



Epidemiology, diagnosis and treatment of the malignant pleural mesothelioma, a narrative review of literature

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Abstract: The malignant pleural mesothelioma is a very aggressive tumor which is arising from mesothelial cells and is associated with asbestos exposure. It is a heterogeneous cancer that shows a complex pattern of molecular changes, including genetic, chromosomal, and epigenetic abnormalities. The malignant pleural mesothelioma is characterized by a silent and slow clinical progression with an average period of 20–40 years from the asbestos exposure phase to the start of the symptoms. Unfortunately, to date, the therapeutic options are very limited, especially if the tumor is detected late. This narrative review provides an extended overview of the present evidence in the literature regarding the epidemiology, diagnostic pathways and treatment approaches of the malignant pleural mesothelioma. The treatment of mesothelioma has evolved slowly over the last 20 years not only from a surgical point of view but also radiotherapy, chemotherapy and immunotherapy play nowadays a key role. Several surgical strategies are available ranging from extrapleural pneumonectomy to cytoreductive surgery but a multidisciplinary approach seems to be mandatory because a single approach has not proved to date to be resolute. New non-surgical treatment options appear to be promising but the results have to be taken in account with caution because clear evidence with high-quality studies is still lacking

Keywords: Malignant pleural mesothelioma (MPM); MARS, pleural disease

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Introduction

Malignant pleural mesothelioma (MPM) is an uncommon but very aggressive intrathoracic carcinoma associated with a poor prognosis (1). In most cases the final cause of death is unclear (2). Eighty percent of patients (3) with MPM have at some point been directly or indirectly exposed to asbestos fibers (4). The MPM stems from mesothelial cells of the pleura, followed by an infestation of the lung, the diaphragm and the pericardium (1). Initially the onset of the disease is gradual with an estimated latency period of 20–40 years after the initial exposure (5). Due to its aggressive nature, MPM is often diagnosed in a late stage of

disease and the remaining survival is significantly decreased. When untreated, less than 5% of patients survive 5 years, the average being 4–12 months post diagnosis depending on various factors such as age, histopathologic subtype, stage of disease, and other pre-existing comorbidities and therapies (6,7). The use of asbestos is nowadays banned in 55 countries worldwide, including the United States, Western Europe and Australia (8). Despite the ban there is still no measurable decrease of MPM, with new cases still appearing due to the late onset of the disease. On the other hand, the use of asbestos in developing countries is still increasing (8,9). Overall, it can also be assumed that there is a high number of unreported cases, especially in developing

countries (10,11). The World Health Organization (WHO) estimates that in 2004 approximately 107,000 people died from asbestos-related diseases like lung cancer, asbestosis and mesothelioma worldwide. It's also estimated that 12 times that amount of people (125 million) are exposed to asbestos fibers at work (12). Driscoll *et al.* showed in 2005 “The Global Burden of Disease Due to Occupational Carcinogens” that annually 43,000 people die from mesothelioma (13). The numbers suggest that every hour 5 to 10 people around the world die from mesothelioma or an asbestos-related disease.

One tragic example of mass exposure to asbestos in the recent past was 9/11. The World Trade Center collapsed, engulfing the streets of New York, thousands of its citizens, dousing them in dust full of asbestos fibers (14). The mass of the effects will show in the decades to come. Because of the late onset of this disease and the further use of asbestos fibers and currently not banned fibers, MPM will continue to be a challenge for healthcare systems worldwide, for decades to come (5). We present the following article in accordance with the Narrative Review reporting checklist (available at <http://dx.doi.org/10.21037/jtd-20-2761>).

Methods

This article is a hand searched narrative review of the literature. We searched PubMed for articles in English language on the following keywords alone or in combination: malignant pleural mesothelioma, treatment, surgery. Relevant papers and linked articles published between 1990 and July 2020 were included and screened.

Epidemiology

Asbestos started being used industrially in the 1880's (4). The use of asbestos became more popular in 1920. In the 1960's there was an increase of MPM due to unknown danger, circulating asbestos in the times before, during and after World War II (9,10). In industrialized countries the production and use of asbestos increased well into the 20th century, where the use of 6 out of 400 potential carcinogen fibers was regulated and banned. The strict regulated fibers can be assigned to two subcategories:

- Serpentine class (chrysotile);
- Amphibole class (amosite, crocidolite, tremolite, actinolite and anthophyllite).

