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Pleural Mesothelioma

Recommendations from the society for diagnosis and therapy of haematological and oncological diseases

DGHO DEUTSCHE GESELLSCHAFT FÜR HÄMATOLOGIE UND MEDIZINISCHE ONKOLOGIE

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- Conflict of interests

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1 Summary

Pleural mesotheliomas are rare tumors of the pleura and are responsible for approximately 1% of cancer deaths in men and 0.3% of cancer deaths in women in Germany. The relative 5-year survival is clearly unfavorable at 8% in men and 13% in women. The average age of onset is 74 for women and 75 for men. Approximately 1,600 people are newly diagnosed with pleural mesothelioma every year. The main risk factor is exposure - usually occupational - to asbestos fibers, especially to asbestos that is only weakly bound to building materials and has a high fiber content.

Clinically, the disease often manifests itself with pleural effusions, thoracic pain and dyspnoea as well as a non-specific reduction in physical performance and/or weight loss. Pleural mesothelioma caused by asbestos can be recognized as an occupational disease by the accident insurance institutions.

The treatment of pleural mesothelioma basically consists of local treatment options and systemic treatment. The procedure primarily depends on the histological subtype and the spread to lymph nodes as well as the age and comorbidities of the patient. Extended pleurectomy/decortication as part of a multimodal treatment approach with the aim of macroscopic complete resection has established itself as the standard option of local treatment. If an epithelioid subtype is present at an early stage and lymph node involvement is excluded or at least still limited, an extended pleurectomy/decortication can be offered together with neoadjuvant or adjuvant systemic therapy - in this case combination therapy with cisplatin and pemetrexed. This approach serves to maximize disease control, howeveer locoregional recurrences are common. In the advanced, metastatic or relapsed stage, therapy involving checkpoint inhibitors should be given irrespective of the histological subtype and are further more primarily recommended in the non-epithelioid subtype.

2 Basics

2.1 Definition and basic information

Pleural mesotheliomas are malignant tumors that derive from the serous membranes of the pleura.

Histologically, 3 types are distinguished: epithelioid, biphasic and sarcomatoid [1, 2]. Biphasic and sarcomatoid mesotheliomas are also summarized under the term non-epithelioid subtypes. The epithelioid type is the most common subtype, occurring in 50-60% of cases. Clinically, the

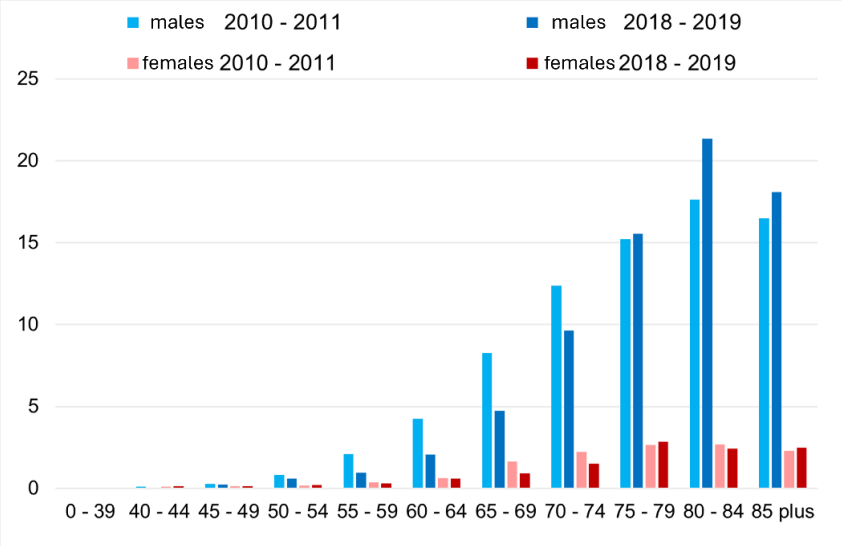
most common site of metastasis is the pleura. Metastasis to the thoracic lymph nodes, lungs and peritoneum is also common.

The other statements in this guideline refer to malignant pleural mesothelioma and not to mesothelioma of the peritoneum (C45.1), the tunica vaginalis testis (C45.7, C63.7), the pericardium (C45.2), or benign mesothelioma (pleura: D19.1, peritoneum: D19.2, other localizations: D19.7).

2.2 Epidemiology

Malignant pleural mesothelioma (C45.0) is a rare malignant tumor that is primarily caused by the inhalation of asbestos fibers. Due to the long latency between frequent occupational exposure and tumor diagnosis, new cases are still occurring more than 40 years after the first legal restrictions and almost 30 years after asbestos processing was finally banned. In 2019, 1,296 cases were recorded in the German cancer registers, most of which affected men (1,057 cases). The number of new cases has only been falling slightly since 2014 (1,425 cases). Figure 1 shows that the incidence rates in the age groups up to 70 years have recently fallen significantly among men, while they are still rising among the over-80s. Accordingly, the mean age of onset has risen from 72 to 76 years in the last 10 years [3, 4].

Figure 1: New cases of malignant pleural mesothelioma in Germany by age and gender, 2010-2011 and 2018-2019.



Comparatively high disease rates are found in north-western Germany at
former shipbuilding sites, e.g. in Bremen and neighboring regions, and in some cases also at steel industry sites, such as in the Ruhr area (3,4,5). Around half of mesotheliomas, the majority of which affect the pleura, are recognized as occupational diseases (2020: 824) [2- 5]. In addition to diffuse mesothelioma (29% in 2019), a histological distinction is made between fibrous (9%), epithelioid (52%) and biphasic (10%) forms [2].

The survival prospects are poor: compared to the general population of the same age and gender, the relative survival rate after 5 years is 9% and after 10 years 5%. The fibrous and biphasic forms have an even worse prognosis, with relative 5-year survival rates of less than 5% [source: Center for Cancer Registry Data at the RKI, based on data from the population-based cancer registries in Germany], see Figure 2 and Figure 3.

