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Turkish Clinical Guideline for Malignant Pleural Mesothelioma

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This guide was approved by Turkish Respiratory Society, Turkish Thoracic Society and Republic of Turkey Ministry of Health General Directorate of Health Research for use in diagnosis and treatment of patients with malignant pleural mesothelioma.

The authors declared that they have no conflict of interest regarding mesothelioma with a pharmacy / medical company or a commercial institution.

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Abstract

Objective: Malignant Pleural Mesothelioma (MPM) is a an important public health problem in Turkey. In order to establish a common ground, Turkish Mesothelioma Working Group was established in 2011. Currently 150 academicians/researches from various disciplines (pulmonary medicine, thoracic surgery, medical and radiation oncology, radiology, pathology, nuclear medicine, public and mineralogy) from 40 universities, 5 training and 2 occupational hospitals have joined this group. The main aim of this effort was to finalize a "Guide for Diagnostic and Therapeutic Standards" that would be used in the epidemiologic evaluation, clinical diagnosis and treatment of MPM patients.

Methods: The group made several consecutive meetings and established panels on four subgroups which were epidemiology, clinical evaluation and diagnosis, pathology and treatment to finalize a guideline. The titles, subtitles and involving academicians/researchers were formed according to the recommendations by the participants. Each panel developed PICOT questions according to the existing literature and proposed their standards. A general council meeting finalized the text of the guidelines, recommendations by the group and the algorithms.

Results: Environmental exposure is a significant problem in rural areas in Turkey besides occupational exposure. A very limited group of people were also exposed to erionite which is a very potent carcinogen. Environmental exposure starts with birth and thus average age of patients is younger with an equal gender distribution. If there is any history of asbestos or erionite exposure and associated pleural effusion or chest pain, MPM should be ruled out using invasive diagnostic procedures. A multidisciplinary diagnosis and treatment team should evaluate the patient and organize the subsequent treatment. Diagnostic and treatment procedures should be performed according to clinical protocols.

Conclusion: Current guideline is expected to establish a basic standard for the diagnosis and treatment of MPM patients in Turkey.

Keywords: Mesothelioma, pleura, diagnosis, treatment

METHOD OF GUIDELINE PREPARATION

This guideline was prepared for forming a "standards guideline" that would be used by clinics in Turkey for the epidemiological evaluation, clinical diagnosis, and treatment of patients with malignant pleural mesothelioma (MPM). Users who we aim to reach are physicians in pulmonary medicine, thoracic surgery, radiology, nuclear medicine, medical and radiation oncology, internal diseases, and family medicine. This guideline does not include non-pleural mesotheliomas, fibrous tumor-benign mesothelioma of the pleura, and metastatic malignant pleural lesions.

The method used in the preparation of similar guidelines was followed for this guideline (1, 2). The titles and subtitles of the standards guideline were determined by the Executive Board of the Turkish Mesothelioma Working Group. Members of the Working Group formed panels on these titles. The panels were created according to the titles of the guideline by the Executive Board of the Turkish Mesothelioma Working Group considering the willingness of participants. The panels identified members who would study on the subtitles. They reviewed existing literature on their subtitles for obtaining related knowledge, and they formed key questions that would be looked for proposals.

While forming the key questions for developing the proposals, the format of "Population, Intervention, Comparison, Outcome, and Time (PICOT)" was taken into consideration. The questions were formed in the way that they had meaning and power that could reveal the proposals for providing content, current information, missing points, and solutions on related topics.

After revealing areas that required the development of proposals through appropriate key questions, the proposals were developed according to the titles and topics. The evidence degrees and proposals levels were decided and marked. The final forms of proposals developed by the panels were discussed in a general meeting and finalized. Evidence formation and development studies were performed in accordance with Appraisal of Guidelines Research and Evaluation Instruments documents (1) and the Turkish Thoracic Society's Instruction for Formation of Guidelines, Reports, and Opinion report (3).

The evidence was graded based on the following information: being able to give clear and definite answers to questions prepared, generalizability of study results, applicability to the targeted patient population, clinical effect of evidence, and the extent of the obtained evidence's practicality. Definitions used for determining evidence levels and degrees are presented in Table 1 and Table 2.

The evaluations formed without evidence but agreed by boards were emphasized as "panel opinion". The proposals and algorithms having been developed include explanations emphasized by all panel members and participants. The points not agreed were not included in the guideline.

The final form of the draft guideline was sent to all members for informing them, and their criticism and suggestions were asked. Finally, the guideline was re-examined by the Executive Board of the Turkish Mesothelioma Working Group, and after being approved, it was submitted for researchers' information on the related link under the web page of www.turkiyemezotelyoma.org. After the publication of the guideline, it was presented to the Turkish Thoracic Society and Turkish Respiratory Society. The use of the guideline was found to be appropriate by the Executive Boards of both societies. It was introduced in the platforms of associations and put on web pages. The guideline, which was introduced to the Republic of Turkey, Ministry of Health, General Directorate of Health Research, was approved for use, and it was allowed to give a name and logo. After the guideline was published as a book and was distributed, it was organized so that it could be published in a journal.

Monitoring Application of the Guideline

The criticisms and suggestions made during its use in clinical practices will be collected by the Executive Board of the Turkish Mesothelioma Working Group. It is planned to renew the guideline after three years.

Stakeholders

Turkish Thoracic Society, Turkish Respiratory Society, other associations for related specialties, occupational and scientific associations, Boards of the Ministry of Health, Boards of the Ministry of Labor and Social Security, and Social Security Institution.

TEXT OF THE GUIDELINE

Epidemiology

At present, two well-known primary causes of MPM are asbestos exposure and erionite exposure, both of which are mineral fibers. While varying according to series, it has been reported that 70–90% of MPM cases are caused by asbestos exposure (4, 5).

Asbestos exposure can occur in occupational or environmental settings. In Turkey, asbestos exposure was seen frequently in some regions until the end of the 1980s. It was observed in rural areas, and its characteristics are well-defined. Although the use of these lands has decreased in recent years, there are some villages still using them (6-11).

In Turkey, our knowledge of data on the results of occupation-induced asbestos exposure is limited except in local area studies. At least 471,000 tons of asbestos were imported in our country over the last 30 years. Production constitutes only approximately 10% of this amount. Hence, from 1983 to 2010, when the use of asbestos was completely prohibited, 500,000 tons of asbestos were used in Turkey (State Planning Organization, the Report of Mining Specialization Commission 1996, 2001, 2009-2013). Accordingly, it is a fact that asbestos exposure still exists in working places using old industrial products and especially in unrecorded small industrial areas. Moreover, unless sufficient precautions are taken during urban-transformation projects, asbestos exposure will continue to occur.

Erionite is a fibrous silicate similar to asbestos. It exists naturally in rock layers near some villages in the region of Ürgüp. People living in these villages used these rocks, which they called Akkuşak Stone,

Table 1. Evidence degrees used during the evaluation of studies in literature

1++	Systematic review of randomized controlled trials and meta-analyses of good quality, or randomized controlled trials with a low margin of error.
1+	Systematic review of well-conducted randomized controlled trials and meta-analyses, or randomized controlled trials with a low margin of error.
1-	Systematic review of randomized controlled trials and meta-analyses, or randomized controlled trials with a low margin of error.
2++	High-quality systematic reviews on case control or cohort studies. High-quality case control or cohort studies with a low margin of error, strong cause-and-effect relationship, or without a limiting factor.
2+	Well-conducted case control or cohort studies with a low margin of error, moderately strong cause-and-effect relationship, or without a limiting factor.
2-	Case control or cohort studies with a high margin of error, limiting factors, or a weak cause-and-effect relationship.
3	Non-analytic studies (case report or case series).
4	(Expert opinion).

Table 2. Evidence levels used while submitting proposals

A	At least one meta-analysis graded as 1++, systematic review on randomized controlled trials, or randomized controlled trial and direct applicability to the targeted population, or A systematic review on randomized controlled trials graded as 1+ or an evidence integrity for studies graded as 1+, direct applicability to the targeted population, and consistency in results to a great extent.
B	An evidence integrity for studies graded as 2++, direct applicability to the targeted population, and consistency in results to a great extent, or evidence obtained from studies graded as 1++ or 1+.
C	An evidence integrity for studies graded as 2+, direct applicability to the targeted population, and consistency in results to a great extent, or evidence obtained from studies graded as 2++.
D	An evidence integrity with the evidence level of 3 or 4, or evidence obtained from studies graded as 2-.

on walls while building their houses many years ago. Therefore, they were exposed to erionite in their homes and streets since the time they were born. Some studies conducted in our country have contributed to world literature by revealing that erionite is carcinogenic and causes high risk of mesothelioma (11, 12). Additional studies on the roles of radiation, simian virus 40 (SV40), and genetic predisposition in the etiology of MPM have been performed by various groups (13). An increase in the incidence of MPM is expected on a global scale within the coming years (14).

The annual mesothelioma incidence rate was found to be 1.6/100,000 persons/year for Turkey in the Report of Asbestos Control Strategic Planning Results (15). In Diyarbakır, including people exposed to asbestos in rural areas, the incidence rate of mesothelioma was 20/100,000 persons/year (16). In a cohort study including villagers with environmental exposure, the mean annual incidence rate of mesothelioma was reported to be 114.8/100,000 people for men and 159.8/100,000 people for women (6).

During the period of planning, it was found that 1,879 of 5,617 cases diagnosed with mesothelioma between 2008 and 2012 had no history of living in a village previously (15). It is clear that these cases will constitute the group of patients with mesothelioma having a high risk of occupational exposure.

