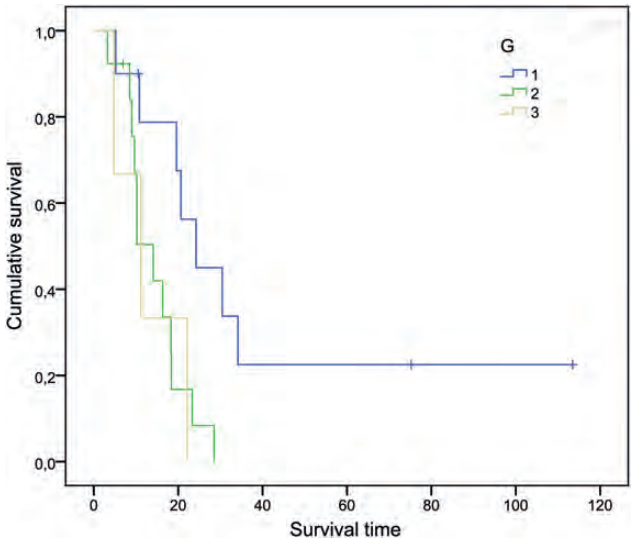

Figure 1: Kaplan–Meier curve showing the median survival of all 61 patients with malignant pleural mesothelioma regarding histologic tumour grading (P = 0.019).

Forty-four patients (72.1%) underwent surgery as the first-treatment modality. P/D was performed in 28 cases (45.9%) and extended P/D in 13 (21.3%), whereas EPP was done in only 3 (4.9%). Additional intracavitary PDT was administered in 20 patients of the surgery group (32.8%): in 17 patients following P/D or extended P/D and in those 3 patients following EPP.

Thirty-four patients were treated with systemic chemotherapy (55.7%): 17 of them had adjuvant chemotherapy following surgery, whereas 17 patients received chemotherapy as definitive treatment instead of surgery. In those cases, chemotherapy was combined with chemical pleurodesis and/or EBRT.

Twelve patients had EBRT (19.7%): 6 of them received EBRT as adjunct treatment after surgery, and 6 patients underwent EBRT as a definitive treatment modality instead of surgery. In those cases, EBRT was combined with systemic chemotherapy and/or chemical pleurodesis.

Finally, chemical pleurodesis was applied in 20 cases (32.8%): Pleurodesis was administered in those 17 patients who were not eligible for surgery. In the remaining 3 cases, chemical pleurodesis was performed postoperatively in order to reduce the temporarily increased pleural effusions through the chest tubes.

In the majority of all cases, several treatment options per patient were applied (Table 1).

In the postoperative period, pneumothorax (n = 8; 13.1%), haemorrhage (n = 6; 9.8%), impaired wound healing (n = 6; 9.8%) and pleural empyema (n = 5; 8.2%) were observed as surgical complications. Ten patients (16.4%) required redo surgery. There was no 30-day mortality.

Table 2 shows a detailed list of complications. No statistically significant influence of complications on survival was found.

Mean overall survival time was 22.3 months (median: 15.4 months). Female patients survived 41.4 months (range 17.6–65.3 months; median: 19.8 months) and male patients, 16.9 months (range: 12.7–21.0 months; median: 14.7 months); (P = 0.06; n.s.). At the end of follow-up, 10 of 61 patients were still alive (16.4%).

Table 1: Incidence of the different applied treatment options within the multimodal treatment regimen for malignant pleural mesothelioma in 61 patients

Treatment options	Number of patients	(%)
Pleurectomy/decortication	28	45.9
Extended pleurectomy/decortication	13	21.3
Extrapleural pneumonectomy	3	4.9
Intraoperative photodynamic therapy	20	32.8
Systemic chemotherapy	34	55.7
External beam radiotherapy	12	19.7
Pleurodesis	20	32.8

Table 2: Postoperative complications after surgery for malignant pleural mesothelioma in 44 of 61 patients

Postoperative complications	Number of patients	(%)
Pneumothorax	8	13.1
Haemorrhage	6	9.8
Impaired wound healing	6	9.8
Mucous obstruction	6	9.8
Pleural empyema	5	8.2
Venous thrombosis	4	6.6
Pneumonia	2	3.3
Chylothorax	2	3.3
Pulmonary embolism	2	3.3
Cardial failure	2	3.3
Myocardial infarction	1	1.6

Neither a history of asbestos exposure nor any kind of co-morbidity had significant influence on survival. Non-smoking patients, however, had significantly higher median survival than smokers (19.6 vs 10.1 months; $P < 0.0001$). No statistically significant influence of age, weight, height or site of the tumour on survival was found.