Figure 2: Incidence and new cases of pleural mesothelioma (Center for Cancer Registry Data Robert Koch Institute) [3] - age-standardized

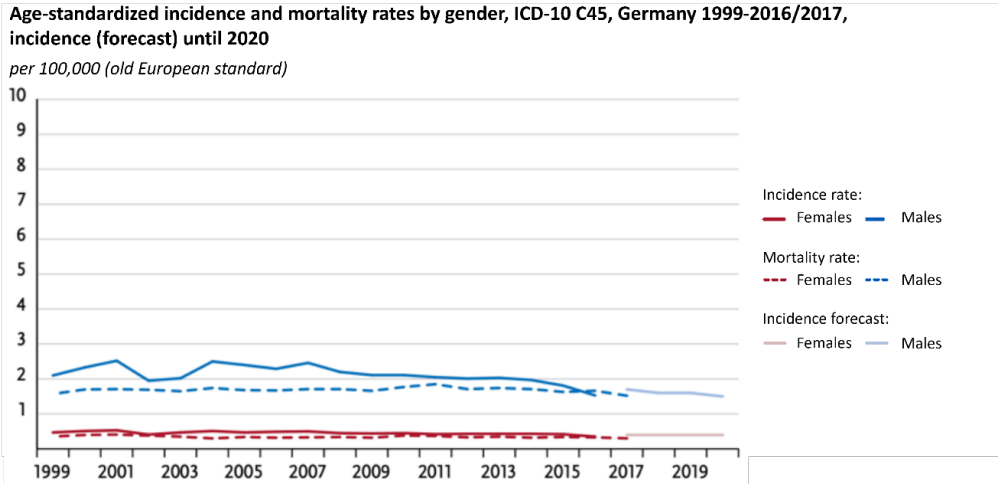
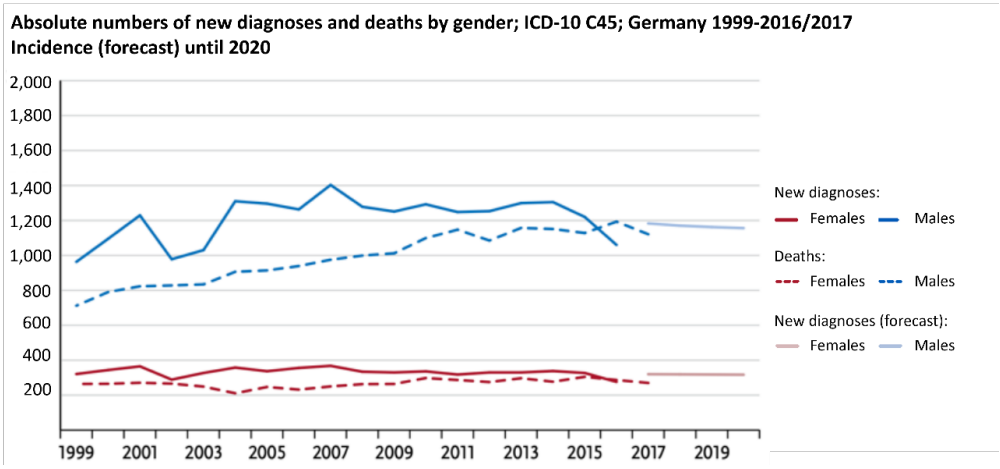


Figure 3: Incidence and new cases of pleural mesothelioma (Center for Cancer Registry Data Robert Koch Institute) [3] - absolute number



2.3 Risk factors

Mesothelioma is mainly caused by fibrous minerals, with asbestos in the form of blue (amphibole) or white (chrysotile) asbestos being the most significant cause in Germany [4]

Other hazardous fibrous minerals such as erionite, certain zeolites and others are practically non-existent in Germany. The fact that artificial mineral fibers can cause mesothelioma has not been explicitly proven in humans. Radiation therapy in the thorax can lead to mesothelioma. Very rarely, chronic inflammatory processes, BAP-1 mutations or an idiopathic genesis can also cause the disease [5]. Asbestos was used in considerable quantities until it was almost completely banned from production and use in Germany in 1993 [7, 8]. The greatest risk today and for the foreseeable future is the improper handling of asbestos-containing materials that are still in use. The geographical distribution of incidences therefore shows an increased incidence where a lot of asbestos was used in the past. A temporal frequency peak of diseases was theoretically predicted due to the ban on asbestos but has not yet been confirmed in reality in Germany [8]. However, a certain uncertainty factor arises from the fact that asbestos processing is still permitted in principle in some countries worldwide even after 1993 [10, 11].

2.4 Recognition as an occupational disease

Asbestos-induced mesotheliomas of the pleura, the peritoneum including the tunica vaginalis testis and the pericardium can be recognized as occupational disease No. 4105 by the accident insurance institutions [12].

In addition to the malignant mesotheliomas of the pleura (C45.0), peritoneum (C45.1), the tunica vaginalis testis (C45.7, C63.7) and the pericardium (C45.2), the rarer benign mesotheliomas (pleura: D19.1, peritoneum: D19.2, other localizations: D19.7) are also included in the clinical pictures covered by BK no. 4105.

Doctors are obliged to report the suspicion of the existence of an occupational disease to the accident insurance institution or the state authority responsible for medical occupational safety (§ 202 SGB VII). In the case of mesothelioma, there is a reasonable suspicion of an occupational cause even without further anamnestic evidence of an asbestos hazard, which is why every mesothelioma must be reported under the suspicion of the existence of an occupational disease.

Details on the assessment as part of the occupational disease recognition procedure can be found in the Falkenstein Recommendation [13].

Between 1994 and 2018, 19,017 men and 1,030 women died because of BK no. 4105 in Germany, more than from any other occupational cancer [14, 15]. Current information can be found on the homepage of the German Mesothelioma Register (www.mesotheliomregister.de/)

3 Prevention and early detection

3.1 Prevention

The most important preventive measure is the consistent application of occupational safety measures and the cessation of asbestos processing. The statutory accident insurance institutions offer preventive measures after the end of occupational exposure to asbestos. According to the Ordinance on Preventive Occupational Health Care (ArbMedVV), follow-up preventive care must be offered after the end of activities in which health disorders may occur after longer latency periods. Insured persons are therefore entitled to receive occupational medical care beyond the end of their working life, even after the end of a job in which they were exposed to asbestos. Employers can transfer their obligation to offer follow-up preventive care to the responsible accident insurance institution after the end of the employment relationship with the consent of the employee. The central service facility of the accident insurance institutions for the organization of follow-up preventive care for asbestos is Gesundheitsvorsorge - GVS [16].

