

European guidelines for the management of malignant pleural mesothelioma

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KEY WORDS

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ABSTRACT

Malignant pleural mesothelioma (MPM) is nearly invariably lethal tumor of the pleura. Significant therapeutic nihilism exists among health professionals. Recent progress has reshaped the clinical landscape in the treatment of MPM. Two European guidelines have been published, one from the task force of the European Respiratory Society and the European Society of Thoracic Surgery, and the other from the European Society of Medical Oncology. With these guidelines and recommendations as a guidepost, this review discusses the major changes and their impact on the management of MPM.

Introduction In 2010, 3 European societies have issued either guidelines or recommendations regarding the management of mesothelioma. The European Respiratory Society (ERS) and the European Society of Thoracic Surgery (ESTS) formed a common task force consisting of 18 experts from 8 disciplines and 8 countries. Based on a set of questions formulated by those experts, a systematic literature review was conducted covering aspects of epidemiology, diagnosis, staging, and treatment. The evidence and the recommendations were graded according to the grading system of the American College of Chest Physicians and voted by the experts. Finally, the manuscript was submitted to external expert peer review by the *European Respiratory Journal*, wherein it was later published.¹

The European Society of Medical Oncology (ESMO) invited 4 experts from 3 disciplines and countries to write statements on the staging and tumor-directed treatment, based on an extensive literature search and using the grading of the American Society of Clinical Oncology. The manuscript was peer-reviewed externally by the *Annals of Oncology*, wherein it was published as a guidelines supplement.²

This article reviews the recommendations as proposed by these scientific societies. **TABLE 1** summarizes the most important recommendations along with their corresponding level of evidence and displays the small differences between the 2 guidelines.

Treatment of malignant pleural mesothelioma (MPM) can be either aimed at symptom relief or have an intention to cure. Radical treatment is reserved for a carefully selected subgroup of patients, and this makes palliative treatments the keystone of care for the vast majority of patients with MPM. But regardless of the initial treatment intention, supportive care should be offered to all patients with MPM.

Treatment with palliative intent MPM has a strong negative impact on the quality of life of patients suffering from this disease. Although it can cause a large number of complaints, its symptom management is mainly aimed at pain relief and improving shortness of breath.

Symptom control Patients with MPM often have troublesome symptoms that significantly decrease their quality of life. These symptoms need addressing, regardless of the institution of active treatment. Offering comprehensive, supportive care is of paramount importance in patients with MPM because the severe symptom burden often causes extreme suffering for both patients and families. The most common symptoms are shortness of breath and pain, affecting over 90% of MPM patients. Other symptoms reported by MPM are tiredness (36%), worry (29%), cough (22%), sweating (22%), and constipation (22%).³

The pain can originate from pleural-based disease or chest wall invasion and consists of

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TABLE 1 Management of malignant pleural mesothelioma. Recommendations from the ESMO and ERS/ESTS guidelines, with corresponding level of evidence. Adapted from Scherpereel A et al.¹ and Stahel RA et al.²