All 6 fibers are grouped under the collective term of “asbestos”. The other fibers are yet to be regulated,

although it seems that many of them could also be carcinogenic (8,9). In the 1980's it was assumed that only commercially used fibers could lead to harmful exposure, due to this, only the previously mentioned 6 fibers were banned (15). Asbestos was primarily used in the building industry due to its resilient nature and low-cost production. More than 3,000 different products with asbestos components were manufactured (4,16). By outlawing asbestos in the European Union and other countries in 1999, world consumption dropped to an all-time low in the late 1990's. Simultaneously consumption increased in Asia, South America and Eastern Europe. Russia and China are currently two of the main producers and consumers of asbestos (8,16). Since 2005, the production and consumption of asbestos is fully banned in the European Union (17,18). Allen *et al.* showed that the ban of asbestos did not have a negative long-term effect on the economy's growth, potentially reducing healthcare cost for the future. The careless handling of asbestos in the past is estimated to result in healthcare expenditures of US \$ 2.4–3.9 billion per year worldwide (16). Lin *et al.* proved with a comparison of data from 1960–1969 and 2000–2004 that the mortality rate of MPM was significant higher for men roughly 37.5 years after the time in which the production/use of asbestos reached its pinnacle (19).

Pathophysiology

Exposure to asbestos can occur during childhood, naturally or environmentally. If the patient is a carrier of an inherited germline mutation, men and women show nearly a 1:1 distribution with an early onset (<55 years) of asbestos related disease and an increase of mesotheliomas (8,9,20,21). Vivero *et al.* compared 36 young [<35 years, w (47%) *vs.* m (53%)] with 48 elderly patients [>35 years, w (13%) *vs.* m (87%)]. The histological transmission in both test groups was not significant. In older patients mostly a biphasic (40%) or sarcomatoid (4%) histology was found. However, in the younger study group most MPM had an epithelioid histology (78%), biphasic (19%) was the second most frequent histology and the least frequent histology was sarcomatoid (3%). Previous radiation therapy was more common in younger patients, as their exposure to asbestos was more limited, than that of older patients. This finding suggests that a previous cancer history and radiotherapy could be a risk factor for developing MPM in young patients (21). Other studies suggest that an inherited BRCA1-associated protein 1 (BAP1) mutation is associated

with an increased probability of MPM after exposure to asbestos, which is also described as gene \times environment interaction [GxE] (9,22). Carbone *et al.* reported that BAP 1 seems to have an important role in the development of mesothelioma. They analyzed two families in which a significantly increased mesothelioma rate occurred. In both families there was an inherited germline mutation of the BAP1 gene found, which seems to have dramatic influence on tumor growth (9).

Furthermore, in more than 60% of the cases a BAP1 mutation seems to be the current most mutated gene in patients with mesothelioma (23). Relating to this, Bononi *et al.* summarizes the important role in tumor growth of BAP1, in form of an influential tumor suppressor gene. They describe that descendants to whom the mutation is inherited, often develop at least one BAP1 associated tumor disease in their life, which is, in most cases, a malignant mesothelioma (24). Baumann *et al.* reported, even if in a small patient collective, that in 40% of cases MPM patients with a germline BAP1 mutation had more than one type of cancer, but that they also had a 2.3-fold improved 5-year survival rate, compared to patients without this mutation. Among other things, this could be because of an earlier diagnosis (25). A mutation in genes which repair damaged parts of the DNA can have devastating effects. Genes like BRCA2, MLH1, MLH3 and TP53 in a damaged form, often result in tumor growth. Recent studies show that oxygen radicals, which are caused by chronic inflammation, from the deposition of the asbestos fibers, could be the reason of tumor expansion (9). This inflammation could induce the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) and the phosphatidylinositol 3-kinase (PI3K) pathways inducing an uncontrolled growth of mesothelial cells.

Histology

Meyerhoff *et al.* showed 2015 in a review, which histological subgroup (sarcomatoid, biphasic and epitheloid) benefited from surgical therapy and which did not. They used data of the Surveillance, Epidemiology, and End Results (SEER) program, this is a program from the United States National Cancer Institute. They analyzed data only from patients with known histology from 2004–2010. Most patients were older than 70 years old, had a MPM on the right side of the chest, where male and fair skinned. Most patients had an epitheloid subtype [811 out of 1,183 (69%)], the second most common was