3.2 Early detection

The early detection of asbestos-related mesothelioma requires the use of further diagnostic methods in addition to the diagnostics used in the follow-up screening, so-called extended screening **offer**, EVA. The Institute for Prevention and Occupational Medicine of the German Social Accident Insurance - Institute of the Ruhr University Bochum (IPA) published the results of the MoMar study [17]. In a prospective design, almost 3,000 subjects with a recognized BK no. 4103 (asbestos dust lung disease (asbestosis) or pleural disease caused by asbestos dust) were repeatedly examined. As a result, the risk of mesothelioma disease was 20 times higher in this high-risk group compared to the general population. The markers calretinin and mesothelin in serum in combination showed a sensitivity of around 45% and a specificity of 98% for pleural and peritoneal mesothelioma. A tumor of the pleura or peritoneum could be indicated up to twelve months before the clinical diagnosis of malignant mesothelioma. In studies, these bio-

markers provided a significantly earlier indication of a tumor but are not an established clinical marker in routine diagnostics.

Various studies on the treatment of mesothelioma show an improvement in prognosis with early treatment [18, 19, 20, 21]. The oncological principle that earlier diagnosis and thus earlier treatment improves the prognosis can therefore also be assumed for mesotheliomas [22, 23]. Early detection of mesothelioma is therefore of particular importance. Regarding the fact that knowledge of the diagnosis, treatment and prognosis of mesothelioma in early detection with biomarkers still needs to be improved, the use of biomarkers in practice should be scientifically monitored. The German Social Accident Insurance (DGUV) has decided to use both biomarkers for the early diagnosis of mesothelioma in high-risk groups as part of an extended screening offer (EVA) and with the consent of the insured persons.

4 Clinical picture

Pleural mesothelioma is often symptomatic due to dyspnoea, chesty cough and thoracic pain. In addition, non-specific symptoms such as fatigue and unintentional weight loss may occur. Sonographic and radiological examinations often reveal a unilateral pleural effusion.

5 Diagnosis

5.1 Diagnostics

5.1.1 Imaging and biopsy

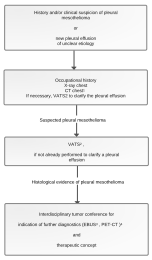
If new pleural effusions occur, a differential diagnosis of pleural mesothelioma should be considered as part of the etiological investigation. The diagnosis of pleural mesothelioma cannot be confirmed or excluded with sufficient certainty based on the patient's medical history, clinical symptoms and radiological procedures. Therefore, if a pleural mesothelioma is suspected, a histological examination should be performed in order to make a sufficient diagnosis. Due to the relatively low incidence of pleural mesothelioma, diagnosis and treatment planning for pleural mesothelioma should be carried out at a center specializing in this disease. If pleural mesothelioma is suspected, an occupational history of both the patient and the spouse should be taken in addition to the clinical history in order to determine possible exposure to asbestos.

In addition to the physical examination and sonography of the pleura, a chest X-ray and a CT chest with contrast medium should be performed, provided there are no contraindications [24, 25]. A pleural effusion should be clarified using video-assisted thoracoscopy (VATS) with pleural biopsy if pleural mesothelioma is suspected, in order to enable a sufficient histological diagnosis [22]. Similarly, if there is clinical and/or radiological suspicion of the possible presence of pleural mesothelioma, histological clarification using VATS should be sought even without the presence of a pleural effusion. When performing the biopsy, it is important to take the subpleural fat tissue to prove invasiveness. If possible, biopsies should be taken at different locations. If possible, the uniportal surgical access route should be placed at the level of a subsequent thoracotomy to avoid implantation metastases. Patients with a histologically confirmed diagnosis of pleural mesothelioma can undergo PET-CT prior to planned curative surgical treatment [25, 26]. If a PET-CT cannot be performed, a CT abdomen should be performed in addition to the CT thorax, in each case with contrast medium if possible. A contralateral VATS or laparoscopy should be considered if there is a radiological suspicion of contralateral or peritoneal involvement with clinical consequences. To clarify infiltration of the thoracic wall - particularly ribs or vertebral body - or to assess the presence of transmural diaphragmatic infiltration, an MRI of the thorax can be performed if there is a therapeutic consequence. Invasive lymph

node staging using endobronchial ultrasound (EBUS) or, if necessary, mediastinoscopy should be performed before planned curative surgical treatment [27, 28].

Figure 4 summarizes the diagnostic procedure for suspected pleural mesothelioma.

Figure 4: Diagnosis of suspected pleural mesothelioma



Legend:
[1] CT - Computed tomography
[2] VATS - video-assisted thorascopy
[3] EBUS - endobronchial ultrasound
[4] PET-CT - positron emission tomography with computed tomography

5.1.2 Pathology

The pathological diagnosis of pleural mesothelioma should be made histologically on a representative tumor sample and is clearly superior to a purely cytological diagnosis, e.g. from a pleural effusion. Immunohistochemically, the mesothelioma markers calretinin, cytokeratin 5/6, Wilms tumor 1 (WT-1) and D-240 should be determined for differential diagnosis against adenocarcinoma of the lung. The adenocarcinoma markers TTF1, CEA, Ber-EP4 should also be evaluated for the differential diagnosis of adenocarcinoma. At least 2 markers for pleural mesothelioma and 2 markers for carcinoma should be tested to diagnose an epithelioid subtype [29]. If a sarcomatoid subtype is suspected, cytokeratin should be tested [29]. The histological subtype of the mesothelioma should be specified, as well as a statement on the certainty of the diagnosis according to the criteria of the European Mesothelioma Panel.

5.2 Classification and staging

The staging of pleural mesothelioma is based on the IASLC/IMIG analyses according to UICC 8 [30, 31, 32]. The TNM classification is summarized in Table 1 and the staging in Table 2.

Table 1: Table 1 Description of the TNM classification according to IASLC*

Category	Stage	Brief description
T (tumor)	Tx	Primary tumor cannot be assessed
	T0	No primary tumor detectable
	T1	Tumor limited to the ipsilateral parietal ± visceral ± mediastinal ± diaphragmatic pleura
	T2	Tumor infiltrates an ipsilateral pleural surface (parietal, visceral, mediastinal, diaphragmatic) and also infiltrates at least one of the following two structures: • Diaphragm muscles • Lung parenchyma per continuitatem from the visceral pleura
	T3	The tumor is locally advanced, but in principle resectable Tumor infiltrates all ipsilateral pleural surfaces (parietal, visceral, mediastinal, diaphragmatic) and also infiltrates at least one of the following two structures: • Infiltration of the endothoracic fascia • Expansion into the mediastinal fat • Isolated, completely resectable part of the tumor grows into the soft tissue of the thoracic wall • Inclusion of the pericardium (non-transmural)
	T4	The tumor is locally advanced but technically not resectable Tumor infiltrates all ipsilateral pleural surfaces (parietal, visceral, mediastinal, diaphragmatic) and also infiltrates at least one of the following two structures: • Diffuse extension or multifocal tumor masses in the thoracic wall ± destruction of adjacent ribs • Direct transdiaphragmatic extension of the tumor to the peritoneum • Direct extension to the contralateral pleura • Direct extension to mediastinal organs • Direct extension into the spinal canal • Direct expansion through the inner surface of the pericardium ± pericardial effusion; or direct expansion to the myocardium
N (lymph nodes)	Nx	Lymph node metastases cannot be assessed
	N0	No lymph node metastases detectable
	N1	Lymph node metastases ipsilateral bronchopulmonary, hilar or mediastinal (including lymph nodes in the area of the internal mammary artery, peridiaphragmatic, pericardial fatty tissue or intercostal lymph nodes)
	N2	Lymph node metastases contralateral bronchopulmonary, hilar or mediastinal or supraclavicular lymph node metastases (ipsi- or contralateral)
M (distant metastases)	Mx	Distant metastases cannot be assessed
	M0	No distant metastases
	M1	Distant metastases