Although it is a local issue for a limited population in Turkey, erionite exposure is also an important factor for mesothelioma. Worldwide, the highest ever MPM incidence rate found is for immigrants from Karain who lived in Sweden. The rate of MPM incidence was detected to be 639/100,000 people/year for men and 1267/100,000 people/year for women. MPM-induced mortality rate was found to be 78%. These rates are 135.5-fold higher among men and 1336.3-fold higher among women compared with those of the Swedish population (17).

In the Report of Turkey Asbestos Control Strategic Planning Results, it was predicted that 15,450 cases would occur in the population exposed to asbestos for a risky period in rural areas between 2013 and 2033 and that the number of cases would increase by 2,511 in the population who would continue to be exposed to asbestos during the same period beginning from 2013, unless necessary precautions would be taken (15). It is possible that if effective measures are taken for exposure in rural areas, the issue of mesothelioma in Turkey may be solved within the next 10 years.

Erionite exposure has led to tragic results in terms of mesothelioma in our country. Erionite exposure has disappeared to a great extent recently. Owing to the small population, a limited number of cases with erionite exposure will be seen and no longer be a problem within the next 10 years.

Pathogenesis

It is suggested that continuous and moderate asbestos exposure is influential in the development of MPM. There is no known safe threshold value or threshold time for exposure. It is assumed that total exposure density increases the risk for MPM (18, 19).

Asbestos fibers taken through inhalation and accumulating in the alveoli reach the pleural space via regional lymphatics or direct penetration, and they accumulate at the openings of parietal pleural lymphatics and they cause pathologic changes. It is thought that mesothelial cells have specific sensitivity to asbestos fibers. Asbestos fibers contact local cells, for example mesothelial cells, and cause chromosome anomalies by damaging the nuclear material of cells during mitosis. It has been reported that chromosome losses, gains, and disorders differ in histologically different types of MPM (epithelioid, sarcomatoid, and biphasic) (20). Asbestos fibers are phagocytosed by macrophages in the regions where they reach. However, because these mineral fibers are too long to be phagocytosed, macrophages are damaged. Oxygen and nitrogen radicals are released. These radicals may lead to mutations. In MPM, mutations are generally seen in tumor suppressor genes. The hypermethylation of these genes and hypomethylation of oncogenes and repetitive elements of the genome have a role in the development of cancer (21). It has been suggested that the methylation profile observed in MPM can be used in differential diagnosis (22). There are some studies indicating that increased histone deacetylation can be restored with histone deacetylase inhibitors and that this can be one of the promising treatment alternatives in the future (23). Furthermore, asbestos fibers cause necrotic cell death in human mesothelial cells (24). Macrophages stimulated by asbestos fibers release cytokines such as tumor necrosis factor-alpha and interleukin-1 beta. The inflammation, having begun in this way, turns into a chronic inflammation, which has an important place in asbestos carcinogenesis over time. Chronic inflammation can also result in other asbestos-induced benign diseases.

It is thought that erionite fibers also have similar effects. The role of SV40 in the development of MPM in humans is controversial. It is suggested that the low level of asbestos exposure will be enough for the occurrence of mesothelioma in people infected by SV40 (25).

Clinical and Laboratory Findings

The mean age for the development of MPM is 60 years (50–70 years) in our country. Because asbestos exposure is more frequently seen in rural areas, the ratio of females/males is similar among patients in clinical series (26). The symptoms in patients with MPM are unclear in the early period due to the structural and positional features of the pleural space. With the progression of disease, symptoms begin to be clearer because of the metastasis of the tumor into the pleura and fluid formation. The time from the beginning of complaints until diagnosis is approximately 3–6 months. The most common respiratory complaints are shortness of breath and/or chest pain. MPM cases rarely present with the signs of paraneoplastic syndrome. Physical examination findings occur depending on intra-thoracic development of the tumor, its localization, and/or the presence of fluid. In the advanced stages of the disease, because the pleura is thickened secondary to the tumor, shrinkage of the hemithorax and a decrease in wall motions are observed. This appearance of collapsed chest, the expansion of which is limited, is defined as "frozen chest". In some cases, a few months after the diagnosis, tumor or nodular lesions can develop due to local tumor extension in the site of the procedure. These lesions are generally asymptomatic (26-28). There is no parameter specific to MPM among parameters studies routinely in either the blood or pleural fluid (4, 29).

Because the initial clinical finding of MPM in patients is mostly pleural fluid, the first diagnostic procedure is thoracentesis (4). In MPM, exudative pleural fluid appears hemorrhagic in almost half of the patients. In some cases, the fluid can be viscous (semi-fluid) due to a high level of hyaluronic acid. In the direct microscopic examination of fluid smears prepared with Wright's stain, the pres-

ence of atypical mesothelial cells showing rapid mitosis, in the form of clusters, (cell ball) is an important indicator for malignant pleural involvement, as well as lymphocyte dominance. Therefore, it is evaluated as a finding indicating further invasive diagnostic methods (4, 30).

In studies on tumor markers for the diagnosis and follow-up of MPM, hyaluronan, osteopontin, mesothelin, megakaryocyte potentiating factor, and fibulin-3 attract the most attention in the serum and pleural fluids (31-35). Many studies have been conducted to reveal the efficiency of these markers in the diagnosis of MPM. It has been demonstrated that mesothelin and megakaryocyte potentiating factor have moderate sensitivity (approximately 60%) and relatively high specificity (approximately 90%) values, in the diagnosis and differential diagnosis of MPM (31, 33). These findings indicate that if the marker level is high in a patient, the risk for the existence of MPM is high, but if the marker level is low, the presence of MPM cannot be denied. It was suggested that fibulin-3 has a high diagnostic value in the study in which it was first presented (35). However, in subsequent studies, its diagnostic value was not as high as that of mesothelin, but it was stated to be related to prognosis (36). As far as we know today, it is not needed to conduct further studies on existing tumor markers. However, these markers should be tested with regard to their efficiency in the evaluation of responses to treatment, analysis of prognosis, and detection of cases through longitudinal studies. Studies should be performed to find out protein, other biochemical, and genetic markers for the same issues and diagnosis/differential diagnosis.

The proposals of the Turkish Mesothelioma Working Group related to clinical and laboratory findings in the diagnosis of MPM are presented in Table 3.

Imaging findings

Radiology

If the findings of pleural fluid or pleural nodular involvement and pleural thickening are observed in the chest radiography of a patient with asbestos exposure, mesothelioma should be considered. In chest radiography, the finding of "frozen chest", volume loss-collapse in the hemithorax, is a significant sign for malignant pleural involvement (37).

Contrast-enhanced computed tomography of the thorax (CTT) is routinely used in treatment and follow-up period for determining the features and localizations of pleural lesions associated with MPM, revealing the prevalence of lesions, and guiding biopsy procedures performed for diagnosis (37-39). In CTTs, pleural pathologies can appear as only pleural fluid, pleural smooth-surfaced thickening, pleural irregular-surfaced thickening, diffuse nodular thickening in the pleura, scattered nodular appearance accompanying pleural thickening, and pleural-based mass. Moreover, the presence of pleural rind, pleural thickening over 1 cm, irregular nodular thickening of the fissure, mediastinal pleural involvement, and local involvement of adjacent structures such as the pericardium and diaphragm in the CTT sections of MPM are also important findings. However, atypical findings can be confused with malignant pleural involvement (38-40).

In addition, magnetic resonance imaging (MRI) is as useful as CTT in the evaluation of malignant pleural involvement. However, MRI can be more beneficial with regard to the demonstration of muscle involvement of the chest wall and non-transmural (not having reached the inner surface) pericardial involvement in malignant pathologies and for the assessment of the diaphragm and its lower parts (41-43).

Ultrasonography (USG) is a portable and inexpensive imaging technique without any side effect, which can be implemented at bedside and used without requiring special expertise for pleural pathologies. In patients with pleural fluid and lesions adjacent to the pleura, it guides pleural interventions including thoracentesis, tube insertion, and needle biopsies. Recently, the use of ultrasound has increased in needle biopsies (44, 45). The most common findings that can be encountered in the thoracic USG of MPM cases are irregular pleural thickening with unclear borders and angles from place to place or nodule(s), if any (46).

Table 3. The proposals of the Turkish Mesothelioma Working Group for clinical and laboratory analyses

Proposals	Evidence Level
While evaluating the patients suspected of having MPM (with possible pre-diagnosis), they should be asked about whether they lived in rural areas or not, where they were born, and where they live.	A
Each patient diagnosed with MPM should be questioned about their occupation in detail, and the type of job should be recorded.	B
The complaint of chest pain is an important sign to suspect MPM in patients exposed to asbestos.	B
In an individual with asbestos exposure, MPM should also be considered among pre-diagnoses when pleural fluid or pleural thickening are detected.	B
In the advanced stages of the disease, shrinkage of the hemithorax and a decrease in wall motions are observed. The appearance of collapsed chest with limited expansion is defined as "frozen chest."	C
There is no laboratory finding specific to the disease in patients with MPM.	A
If pleural fluid is detected in a patient exposed to asbestos, the risk of MPM should be taken into consideration while conducting examinations.	A
Mesothelin and megakaryocyte potentiating factor have moderate sensitivity and high specificity values in the diagnosis and differential diagnosis of MPM from other pleural diseases. Moderate sensitivity and high specificity values show that the presence of MPM cannot be denied when these markers are found to be negative.	B

MPM: Malignant pleural mesothelioma

Table 4. Proposals of the Turkish Mesothelioma Working Group for the radiological evaluation of malignant pleural mesothelioma