the sarcomatoid subtype [224 out of 1,183 (19%)] and least frequent was the biphasic subtype [148 out of 1,183 (12%)]. The median overall survival differed, patients with sarcomatoid histology died earlier (within 4 months), then the patients with biphasic histology (10 months) and patients with epitheloid histology (14 months) (9,26). Compared to patients, which had a surgical treatment showed a median survival of 4 months with sarcomatoid histology, 12 months with biphasic histology and 19 months in the group of patients with epitheloid histology. In the group of Patients with no surgical treatment median survival was 3 months in patients with sarcomatoid histology, 10 months with epitheloid histology and 12 months with biphasic histology. Although the number of cases was not the same for all groups, results suggest that patients with epitheloid histology could possible benefit the most from surgical treatment, and patients with biphasic histology may could be at a disadvantage. The authors also reported data from the IASLC, of patients which underwent an operation, this data indicates a median survival of 8 (sarcomatoid histology), 13 (biphasic histology) and 19 (epitheloid histology) months (26). Brims *et al.* reported of a median survival of 7.5 months in patients with sarcomatoid histology, 9.1 months in Patients with biphasic histology and 14.8 months in patients with epitheloid histology (27). Recent studies show a subgrouping of the individual histologies (C1 and C2). With different molecular profiles, gene modifications and survival outcomes (28).

Diagnostic

The manifestation of the MPM is displayed with unspecific symptoms such as shortness of breath (caused by pleural effusion), chest pain, fatigue and a dry cough. However, the typical B symptoms can also appear. The next step, after an accurate medical history and physical examination, should be an X-ray and/or CT of the thorax, or a non-invasive ultrasound of the pleura. Pleural plaques on X-ray were evident in more than 80% of cases from patients with asbestos exposure and MPM. It is common after the first line of diagnostic, to scrutinize the pleural effusion by a cyto-/histological examination. Because of low sensitivity, fine needle biopsy is commonly not recommended (29). For Carbone *et al.*, pleural effusion is the first material to be obtained, here the experience of the examiner is crucial, because the sensitivity can vary from <5 to >90%. A Thoracoscopic biopsy is a possible means to drastically

improve accuracy. After the diagnosis of MPM, a second assessment should be carried out by an experienced specialist, but even when using highly sensitive and specific methods such as immunohistochemistry (IHC), a misdiagnosis cannot be ruled out (9). As stated by the ERS/ESTS/EACTS/ESTRO task force, VATS pleural biopsies (similar to the medical thoracoscopy) carry a sensitivity of 95%, specificity of 100% and negative predictive value of 94% offering the possibility to secure a pathological diagnosis, assess the pleural cavity for staging purposes and perform a talc poudrage (30). There are three known histological subtypes of MPM: epithelioid, sarcomatoid and biphasic. According to the recommendations of the American Society of Clinical Oncology, an individual patient-specific diagnosis should be made. To carefully differentiate an MPM from a carcinoma or sarcoma, a cytological and immunohistochemical examination is crucial because a misdiagnosis would have far-reaching consequences for a patient. If symptomatic pleural effusions are present, ultrasound-guided thoracentesis with subsequent cytopathological examination should be performed as one of the first diagnostic steps; however, owing to its low sensitivity, a cytopathological examination of the pleural effusions can correctly diagnose only less than one-third of MPM cases (31) [it is most sensitive in patients with epithelioid histology (32)]. Furthermore, a drainage of the pleural effusions helps to reduce symptoms such as chest discomfort or dyspnea. With the requirement of making as few incisions as possible in the area of the subsequent operation side in order to prevent parietal tumor spreading, if these procedures are not possible, a fine needle biopsy is recommended despite its low sensitivity. Thoracoscopic biopsy, open pleural biopsy or fine needle biopsy helps to conclude the clinical staging to determine the histology. Cases should be subdivided according to histological differentiation, because for example, the SEER database indicates that among patients who underwent surgery, patients with an epithelial subtype had a median survival of 19 months, whereas patients with biphasic and sarcomatoid subtypes had a median survival of 12 and 4 months, respectively. IHC could be used as a tool for differentiating between MPM and other carcinomas. For example, in MPM, positive immunohistochemical results are observed with Wilms tumor protein 1, keratins 5/6, podoplanin and calretinin. However, patients with MPM with a loss of BRCA1-associated protein (BAP1) seem to have a better prognosis (33). On the other hand, there are negative immunohistochemical results in patients with

MPM, for example, epithelial cell adhesion molecule, carcinoembryonic antigen, blood group 8, napsin A, thyroid transcription factor 1 and Claudin 4. Another approach to differentiate between MPM and other carcinomas is to test for specific markers for differential diagnosis (34,35). Furthermore, fluorescent *in situ* hybridization could indicate a genomic loss of p16/CDKN2A locus at 9p21 in patients with MPM (36).