Legend:
**according to [27, 28, 29]*

Table 2: Classification of tumor stage according to IASLC/UICC 8 in pleural mesothelioma [29]

Stage	Primary tumor (T)	Lymph nodes (N)	Distant metastases (M)
0	T0	N0	M0
IA	T1	N0	M0
IB	T2-3	N0	M0
II	T1-2	N1	M0
IIIA	T3	N1	M0
IIIB	T4 Each T	N1 N2	M0 M0
IV	Each T	Each N	M1

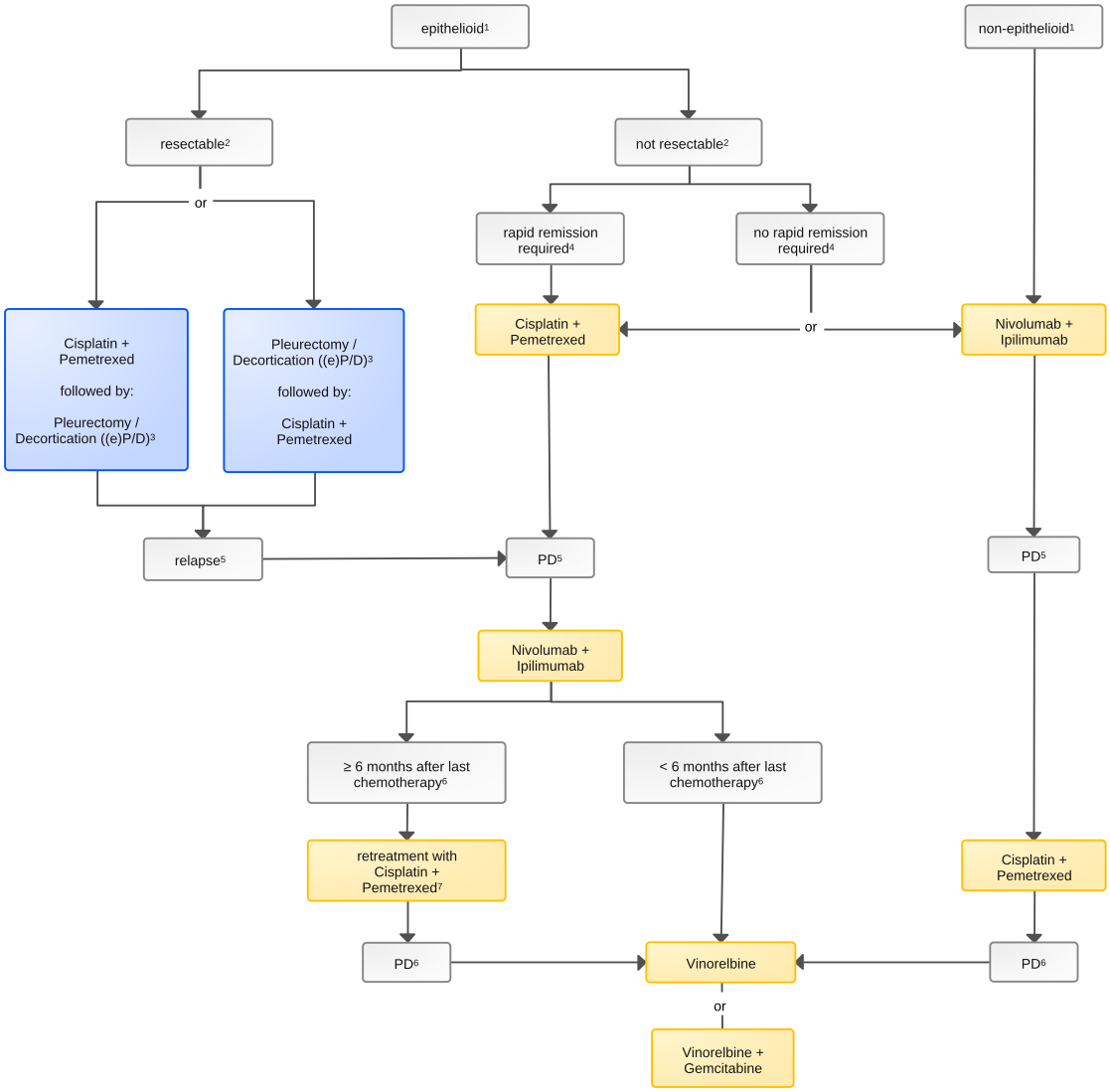
6 Therapy

6.1 Therapy structure

The treatment of pleural mesothelioma depends on the stage and the histological subtype. The patient's general condition and comorbidities must be taken into account when choosing the therapy and determining the overall therapeutic concept. The overall therapeutic concept should be determined in an interdisciplinary tumor board at an institution experienced in mesothelioma therapy.

An algorithm for the treatment of pleural mesothelioma is shown in Figure 5.

Figure 5: Treatment of pleural mesothelioma



Legend:
[1] For pathohistologic diagnostics, see chapter 5.1.2.
[2] Assessment based on imaging and consultation in the interdisciplinary tumor board
[3] (e)P/D - extended pleurectomy and decortication
[4] depending on the clinical symptoms and disease progression
[5] PD - progressive disease (progressive disease)
[6] Off-label use - drug not approved for this indication

6.1.1 First-line therapy in the resectable stage with epithelioid histology

Systemic therapy is of particular importance in the treatment of pleural mesothelioma, as a complete resection of the tumor is practically impossible to achieve even in localized stages, so that the treatment of systemic micro metastasis is relevant for the best possible long-term prognosis.