5 year survival was 17% in the epitheloid histology group (mean: 25.9 months; median: 18.3 months), whereas patients with other subtypes survived for a maximum of 20.6 months (mean: 10.1; median: 10.8 months). The difference was statistically significant ($P = 0.029$; Fig. 2).

Thirty-two of 61 patients had distant metastases at the time of diagnosis. They had a mean survival of 18.2 months (median: 14.7) compared with 25.6 months (median: 18.3) in patients without distant spread. The difference was not statistically significant ($P = 0.531$). At the time of death or at the last follow-up, a further 17 patients had developed distant spread.

Spread to the mediastinal lymph nodes was observed in 32 of 61 patients. Their mean survival was 19. Two months (median: 15.6 months) compared with 24.1 months (median: 14.2 months) without lymphatic spread ($P = 0.95$; n.s.). In the course of complete mediastinal lymphadenectomy, a mean number of eight lymph nodes had been dissected in every patient who had undergone surgery.

Neither surgical procedure had statistically significant influence on survival.

If the 48 patients with epithelioid subtype were considered separately, a statistically significant better survival of female

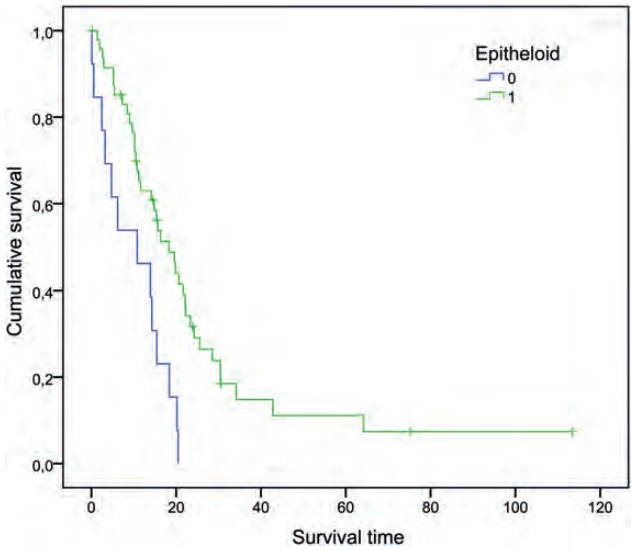

Figure 2: Kaplan–Meier curve showing the median survival of all 61 patients with malignant pleural mesothelioma regarding histologic subtype ($P = 0.02$).

patients was observed (median: 23.3 vs 15.3 months; $P = 0.029$). Patients with epitheloid histology treated with P/D survived longer than those treated otherwise (mean: 30.4 vs 14.2 months; median: 19.8 vs 14.7 months), however, the difference did not reach statistical significance ($P = 0.055$). The 3 patients who underwent EPP had a mean survival of 11.9 months (median: 11.1) compared with those treated otherwise (mean: 26.3; median: 25.6) ($P = 0.652$).

If only those 41 patients who had P/D were considered, it turned out, that neither additional chemotherapy, additional EBRT or intraoperative PDT had no statistically significant impact on survival.

Patients with epithelial subtype treated with chemotherapy but without P/D had a mean survival of 19.1 months (median: 23.3) compared with a mean of 10.4 (median: 10.7) in those who had no chemotherapy. The difference was statistically significant ($P = 0.049$; Fig. 3). In patients with other histological subtypes, chemotherapy showed no statistically significant benefit, regardless of the type of local treatment.

DISCUSSION

It has been shown that female patients had a better prognosis than men, and the epitheloid subtype showed that the best sarcomatoid subtype had the worst outcome, which could be confirmed by the findings in our study [5]. Although currently smoking is not considered to be a major causative factor in the pathogenesis of MPM, it seems to play a statistically highly significant role in survival. In non-smokers, we found a median survival 9 months longer than that of smokers ($P = 0.000$).