Staging

Staging-scores and systems were numerous in the last decades. Due to poor data availability, the International Association for the Study of Lung Cancer (IASLC) has set itself the task to build a proofed and validated database. The current 2nd Edition by IASLC 2016, includes data from 1995-06/2013. For the 8th Edition of the Lung Cancer Staging System, by the IASLC, the data of 2,460 out of 3,519 Patients with MPM from 29 Institutes, from 4 different continents were analyzed. The collected data serve as the basis for the changes in the staging and TNM categories of MPM, which are presented in the 8th Edition of the Lung Cancer Staging System, by the IASLC. As with other tumor diseases, the MPM is classified according to a TNM classification, which then results in a stage classification from Stage IA - Stage IV (37). Owing to the small number of cases, it is difficult to create a staging system that is widely accepted. The first staging step should be a CT scan of the thorax and the upper abdomen with IV contrast medium in order to identify baseline characteristics. If the clinical radiologist is familiar with modified Response Evaluation Criteria in Solid Tumor (RECIST) and has the expertise available, T-staging can be performed by measuring according to modified RECIST for mesothelioma (38-40). Data of measurements of tumor thickness (TT) can be used to demonstrate the response of the ongoing therapy. To avoid inter-observer variability, a single radiologist or a defined team of radiologists should perform the analysis for all patients (40,41). In patients who are candidate for surgery a FDG PET/CT should be performed because, in approximately 10% of cases, it could identify metastatic spread, which is not detected by CT scan. FDG PET/CT helps to distinguish malignant differentiations from benign forms (42,43). Furthermore, the extent of FDG absorption is prognostic for outcome. If CT scan of the thorax/abdomen or PET/CT shows structures suspected to be metastatic, a CT scan of the abdomen with IV and oral contrast media is recommended.

However, cerebral metastases are rare and should therefore be explored only in the presence of symptoms. Because symptoms of MPM such as dyspnea and shortness of breath, are promptly clarified, there is often no distant metastasis at the time of diagnosis. However, the ipsilateral chest wall, contralateral pleura and peritoneum may be affected at the time of diagnosis. Particularly, if the carcinoma has invaded into the mediastinum, diaphragm, thorax or other areas, a CT scan is often not as accurate as required. In such cases, if the patient is still a candidate for surgery, an MRI with IV contrast medium should be performed to reveal infiltrative structures in the soft tissue; however, the MRI is more expensive and needs more expertise of the observer, than a CT scan (44). In addition to radiological examinations, invasive staging techniques are required to confirm the radiological diagnosis with a subsequent cytopathological analyses. For example, EBUS-guided fine-needle aspiration has a higher specificity and sensitivity in nodal variations than cervical mediastinoscopy (45). Thoracoscopy provides crucial information's about histologic subtype and molecular expression but, in cases of radiologically suspected mediastinal lymph nodes metastasis or contralateral carcinoma, it could play a key role in the decision-making process. Moreover, laparoscopy can be used as a staging method to supplement the data from radiological imaging, especially in cases in which the carcinoma extends through the diaphragm [T4] or if intraabdominal manifestation is expected (46,47). According to the IASLC, an ipsilateral involvement of intrathoracic lymph nodes indicates N1 disease. Because most lymph nodes are difficult to access, the accuracy of clinical diagnosis is limited. T-staging can be challenging, especially in the early stages of the disease, because there is often a discrepancy between radiological diagnosis and pathological staging. In radiological examinations, it is often difficult to measure the exact depth and spread in the pleural space, indicating that patients with clinical stage I/II cancer may need intraoperative upstaging. On the contrary, usually only a CT scan of the thorax is needed for patients who are not candidate for surgery but are suitable for chemotherapy alone and/or radiotherapy and/or immunotherapy in order to evaluate the response to treatment.