The first proof of efficacy of a combination therapy consisting of cisplatin and pemetrexed with a median of 6 cycles was provided in a phase III trial in non-resectable patients by Vogelzang et al. with an improvement in overall survival of 12.1 vs. 9.3 months (HR: 0.77; p-value = 0.02) and progression-free survival of 5.1 vs. 3.9 months (p-value = 0.001) and a response rate of 41.3% vs. 16.7% (p-value < 0.0001) [33].

Since then, the neoadjuvant or adjuvant application of 4 cycles of cisplatin and pemetrexed has been an *empirically clinically* recognized standard.

If there are contraindications to cisplatin and/or pemetrexed, pemetrexed can be replaced by vinorelbine or gemcitabine, for example, and if there are clear contraindications to cisplatin, this can be replaced by carboplatin if necessary [34, 35, 36].

Studies evaluating the significance of checkpoint inhibitors for this disease situation have not yet been conclusively evaluated. However, due to the efficacy of checkpoint inhibitors in the non-resectable situation, an extension/adaptation of the therapeutic approach is not unlikely once these studies have been finally evaluated.

The surgical procedure of choice today should be extended pleurectomy/decortication ((e)P/D), i.e. complete removal of the parietal and visceral pleura while preserving the lung parenchyma, possibly extended by diaphragmatic and/or pericardial resection. The aim of surgical resection is the macroscopically complete removal of the tumor in the sense of maximum possible cytoreduction. Outside of clinical studies, procedures such as extrapleural pneumonectomy (EPP) should only be considered if strictly indicated and if there is sufficient functional reserve. In justified exceptional cases, EPP can be performed at sufficiently experienced centers as part of individual therapy concepts.

Histologic confirmation and staging should be performed as described in section 5.1. Patients in a good general condition (ECOG 0) suffering from epithelioid mesothelioma in localized stage I-IIIA can be offered (e)PD either after neoadjuvant chemotherapy or primarily and followed by adjuvant chemotherapy with cisplatin and pemetrexed if pulmonary functionality is sufficient.

In this context, it should be noted that the neoadjuvant chemotherapy of 4 cycles of platinum combination can usually be applied much better than adjuvant therapy after (e)P/D, in which the dose density usually has to be reduced due to postoperative restrictions. On the other hand, it should be borne in mind that the postoperative recovery time after neoadjuvant chemotherapy is usually significantly longer. An EORTC study (NCT02436733), which had not yet been evaluated at the time of writing the guidelines, compares neoadjuvant with adjuvant application.

The therapeutic goal of the combination of surgical cytoreduction and systemic therapy is to control the disease for as long as possible while maintaining a good quality of life. A formally curative therapeutic approach with radical (R0) tumor resection is practically impossible in malignant pleural mesothelioma. In individual cases, long progression-free courses >10 years can be achieved, but in the long-term course there is practically always a mostly local recurrence. Depending on the localization and extent of the recurrence, local therapeutic approaches may then be offered again in combination with systemic therapy.

The therapeutic concept should be developed in an interdisciplinary conference in a facility experienced in the treatment of pleural mesothelioma, ideally in a DKG-certified lung cancer center with a mesothelioma unit.

6.1.2 First-line therapy for non-epithelioid histology and for epithelioid histology in non-resectable or relapsed stages

In the non-resectable situation and/or in the presence of *non-epithelioid histology,* a therapy consisting of the combination of the checkpoint inhibitors nivolumab and ipilimumab is considered the current first-line standard. In the randomized phase III CheckMate743 trial, the checkpoint inhibitor combination showed significant superiority in overall survival in patients with *non-epithelioid histology* compared to cisplatin/carboplatin and pemetrexed, with an extension of the median overall survival time by 9.3 months (18.1 vs. 8.8 months; HR: 0.46)) [37]. In patients with epithelioid histology, median overall survival tended to be better compared to treatment with cisplatin/carboplatin and pemetrexed, but was not statistically significant, and amounted to 18.7 months in the checkpoint inhibitor arm and 16.5 months in the chemotherapy arm (HR: 0.86). For the entire patient population, the median overall survival of 18.1 vs. 14.1 (HR: 0.74; p-value = 0.002) months was also longer in the immunotherapy arm than in the chemotherapy arm. Regardless of the histological subtype, in a retrospective subgroup analysis, patients with PD-L1 expression of ≥ 1% on the tumor surface (TPS) benefited more from the immunotherapy combination than patients with PD-L1 expression of < 1% on the tumor surface (TPS). (PD-L1 ≥ 1% TPS: median overall survival 18.0 vs. 13.3 months (HR: 0.69); PD-L1 <1% TPS: median overall survival 17.3 vs. 16.5 months (HR: 0.94)). Due to the retrospective nature of the subgroup analysis and the small number of cases, a treatment decision based on PD-L1 status is not recommended.

Median progression-free survival was comparable for the entire patient population in both study arms (6.8 months in the immunotherapy arm and 7.2 months in the chemotherapy arm (HR: 1.00)). However, progression occurred more frequently in the first 6 months in the checkpoint inhibitor arm than in the chemotherapy arm [37].

The median duration of response in the entire patient population was 11.0 months in the checkpoint inhibitor arm and 6.7 months in the chemotherapy arm, meaning that patients benefited longer from a response to checkpoint inhibitor therapy. In both study arms, the objective response rate was comparable with 40% in the checkpoint inhibitor arm and 43% in the chemotherapy arm.

In the CheckMate743 study, the checkpoint inhibitor arm showed better control of the disease-associated symptoms anorexia (HR: 0.51), fatigue (HR: 0.43), pain (0.55), dyspnoea (HR: 0.75) and cough (HR: 0.78) and a better general quality of life measured in the standardized questionnaires LCSS-Meso ASBI (HR: 0.52) and LCSS-Meso 3-IGI (HR: 0.61) [38].

Since the study met the primary endpoint (improvement in overall survival in the entire study population), patients can benefit from the possibility of a longer-lasting treatment response and symptom control and quality of life were more favorable in the checkpoint inhibitor arm, treatment with nivolumab and ipilimumab can be *considered* as a *possible* treatment option for both histological subtypes. However, for patients with a high pressure of treatment and need of a remission and epithelioid histology, treatment with cisplatin and pemetrexed should continue to be used as the standard of care based on the data presented above [33]. Patients with a contraindication to checkpoint inhibitor therapy should also receive cisplatin and pemetrexed as first-line therapy if there are no contraindications [33].