ESMO	Level ^a	ERS/ESTS	Level ^b
symptom control			
palliative local procedures to control pleural effusions includes parietal pleurectomy or talk pleurodesis	NA	every patient should be offered supportive care pleurectomy/decortication should not be proposed with a curative intent but can be considered in patients to obtain symptom control, especially symptomatic patients with entrapped lung syndrome who cannot benefit from chemical pleurodesis	2C
palliative radiotherapy			
radiotherapy can be delivered locally in view of pain control or prevention of obstructive symptoms	IVC	palliative radiotherapy aimed at pain relief may be considered in cases of painful chest wall infiltration or nodules	2C
prophylactic irradiation of tracks			
impossible to draw definitive conclusions regarding its efficacy	IIC	its value is questionable	NA
first-line chemotherapy			
platinum analogues, doxorubicin and some antimetabolites (methotrexate, raltitrexed, pemetrexed) have shown modest single-agent activity	IIIB	when a decision is made to treat patients with chemotherapy, subjects in a good performance status (PS >60% on the Karnofsky scale or <3 on the ECOG scale) should be treated with first-line combination chemotherapy consisting of platinum and pemetrexed or raltitrexed	1B
the combinations of both pemetrexed/cisplatin, and to a smaller extent raltitrexed/cisplatin, have been shown to improve survival as well as lung function and symptom control, in comparison with cisplatin alone in randomized trials	IIA	alternatively, patients could be included in first- and second-line clinical trials	NA
the combination of pemetrexed/carboplatin is an alternative effective therapy	IIIA	administration of chemotherapy should not be delayed and should be considered before the appearance of functional clinical signs	1C
		chemotherapy should be stopped in case of progressive disease, grade 3–4 toxicities, or cumulative toxic doses, or following up to 6 cycles in patients who respond or are stable	1A 2C
second-line chemotherapy			
pemetrexed-naïve patients: pemetrexed	NA	patients demonstrating prolonged symptomatic and objective response with first-line chemotherapy may be treated again with the same regimen in the event of recurrence	2C
patients demonstrating prolonged symptomatic and objective response with first-line chemotherapy may be treated again with the same regimen in the event of recurrence	IIC	inclusion of the patients in clinical trials is encouraged	2C
otherwise: vinorelbine	IIIA		
inclusion of the patients in clinical trials is encouraged	IIC		
radical surgery			
surgery, the appropriateness of which is still under consideration, should only be performed on selected patients by experienced thoracic surgeons in the context of a multidisciplinary team and preferably as part of a clinical trial	IIIA	radical surgery (EPP) should be performed only in clinical trials, in specialized centers as part of multimodal treatment	NA
PORT			
caution must be exercised regarding the exposure of the contralateral lung to low-dose irradiation, especially when using IMRT	IIIB	PORT should not be performed after pleurectomy or decortication	1A
multimodality treatment including chemotherapy			
if extrapleural pneumonectomy is planned, platinum-based neoadjuvant or adjuvant combination chemotherapy should be considered	NA	patients who are considered candidates for this multimodal approach should be included in prospective randomized trials in an experienced center	NA

a level of evidence; American Society of Clinical Oncology grading system⁴

b level of evidence; American College of Chest Physicians grading system⁵

Abbreviations: ECOG – Eastern Clinical Oncology Group, EPP – extrapleural pneumonectomy, ERS/ESTS – European Respiratory Society/European Society of Thoracic Surgery, ESMO – European Society of Medical Oncology, IMRT – intensity-modulated radiotherapy, NA – not available, PORT – postoperative radiotherapy, PS – performance status

a complex of nociceptive, neuropathic, and inflammatory components, being referred to as the costopleural syndrome. The nociceptive pain caused by chest wall involvement can be treated with opioids; as for the inflammatory part, nonsteroidal anti-inflammatory drugs are useful. Treatment of neuropathic pain, induced either by disease or chemotherapy, includes the usual agents used in patients with neuropathic pain of any etiology (anticonvulsants, corticosteroids, tricyclic antidepressants, and α_2 -agonists).⁶ Due to the complex nature of the pain and relatively large innervations of the chest wall and pleura, pain in MPM is often hard to control, with pain medication escalating rapidly on the World Health Organization's analgesic ladder. For strictly selected patients with refractory or uncontrolled pain with analgesics, percutaneous cervical cordotomy in an experienced center can be considered.^{7,8}

The cause of dyspnea is often multifactorial, including pleural fluid, a trapped lung or preexisting comorbidity, and a number of treatment modalities may be required to address this symptom. Pleurodesis is useful in preventing recurrent effusions, and repeated thoracentesis can be avoided if pleurodesis is performed early in the disease process, before the effusion has become loculated and/or the lung fixed and unable to expand fully. For a successful pleurodesis, pleural sheets need to be approximated and sterile talc is the most effective chemical sclerosant, but no significant differences between a medical or thoracoscopic procedure have been demonstrated. It is of paramount importance that sufficient tissue for the diagnosis of MPM has been obtained before performing a pleurodesis.⁹

For very frail patients, however, repeated aspiration may still be the most practical way to manage recurrent effusions, or, alternatively, an indwelling chest drain can be placed. Other strategies include pleurectomy/decortication for patients with a trapped lung syndrome and failure of pleurodesis, as discussed in the next paragraph.