Prognostic factors

Different scoring systems can be found in the international Literature even if they have been extrapolated from retrospective studies. The greatest advantages given by

prognostic scores is the possible use of an individual case based, patient-oriented therapy, which could improve outcomes (29). Brims *et al.*, reported in their publication, with a collective of 482 patients including patients with MPM from 2005–2010 and from 2011–2014, weight loss (classified as significant by a medical professional) as one of the most important predictive factors. Patients who did not lose weight, had a hemoglobin >153 g/L and a serum albumin >43 g/L, had the best survival rate at 18 months and a median survival of 34 months. Patients with sarcomatoid histology and recorded weight loss only had a median survival of 7.5 months (27). Opitz *et al.*, presented their Multimodality Prognostic Score (MMPS) which names 3 prognostic factors pre-chemotherapy: volume of the MPM (>500 mL), CRP >30 mg/L and a confirmed histological non-epithelioid subtype. A progressive disease of MPM as a negative prognostic post-chemotherapy factor in their score is also mentioned. The analyses showed a significantly shorter overall survival of patients, with a score greater than 3 (48). Sugarbaker *et al.*, analyzed other prognostic factors in 2010: female gender, age of 56 years or younger, histological secured epithelial tumor, normal blood parameters (hemoglobin, white blood cells and platelets) before operation (1). In addition, there are prognostic factors mentioned in other publications like the restriction of the tumor to one half of the thorax, missing evidence of histological lymph node involvement and a slight cancer spread (29). de Perrot *et al.*, showed in their data analysis the possible role of the TT on the survival rate. The patients underwent an extra pleural pneumonectomy (EPP) after a high-dose radiation of the affected thorax. In their data analysis, they found that both tumor volume (<500 cm³ + epithelioid histology) and diaphragmatic TT (<2 cm) had an impact on median and disease-free survival (49).

Surgical treatment

The actual importance of surgical treatment is unclear, it seems that only some patients benefit from an aggressive therapy, but it appears reasonable to perform mesothelioma surgery only in MPM high volume centres, due to the perioperative risks and different experiences (50). Sugarbaker *et al.*, showed in 2010 that a multimodal therapy of patients with MPM, with a surgery-based therapy (EPP) was associated with a long-term survival rate over 3 years in 18% of the patients (117 of 636) (1). The role of surgical treatment was shown by an end result study of 14,228 patients published in 2015, which showed that a surgical

treatment alone, was significantly associated with survival. Patients who undergo surgery lived significantly longer if compared with patients who undergo radiotherapy or do not receive any therapy (51). An EPP is an extended operation, which includes an *en bloc* resection of the entire lung, the visceral and parietal pleura, the pericardium and diaphragm. Furthermore, it is necessary to resect lymph nodes, which are found along the intercostal structure in the mammary chain, in addition a radical mediastinal lymphadenectomy is needed. To prevent herniation, it is of utmost importance to reconstruct the pericardium and diaphragm with patches. Some surgeons believe that the maximal macroscopic cytoreduction (MCR) of the tumor should be the goal of the surgical treatment as in other oncological treatment settings (29). Brims *et al.*, reported in their publication about a small group of 12 patients who underwent EPP with a median survival of 19.5 months (5.5–33.5) (27). It also seems that patients could benefit from a combination of therapy options. In addition to the MCR due to EPP, therapy of micro metastasis is paramount. This result is only reachable with a multimodal therapy of the MPM (52). With advanced operative techniques, the perioperative care is very important. Invasive hemodynamic monitoring and a selective use of bronchoscopy is common. Furthermore, a protective lung ventilation is needed to prevent acute respiratory distress syndrome. An adequate perioperative management also includes an intensive care unit team with understanding of the special needs of patients after pneumonectomy (29). Sugarbaker *et al.* reported in a study with 328 patients that the most common complication after extrapleural pneumonectomy is reversible atrial fibrillation, which was seen in 145 out of 328 patients, this shows the importance of a prophylaxis of atrial fibrillation which was not part of this study. The most common postoperative complications associated with death are pulmonary embolism, ARDS and myocardial infarction (53). Opitz *et al.* name heart failure, pulmonary embolus, septic multiple organ dysfunction syndrome (MODS), pneumonia and gastric necrosis as death-associated causes after EPP (48). The ERS/ESTS/EACTS/ESTRO task force which included several experts in MPM research and management elaborated an algorithm where the central point is: is the patient suitable for a macroscopic surgical resection (MCR) in the context of a multimodality treatment including chemotherapy and radiotherapy. If the patient is too frail for MCR, a partial resection with a palliative surgical approach is possible. The MPM (MesoVATS) trial was published in *Lancet* in 2014, it was