Proposals	Evidence Level
The concern of MPM should be taken into consideration in the presence of pleural fluid or pleural nodular involvement/thickening in the chest radiography of a patient with asbestos exposure.	B
CTT and MRI are the techniques providing anatomical images and also information on morphology.	A
Contrast-enhanced CTT can be used for revealing the localization of MPM-induced pleural lesions and prevalence of lesions and for the follow-up period after treatment.	A
MRI is more sensitive to demonstrate the chest wall, diaphragm, and pericardium involvement.	C
CTT or ultrasonography should guide pleural needle biopsies.	B
While taking CTT of patients with a diagnosis of MPM, it is appropriate to use a contrast agent and perform CTT of the thorax and upper abdomen together, unless there is any contraindication.	B

CTT: Computed tomography of the thorax; MRI: magnetic resonance imaging; MPM: malignant pleural mesothelioma

Table 5. Proposals of the Turkish Mesothelioma Working Group for PET-CT evaluation

Proposals	Evidence Level
If tumor burden is not high in patients with MPM, PET can give a negative finding when pleural thickening-pleural lesions are smaller than 1 cm. This situation is important in the diagnostic stage. In the presence of clinically and/or radiologically suspected MPM, efforts for diagnosis should be continued despite PET negativity.	B
PET and CT should be used together in patients with MPM, and fusion images should be obtained.	A
PET-CT is more appropriate for distant metastasis and when necessary, for mediastinal lymph node evaluation.	A
In patients who will undergo radical surgical treatment, evaluation should be conducted using PET-CT.	B
If there is no consistency between PET and CT in the evaluation of the mediastinum, invasive evaluation should be performed.	B
In patients for whom the evaluation of response to chemotherapy with CTT is insufficient, it is appropriate to re-measure with PET-CT.	C

CTT: Computed tomography of the thorax; MPM: malignant pleural mesothelioma; PET-CT: positron emission tomography-computed tomography

Nuclear Medicine

The routine use of standard oncologic 18-F fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) in the diagnosis of MPM is restricted. It is more useful in the discussions of MPM and benign asbestos pleurisy and especially in demonstrating distant metastases. The confirmation of the absence of distant disease in patients who will receive multimodal treatment is preferably conducted with PET/CT imaging. However, due to the restricted use of PET/CT in the determination of transpericardial and transdiaphragmatic desease, these regions must be evaluated more carefully with the help of other imaging techniques. Because talc pleurodesis causes serious inflammation, PET/CT examination must be performed before pleurodesis. Furthermore, the FDG affinity of epithelial type MPM is lower than sarcomatous and mixed-type histopathology, which is a restrictive problem (47-50).

Because FDG PET/CT is based on metabolic measurement in morphological lesions, it can also be used for detecting the response to treatment and anticipating survival and recurrence (49).

The proposals of the Turkish Mesothelioma Working Group on radiological imaging and nuclear medicine imaging techniques are presented in Table 4 and Table 5, respectively. Algorithms recommended to be followed for diagnosis according to proposals on laboratory and imaging techniques are given in Figure 1 and Figure 2.

Invasive Methods for Diagnosis

Invasive procedures are needed in clinical/differential diagnoses because the diagnosis of MPM requires the histopathological examination of tumor tissue, except in special cases. To obtain samples for the cyto-histopathological diagnosis of MPM, thoracentesis, closed pleural needle biopsy (PNB) (percutaneous pleural biopsy), medical thoracoscopy (MT), videothoracoscopic surgery (VATS), thoracotomy, endoscopic ultrasonography-guided needle biopsy in special cases, and biopsy from metastasis regions when necessary can be used.

In the cytological examination of pleural fluid samples taken by thoracentesis, the diagnostic rate of MPM has been reported to be low as 15–40% (51). Repeating the procedure several times or increasing the amount of fluid sample is not useful for raising the diagnostic success rate. PNB is performed using Abrams, Cope, or Tru-cut needles. The success rate of diagnosis is approximately 40–50% with blind PNB (52). The main problem in this technique is that samples are randomly taken without seeing the pleura. The performance of PNB under the guidance of CTT or ultrasonography increases the sensitivity of diagnosis (53-55).

The sensitivity of CTT-guided PNB for the diagnosis of mesothelioma was reported to be between 77% and 93%, and its specificity was reported range from 88% to 100% (53, 55-57). In a randomized trial comparing the safety and diagnosis efficiency of CT-PNB with

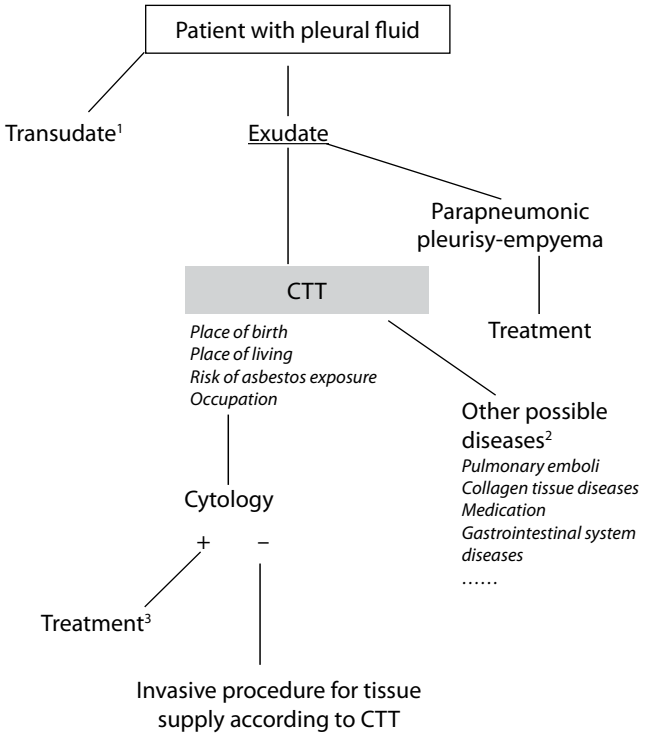

Figure 1. Algorithm recommended for the management of invasive diagnosis in patients having pleural fluid according to the proposals of clinical, laboratory, and imaging techniques

[1]If the clinical picture of the patient and transudation result are not consistent, biochemical fluid analyses are performed for the second time. If the results are again found to be inconsistent and a problem that will be a clinical cause of transudation occurs, the fluid is accepted as exudate. [2]If no result is obtained with regard to other diseases, the cytological examination period is restarted. [3]If the suspicion of malignant pleural mesothelioma is not completely differentiated as a result of cytological examination, tissue diagnosis is recommended.
CTT: Computed tomography of the thorax

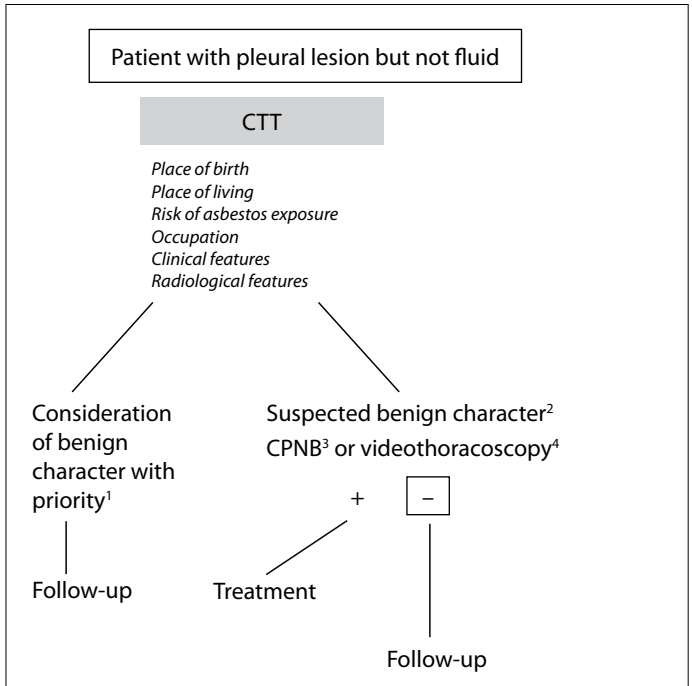

Figure 2. Algorithm recommended for the management of invasive diagnosis in patients without pleural fluid according to the proposals on clinical, laboratory, and imaging techniques

[1]Evaluation performed by a radiologist. [2]In the absence of clinical, laboratory, and radiological consistency about benign pleural pathology of pleural lesions, invasive diagnosis procedures should be initiated. PET can also help this issue. However, PET negativity is insufficient for deciding on benign character due to the distribution of pleural lesions, their localization, thickness, and frequency of adenocarcinoma in cancer involvement. [3]CPNB should be performed with a cutting needle under the guidance of CTT or ultrasonography. [4]If CPNB reveals fibrinous pleuritis, VATS can be performed due to the risk factors in such a patient or patient is scheduled for follow-up.
CPNB: Closed pleural needle biopsy; CTT: computed tomography of the thorax; PET: positron emission tomography; VATS: videothoracoscopy

Abrams needles to MT, the diagnostic sensitivity rates of CT-PNB and MT were found to be 85.7% and 94.1%, respectively, and no significant difference was detected between them (57). In studies in which cutting needles were used for CTT-guided PNB, sensitivity was reported in the range of 76–88%, and specificity was reported as 100% for malignant pleural pathologies (58). Cutting needles can be safely used in patients with pleural thickening but without pleural fluid or with a little pleural fluid and in patients having only pleural mass. The biopsy puncture site should be determined through USG in patients without pleural lesions and only with a little or moderate fluid (59).

Pleural biopsies performed under the guidance of imaging techniques have low rates of complications, and major complications are not expected (55, 56).