Independent of the cause, low-dose oral morphine may be useful in reducing dyspnea and accompanying anxiety. Oxygen can be helpful but should not be used unless there is evidence of reduced oxygen level.¹⁰

Debulking pleurectomy/decortication Debulking pleurectomy/decortication can be defined as significant but incomplete macroscopic clearance of pleural tumor. The aim of the operation is to relieve an entrapped lung by removing the visceral tumor cortex. Subtotal parietal pleurectomy provides lasting and effective pleurodesis and gives an opportunity to obtain large volumes of tissue in cases of difficult histological diagnosis. Removal of the parietal tumor cortex may also relieve a restrictive ventilatory deficit and reduce chest wall pain. Unfortunately, when performed through a thoracotomy, it has been associated with significant morbidity.^{11,12} However, there is emerging

evidence that the use of video-assisted thoracoscopic pleurectomy may provide symptom control with lower morbidity and may even have an effect on survival.¹³ It can be considered in symptomatic patients with entrapped lung syndrome who cannot benefit from chemical pleurodesis and have an expected survival of more than 6 months. No randomized trials have been conducted, but there is an ongoing trial in the United Kingdom comparing video-assisted thoracoscopic surgery debulking with chemical pleurodesis.

Palliative radiotherapy Palliative radiotherapy aimed at pain relief can be considered in cases of painful chest wall infiltration or nodules.¹⁴ The initial effect is often encouraging, but responses are generally short-lived.¹⁵ Combining radiotherapy and hyperthermia resulted in higher response rate in patients who received additional hyperthermia.¹⁶ Further validation of this cumbersome technique is needed before its routine use can be advised. Hyperthermia is currently limited to a few specialized centers.

Prophylactic radiotherapy The diagnosis of MPM is often established by invasive procedures. Regardless of the procedure, tumor cell seeding that leads to metastases at the biopsy sites occurs in up to 20% of the patients. Prevention of malignant seeding with prophylactic radiotherapy along the tracts of these procedures has therefore received much attention. Randomized trials showed contradictory evidence. The results of 3 trials have been pooled in a recent meta-analysis that showed no significant reduction of the relative risk of tract metastases.¹⁷ The discrepancies between these results may be partly attributed to different techniques of radiotherapy and the emergence of effective systemic therapies delaying the occurrence of tract metastases. Because of these conflicting data and the availability of adequate systemic therapies and palliative radiation schemes in case of tract seeding, the value of prophylactic radiotherapy is questionable. A large randomized trial regarding the efficacy of prophylactic radiotherapy is proposed in the United Kingdom.

Palliative chemotherapy Recently, there have been important developments in the use of chemotherapy for mesothelioma. The largest randomized trial of chemotherapy in MPM to date compared a combination of pemetrexed, a multi-targeted antifolate, and cisplatin with cisplatin alone in 456 patients. Median survival with the pemetrexed and cisplatin combination was 12.1 months, significantly longer than the 9.3 months with cisplatin alone. In vitamin supplemented patients, there was significantly lower hematological toxicity. Partly because of this trial, vitamin B₁₂ and folate supplementation was introduced in pemetrexed therapy. Symptom relief was also better with pemetrexed therapy, although no full quality-of-life data have been published.¹⁸

Similar results were achieved in a randomized trial comparing raltitrexed, another antifolate, plus cisplatin with cisplatin alone in 250 patients.¹⁹ Further studies with pemetrexed have shown that similar results may be obtained by combining it with carboplatin rather than cisplatin, with reduced toxicity and greater convenience of administration.²⁰

No studies have compared chemotherapy with best supportive care alone and none has compared different combination chemotherapy regimens with each other. In the light of the still limited evidence of efficacy of chemotherapy, the decision to administer chemotherapy should be discussed with patients and their relatives on a case-by-case basis, like all other palliative treatment modalities. When a decision is made to treat patients with chemotherapy, only subjects in good performance should receive first-line combination chemotherapy consisting of platinum analogue and an antifolate (pemetrexed or raltitrexed).

Other cisplatin-based combinations have been tested in phase II studies and a meta-analysis showed promising response rates of approximately 25% to 30% (TABLE 2).^{21,22} Equipose between these regimens is therefore possible. While some single agents have shown modest activity in patients with MPM, they should not be considered as the standard of care for first-line treatment.²²

There is uncertainty regarding the optimal timing of chemotherapy. A common tendency is to defer treatment while the patient feels relatively well after initial effective management of a pleural effusion by pleurodesis. The drawback is that the transition from “too well for chemotherapy” to “too ill for chemotherapy” can be unexpectedly rapid, so many patients miss the opportunity to benefit from chemotherapy. A small randomized study found a survival advantage for early rather than delayed chemotherapy without reaching statistical significance.²³ There is also limited evidence for better efficacy of chemotherapy in small tumor volumes.²⁴ Administration of chemotherapy should therefore not be delayed and should be considered even before the appearance of functional clinical signs.