designed as a multicenter, controlled and computer randomized open label trial. It compares the costs and the overall survival of patients after different therapy options. In this trial a talc pleurodesis was compared with a video-assisted thorascopic partial pleurectomy (VAT-PP). 196 Patients were recruited from 10/2003–01/2012, 175 of them had a confirmed pleural mesothelioma. In the end out of 175 patients, 73 patients were treated with talc pleurodesis and 78 with VAT-PP. The cohort of the talc pleurodesis had a better overall survival after the first year with 57%. In the VAT-PP group the 1-year survival was merely 52%. Furthermore, the talc pleurodesis cohort had less surgical complications (14%) than the VAT-PP cohort (31%). Besides that, VAT-PP treatment was 5,000\$ more expensive than the comparable costs of a talc pleurodesis. However, the study showed that the quality of life of those from the VAT-PP cohort was better after 6 months, than in patients who underwent a talc-pleurodesis. In synopsis of all results the authors does not recommend VAT-PP for treatment in patients with malignant pleural mesothelioma. Talc pleurodesis is considered a better option due to a lower complication rate and a shorter hospitalization (54). If the patient is fit enough MCR should be performed. The MARS trial tries to answer the question which surgical technique has the best outcome. The Mesothelioma and Radical Surgery (MARS) trial, published in 2011, compares the survival of patients who undergo a triple therapy (a combination of chemotherapy plus EPP plus radiotherapy) with patients who undergo chemotherapy and no EPP. The MARS trial was a multicenter randomized controlled trial, which showed a median survival of the EPP cohort of 14.4 months (5.3–18.7) and a median survival of the no EPP cohort of 19.5 months (13.4–lifetime exceed observation time). In this study patients undergo a triple therapy; 112 patients were included from 10/2005 to 11/2008 and all of them had a platinum-based chemotherapy. Less than half of patients [50] were computer based randomized, 24 should get an EPP, in the end 16 patients underwent an EPP and 8 of them got radiotherapy. Two patients died in less than 30 days and one patient died during hospitalization. Twenty-six of fifty patients had no EPP. The quality of life analysis showed no significant difference in either cohort, patients of the EPP cohort however had a worse outcome than patients of the no EPP cohort. In summary, the authors concluded that EPP is not a recommended treatment for the next trial, it seems that a triple therapy does not offer advantages, rather it may impair patients (55). The results of this study show one time more, that a

randomized trial seems to be difficult or not to be workable and that selection bias are more common in trials with small patient collectives. Due to results from the previous MARS trial, there is currently a new trial, the MARS 2 study which compares standard chemotherapy (combination of pemetrexed and cisplatin) alone with surgical treatment [extended pleurectomy decortication (EPD)] including the standard chemotherapy, designed as a randomized trial. The aim of an EPD is the removal of all macroscopic visible tumor mass, a decortication of the lung and the pleura. If there is tumor mass at the diaphragm and/or pericardium it will also be removed. We expect results from the current study in the next few years (56). A long-term Meta-Analysis, which spanned a period of almost 30 years showed, that the median overall survival in the pleurectomy/decortication (P/D) group and the 30-day mortality in the EPP group is significantly higher (57-59). In addition, there were more perioperative complications in the group of EPP patients (57,58,60), besides that patients after P/D have a higher forced vital capacity (FVC), forced expiratory volume (FEV1) and quality of life (QoL) (61). Even if the results seem devastating, there is still a place for EPP today. Trials show also acceptable mortality and morbidity rates for a selected group of patients in the context of multimodal therapy at high-volume centres (62-64). The MesoTRAP trial was published in 2018, it's a randomized controlled, pilot multicenter feasibility study. Which compares the treatment of video-assisted thoracoscopic partial pleurectomy decortication (VAT-PD) with an indwelling pleural catheter (IPC) in patients with pleural effusion and significant trapped lung by confirmed MPM. Included in the trial were only patients eligible for both treatment options. In the advanced stage of the disease many are affected by and suffer severe respiratory symptoms, therefore their aim is to specifically explore treatment of patients with trapped lung within MPM. The Aim of the feasibility study was to randomize and recruit 38 patients within 18 months, if these patients aren't impaired by trial interventions, they would like to set up a phase III trial. The main goal of the feasibility study is to determine the standard deviation (SD) of VAS scores for dyspnea, over the entire observation period. The main subordinate goals are the exploration of the subjective quality of life during different phases of the study and the survival rates of the patients. Results from current studies are expected in a few years (65). A study by Opitz *et al.*, examined the approach of a fibrin-cisplatin mixture, for intracavity application after (extended) pleurectomy/decortication. Twelve patients were included

