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Guidelines of the European Respiratory Society and the European Society of Thoracic Surgeons for management of Malignant Pleural Mesothelioma

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Abstract

Malignant pleural mesothelioma (MPM) is a rare tumour but with increasing incidence and a poor prognosis. In 2008, the ERS/ESTS Taskforce brought together experts to propose practical and up-to-dated guidelines on management of MPM. *Diagnosis*: to obtain an earlier and reliable diagnosis of MPM, the experts recommend performing thoracoscopy except in case of preoperative contraindication or pleural symphysis. *Pathology*: standard staining procedures are insufficient in about 10% of cases. Therefore we propose using specific immunohistochemistry markers on pleural biopsies. *Staging*: in the absence of a uniform, robust and validated staging system, we advice to use of the most recent TNM based classification, and we propose a three steps pre-treatment assessment. *Monitoring*: Patient's performance status and histological subtype are currently the only prognostic factors of clinical importance in management of MPM. Other potential parameters should be recorded at baseline and reported in clinical trials. *Treatment*: MPM exhibits a high resistance to chemotherapy and only few patients are candidate for radical surgery. New therapies and strategies have been reviewed. Because of limited data on the best combination treatment, we emphasize that patients who are considered candidates for a multimodal approach should be included in a prospective trial in specialized centres.

Introduction

Previously considered to be rare, malignant pleural mesothelioma (MPM) is a highly aggressive tumour that has become a very important issue over recent years[1]. Asbestos exposure is the main factor involved in pathogenesis, which can explain the rise in incidence of MPM since the 1960s. Despite the prohibition of asbestos use in Europe in 2005, as in most other developed countries, epidemiological projections estimate that the incidence of MPM still increases and will peak within the next ten years[1,2]. In addition, some countries still produce large amounts of asbestos, with the "top five" including Russia which is by far the larger producer, China, Kazakhstan, Brazil and Canada. Asbestos is used in these countries as well as in other emerging countries such as India, and less-developed nations[3].

The diagnosis of MPM is difficult because the disease may occur up to 30 to 40 years after asbestos exposure, and the differential diagnosis on pleural biopsy between MPM and pleural benign disease or metastasis of adenocarcinoma may be difficult in some cases, even with the use of immunohistochemistry[4,5]. Since MPM patients have a poor outcome and an optimal treatment is not clearly defined, including in the recent guidelines from the French speaking Society for Chest Medicine (SPLF), from the British Thoracic Society (BTS) or from the European Society of Medical Oncology (ESMO)[4-7], MPM will remain a major public health problem for many years.

Therefore the European Respiratory Society (ERS) in collaboration with the European Society of Thoracic Surgeons (ESTS) brought together experts on mesothelioma from different scientific Societies between May 2007 and November 2008 to draw up recommendations in order to provide clinicians with clear, concise, up-to-date guidelines on management of MPM.

Methods

A systematic analysis of the literature from 1990 to 2009 (except for the chemotherapy chapter, 1965-2009) was realized by the experts using the following databases: Medline (National Library of Medicine, USA), Embase (Elsevier, Netherlands), Cochrane Library (Great Britain), National Guideline Clearinghouse (USA), HTA Database (International Network of Agencies for Health Technology Assessment - INAHTA), NIH database (USA), International Pleural Mesothelioma Program - WHOLIS (WHO Database). Following key-words were used for the search in the literature: pleura, cancer, mesothelioma, guidelines, asbestos, treatment, surgery, chemotherapy, radiotherapy.

Each recommendation was graded by the experts, based on the official proposal for evidence-based medicine, provided by the ACCP[8] [see Table 1 in Annex – online material]. Briefly, the strength of any recommendation of the ACCP system depends on the following two factors: the tradeoff between the benefits and the risks and burdens (clear in category 1, or not clear in category 2); and the quality of the evidence regarding treatment effect, graded following three categories: (a) randomized controlled trials (RCT) that show consistent results, or observational studies with very strong treatment effects; (b) RCT with limitations, or observational studies with exceptional strengths; and (c) observational studies without exceptional strengths and case series. Thus the ACCP system [Table 1 in Annex] generates recommendations from the very strong (unequivocal benefit/risk ratio, high-quality evidence, grade 1A) to the very weak (questionable benefit/risk ratio, low-quality evidence, grade 2C). Each recommendation was voted by all experts: if less than 85% of the experts were in total agreement with one proposal, the corresponding recommendation was modified after a new discussion. These recommendations appear following bullets (dots) in the text below.