According to several studies, tri-modality treatment seems to offer a realistic chance to prolong overall survival [1, 6]. However, aggressive surgery had been postulated as the ultimate approach, promising a chance for cure [7]. It turned out that EPP was associated with increased mortality and morbidity if compared with D/P [8]. Therefore, the therapeutic approach for MPM has changed during the last 10 years and the pre-

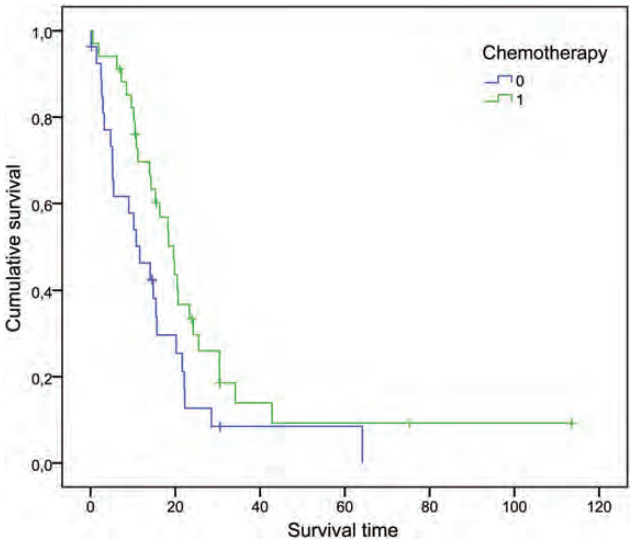

Figure 3: Kaplan–Meier curve showing the median survival of all 61 patients with malignant pleural mesothelioma regarding administration of systemic chemotherapy ($P = 0.049$).

eminence of aggressive and radical surgery has been widely abandoned in favour of a multimodal therapeutic approach [9].

Apart from functional considerations, most authors agree, that surgery for MPM should be reserved for patients with epitheloid histology reporting prolonged survival, which is comparable to our own results [5, 10]. P/D does not compromise survival and should be performed in favour of EPP [11, 12]. In spite of some enthusiastic reports, the question whether EPP is really superior to P/D is a matter of debate [13, 14]. It was found though that involvement of N2 nodes was associated with an accelerated course of disease and is therefore a contraindication to EPP [15].

In our opinion, the supreme goal of surgery for MPM should be to provide a complete resection of visible tumour tissue ('cyto-reductive surgery'), conditioning the patient for further treatment. This hypothesis is corroborated by Bölükbas who advocates P/D as a lung-sparing surgical option within the trimodality regimen with promising results in long-term survival, morbidity and mortality. P/D yields comparable results, while the patient's physiological reserve is maintained for further treatment options [16].

Despite attempts to use different multimodality therapies, MPM recurs in most patients because the mostly diffuse tumourous infiltration of the surrounding tissue strictly prevents a radical resection with histologically free resections margins corresponding to R0 resection. Even by applying extensive resection procedures like EPP, truly 'radical' resection without microscopic residual tumour will never be achieved, and even this ambitious type of surgery still remains a palliative one.

Depending on the extent of surgery for MPM and particularly in the case of EPP, postoperative morbidity and mortality may be increased unreasonably hazardously for the patient [8]. This is confirmed by the findings of treasure in the course of the MARS trial, which gives strong evidence that EPP offers no benefit and possibly harms patients [17]. This is why P/D had a better outcome than EPP with longer survival time when the resection was part of a multimodal approach [16, 18–19]. In our study, a prolonged survival of epitheloid MPM was observed following P/D and chemotherapy if compared with P/D alone.

Even without adjuvant non-surgical oncological treatment, radical P/D leads to a higher median survival than best supportive care (14.5 vs 4.5 months) and non-radical decortication (15.3 vs 7.1 months; $P < 0.000$), confirmed by Zahid [20]. For this reason and considering increased morbidity and mortality related to EPP, P/D has become the predominating surgical option for MPM at our department.

We decided on P/D in functionally fit patients with epitheloid subtype and IMIG stage I or II. Compared with non-resective treatment, a longer, but statistically not significant, survival was achieved.

Patients with non-epitheloid subtype and IMIG III or IV, reduced functional assessment and/or advanced age were considered ineligible for surgery and provided with best supportive care. Non-resective palliative procedures aim at an improvement of breathing, analgesia and a slowing-down of tumour growth. In our patients, chest tube drainage and pleurodesis, EBRT and chemotherapy were administered in a reasonable sequence.

Referring administration of systemic chemotherapy, the combination of pemetrexed and cisplatin has become the current standard of care [21].

Vogelzang could demonstrate that in patients ineligible for surgery, first-line treatment with pemetrexed plus cisplatin could significantly improve survival time, time to progression and response rate when compared with treatment with cisplatin alone [22].