The optimal duration of chemotherapy is also controversial; the scanty evidence available at the moment shows no significant benefit for more than 6 cycles of chemotherapy. So chemotherapy should be stopped in case of progressive disease, grade 3–4 toxicities or cumulative toxic doses, or after up to 6 cycles in nonprogressive patients.

Unfortunately, nearly all MPM patients progress during or after first-line treatment. Second-line therapies are being increasingly used in the clinical practice because patients often have good performance scores at the time of disease progression. In pemetrexed-naïve patients, data from a randomized trial vs. best supportive care suggest the use of single-agent pemetrexed as a standard second-line treatment.²⁵ There is still

no standard approach for the growing population of pemetrexed-pretreated patients. In selected cases with a prolonged response to first-line pemetrexed-based chemotherapy, re-treatment with a pemetrexed-based regimen should be considered. When a trial is not available or patients are not eligible for an experimental approach, single-agent vinorelbine can be a reasonable option for palliation. However, the role of these treatments in MPM is unproven, and the optimal regimen still remains to be defined. This makes second-line therapy in MPM an ideal field in which to test new chemotherapy agents as well as new therapeutic strategies.

Recommendations Patients demonstrating prolonged symptomatic and objective response with first-line chemotherapy may be treated again with the same regimen in the event of recurrence. Pemetrexed-naïve patient may be treated with pemetrexed, in other cases inclusion of the patients in clinical trials is encouraged.

Despite a number of signaling pathways being dysregulated in MPM, targeted therapeutic agents have demonstrated disappointing effects so far in the treatment of MPM. Agents aimed at the inhibition of specific targets, such as angiogenesis, epidermal growth factor receptor, histone deacetylase, and ribonucleases, have failed to induce substantial responses. Immunomodulating agents, targeted biotherapies and vaccines should therefore not be used in the treatment of MPM outside clinical trials.

For assessment and follow-up of MPM, a chest computed tomography (CT) scan is recommended. In addition to CT, contrast-enhanced magnetic resonance imaging as another anatomic imaging method has also been evaluated and found to give comparable results to CT.²⁶ Recently, metabolic 18FDG-positron emission tomography imaging has been proposed as a promising alternative for response evaluation in MPM.^{27,28} If a patient has had pleurodesis, a chest CT scan should be performed again before the start of chemotherapy to better evaluate the response to treatment.

The growth pattern of MPM provides a challenge for measuring response to chemotherapy and standard response criteria have been felt to be inadequate for response evaluation. However, the modified Response Criteria In Solid Tumours for MPM have been proposed by Byrne et al.²⁹ based on 2 CT measurements of tumor thickness perpendicular to the chest wall at 3 different levels and have become widely accepted.

Treatment with radical intent **Surgery** Radical surgery is illustrated by extrapleural pneumonectomy (EPP), which involves en bloc removal of tissues in the hemithorax (including the pleura, lung, mediastinal lymph nodes, diaphragm, and pericardium) in order to remove all gross disease. In experienced centers, the mortality rates with EPP have decreased to around 4%; however,

TABLE 2 Selected regimens of combination chemotherapy in malignant pleural mesothelioma. Adapted from Sørensen JB²² and van Meerbeeck et al.³⁰

Author, year	Regimen	n	Response rate, %	Median survival, mo	Median progression-free survival, mo	1-year survival, %
van Meerbeeck, 2005	CDDP + raltitrexed	126	24	11.4	5.3	46
Vogelzang, 2003	CDDP + pemetrexed	226	41	12.1	5.7	51
Obasaju, 2007	CDDP + pemetrexed	728	21	10.8	NA	45
Santoro, 2007	CBDCA + pemetrexed	861	22	NA	NA	64
Ceresoli, 2006	CBDCA + pemetrexed	102	19	12.7	6.5	52
Andreopoulou, 2004	CDDP + MMC + VBL	150	15	7	NA	31
Byrne, 1999	CDDP + gemcitabine	21	48	10	NA	NA
van Haast, 2002	CDDP + gemcitabine	32	16	9.6	6	36
Favaretto, 2003	CBDCA + gemcitabine	50	26	14.7	8.9	53
Berghmans, 2005	CDDP + epirubicin	69	19	13.3	NA	50
Hillerdal, 2008	CBDCA + gemcitabine + liposomal doxorubicin	173	33	13	–	52
Sørensen, 2008	CDDP + vinorelbine	54	30	16.8	7.2	61
Sørensen, 2010	CBDCA + vinorelbine	47	30	14.6	7.2	55