MT is a safe, highly efficient, and cheap technique implemented by pulmonologists or thoracic surgeons (60, 61). It can be performed in bronchoscopy rooms having basal equipment, under local anesthesia and mild sedation, and during voluntary ventilation (17-19). Recently, MT has begun to be used for ambulatory care conditions (62). In series comprising malignant pleural pathologies, the diagnostic sensitivity of MT was detected to be 90–95% and specificity was reported to be 100% (60-64). Contraindications for MT are limited, and a considerable part is relative. Absolute contraindications are as follows: insufficient pleural space, comatose or unconscious patient, type II severe respiratory failure, superior vena cava syndrome, end-stage pulmonary fibrosis, and patient's denial of the procedure. For the procedure to be performed, there must be adequate space for the thoracoscope to turn to the sides. The 10 cm space is adequate for this aim (60, 63).

The complication rate of MT is low. In patients in whom the procedure was carefully conducted, the rate of major complications such as prolonged air leak, subcutaneous emphysema, and entry site infection was reported to be 3–4%, and the rate of minor complications such as pain and tachycardia was 8–14%; mortality rate was reported to range from 0.01% to 0.24% (60-63).

VATS is an efficient and reliable technique for the diagnosis and treatment of pleural diseases. Its area of utilization is gradually increasing mainly in surgical treatment and sometimes in diagnosis in special cases. The success rate of VATS in the diagnosis of pleural pathologies is approximately 95%. It is successfully used in bullous lung surgeries, solitary pulmonary lesion treatment, wedge resections, pneumonectomy surgeries, lung resections, pleurectomy, decortication, and pleuroperitoneal shunt applications (64, 65).

Table 6. Proposals of the Turkish Mesothelioma Working Group for the invasive diagnosis of MPM

Proposals	Evidence Level
In patients not being given antitumoral treatment, the appearance of atypical mesothelial cells in a cytological examination is sufficient for diagnosis.	C
In the diagnosis of MPM, medical thoracoscopy or videothoracoscopy are the recommended diagnostic techniques in the case of an appropriate clinical state.	A
In patients with local lesions or pleural thickening, pleural needle biopsy under the guidance of an imaging technique can be performed as the initial procedure.	B
Pleural needle biopsy should be avoided as a blind procedure, except for patients with a high clinical concern of pleural tuberculosis, and it should generally be used under the guidance of CTT or ultrasonography in all patients.	A
If imaging techniques give contradictory data on mediastinal lymph node involvement in MPM cases, EBUS-FNA/ EUS-FNA can be the invasive method that can be initially preferred for mediastinal lymph node sampling.	C
If in the evaluation of mediastinal lymph nodes determined through imaging techniques, EBUS-FNA/EUS-FNA does not reveal mediastinal lymph node involvement in patients having a surgical chance, the mediastinum should be evaluated with cervical mediastinoscopy.	A

CTT: Computed tomography of the thorax; EBUS-FNA: endobronchial ultrasonography-guided fine needle biopsy; EUS-FNA: esophageal ultrasonography-guided fine needle biopsy; MPM: malignant pleural mesothelioma

Owing to developments in MT and VATS applications, thoracotomy is rarely used at present for diagnosis. It is mostly used in patients who cannot be diagnosed with other techniques and who can simultaneously undergo a surgical procedure for diagnosis and treatment at the same session (66).

We have inadequate knowledge for forming standards on endobronchial ultrasonography-guided fine needle biopsy (EBUS - FNA) and esophageal endoscopic ultrasonography-guided fine needle biopsy (EUS - FNA) in the case of the determination of lymph nodes with appropriate localization. However, the use of these procedures in the following situations can give useful information: when imaging techniques give contradictory data for mediastinal lymph node involvement, EBUS-FNA/EUS-FNA can be the invasive method that can be preferred in the first step for mediastinal lymph node sampling. Moreover, in clinics following MPM cases, when a concern of mediastinal lymph node metastasis occurs, the first procedure for evaluating recurrence can be EBUS-FNA/ EUS-FNA (67).

Table 6 shows the proposals of the Turkish Mesothelioma Working Group for invasive diagnosis, and Figure 3 includes algorithms developed according to these proposals to obtain tissue samples for histopathological analyses.

Clinical Staging

This stage is one of the most important factors that determine the type of treatment and prognosis (1, 2). The most common staging system used for MPM today is the tumor node metastasis-(TNM) based International Mesothelioma Interest Group staging system (68).

CTT is the basic imaging technique providing valuable data in the clinical staging of MPM despite its disadvantages. In these patients with MPM, CTT should be performed with a spiral technique using intravenous contrast agents and covering the whole thorax and upper abdomen, at least up to the level of the kidney, and if possible, after fluid drainage. The relationship between tumor and the mediastinum, pericardium, chest wall, and diaphragm is observed better in coronal images (69-71).

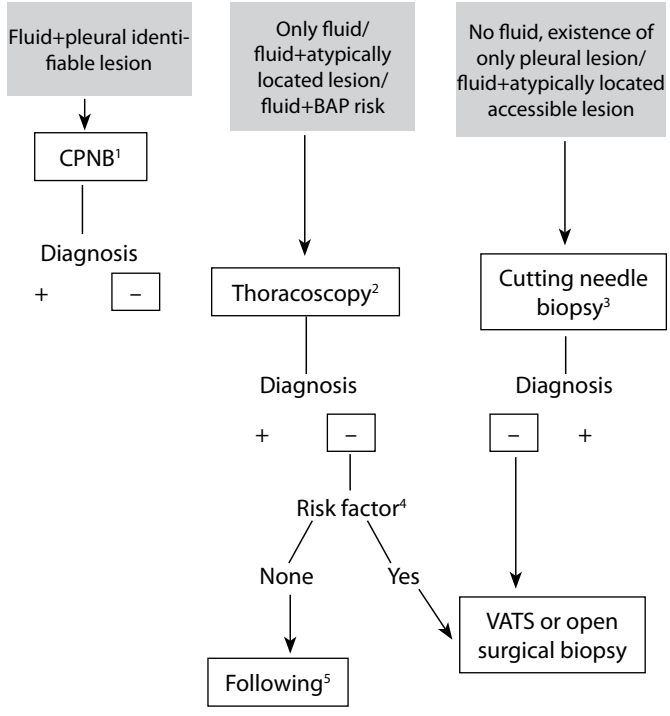

Figure 3. Algorithm recommended by the Turkish Mesothelioma Working Group for obtaining tissue samples for histopathological analyses in the diagnosis of MPM

[1]CPNB should be performed under the guidance of imaging techniques [2]Thoracoscopy can be performed with MT in applicable regions and with VATS in inapplicable regions. If the result of MT is reported as "fibrinosis pleuritis, "VATS is recommended in the presence of a risk factor. [4]The risk factor should be evaluated by clinics according to the features of patients and the region. [5]The patient can be followed-up if there is no risk factor. The follow-up should last for at least three years (two times with three-month intervals, then two times with six-month intervals, and then with a 12-month interval).
BAP: Benign asbestos pleurisy, CPNB: closed pleura needle biopsy with Abrams needle, MT: medical thoracoscopy, VATS: videothoracoscopy

MRI of the thorax is not routine and is a technique used for cases with suspicion in CTT. Oil-based contrast-enhanced T1-weighted series are sufficient for determining the invasion of tumors into adjacent structures and interlobar fissures. Although findings used for evaluating the local extension of tumors can be found by both MRI and CTT, MRI can be superior to CTT in some situations (71, 72).

It is accepted that PET-CT, which enables anatomical and metabolic evaluation together, has a more accurate staging by increasing the sensitivity of CT and specificity of PET. Although PET-CT is beneficial for the detection of distant organ metastasis, it partially fails to determine lymph node metastasis, lymph node local tumor metastasis, and tumor invasion into the mediastinum, chest wall, and diaphragm (73-75). The main expectation from PET-CT is to increase the possibility of preventing unnecessary thoracotomy procedures. It should be kept in mind that talc pleurodesis can affect the accuracy of PET-CT in staging (74, 75).

In a few studies that used EBUS and/or EUS, the sensitivity values of these techniques for determining mediastinal lymph node involvement were found to be 29% and 59%, respectively. Their negative cut-off values were revealed to be 58% and 57%, respectively (67). There are still studies being conducted on the roles of both techniques in invasive staging of MPM, especially in the evaluation of mediastinal lymph node.

The proposals of the Turkish Mesothelioma Working Group for staging studies are presented in Table 7. Algorithms recommended for deciding the therapy after diagnosis and clinical staging examinations are shown in Figure 4.