in their study, 8 of whom had previously received a systemic cisplatin and pemetrexed based chemotherapy. Out of the 12 patients there were 5 subgroups with 4 different concentrations of fibrin-cisplatin mixture. Initially, all patients underwent an (extended) pleurectomy/decortication. Thereafter, all resection surfaces were sprayed with a fibrin-cisplatin mixture under video assistance. After surgery and the spraying of the fibrin-cisplatin mixture, there was no other treatment. Compared with other trials, which use hyperthermia, which was not used in this trial, and intracavitary cisplatin perfusion, the renal toxicity was reduced. No fatalities were observed in the first 90 days of observation. Furthermore, the trial showed an overall survival of 10–31 months with a median of 21 months. However, the available data show that an intracavitary therapy with a mixture of cisplatin and fibrin is safe up to the maximum concentration of 44 mg/m², which was tested in this trial. Due to the limited test group, the results are of limited use. For this reason, a phase II study is currently being run to generate more data and to confirm the effectiveness of this new therapy option (66).

Chemotherapy

A multimodal therapy regime also can include a chemotherapy, besides that chemotherapy could be an option in macroscopic or radiological not respectable MPM. Different combinations of chemotherapy are used; Vogelzang *et al.*, reported that a combination of cisplatin and pemetrexed can help to improve the overall survival, progression-free survival and response rate compared with a single-agent therapy with cisplatin (67). The South West Area Mesothelioma and Pemetrexed (SWAMP) trial compared patients who received a combination of cisplatin and pemetrexed with patients who chose best supportive care (BSC), demonstrating that patients treated with the combination therapy had fewer symptoms and improved HR QoL at 16 weeks (68). In the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS), triple therapy (standard pemetrexed/cisplatin + bevacizumab) showed improved overall survival and progression-free survival (69). However, because of insufficient data, there is no clear recommendation; it may improve survival in certain groups of patients without contraindications to bevacizumab. In patients responding to therapy or with stable disease, pemetrexed-based chemotherapy should be performed with pauses after 4–6 cycles. A multicenter trial showed that patients treated with a combination therapy of EPP,

adjuvant hemithoracic radiation therapy and neoadjuvant chemotherapy with platinum/pemetrexed had a 2-year overall survival of approximately 61% with a median survival of 29.1 months (70). Another trial showed that combination therapy with raltitrexed/cisplatin also improved the overall survival of patients compared with treatment with cisplatin alone (71,72). In patients with unresectable MPM who cannot tolerate cisplatin, it is possible to substitute cisplatin by carboplatin as data suggest a similar effectiveness. A Chemotherapy can significantly reduce symptoms such as pain and dyspnea, thus improving the quality of life (QoL). In a previous study, in patients with a ≤ 2 performance status (PS), systemic combination chemotherapy with platinum plus pemetrexed, with vitamin (B12) and folic acid supplementation to reduce toxicity, was used as first-line therapy, which led to nausea (14.6%), leukopenia (17.7%) and grade $\frac{3}{4}$ neutropenia (27.9%). Compared with a cohort treated with single-agent therapy with cisplatin, the cohort treated with combination therapy showed a higher response rate (41.3% vs. 16.7%; $P < 0.001$), median overall survival (12.1 vs. 9.3 months; $P = 0.020$) and progression-free survival (5.7 vs. 3.7 months; $P = 0.001$). The median number of cycles of the combination therapy was six (67). Other therapy options can be offered as part of clinical studies. In the case of patient groups with a worse performance status ($PS \geq 2$), single-agent chemotherapy—for example, with pemetrexed, vinorelbine or gemcitabine—is feasible. Patients who are not eligible for therapy should receive palliative care. If the PS of the patient is ≥ 3 , palliative care is indicated. For patients who reach disease control with pemetrexed-based chemotherapy as first-line therapy and need second-line therapy, pemetrexed-based chemotherapy is an option (73,74). Ideally, these therapies should be given in clinical trials. In all other cases, vinorelbine treatment may be used (75). In certain cases, with epithelial histology and asymptomatic patients, an observational trial with close monitoring can be carried out before starting therapy. However, O'Brien *et al.*, showed that early chemotherapy helps to extend survival and increase the period of symptom control (76).