In patients with very significant comorbidities, a very severely reduced general condition or refusal of therapy by the patient, it may be appropriate, as part of a joint, individual decision by

the patient and therapist, not to carry out active tumor therapy but to pursue a purely palliative concept of "best supportive care". However, this is always an individual decision for which no generally valid recommendations can be made due to a lack of randomized data.

6.1.3 Systemic therapy options of the second and further lines

At the time of writing this guideline, there are no evaluated phase II or III studies on treatment options after progression under first-line therapy with checkpoint inhibitors.

For patients who have not received treatment with nivolumab and ipilimumab as first-line therapy in the non-operable disease situation, treatment with nivolumab and ipilimumab should be considered as part of an "off-label use" due to the overall good data from the CheckMate743 study [37], in the absence of contraindications. An application to the payer is required to secure cost coverage.

In the event of progression during/after treatment with ipilimumab and nivolumab, treatment with cisplatin and pemetrexed should be administered for up to six cycles, for which a possible overall survival of 12.1 months has been described in first-line therapy [33], see Chapter 6.1.1 Maintenance treatment with pemetrexed showed no clinically relevant or statistically significant advantage in progression-free or overall survival in a randomized phase II trial (CALGB 30901) [39] and cannot currently be recommended. Switch maintenance with gemcitabine after first-line treatment with platinum and pemetrexed showed a prolongation of median progression-free survival from 3.2 to 6.2 months (HR: 0.44; p-value <0.0001) compared to best supportive care [40]. However, the data for a general recommendation of switch maintenance therapy with gemcitabine are not yet sufficiently robust.

In a multicenter retrospective analysis, re-exposure to pemetrexed at progression showed a disease control rate of 66% with a reduction in pain in 43% of patients, a time to progression of 5.1 months and an overall survival of 13.6 months in patients with a treatment response of at least 6 months to first-line treatment with platinum and pemetrexed [41]. Another multicenter, retrospective analysis by Zucali et al. showed a disease control rate of 70.7%, a progression-free survival of 6.2 months and an overall survival of 10.6 months for patients previously treated with pemetrexed [42]. In this retrospective analysis, patients pretreated with pemetrexed also received second-line therapy consisting of pemetrexed and a platinum derivative [42]. The group of patients who were re-treated with platinum and pemetrexed achieved a longer median overall survival (13.4 vs. 4.2 months; p-value <0.001) and a longer median progression-free survival (6.4 vs. 2.4 months; p-value = 0.003) compared to patients treated with pemetrexed as a single agent.

A case series of four patients who had been treated with platinum and pemetrexed in first-line therapy described partial remission and stable disease in three cases after re-therapy with platinum and pemetrexed [43].

Another case series described a progression-free survival of 5.0 and 8.2 months in four comparable patients who responded to re-therapy with platinum and pemetrexed [44]. A single-arm observational study showed a median overall survival of 10.5 months and a median progression-free survival of 3.8 months in 31 patients who had been re-treated with platinum and pemetrexed (16 patients) (second or higher line of therapy) [45]. The duration of progression-free and overall survival correlated with the duration of response to first-line treatment with platinum and pemetrexed [45].

This means that patients who have achieved a response or disease stabilization period of at least 6 months following treatment with platinum and pemetrexed can be re-exposed to pemetrexed as a monosubstance or in combination with a platinum derivative in the event of progression. The decision as to whether treatment should be carried out as monotherapy or combi-

nation therapy should depend on the presence of side effects from the previous line of therapy, e.g. polyneuropathy or hypoacusis, as well as comorbidities and the patient's general condition.

Patients who have achieved a treatment response or disease stabilization of less than 6 months under treatment with platinum and pemetrexed, or who cannot receive treatment with pemetrexed due to contraindications, should be treated with vinorelbine or gemcitabine as monotherapy or in combination [46, 47, 48, 49, 50,51]. The advantage or disadvantage of combination therapy compared to monotherapy has not been proven by randomized data.

In the randomized phase 2 VIM study, oral vinorelbine and active symptom control provided a statistically significant benefit in progression-free survival of 4.2 versus 2.8 months [HR 0.60; p = 0.002)] [50].

For vinorelbine, a median progression-free survival of 1.7 and 2.3 months and a median overall survival of 5.4 and 6.2 months have been documented in two retrospective analyses in the second or higher line of therapy [46, 47].

In a retrospective analysis, monotherapy with gemcitabine in the second or more advanced line of therapy resulted in a progression-free survival of 1.6 months and a median overall survival of 4.9 months [46].

The randomized phase II RAMES study compared gemcitabine plus placebo with a therapy consisting of gemcitabine and the anti-VEGF antibody ramucirumab in second-line therapy [48]. In this study, the median overall survival for gemcitabine and placebo was 7.5 months compared to 13.8 months in the gemcitabine and ramucirumab study arm (HR: 0.71; p-value 0.028). In the gemcitabine and ramucirumab arm, median progression-free survival was 6.4 months compared to 3.3 months in the gemcitabine and placebo arm (HR: 0.79; p-value= 0.082).

However, at the time of writing this guideline, there is no approval for ramucirumab in pleural mesothelioma in Germany, Austria and Switzerland (off-label use).

The randomized phase III trial ETOP9-15 (PROMISE-Meso trial) compared a chemotherapy arm in which either gemcitabine or vinorelbine (investigator's choice) was administered with the PD-1 inhibitor pembrolizumab [51]. Median progression-free survival was 3.4 months in the gemcitabine or vinorelbine arm compared to 2.5 months in the pembrolizumab arm (HR: 1.06; p-value= 0.76). A median overall survival of 12.4 months was reported in the gemcitabine or vinorelbine arm compared to 10.7 months in the pembrolizumab arm (HR: 1.12; p-value = 0.59).

The anthracyclines doxorubicin and epirubicin have been described to be effective in non-resectable pleural mesothelioma [52, 53, 54, 55]. Due to more effective substances with a better study situation, doxorubicin or epirubicin are now only administered as monotherapy, if at all, in advanced therapy situations after the failure of checkpoint inhibitors, platinum derivatives with pemetrexed, gemcitabine and vinorelbine.

Doxorubicin showed a median overall survival of 8.2 and 10 months in two phase III trials in first-line therapy [52, 53]. Epirubicin showed a median overall survival of 7.5 and 10 months and a response rate of 5% and 15% in two single-arm phase II trials in first-line therapy [54, 55].