Abbreviations: CBDCA – carboplatin, CDDP – cisplatin, MMC – mitomycin C, VBL – vinblastine, others – see [TABLE 1](#)

morbidity remains significant.³¹ The role of EPP in the management of MPM remains controversial due to the lack of randomized evidence and because the eradication of all microscopic disease is theoretically unattainable. MPM is a diffuse disease affecting the entire mesothelial lining of the hemithorax, so surgery alone will only rarely achieve adequate microscopically tumor-free resection margins. Despite a radical surgical approach, EPP as a single modality frequently cannot prevent local recurrences. A retrospective analysis of 36 patients referred for radical surgery demonstrated a comparable median survival in patients that underwent EPP and non-EPP patients (20.4 vs. 20.7 months). However, the only longtime survivors with MPM are those that underwent an EPP as part of their treatment. Radical surgery (EPP) should be limited to clinical trials, in specialized centers and as part of a multimodal treatment.³²

Radiotherapy Radical radiotherapy is limited by the same characteristic of MPM that radical surgery faces, namely the widespread nature of the tumor. Radiation therapy to the full hemithorax affects many organs at risk of radiation damage, particularly the lung, liver, and heart, but also the spinal cord and the esophagus. Therefore, it is difficult to administer a radical dosage, and even if a potentially curative schedule can be given, no survival benefit has yet been demonstrated when comparing radical radiation of the hemithorax to best supportive care.^{33,34} However, conventional radical radiotherapy does result in significant toxicity, including radiation-induced pneumonitis, fibrosis, and fistula. Conventional radical radiotherapy is thus limited by large radiation fields; it failed to show a survival benefit and cannot presently be recommended as single-modality treatment in a curative setting.

Multimodality treatment The failure of single-modality treatments with an intention to cure to induce curation or even significant prolongation of overall survival has led to the interest in multimodality treatments. The main multimodality strategies are surgery and postoperative radiotherapy (PORT) with or without chemotherapy. Long-term survival has been described in carefully selected patients with locoregional extension of MPM who receive these aggressive multimodality strategies.³⁵

Surgery and postoperative radiotherapy PORT can be given after a pleurectomy or EPP. Retrospective studies demonstrated similar survival data in patients receiving pleurectomy, whether or not it was followed by PORT, and the addition of conventional radiotherapy only resulted in added morbidity (28% grade III–IV toxicity).³⁶ For this reason, curative radiotherapy should not be performed after pleurectomy or decortication.

Although the removal of the ipsilateral lung during EPP eliminates the lung from the radiation treatment field, the complex target volume of the postoperative hemithorax remains a serious challenge for PORT. Phase II trials including PORT after EPP showed varying results with vast differences in local and systemic recurrences, most likely reflecting different radiation techniques and the dosages administered.^{37,38} No phase III randomized trials of PORT post-EPP exist, but a randomized multicenter European study is ongoing (SAKK study).

In the absence of robust evidence of the efficacy of adjuvant PORT after EPP, it should only be proposed in clinical trials, in specialized centers and as part of a multimodal treatment.

Intensity-modulated radiotherapy Intensity-modulated radiotherapy (IMRT) is a mode of

radiotherapy that theoretically combines good local control with protection of organs at risk.³⁹ Initial studies have shown IMRT after EPP to be feasible; however, some centers reported severe pulmonary toxicity with IMRT with up to 46% of patients developing fatal radiation pneumonitis.⁴⁰ The V20 for the contralateral lung was the only independent determinant for risk of pulmonary-related death, implying that the V20 should be kept as low as possible after EPP. The potentially serious adverse effects restrict IMRT to expert centers.