Radiation therapy

In special cases, adjuvant/neoadjuvant radiation therapy can be offered to patients who are planned to undergo EPP. Ideally, this therapy should be carried out in trials at experienced centers (77,78). The Intensity modulated pleural radiation therapy (IMPRINT)-trial showed an

effect of radiotherapy who underwent a multimodal Therapy with chemotherapy and P/D (Phase II Study of Hemithoracic Intensity-Modulated). Especially patients with a respectable epithelioid MPM can benefit from an accelerated hemithoracic intensity modulated radiation therapy (IMRT) followed by an EPP (Accelerated hemithoracic radiation followed by extrapleural). Radiation techniques such as IMRT or three-dimensional (3D) conformal radiation therapy (CRT) can help to precise and control the radiation dose (79,80). Clinical trials have reported dissimilar results; Rusch *et al.*, reported a local control of up to 97% (78), whereas other trials reported a local control of up to 40–71%, with a 2-year overall survival of up to 18–57% (64,81–83). Side effects of radiation therapy include radiation-related lung damage in particular, which often affects the contralateral lung (84); reduced toxicity was observed, by decreasing radiation doses in combination with rising experience (80,85). Patients who undergo a surgical procedure such as lung-sparing cytoreductive surgery (P/D or extended P/D) should not be given neoadjuvant radiation therapy owing to the high toxicity. However, adjuvant intensity-modulated radiation therapy in clinical trials at experienced centers is feasible in certain cases. New techniques such as IMRT make it possible to reduce the toxicity for untreated tissues through targeted use of radiation. Rosenzweig *et al.* reported that the risk of pneumonitis grade 3 or higher is approximately 20% (86). The larger the irradiated area (≥ 5 Gy), the greater the risk of radiation damage to the lungs with the development of pneumonitis (87). Taking into account the standard dosimetric guidelines for organs, adjuvant or neoadjuvant hemithoracic radiation therapy with techniques such as IMRT, 3D CRT or proton therapy may be offered at specialized centers and/or in clinical trials. Preventing implantation metastasis with prophylactic irradiation is not recommended. There is no significant effect of survival or quality of life after prophylactic radiotherapy, in patients with MPM after a pleural intervention (88,89). On the other hand, Boutin *et al.* showed with a small collective of patients that there were more subcutaneous nodules in the patients who did not undergo a prophylactic radiotherapy (90). However, for patients with implantation metastasis, as observed in histological examination, adjuvant radiation therapy should be offered. On the other hand, small trials did not show statistically significant results. The proponents of this therapy option cite a study by Boutin *et al.*, which reported that patients who received radiotherapy (21 Gy in three consecutive fractions) together

with thoracoscopic intervention had no implantation metastasis 10–15 days post intervention; without radiation, metastasis was observed in 40% of the cases (90). If radiation therapy is used, electrons are effective for superficial targets and implantation metastasis. In cases of local asymptomatic recurrence, patient-adapted therapy should be used. A decision should be made by a multidisciplinary team; all therapy options should be considered, and the best option should be offered to the patient. Radiation therapy can help to achieve local control, for example, with IMRT at centers of excellence. Radiation therapy (2D, 3D, IMRT, or electron) can be used in palliative care to reduce symptoms. Standard procedures used for other diseases can be used, for example, 3 Gy × 10 fractions, 4 Gy × 5 fractions or 8 Gy × 1 fractions. In patients who undergo a palliative care, long-term toxicity as with stereotactic body radiation therapy lose importance (91-93). Data from the Symptom Study of Radiotherapy in Mesothelioma (SYSTEMS-1) showed optimal results for pain reduction in 47% of patients with a total dose of 20 Gy in five fractions (4 Gy × 5 fractions) (93).

Conclusions

Although therapies are improving and mortality rates are decreasing “the most efficient way to eliminate asbestos-related diseases is to stop using all types of asbestos.” Statement WHO 2014 (94). Desirable would also be if further large-scale studies on the treatment options of the MPM were carried out. In the future the histology and genotype should be a main focal point. Furthermore, patients with MPM should, if possible, be treated as part of study protocols at high-volume centers in order to collect further data for the future. If that’s not possible data of the patients should be collected and presented in the context of smaller studies or case reports. For the best possible data collection and best prognosis of the patient, the therapy of patients with MPM should be discussed by an interdisciplinary team of pathologist, oncologists, radiotherapists and surgeons at a medical center with special knowledge or as a part of a study. Histological differentiation should be part of a therapy concept of MPM, as shown some histological subtypes affect the outcome of the therapy.

Discussion

This article is a narrative review. Therefore, a certain

subjectivity in choice of studies included is likely. In narrative reviews like this one, the large number of sources and studies which are cited accepts that there is a complexity of interactions. The identification and integration of those could be difficult.

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