Due to the limited efficacy of treatment options in the second and later lines of therapy for pleural mesothelioma, it is generally recommended that patients be included in clinical trials.

6.1.3.1 Supplementing systemic therapy with Tumor Treating Fields (TTF)

Tumor Treating Fields are a non-invasive technology that applies alternating electric fields with a field strength of approx. 150 kHz to the pleural mesothelioma area via local arrays on the body surface. This disrupts the spindle apparatus in tumor cells during mitosis. The cell cycle of healthy cells is generally hardly affected by the TTF. The devices have received a CE certificate in Germany. In a single-arm phase II trial (Stellar), a median overall survival of 18.2 months was achieved in patients with inoperable pleural mesothelioma using TTF in combination with first-line therapy consisting of cis/carboplatin and pemetrexed [56]. The most common side effects documented with the application of TTF in the study were skin irritations [56].

At the time of writing the guideline, cost coverage by the payers has not been clarified, but patients can receive therapy with TTFields in addition to systemic therapy as part of the TIGER Meso registry study (NCT05538806).

Due to the currently rather sparse data available, it is not yet possible to make a clear recommendation on the position of TTF in the current multidisciplinary therapeutic spectrum.

6.2 Operation/surgical procedure

Surgical procedures are used for diagnosis (see Chapter 5.1) and for the treatment of patients with an epithelioid subtype in good general condition in the early stages. If a non-epithelioid pleural mesothelioma is present, surgical procedures outside of diagnosis should be limited to individual concepts following an interdisciplinary tumor board decision at an experienced center. Therapeutic surgical interventions should take the form of extended pleurectomy and decortication ((e)PD). The indication for extended surgical procedures such as extrapleural pneumonectomy (EPP) should be made on an individual, interdisciplinary basis, taking relevant comorbidities into account. The indication for surgical therapy should be supported by an interdisciplinary tumor board and performed at experienced centers. Therapeutically intended surgical procedures should be accompanied by four to five cycles of systemic therapy consisting of cisplatin and pemetrexed in neoadjuvant or adjuvant application.

6.3 Radiotherapy

Radiotherapy is effective in palliative indications for pleural mesothelioma and is of great clinical importance, particularly in the case of tumor infiltration of the spine. It should be carried out in good time before spinal symptoms occur. In larger retrospective and one prospective study, partial remissions of pain symptoms were found in approx. 50% of patients as early as 2 weeks after radiotherapy [57, 58]. Effective doses are 10-12 x 3 Gy per fraction, 5 fractions per week, or 4 Gy per fraction up to a total dose of at least 20 Gy. Objective resizing of pleural mesothelioma manifestations in the sense of partial remission after Recist was found in 45% of patients with a dose of 12 x 3 Gy per week or a higher effective dose [57, 59]. In sarcomatoid pleural mesotheliomas, lower response rates were found than in epithelioid mesotheliomas [60]. On the other hand, radiotherapy has been reported to be particularly effective in biphasic pleural mesothelioma with a high proportion of sarcomatoid component [60].

The use of radiotherapy for oligoprogression in up to 3 localizations after first-line therapy has been investigated in retrospective studies. This focal radiotherapy, often performed using the stereotactic technique, results in local tumor control rates of 75% after one year if the dosage is sufficient, so that its use for circumscribed oligoprogression can be recommended as an individual treatment option in individual cases [61, 62].

More recently, radiotherapy of the ipsilateral pleural space after pleurectomy/decortication has been investigated using the intensity-modulated technique in compliance with strict dose-volume limits for the lung [63, 64]. In a randomized Italian study with 108 patients, a survival advantage was found with the early use of pleural space irradiation up to 50 Gy in conventional fractionation after pleurectomy/decortication and chemotherapy compared to palliative small-volume radiotherapy. All patients in this study still had a macroscopic residual tumor postoperatively, to which an additional boost of up to 60 Gy was applied using the simultaneous integrated technique. Distant metastases and contralateral mediastinal lymph nodes were an exclusion criterion for this study [67]. Pleural irradiation proved to be safe to perform in experienced centers. However, the results of the randomized NRG Oncology Group study (NRG-LU-006) on this method should be awaited before wider use of this demanding technique outside of clinical trials.

As EPP is being used with increasing restraint, radiotherapy of the affected hemithorax in addition to EPP has only limited potential. It can be used postoperatively after macroscopically complete resection but should only be carried out in experienced centers in strict compliance with the tolerances for the surrounding organs. In a single-arm phase 2 trial (SMART) [65], 96 patients with histologically confirmed, resectable, previously untreated pleural mesothelioma received radiotherapy of the hemithorax with 25 Gy (boost of risk areas with 5 Gy) followed by EPP. In the case of lymph node involvement, adjuvant chemotherapy was offered. 49% of patients suffered a grade 3-4 adverse event within the first 30 days after surgery. The cumulative 5-year incidence of distant recurrence was 63.3%.

In the past, radiotherapy of the access routes after thoracotomy, thoracoscopy or insertion of larger pleural drainage tubes was carried out more frequently. However, according to recent prospective studies, the incidence of implantation metastases in the access routes is only about 15% after 18 months. Given the high competing risks of tumor progression at other sites, the benefit of additive radiotherapy of the access routes was negligible in the randomized studies conducted, so that its use is not recommended.

6.4 Drug tumor therapy

6.4.1 Substances in alphabetical order

6.4.1.1 Bevazicumab

Bevazicumab improved overall survival by 2.7 months (18.8 vs. 16.1 months; HR: 0.77, p = 0.0167) in patients with non-resectable pleural mesothelioma as first-line therapy in combination with cisplatin and pemetrexed compared with cisplatin and pemetrexed without bevazicumab in a phase 3 trial [66].
In a retrospective single-center analysis, the addition of bevacizumab to induction chemotherapy with platinum and pemetrexed significantly improved the overall response rate after mRECIST in patients with resectable pleural mesothelioma compared to induction therapy with platinum and pemetrexed (p = 0.046) [67]. Bevacizumab is not approved for the EU in this indication.

6.4.1.2 Carboplatin

If there are clear contraindications to cisplatin, carboplatin can be used in the neoadjuvant, adjuvant or palliative situation, see Chapter 6.1.1 and Chapter 6.1.3 [36]. Possible combination partners are pemetrexed, vinorelbine or gemcitabine. When combining with gemcitabine, the pronounced myelotoxic effect with an increased risk of high-grade anemia and thrombocytope-

nia must be taken into account. Common side effects of carboplatin are nausea and vomiting, as well as anemia, thrombocytopenia and leukocytopenia.