Pathological Examination Methods

The World Health Organization (WHO-2004) classified MPM into four groups according to the microscopic appearance of dominant malignant

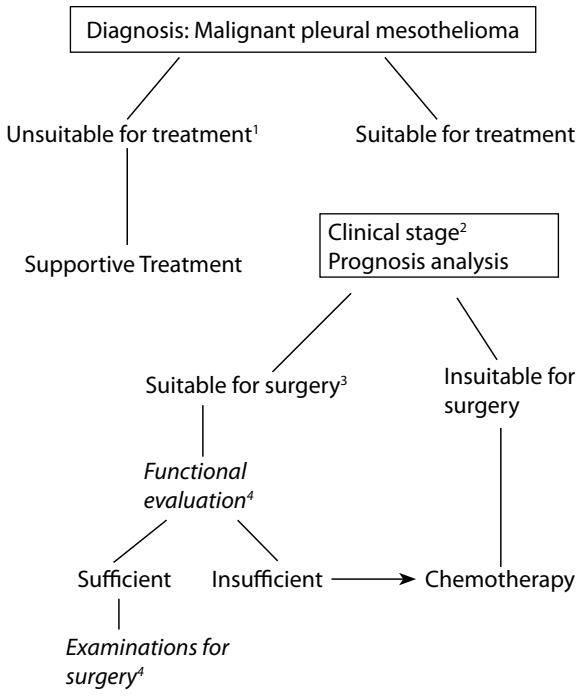

Figure 4. Algorithm recommended for making decisions on treatment after diagnosis and clinical staging examinations

[1]Patient may be unsuitable for treatment due to poor performance status and severe comorbidities or may refuse the options of antitumoral treatment. [2]Patient is clinically staged with the techniques mentioned above in the related section. [3]Patient is evaluated for suitability to undergo surgery with regard to clinical stage and functions of the lung, heart, and other organs. [4]According to the options of surgical treatment, respiratory and cardiac function tests, and if necessary, PET, EBUS, mediastinoscopy, bilateral thoracoscopy, and laparoscopy can be performed. EBUS: Endobronchial ultrasonography; PET: positron emission tomography

Table 7. Proposals of the Turkish Mesothelioma Working Group for clinical staging

Proposals	Evidence Level
The initial evaluation of staging should be performed through multidetector and contrast-enhanced CTT.	A
If multi-camera CTT cannot be used in the presence of suspected chest wall, pericardium, and diaphragm invasion, MRI should be performed.	B
It is not necessary to perform PET-CT, cerebral MRI, or bone scintigraphy for screening unless patients, who are not suitable for surgery with distant metastasis in cases of epithelial mesothelioma and relevant clinical complaints, signs, and laboratory findings. However, in patients having clinical or laboratory findings for distant metastasis, the examination should be done with a suitable technique. There is inadequate information on this issue for biphasic mesothelioma.	B
If PET-CT cannot be performed for patients with clinical complaints or clinical or laboratory findings, bone scintigraphy should be performed.	A
Contrast-enhanced MRI should be performed in patients with clinical finding of cerebral metastasis.	A
PET-CT and cerebral MRI should be performed in patients with sarcomatoid mesothelioma.	C
If imaging techniques and PET-CT are not consistent with each other for the absence of mediastinal lymph node involvement, EBUS/FNA should be performed.	C
If EBUS/FNA does not reveal mediastinal lymph node involvement in the evaluation of mediastinal lymph nodes determined by imaging techniques for patients having surgical chance, the mediastinum should be evaluated through mediastinoscopy.	A

CTT: Computed tomography of the thorax; EBUS-FNA: endobronchial ultrasonography-guided fine needle biopsy; MRI: magnetic resonance imaging; PET-CT: positron emission tomography-computed tomography

elements: epithelioid mesothelioma, sarcomatoid mesothelioma, desmoplastic mesothelioma, and biphasic mesothelioma (mixed) (76, 77).

Pleural fluid cytology is generally the first diagnostic examination. However, cytological examination is often insufficient for the diagnosis of MPM because the most important criterion in the microscopic diagnosis of MPM is the presence of an invasion. Hence, tissue confirmation is definitely recommended for MPM diagnosis, except in special cases. Only the results of cytological examinations can be used for evaluating the recurrence of disease or metastatic disease.

Samples taken with fine needle biopsies should be at a representative amount and quality. This amount should also be sufficient for immunohistochemical examinations.

The purposes of immunohistochemical examinations are to differentiate lung adenocarcinoma and other metastatic tumors from epithelioid mesotheliomas, reactive mesothelial cell proliferations from epithelioid mesotheliomas, and metastatic or primary sarcomas from sarcomatoid mesotheliomas. Because there is no standard immunohistochemical marker for sensitivity and specificity in mesothelioma, a panel study is recommended. The International Mesothelioma Panel proposals are as follows: For the differential diagnosis of epithelioid mesothelioma-lung adenocarcinoma and other metastatic tumors, it is recommended to perform a panel implementation including at least two epithelial and two mesothelial immunohistochemical markers; and to study broad-spectrum cytokeratins, at least two mesothelial markers, calretinin, cytokeratin (CD) 5/6, D2-40, and TTF-1 marker positive in at least two lung adenocarcinomas and negative in mesothelioma, CEA, Ber-Ep4, Leu M1, and MOC 31 (78-80). Calretinin WT-1 (Wilms' tumor antigen-1), Leu-M1 and TTF-1 (thyroid transcription factor-1) combination can be given as an example. The most common marker used in the diagnosis of sarcomatoid mesothelioma is cytokeratin. In these tumors, calretinin positivity can be found at varying degrees. Desmin, epithelial membrane antigen, p53, and GLUT-1 markers can be used in the differential diagnosis of mesothelioma and reactive mesothelial cell proliferations, but their sensitivity and specificity are low (70, 77, 80).

The investigation of p16/CDKN2A deletion using Fluorescence in situ Hybridization (FISH) for genetic analysis is useful in the differentiation of mesothelioma and benign reactive mesothelial proliferations. It is possible to explore (CDKN2A) p16 deletion through FISH (77). Electron microscopy is not included in routine practices.

In Table 8, proposals developed for cyto-histopathological diagnosis by the Turkish Mesothelioma Working Group are presented.

Chemotherapy in Treatment

First-line Chemotherapy

A cisplatin–pemetrexed regimen in patients with MPM displayed a longer median survival (12.1 vs 9,3 months) and time to progression (5.7 vs 3.9 months), and higher rate of objective responses (41.3 vs 16.7%) compared with those of only cisplatin. For reducing the risk of any side effect before the administration of pemetrexed, folic acid, vitamin B12 support, and premedication with dexamethasone are given (81). Compared with single cisplatin therapy, a cisplatin and raltitrexed regimen provided a longer median survival (11.4 months and 8.8 months), higher annual survival rate (46% and 40%), and higher rate of objective responses (23.6% and 13.6%). At present, the standard approach for the primary chemotherapy of patients with MPM is 4–6 regimens of cisplatin–pemetrexed or raltitrexed combination chemotherapy. If these combinations cannot be used, cisplatin–gemcitabine can be considered as an alternative. For reducing toxicity, carboplatin can be preferred instead of cisplatin (70, 83, 84).

Table 8. Proposals developed for cyto-histopathological diagnosis by the Turkish Mesothelioma Working Group

Proposals	Evidence Level
The complete sample taken for a pleural fluid cytological examination should be sent.	A
Direct smear and liquid-based cytology can be applied. Air drying-Giemsa based stain and alcohol fixation-PAP staining or, if possible, both can be used.	B
Cell block should be done in the pleural fluid sample.	B
When necessary, immunohistochemical examination can be tried by fading routine stain in smears (especially nuclear stains).	B
All materials sent for diagnostic histopathological examinations are followed.	A
Macroscopic features are recorded.	B
After planning techniques, sections are prepared for a routine examination and histochemical and immunohistochemical evaluations. Staining is gradually performed and the tissue is protected.	A
All sections can be done on to coated slides, and serial sections should be prepared at the beginning.	A
Electron microscopy is not recommended for small biopsies.	B
If genetic examinations are planned, the tissue is protected.	B
For the immunohistochemical staining panel, each laboratory can use its best working panel under control.	B
The differential diagnosis of reactive proliferation and mesothelioma has lower sensitivity and specificity than the differentiation of epithelium and mesothelioma.	B
The frozen section cannot be used for primary diagnosis. In diagnosed cases, the frozen section procedure is performed when needed during the surgical procedure.	A

In patients who respond to the combination of pemetrexed and platin or who are stable, the benefit of maintenance treatment with pemetrexed has not yet been revealed. The use of immunomodulators, targeted biotherapies, and vaccines out of clinical study protocols are inappropriate for MPM.

Second-line Chemotherapy

When recurrence is observed in patients who have not previously received pemetrexed therapy or have taken first-line platin–pemetrexed and whose lifetimes without progression have been longer than 12 months, pemetrexed can be preferred as a single drug or in combination with platin in second-line chemotherapy. If lifetime without progression is shorter than 12 months in these patients, gemcitabine or vinorelbine can be preferred in the second and third lines (83-86). The benefit of targeted drugs, biological agents, and immunotherapy has not yet been proven in the second and third-line therapies of MPM (87, 88).

Neoadjuvant Chemotherapy

Neoadjuvant chemotherapy is the therapy applied before radical surgery as a part of multimodal treatment in MPM. It has been observed in neoadjuvant chemotherapy implementations that 80–95% of patients complete three or four regimens of chemotherapy with acceptable toxicity rates and objective responses are obtained from 30-40% of patients (89-92). However, patient choice is highly important in this process. The regimen recommended for neoadjuvant chemotherapy is cisplatin–pemetrexed. Some researchers also state that cisplatin–gemcitabine or cisplatin–vinorelbine regimens can also be used (89-94). Today, data on raltitrexed are insufficient.

Adjuvant Chemotherapy

Adjuvant chemotherapy is the therapy administered in multimodal treatment protocols after surgical therapies such as pleurectomy/decortication (P/D) or extrapleural pneumonectomy (EPP). The preferred chemotherapy regimen is cisplatin–pemetrexed. No study including raltitrexed is available. In patients preoperatively receiving chemotherapy, the total number of regimens can be 4–6. In patients not receiving preoperative chemotherapy, four regimens can be given (70, 84, 91).

The proposals of the Turkish Mesothelioma Working Group for chemotherapy applications in MPM treatment are presented in Table 9.