It should be noticed that the authors of the ACCP system also stated: “whatever the grade of the recommendation, clinicians must use their judgment, considering both local and individual

patient circumstances, and patient values, in making individual decisions. In general, however, they should place progressively greater weight on expert recommendations as they move from grade 2C to grade 1A" [8]. This explains why the ERS/ESTS experts used different terms in their recommendations ("should" or "may" for example) to modulate the strenght of each recommendation to the reader in the clinical practice.

Epidemiology of malignant mesothelioma

1) What are the risk factors associated with malignant pleural mesothelioma (MPM)?

ASBESTOS

Asbestos is the principal etiological agent of MPM. This term refers to a group of six silicate minerals able to form very thin fibres: chrysotile, crocidolite, amosite, anthophyllite, tremolite and actinolite. Chrysotile belongs to the serpentine group and the other ones to the amphibole group of minerals. Chrysotile is less biopersistent in the lungs than amphiboles. Chrysotile, amosite and crocidolite have been widely used for industrial purposes.

The first studies on the association between asbestos and MPM were published in the 1960s[9]. Since most asbestos exposure is work-related, mesothelioma is an occupational disease in the majority of cases. The background incidence is very low. Because past exposure to asbestos was more common in occupations with a predominantly male workforce, the current incidence of MPM is higher among men than among women. For example, according to the French National Mesothelioma Surveillance Program, the risk fraction attributable to occupational asbestos exposure is higher than 80% in men, and lower than 40% in women[10]. This gender difference in risk fraction attributable to occupational exposure to asbestos has also been reported in other countries.

Over the last decades, a shift has been observed in the exposure history of mesothelioma cases, from primary asbestos workers (handling raw asbestos material) to end-users often exposed when installing asbestos products or handling asbestos materials still in place (construction workers, electricians, plumbers, heating worker…). Even if the occupations with the highest risk of mesothelioma belong to the first group, the number of subjects at risk of MPM is presently much larger in the latter.

Environmental mesotheliomas are linked either with a "natural" exposure in areas of the world where asbestos (generally tremolite) exists as a geological component of the soil (Turkey, Corsica, Cyprus, New Caledonia) with sometimes local use for white-washing of walls of houses or with neighbourhood exposures in people living close to asbestos mines or factories[11,12]. Para-occupational cases are described in households of asbestos workers, mainly because of domestic exposure via clothes used at work.

A dose-effect relationship has been demonstrated, but it is impossible to define a threshold of cumulative exposure below which there is no increased risk[13]. Therefore, all individuals who have been exposed to asbestos are considered as a population at risk. The mean latency of

MPM after exposure to asbestos is around 40 years (range 15 to 67 years). In a review of 1,690 cases, latent period was more than 15 years in 99%[14].

Among commercially used fibres, crocidolite and amosite have a higher carcinogenic pleural potency than chrysotile fibres. The carcinogenic potency of short asbestos fibres cannot be ruled out at present time**.**

MPM may be observed in exposed individuals without any other asbestos-related disease (lung or pleural fibrosis). Pleural plaques are a sign of asbestos exposure in the past in most of the cases, and it has been reported that they are associated with a greater risk of mesothelioma. Indeed, it is expected that mesothelioma is more frequent in subjects having pleural plaques than in the general population because both diseases are strongly associated with asbestos exposure. Such association has been reported in some necropsy or cohort studies. By contrast, other cohort studies did not report such association. In a cancer prevention programme at the crocidolite mining and milling town of Wittenoom, Australia, pleural thickening was not associated with an increased risk of pleural mesothelioma after adjusting for time since first exposure, cumulative exposure and age at the start of the programme. The same authors reported an excess of peritoneal mesothelioma in this population[15]. Therefore there is overall no clear evidence that pleural plaques increase by themselves the risk of pleural mesothelioma.