6.4.1.3 Cisplatin

Cisplatin in combination with pemetrexed is the current standard of care in the neoadjuvant or adjuvant situation, see section 6.1.1 [30]. In the non-resectable situation, in the presence of contraindications to checkpoint inhibitors or epithelioid histology and remission pressure, the combination of cisplatin and pemetrexed can be used as first-line therapy [33] or applied as second-line therapy after progression during first-line therapy with checkpoint inhibitors, see section 6.1.3 [33]. In the non-resectable situation, a median overall survival of 9.3 months or 12.1 months in combination with pemetrexed and a response rate of 16.7% (monosubstance) or 41.3% (in combination with pemetrexed) was achieved with cisplatin as a monosubstance [33]. Common side effects of cisplatin are nausea and vomiting, as well as anemia, thrombocytopenia and leukocytopenia. There is also a risk of neurological side effects such as hypoacusis and polyneuropathy. Due to potential nephrological side effects, renal function should be monitored during therapy and care should be taken to ensure adequate hydration during application. If necessary, tolerability can be improved by applying a split dose (2-3 divided doses), as proven by studies in non-small cell lung cancer.

6.4.1.4 Doxorubicin

The anthracycline doxorubicin showed a median overall survival of 8.2 and 10 months in two randomized phase III trials in first-line therapy [52, 53]. Due to more effective substances with a better study situation, doxorubicin is now only administered as monotherapy, if at all, in advanced therapy situations after the failure of checkpoint inhibitors, platinum derivatives and gemcitabine and vinorelbine. Common side effects are nausea and vomiting, as well as anemia, thrombocytopenia and leukocytopenia. Cardiac toxicity must also be closely monitored. Due to tissue necrosis in the event of extravasation, care must be taken to ensure a secure venous access during administration.

6.4.1.5 Epirubicin

The anthracycline epirubicin showed a median overall survival of 7.5 and 10 months and a response rate of 5% and 15% in two single-arm phase II trials in first-line therapy [54, 55].
Due to more effective substances with a better study situation, epirubicin is now only administered as monotherapy, if at all, in advanced therapy situations after the failure of checkpoint inhibitors, platinum derivatives and gemcitabine and vinorelbine. Common side effects are nausea and vomiting, as well as anemia, thrombocytopenia, and leukocytopenia. Cardiac toxicity must also be closely monitored. Due to tissue necrosis in extravasations, care must be taken to ensure a secure venous access during administration. Epirubicin is not approved for this indication in the EU.

6.4.1.6 Gemcitabine

Gemcitabine can be administered as a monotherapy or in combination with platinum derivatives or vinorelbine in the second-line situation or in a later line of therapy, Chapter 6.1.3. As monotherapy in the second and later lines of therapy, gemcitabine has been shown to achieve a median overall survival of 4.9 - 12.4 months [46, 47, 48], see Chapter 6.1.3. Common side effects of gemcitabine are nausea and vomiting, as well as anemia, thrombocytopenia, and leukocytopenia.

6.4.1.7 Ipilimumab

Together with nivolumab, the anti-CTLA4 checkpoint inhibitor ipilimumab has been approved as a first-line systemic therapy in the non-resectable disease setting. Here, ipilimumab in combination with nivolumab showed a prolongation of median overall survival of 4 months compared to a combination therapy of platinum and pemetrexed (18.1 vs. 14.1 months (HR: 0.74; p-value = 0.002) [37]. Regarding differentiated use and study data, see Chapter 6.1.2. Common side effects of checkpoint inhibitors are fatigue, pruritus, hypo- or hyperthyroidism and diarrhea. In addition, autoimmune inflammatory reactions such as pneumonitis, colitis, nephritis, hepatitis, hypophysitis, myositis, cardiomyopathy and arthralgia may occur in rarer cases.

6.4.1.8 Nivolumab

Nivolumab is an anti-PD-1 checkpoint inhibitor. Data on approved indications, study data and possible side effects are presented in chapter 6.4.1.7 Ipilimumab and chapter 6.1.2.. Actually it is approved in combination with ipilimumab as a first-line systemic therapy in the non-resectable disease setting .

6.4.1.9 Pemetrexed

Pemetrexed can be administered neoadjuvant or adjuvant in combination with a platinum derivative [33]. It can also be administered in the non-resectable situation in combination with a platinum derivative or as monotherapy in case of contraindications [33, 39], see Chapter 6.1.3. In the non-resectable situation, the addition of pemetrexed to cisplatin improved median overall survival from 9.3 to 12.1 months and progression-free survival from 5.1 vs. 3.9 months compared to monotherapy with cisplatin and led to a response rate of 41.3% vs. 16.7% [33], see Chapter 6.1.1 and Chapter 6.1.3.

Supportive concomitant medication with folic acid and vitamin B12 should be taken in accordance with the approval. Possible side effects include nausea and vomiting, as well as anemia, thrombocytopenia, leukocytopenia, stomatitis, mucositis and renal damage.

6.4.1.10 Vinorelbine

Is a vinca alkaloid and can be administered as monotherapy or in combination with gemcitabine in the second-line situation or in a later line of therapy, see Chapter 6.1.3. Vinorelbine can achieve a median overall survival of 5.4-12.4 months as monotherapy in the second and higher lines of therapy (46, 47, 49,50), see Chapter 6.1.3.. Common side effects are nausea and vomiting, as well as anemia, thrombocytopenia and leukocytopenia and a polyneuropathy. Due to tissue necrosis in the event of extravasation, care must be taken to ensure a secure venous access during administration.

7 Rehabilitation

After completion of a curative or palliative therapy, a rehabilitation measure can be carried out to improve physical resilience - especially cardio-pulmonary function - and possible side effects of therapy if there are no signs of recurrence/progression and no acute indication for therapy. The rehabilitation measure must be applied for from the relevant cost bearer, either the accident insurance provider or the health insurance fund.

8 Follow-up and aftercare

During systemic therapy, radiological checks of the success of the therapy should be carried out every 6-8 weeks with CT thorax/abdomen. Patients who have undergone resection of pleural mesothelioma should be followed up with CT chest/abdomen every three months for a period of two years after completion of treatment. Thereafter, the interval can be extended to six months depending on the individual risk constellation.

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11 Systemic Therapy - Protocols

- Pleural mesothelioma - Treatment protocol

13 Certification Status

- Pleural mesothelioma - Approval status

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16 Disclosure of Potential Conflicts of Interest

according to the rules of the responsible Medical Societies.