Table 9. The proposals of the Turkish Mesothelioma Working Group for chemotherapy applications in MPM treatment

Proposals	Evidence Level
The standard approach for the primary chemotherapy of MPM patients with good performance, who are not candidates for surgical treatment, or who cannot be operated due to any reason is 4–6 regimens of cisplatin–pemetrexed or raltitrexed at present.	B
If cisplatin–pemetrexed or raltitrexed cannot be used, cisplatin–gemcitabine can be considered as the alternative.	C
The use of carboplatin is recommended for patients who cannot use cisplatin.	B
It has not been proved that combinations not including platin are more efficient than combinations including platin.	B
The benefit of maintenance treatment has not yet been demonstrated.	B
The use of immunomodulators, targeted biotherapies, and vaccines out of clinical study protocols is inappropriate.	A
If lifetime without progression is longer than 12 months in patients receiving first-line platin–pemetrexed, pemetrexed can be preferred as the single drug or in combination with platin in second-line chemotherapy.	C
In patients receiving other drugs instead of pemetrexed in first-line chemotherapy, pemetrexed can be preferred in second-line chemotherapy.	B
The benefit of targeted therapies, biological agents, and immunotherapy has not yet been demonstrated in second- and third-line chemotherapies.	A
Agents used in neoadjuvant chemotherapy can be primarily cisplatin–pemetrexed and cisplatin–gemcitabine. Data on the use of raltirexed for this aim are insufficient.	B
It is stated that vinorelbine schema can also be preferred in second-line chemotherapy.	D
Considering the data available, despite the absence of prospective randomized trials on this topic with high evidence level and large series, operable patients who are appropriate with regard to age, comorbidity, and performance and who have epithelioid-type histology and other good prognostic factors are candidates for multimodal treatment.	B
Although induction (neoadjuvant) chemotherapy is recently recommended more often because its treatment tolerance is better, postoperative adjuvant chemotherapy is also recommended for operated patients.	B
Considering series using adjuvant chemotherapy, the chemotherapy regimen that should be preferred is cisplatin–pemetrexed. At this point, no study including raltitrexed is available.	B
The regimen number of adjuvant chemotherapy can be 4–6 in patients receiving chemotherapy in the preoperative period and four in patients not given preoperative chemotherapy.	B
For reducing the frequency and severity of skin reactions in patients administered with pemetrexed, dexamethasone is given. Folic acid and vitamin B12 are also given for decreasing toxicity.	B
No premedication or vitamin support is recommended for patients receiving raltitrexed.	B

MPM: Malignant pleural mesothelioma

Measurement of Response to Chemotherapy

The determination of response to chemotherapy in MPM is generally performed through CT. For this aim, the modified criteria of the Response Evaluation Criteria in Solid Tumors (RECIST), which is a one-dimensional measurement method, are currently used (95).

Before measuring the responses, the lesions should be differentiated as measurable or non-measurable. A measurable lesion must be correctly measured at a certain size at the beginning, and the smallest size must be 10 mm in CTT (section thickness is preferred to be 5 mm), 10 mm in the physical examination, and 20 mm in the chest radiography. The short axis of measurable lymph node is ≥15 mm in CTT. Other smaller lesions not consistent with these definitions, pleural or pericardial fluid, acid and lymphangitic involvement of the lung are non-measurable lesions (96). In transverse CT sections, a total of six measurements are performed in accordance with the modified RECIST criteria in three different sections at least 1 cm away from each other and in two positions vertical to the mediastinum or chest wall. While measuring, some anatomical benchmarks are identified for the next evaluations at the same points and measurements after treatment according to these benchmarks. Nodal or subcutaneous measurements are included in these evaluations.

The definitions in response measurement are as follows: Complete response: Disappearance of all targeted lesions. Partial response: A decrease of at least 30% in total tumor measurements. Stable disease: Decrease of less than 30% and increase of less than 20% in total tumor measurements. Progressive disease: An increase of at least 20% in total tumor measurements or the occurrence of one or more new lesions (1). RECIST version 1.1 can be used for non-measurable lesions (96). According to that, complete response is the disappearance of all lesions and short axis of lymph nodes smaller than 10 mm; progressive disease is the progression of existing lesions or occurrence of new lesions; and stable disease is the continuance of the clinical picture with determined lesions (96).

There are some centers evaluating tumor responses with PET-CT in MPM cases. Especially decreased glycolytic activity after treatment is considered to be the criterion for evaluating the response. However, strong evidence on this method has not yet been presented. There are no data that can help develop distinct proposals for response evaluation with biological markers or volumetric methods using special software in CTT devices (70).

The proposals of the Turkish Mesothelioma Working Group are presented in Table 10.

Radiotherapy in Treatment

Radiotherapy applications in MPM cases include adjuvant or neoadjuvant, palliative, and prophylactic administrations in multimodal treatment (97-100). To increase local control rates in multimodal treatment, high-dose ipsilateral hemithoracic radiotherapy is performed (97, 99).

Conventional radiotherapy and radical radiotherapy can result in troublesome side effects due to the size of targeted volume, its shape, and the presence of adjacent critical organs. However, local recurrences can also be seen in regions with low-dose RT (97, 101, 102). Therefore, considering a large region, targeted volume excess, and anatomical adjacency of high-risk tissues, the adjustment of intensity with intensity modulated radiotherapy (IMRT) will allow better dose distribution, risky tissues to take less drug and be effected less, and lower rate of pulmonary toxicity. IMRT should be administered within clinical protocols and to patients whose lungs have been removed through EPP (103-107). However, some experienced centers administer radiotherapy over 60 Gy by paying attention to adjacent tissues if R2 resection was performed and large tumoral tissues were left behind in patients (107).

The administration of radiotherapy in patients who did not undergo pneumonectomy is not standard. There are a few single-center studies reporting that successful results can be obtained when high-tech treatments are applied in strict dose limitations (107-109).

Palliative radiotherapy can be used for the control of primary disease-induced pain and also for the palpation of symptoms associated with pressure on adjacent structures. Although palliative radiotherapy does not affect survival rate, it can contribute to the quality of life (98). While there are some studies showing that prophylactic radiotherapy given to intervention sites in the chest wall is beneficial for the prevention of local tumor invasion, others suggest the opposite. It is difficult to develop a proposal based on current data (110, 111).

The proposals of the Turkish Mesothelioma Working Group for radiotherapy are shown in Table 11.

Surgery in the Management of MPM

Surgical techniques have an important place in the diagnosis, staging, treatment, and symptom control of MPM (112).

Surgery in Diagnosis, Staging, and Symptom Control

Because the most important factor for MPM prognosis is extrapleural and mediastinal lymph node metastasis, some specialized centers recommend mediastinoscopy for patients planned to receive advanced surgical treatment (113, 114). The necessity of VATS evaluation in MPM staging before surgical treatment is still controversial. The differentiation of T1a and T1b can be conducted only with VATS. Moreover, VATS allows evaluating the presence of ipsilateral lymph nodes and chest wall invasion (115).

Pleurectomy is a technique that can be useful in the palpation of

Table 10. The proposals of the Turkish Mesothelioma Working Group for measurement of response to chemotherapy

Proposals	Evidence Level
The evaluation of response to chemotherapy should be performed with the modified RECIST method in patients with MPM.	B
In patients who are thought to be inappropriate for the administration of the modified RECIST method, the decision should be made with the observation of two readers (one clinician and one radiologist).	B

MPM: Malignant pleural mesothelioma

Table 11. The proposals of the Turkish Mesothelioma Working Group for radiotherapy applications in MPM treatment

Proposals	Evidence Level
It is appropriate to administer high-dose ipsilateral hemithoracic radiotherapy for increasing local control rates in patients who underwent EPP.	B
The administration of treatment with intensity-adjusted radiotherapy due to large region and volume and anatomical adjacency of risky tissues allows the better distribution of dosage and risky tissues to take a less dose.	C
Intensity-adjusted radiotherapy should be performed within clinical protocols.	B
The administration of radiotherapy in patients who did not undergo pneumonectomy is not standard.	C
If R2 resection was performed and large tumoral tissues were left behind, radiotherapy over 60 Gy can be given by paying attention to adjacent tissues. However, this procedure should be performed in experienced health centers within clinical protocols.	D
Palliative radiotherapy, which is performed for pain control, does not contribute to survival rate, but positively affects the quality of life.	C
It is difficult to develop a proposal for prophylactic radiotherapy according to existing data. Centers should decide depending on their experience.	
EPP: Extrapleural pneumonectomy	B

MPM. During pleurectomy, parietal and visceral pleura are removed completely or partially advancing down to the costodiaphragmatic sulcus. The aim of this procedure is to provide a more comfortable respiration and to reduce the possibility of re-accumulation of fluid in the pleural space by removing the tissue surrounding the lung and pleura. In MPM, because the intercostal spaces, ribs, and diaphragm cannot move due to tumor fixation, parietal pleurectomy enables these functions to be regained and thus contributes a decrease in dyspnea. In addition, pain arising can be relieved (116, 117).

Surgery for Tumor Treatment

For potential curative treatment of MPM, two types of surgical approaches, both of which must be applied within the scope of multimodal therapy, are accepted: P/D and EPP surgeries.

As stated above, pleurectomy involves separating the pleura from the chest wall and removing it. Decortication constitutes the second part of the operation. The goal of this stage is to peel the layer of the lung and to allow the lung to re-expand (118). If macroscopic tumor cleaning is aimed in P/D surgeries, the diaphragm and pericardium must also be removed with the pleura. This phase, in which only the lung is left, is called "extended P/D". It is suggested in multimodal therapy schemas that extended P/D provides the same survival rate as EPP (119-122). While potential curative surgical procedures can be performed with open thoracotomy, palliative procedures are performed with VATS or open thoracotomy (70).

In EPP, for removing the entire tumor, the pleura, diaphragm, lung in the hemithorax, and when necessary, the pericardium are removed. In the cancer treatment guideline of USA, it is stated that EPP can be an efficient treatment technique for early-stage patients with epithelioid histology, pleura-bordered mass, and without mediastinal lymph node involvement (47). For the procedure to be implemented, the disease must be restricted to the hemithorax, and there should not be transdiaphragmatic, transpericardial, and diffuse chest wall invasion. It is specified that the morbidity rate of EPP is high, but its mortality has decreased to acceptable rates. The most common pulmonary complications of this procedure are acute pulmonary damage and adult respiratory distress syndrome (ARDS). Bronchopleural fistula incidence after EPP is the same with standard pneumonectomy surgery (122-124). Due to the potential mortality and morbidity risks of EPP, it is recommended to be performed within clinical protocols in clinics with experienced staff.