Trimodality treatment The most aggressive multimodality treatment with curative intent currently consists of the sequential combination of 3 modalities: chemotherapy, PORT, and surgery, with PORT and surgery primarily aimed at achieving locoregional control and chemotherapy at preventing systemic disease. Recent phase II trials have shown a median survival of 29 months for patients who complete trimodality treatment.^{41,42} This approach, however, has not been tested in a multicenter fashion and a small retrospective study failed to show any benefit of combining chemotherapy and PORT with EPP vs. EPP alone.³² These trimodality treatments are also very challenging with considerable morbidity and even mortality, for a large part caused by the inclusion of surgery (EPP). Even after a strict selection, only a minority of patients can finish all 3 modalities and treatment failure is either iatrogenic or disease-related. In conclusion, the available data on trimodality treatment is limited and weak. Until the data from prospective multicenter randomized trials becomes available, patients who are considered candidates for this multimodal approach should be included in these trials in specialized centers.

Patient selection for multimodality treatment Multimodality treatment is feasible, but strict patient selection is mandatory. To aid patient selection, the following criteria are proposed:

- 1 biopsy-proven MPM of nonsarcomatoid cell type
- 2 clinical and/or pathological stage T1–3, N0–1, M0 (some centers include patients with N2 disease)
- 3 fit for pneumonectomy by virtue of sufficient respiratory reserve
- 4 absence of other (moderately) severe comorbidity, especially cardiovascular
- 5 fit to receive neoadjuvant/adjuvant chemotherapy
- 6 fit to receive adjuvant radical hemithorax irradiation.

Conclusion The ERS-ESTS and ESMO guidelines are a first step in harmonizing the management of pleural mesothelioma in Europe. They are multidisciplinary and cover a broad spectrum of issues. Transparency and representation can certainly be improved, as well as the use of a uniform

European grading system. Compared with the recently published National Comprehensive Cancer Network clinical practice guideline, they are more evidence-based, moderate, and less aggressive.⁴³ As is the case with every guideline, the implementation will be the Achilles' heel and indicators of implementation will have to be developed. Furthermore, the advances in management should be regularly assessed and incorporated, calling for a periodic revision of the recommendations. This revision should preferably be conducted by representative experts of all the European societies involved and should result in true multidisciplinary guidelines. The issues addressed should pop up by a broad survey of the actual people at the patient's bed (bottom up) instead of being imposed by a few experts. Finally, the guidelines will have to be translated and distributed in Europe's different languages in order to reach the practitioner. The costs associated with this enterprise should not be underestimated.

Key notes Every patient with MPM should receive at least best supportive care.

In the light of limited evidence of efficacy of chemotherapy, the decision to administer chemotherapy should be discussed with patients and their relatives on a case-by-case basis, like all other treatment modalities without curative purposes.

When a decision is made to treat patients with chemotherapy, subjects in a good performance status should be treated with first-line combination chemotherapy consisting of platinum and pemetrexed or raltitrexed.

Pleurodesis is useful in preventing recurrent effusions. Sterile talc is preferred to other agents and pleurodesis is most effective when performed early in the disease process, but it should not be performed before sufficient tissue has been obtained for diagnosis.

Carefully selected patients can be offered a potentially curative multimodal approach, but no clear survival benefit has yet been demonstrated and eligible patients should be included in a prospective randomized trials in specialized centers.

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Europejskie wytyczne postępowania u chorych z międzybłoniakiem opłucnej

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SŁOWA KLUCZOWE

leczenie, międzybłoniak, opłucna, wytyczne

STRESZCZENIE

Międzybłoniak opłucnej (*malignant pleural mesothelioma* – MPM) jest nowotworem opłucnej, który prawie zawsze prowadzi do zgonu. Postawę pracowników ochrony zdrowia w stosunku do chorych często można określić jako „nihilizm terapeutyczny”. Postęp wiedzy w ostatnim czasie spowodował zmianę perspektyw w terapii MPM. Opublikowano dwa dokumenty wytycznych europejskich: jeden przygotowany przez grupę roboczą European Respiratory Society wraz z European Society of Thoracic Surgery i drugi, przygotowany przez European Society of Medical Oncology. Te wytyczne i rekomendacje stanowiły podstawę do przygotowania niniejszej pracy przeglądowej, w której omówiono istotne postępy wiedzy oraz ich wpływ na postępowanie w przypadkach MPM.

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