These data were similar to the results of our study where in patients with epitheloid MPM, considerable prolonged survival with P/D and chemotherapy could be yielded, whereas statistically significant increased median survival was obtained with early chemotherapy alone ($P = 0.049$).

However, intraoperative PDT seems to experience a renaissance in the multimodal treatment of MPM. Since the beginning of 2000, several studies, even conducted at our department, documented the feasibility and the clinical impact of PDT, particularly in the palliation of MPM, resulting in statistically significant prolonged survival and symptom control [4, 23].

Friedberg and his group corroborated intracavitary PDT as an adjunctive component in the surgery-based multimodal treatment regimen allowing not only local tumour control but rather a PDT-induced stimulation of the patient's immune system resulting in a tumour-directed immune response [24].

In our series, we decided on intracavitary PDT in every patient after the preceding EPP, and in selected cases after P/D and extended P/D before the chest had been closed again. The main reason for PDT after EPP was to complete that way of extensive and radical surgery by the local as well as systemic antitumourous effect induced by PDT. After P/D or extended P/D, intracavitary PDT was provided for those patients who were eligible for surgery but not suitable for further adjuvant systemic treatment modalities (i.e. chemotherapy) due to advanced age, increased cardiac impairment or renal insufficiency, respectively. This is why intraoperative PDT was done in just 17 patients and not in all 41 cases of (extended) P/D.

However, the depth of penetration of the monochromatic laser light used (~5–7 mm) limits the active range of the cytotoxic effect of PDT, so the treatment effect is almost superficial. This is why, in our opinion, the most important aim of surgery for MPM should be to provide a complete resection of visible tumour tissue as much as possible. Nevertheless, PDT represents an ideal treatment for tissue surfaces and body cavities after

surgical treatment, which predisposes PDT as an effective adjunctive component to surgery for MPM allowing a sustainable anti-tumourous impact on the patient's disease-free survival as well as on the median overall survival.

We were able to confirm those clinical advantages of intraoperative PDT in case of MPM by the positive and encouraging results of two prospective trials conducted at our department some years ago [3].

Moreover, the multimodal approach will be completed by postoperative EBRT as an adjunctive treatment option following intracavitary PDT as we do at our department. MPM responds to EBRT and may be used for local tumour control, for the treatment of tumour-related chest pain and as a prophylaxis against tumour seeding at the sites of drainage.

Although a large number of publications describing its use as a supportive component within the multimodal treatment regimen are available, no randomized data exist considering the additive impact of EBRT after cyto-reductive surgery [25]. The limiting factors of EBRT are the irregular growth of the tumour along large surfaces and the necessity for high radiation doses resulting in dose-related toxicity to the underlying radiosensitive tissues [10]. In our collective, no statistically significant benefit of EBRT could be demonstrated.

However, the following conclusions should be drawn very carefully because of the relatively small sample size of our study group on the one hand and the heterogeneity of the patient's population on the other hand.

Considering our own findings, the main prognostic factors associated with statistically significant prolonged median survival are female gender, epitheloid subtype, high tumour grading and a history of non-smoking.

We may conclude that interdisciplinary treatment of MPM may result in improved median survival time with an acceptable quality of outpatient life, if a multimodal approach is chosen. The treatment options have to be tailored to the specific particular needs of each patient considering functional assessment as well as individual comorbidity, the histological subtype and the tumour stage, respectively.

Regarding the results of our study, we can postulate in accordance with recent international literature, that only patients with epitheloid MPM and IMIG stage I and II should undergo lung-sparing surgery within the multimodal treatment regimen.

There might be strong evidence that, particularly in patients with epitheloid subtype, prolonged survival can be obtained when P/D and chemotherapy are performed in combination.

Furthermore, we could clearly confirm that patients with epitheloid histology of MPM who were treated with P/D survived obviously longer when compared with those who were treated otherwise (mean 30.4 vs 14.2 months).

Due to the fact that our EPP group consisted of just 3 patients, this sample size is too small and allows no serious comparison with other groups. Therefore, we agree that EPP should be avoided in favour of P/D due to its increased morbidity and mortality, which is mainly based on the findings in recent literature [8, 17–19].

Considering our own findings, we could demonstrate that statistically significant increased survival was obtained when chemotherapy was applied as the sole palliative treatment in non-resectable patients. In our opinion, this fact clearly underlines the essential need for systemic treatment of MPM.

Innovative treatment options such as immunotherapy, gene or targeting therapy offer an experimental molecular approach and are still the subjects of further investigations that are definitely required.

Conflict of interest: none declared.

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