Hyperthermic perfusion chemotherapy (HIPEC) was used as complementary treatment to surgery for various types of cancer for many years. HIPEC was applied by some researchers in MPM surgery for microscopic or macroscopic tumor focuses that probably left after EPP and P/D because high temperature was demonstrated to have a destructive effect on tumor cells and high temperature increased the penetration of chemotherapeutic agents into cancer cells; positive results were reported. However, extensive clinical practices have not yet begun (125, 126).

The proposals of the Turkish Mesothelioma Working Group for surgical implementations in the management of MPM are presented in Table 12. The algorithm developed for surgical diagnosis and treatment procedures considering these proposals is shown in Figure 5.

Multimodal Treatment

The logic behind multimodal, in this case trimodal, treatment is to remove macroscopic tumor with radical surgery, to provide local control with radiotherapy, and to reduce the frequency of distant metastases or to dissolve micrometastases with chemotherapy. There are three main techniques in multimodal treatment:

1. Adjuvant sequential radiotherapy and chemotherapy after EPP (101, 113).
2. EPP and radiotherapy after neoadjuvant chemotherapy (127).
3. Adjuvant chemotherapy, IMRT, or prophylactic radiotherapy after extended pleurectomy (128, 129).

Some promising results showing extended survival up to 29 months especially in early-stage, epithelial type MPM patients without lymph node involvement and five-year survival rate exceeding 50% with multimodal treatment are reported (101, 113). However, P/D is being preferred in some health centers instead of EPP in multimodal treatment after the MARS study. Discussions on this issue are ongoing,

Table 12. The proposals of the Turkish Mesothelioma Working Group for surgical implementations in the management of MPM

Diagnosis and staging practices	Evidence Level
If preoperative pleural space exists in patients who are to undergo surgery, biopsy with VATS is recommended.	B
The entry sites of interventional procedures should be chosen thinking about further surgical incision.	A
In the presence of the clinical suspect of accessible extrapleural lymph node metastasis, the evaluation should be conducted with mediastinoscopy and/or EBUS/FNA.	B
If the result of EBUS/FNA is negative in the presence of suspected mediastinal involvement, mediastinoscopy should be performed.	A
In case of clinical suspicion, contralateral VATS and/or biopsy with laparoscopy are recommended.	C
In surgical staging, at least 6–10 biopsy samples should be taken with VATS, and these biopsy specimens should be from the diaphragm and visceral and parietal pleura.	B
General complications of surgical treatment	**Evidence Level**
Surgical technique is chosen through preoperative radiology, clinical staging, and finally, intraoperative exploration.	C
Surgical treatment can be administered to patients who are appropriate for R1 resection with regard to clinical staging and physiological capacity.	B
In non-epithelial histology, non-surgical and experimental therapies can be preferred.	C
Neoadjuvant treatment is recommended for patients whose tumor is clinically local resectable but who have extrapleural lymph node metastasis.	B
Potential curative surgical methods should be applied as a component of multimodal treatment.	B
Proposals for pleurectomy	**Evidence Level**
Partial pleurectomy includes the resections of the entire pleura, in which a large tumor tissue is left in the thorax.	C
Total pleurectomy includes total pleural resections in which diaphragm and pericardium resections are not performed, but R1 resection is possible.	B
Extended pleurectomy includes pleural resections in which diaphragm and/or pericardium resections and reconstruction are implemented and gross tumor tissue is not left (R1).	B
Proposals for extrapleural pneumonectomy	**Evidence Level**
Extrapleural pneumonectomy is the procedure in which the lung, diaphragm, and pleura in the hemithorax are all removed. The decision of whether to remove the pericardium and/or peritoneum is made during surgical exploration.	A
In patients thought to be given radical treatment, pulmonary and cardiac function tests should be evaluated, and the psychosocial state of the patient should be taken into consideration for this treatment.	A
In the case of suspected recurrence, the first evaluation can be done with computed tomography of the thorax.	B

EBUS/FNA: Endobronchial ultrasonography-guided fine needle biopsy; VATS: videothoracoscopic surgery; MPM: malignant pleural mesothelioma

Table 13. The proposals of the Turkish Mesothelioma Working Group on multimodal treatment practices for MPM

Proposals	Evidence Level
Pulmonary and cardiac function tests should be evaluated in patients for whom multimodal treatment is planned; the psychosocial state of the patient should also be taken into consideration.	A
In patients who are to undergo resection, surgery should be performed with other treatment modalities.	B
Radiotherapy is essentially implemented as adjuvant treatment.	B
Neoadjuvant chemotherapy is implemented in the presence of extrapleural lymph node metastasis and locally advanced disease.	B
Intrapleural treatment can be implemented as experimental.	C
Multimodal treatment should be conducted in specialized centers with educated and experienced staff in this area.	A
It is recommended that patients who are to receive multimodal treatment should be included in prospective studies.	C

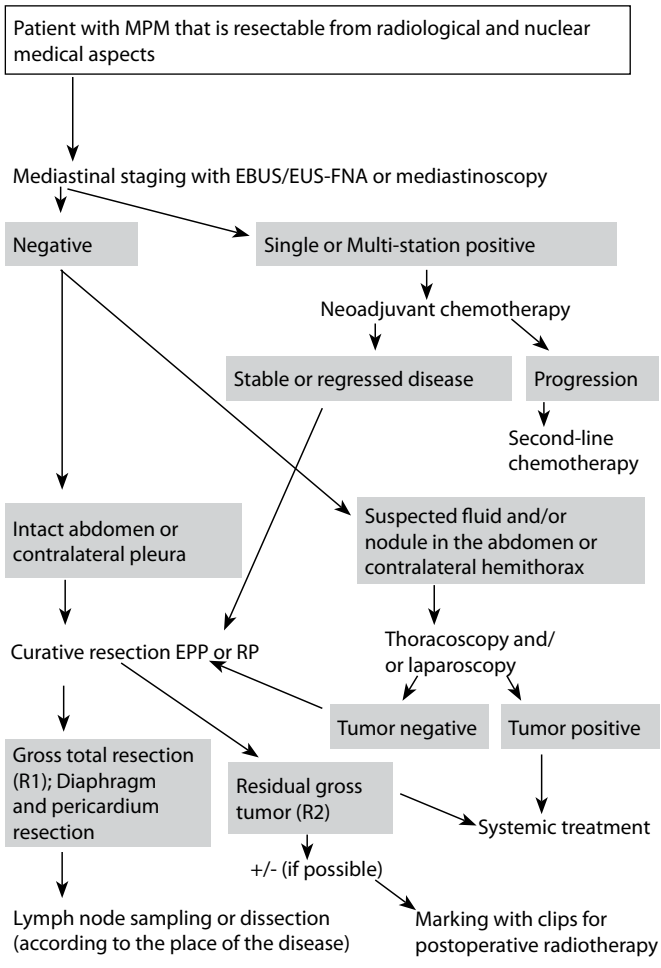

Figure 5. Algorithm developed for surgical diagnosis and treatment practices by considering the proposals of the Turkish Mesothelioma Working Group on surgical treatment in the management of MPM

EBUS: Endobronchial ultrasonography; EUS: esophageal ultrasonography; FNA: fine needle aspiration

and a consensus has not yet been achieved (99, 114, 130).

The implementation of high-dose radiotherapy to the hemithorax after EPP can be beneficial for long-term local control in multimodal treatment (99). It is also reported that IMRT can be applied after extended pleurectomy. However, this technique must be performed in accordance with clinical protocols (99, 130). In a recent study, patients were first given radiotherapy with IMRT and then EPP was performed. Adjuvant chemotherapy was applied to patients with postoperative lymph node metastasis (N2), and with this treatment, the cumulative three-year survival rate was found to be 84% in patients with epithelial-type tumor; however, this rate remained 13% in mixed mesothelioma cases (131). Besides that, this method is an experimental approach, and its long-term results are unknown.

The proposals of the Turkish Mesothelioma Working Group on multimodal treatment practices for MPM are shown in Table 13, and the algorithm developed according to these proposals is presented in Figure 6.

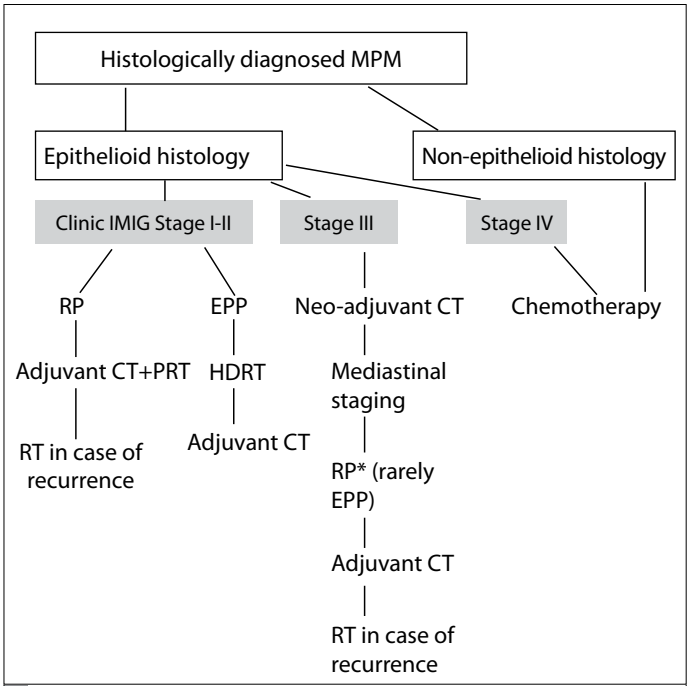

Figure 6. Algorithm recommended for multimodal treatment

*Intrapleural treatments can be added.

CT: Chemotherapy; EPP: extrapleural pneumonectomy; HDRT: high-dose radiotherapy; MPM: malignant pleural mesothelioma; PRT: prophylactic radiotherapy; RP: radical pleurectomy; RT: radiotherapy

Supportive Treatment

Supportive treatment in the management of MPM includes all therapeutic approaches complementing antitumoral treatment, without the requirement of non-response to active and antitumoral treatments. The aim of supportive care for MPM is to ameliorate the health, comfort, and functional state of patient to the best point and to protect and to improve life qualities of patient and his/her family. At this point, the management of MPM requires a team-treatment approach. In the team, cancer nurse, psychologist, psychologist of religion, physiotherapist, dietician, and social service specialist should be included as well as pulmonologist or oncologist. Cancer nurse coordinates the team. The goal of the team is to help MPM patients to live their last days in comfort and to help providing a death without pain. Unless supportive care is given by a team and turned to be a routine procedure in the management of patient, a successful MPM management cannot be mentioned (132, 135).

The treatment of symptoms, treatment of problems associated with antitumoral therapy, and psychosocial support are important within the scope of supportive care. During the terminal stage, patient and family must be made suitable for home care pharmacologically and psychosocially and patient should be enabled to spend the last days with his/her family (136-142).

The proposals of Turkish Mesothelioma Working Group on supportive care practices are included in Table 14.

Pleurodesis

Determinant factors for the decision of pleurodesis in MPM are shortness of breath, tumor burden, recurrence of fluid, lung expansion when fluid is taken, and life expectancy of patients. Sclerosing agents that are commonly used for pleurodesis at present are talc

and tetracycline (143, 144). Talc that will be used for pleurodesis must have large particles (>15 μ) (143-145). Talc can be added to the pleural space as dissolved in water (slurry) or through MT with pulverization (poudrage) through a chest tube (143, 146). Talc is activating by causing inflammation on pleural surfaces (147, 148). The success rates of talc in pleurodesis have been reported to vary between 81% and 100% in various studies (143, 145, 146).

If pleurodesis procedure is planned to be performed through a chest tube, it must be conducted after daily fluid drainage decreases to approximately 150 ml and full expansion of the lung is radiologically enabled. The width of the tube is not important for the success of pleurodesis. It is recommended that patients should be given various positions (supine, prone, lateral) during the procedure, but there are different opinions on this issue. After unsuccessful tube thoracostomy pleurodesis, thoracoscopic pleurodesis can be tried (143, 149-151).
In talc poudrage, 4–5-g talc powder is intrapleurally implemented via a pulverizer through MT. In a randomized clinical trial comparing talc poudrage with talc slurry in malignant pleural fluids, it was reported that 30-day success rates were higher in talc poudrage group (78% vs 71%) and that the complaint of respiratory failure was higher in the talc poudrage group (8% vs 4%) (146). If the lung does not expand after the procedure, pleurodesis will not be successful because two pleural leaves cannot be in contact. Moreover, diffuse tumoral invasion on pleural surfaces also negatively influences the success of pleurodesis (150-152).

The success of pleurodesis is measured during the early (seven days) and late (one month) periods. The late period is considered. No specific markers are available for demonstrating the success of pleurodesis. However, if the pH level of pleural fluid is below 7.20 and/or glucose level of pleural fluid is below 60 mg/dL, the likelihood of failure is considered to be high (153). Pleural elastance more than 19 cm

Table 14. Proposals on supportive care practices

Proposals	Evidence Level
The treatment of MPM should be done by an educated team including cancer nurse, researcher, psychologist, psychologist of religion, physiotherapist, dietician, and social service specialist as well as physicians from related disciplines.	A
Treatment should be given considering the recommendations of the World Health Organization for pain control.	B
Palliative radiotherapy is recommended if the region of pain is localized.	C
Oxygen therapy can be useful for decreasing the shortness of breath.	D
Low-dose opioids can be useful for decreasing the shortness of breath.	B
Nutrition and sleep problems of patients should be tackled for treatment.	B

MPM: Malignant pleural mesothelioma

Table 15. The proposals of the Turkish Mesothelioma Working Group on pleurodesis practices

Proposals	Evidence Level
Pleurodesis for the control of fluid in the case of recurrent pleural fluid should be implemented for patients whose diseases are in the early-stage, fluid is intense, and shortness of breath is associated with fluid.	B
If chemotherapy is not planned to be given after pleurodesis, prophylactic radiotherapy can be beneficial for the prevention of local tumor extension in the site of procedure.	D
In advanced-stage cases with high tumor burden and "frozen lung", pleurodesis will not provide benefits.	B
The measurement of pleural elastance can be leading in cases when a decision cannot be made on the administration of pleurodesis.	C
Pleurodesis should not be implemented for patients who are to undergo pleurectomy.	A
Pleurodesis can be applied to patients who are to undergo extrapleural pneumonectomy.	B
The most appropriate agent for pleurodesis is talc.	B
If pleurectomy is not planned for the treatment of patients who underwent thoracoscopy, talc poudrage application should be performed during the procedure.	B
After slurry talc application, the patient should be turned into the right–left and prone–supine positions in bed.	C
The data on the use of tunneled catheter instead of pleurodesis in patients with MPM are insufficient.	A
In patients whose physiological capacities are inadequate for surgical treatment and who have recurrent fluid, pleurodesis should be performed with MT or VATS, preferably using talc. In patients who are not suitable for thoracoscopy, pleurodesis should be done with a chest tube at bedside.	A
In the presence of recurrent pleural fluid, partial pleurectomy and/or shunt treatments should be decided for controlling according to the patient's condition.	D

MT: Medical thoracoscopy; VATS: videothoracoscopic surgery; MPM: malignant pleural mesothelioma

Table 16. The proposals of the Turkish Mesothelioma Working Group on the evaluation of prognosis

Proposals	Evidence Level
Early stage, epithelial cell type, and good clinical performance are important factors related to a good prognosis.	A
There are different evaluations for LDH, white blood cell count, platelet count, hemoglobin level, weight loss, and pain.	B
Quantitative PET, high SUV, or high tumor glycolytic volume can indicate a poor prognosis. However, further studies are needed for determining quantitative values on this issue.	C
N2 disease is an indicator of poor prognosis for surgical treatment.	B
Biological markers are promising, but their routine clinical use is now inappropriate.	A

PET: positron emission tomography; SUV: standardized uptake value; LDH: lactate dehydrogenase

H_2O/L, which is measured via a pleural manometer, indicates trapped lung (152). The use of non-steroid anti-inflammatory drugs or steroids must be stopped at least 48 h before pleurodesis, and these drugs must be avoided for 3–4 days after the procedure (154, 155).

Complications related to talc usage in pleurodesis are rare when sterile and large-particle talc is used. The most serious side effects that can develop after talc application are respiratory failure and ARDS, but they develop after small-particle talc application (143, 156, 157).

The proposals of the Turkish Mesothelioma Working Group on pleurodesis practices are demonstrated in Table 15.

Evaluation of Prognosis

The evaluation of prognosis is important both for making a decision on treatment and for predicting the outcome. The median lifetime for MPM cases is approximately 12 months. Antitumoral treatment options provide a moderate palpation and restrictedly prolonged lifetime (47, 68, 158, 159). While one-year survival expectancy is 40% for the case group without a bad prognostic factor, this rate is 12% for the group with a bad prognostic factor (160).

In studies on clinical prognostic factors for MPM, epithelial cell type, early-stage disease (stage I and II), young age, and high Karnofsky Performance Index are good prognostic factors that are generally agreed. Moreover, antitumoral treatment has been specified to be a good prognostic factor compared with patients not receiving treatment (158, 161-164).

In three studies with large series, different prognostic scores were developed: CALGB and two EORTC studies (70, 161, 165, 166). In the CALGB study, decreased clinical performance score, age≥75, presence of chest pain, platelet count at ≥400×10^9/L, and LDH serum level at ≥500 IU/L were found to be consistent with poor prognosis (165). On the other hand, in the early study of EORTC, decreased clinical score, non-epithelial cell type, male gender, and leukocyte count at ≥8.3×10^9/L (161) were consistent with a poor prognosis. In the next study, stage 3 and 4 of the disease, non-epithelial cell type, delayed diagnosis for more than 50 days, platelet count at ≥350×10^9/L, a change of >1 g/dL in hemoglobin value in the last month, and the presence of pain and loss of appetite were found to be related to a poor prognosis (166).

An inverse correlation has been observed between the severity of inflammation and lifetime in patients with MPM, but inflammatory markers for differentiating this relationship have not been developed, yet (167, 168). High SUV detected in tumor and tumoral regions through PET-CT have been found to be related to short median survival (169-171). There are studies reporting the relationship between high levels of mesothelin, osteopontin, hyaluronan, and fibulin-3 and a poor prognosis (36, 172-174). However, a marker that can be routinely used has not yet been defined. Discussions on this issue are ongoing.

Antitumoral treatment increases the median survival for patients receiving only supportive care and the survival rates (166, 175-177). In a study, a group receiving chemotherapy and another group receiving good supportive care were compared with regard to lifetime and prognostic characteristics, and it was found that chemotherapy significantly increased lifetime in stage 3 and stage 4 patients with epithelial cell type (175). This situation is also valid for multimodal treatment (101, 113).

The proposals of the Turkish Mesothelioma Working Group on the evaluation of prognosis are presented in Table 16.

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