Evidence

The global attributable proportion of MPM to asbestos is more than 80% in males but much less in females. A dose-response relationship is clearly established for asbestos and MPM, but the disease may be observed in subjects having low dose cumulative exposures. MPM is mainly observed following asbestos exposure from occupational origin, but it is also observed for para-occupational and environmental exposures to asbestos. Most amphibole fibres, particularly crocidolite, also amosite and tremolite have a higher carcinogenic pleural potency than chrysotile fibres. Most workers have experienced a mixed exposure to various asbestos types. Mesothelioma has been associated with chrysotile exposure, but in most cases, chrysotile was contaminated or associated with amphibole fibres. The carcinogenic potency of short asbestos fibres cannot be ruled out at present time. Pleural plaques are a sign of past asbestos exposure in most of the cases. There is no clear evidence that they would increase by themselves the risk of MPM. MPM may be observed in exposed individuals without any other asbestos-related disease.

Statement

- The low proportion of MPM attributable to asbestos in females is not yet fully understood and merits further investigations, including search for occult asbestos exposure and/or for other etiological factors (grade 2B).

OTHER FACTORS

Agents other than asbestos are considered as recognized or potential risk factors or cofactors for MPM, namely exposure to other natural (erionite, fluoro-edenite) or man-made (refractory ceramic) fibres, ionizing radiation, and SV 40 virus. Tobacco is known not to play a role in the development of mesothelioma. From available published data, there is no evidence of pleural carcinogenic potency of man-made (vitreous) fibers such as mineral wool (rockwool, glasswool, slagwool) fibres in humans. Genetic factors, which could increase susceptibility, may contribute to the development of MPM, consistently with familial clusters of mesothelioma. A study has suggested that genetic predisposition influences mineral fiber carcinogenesis in Karain (Turkey) where erionite is implicated in an extremely high incidence of the disease[16,17].

Evidence

For some agents, the level of evidence is highly in favor of a causative role in MPM: erionite, therapeutic irradiation (e.a. for breast cancer or lymphoma). For some other agents or situations, there is still controversy or a lower level of evidence in humans: refractory ceramic fibres, SV40 virus. From available published data, there is no evidence of pleural carcinogenic potency of mineral wool (rockwool, glasswool, slagwool) fibres in humans. Tobacco smoking is not carcinogenic to the pleura.

2) What are the future trends in the epidemiology of MPM?

There are prominent differences in incidences reported from different countries worldwide[18]. The incidences vary from 7 per million (Japan) to 40 per million (Australia) inhabitants per year[19]. In Europe, the incidence is around 20 per million. It is reasonable to accept that these differences are mainly due to differences in historical asbestos import and consumption but an influence of diagnostic practices and awareness may also interfere.

For the future, epidemiologists expect peak incidences in the very next decades. Preliminary projections in the nineties were recently reevaluated and date of peak incidence and number of cases were generally less than previously anticipated[2,20-22]. The peak is expected between 2015 and 2020 in Europe[19], and may already have been reached in some countries (USA, Sweden).

Evidence

There are differences in MPM incidence between countries, which mainly reflect differences in asbestos consumption over the past decades in these countries. Because of the long latency of MPM and of national differences in the timing of reduction or ban of asbestos use, the timing of the peak incidence of MPM cannot be predicted precisely and may vary from one country to another. Epidemiological projections have suggested that the incidence of MPM could still increase in Europe for the next ten years. In countries that continue to use asbestos in the 21st century, the incidence of MPM is expected to increase in the next decades.

3) What are the available methods to evaluate exposure to asbestos?

Several methods and tools exist to evaluate cumulative exposures by occupational questionnaires and by the use of job/exposure matrices (Evalutil, Fäser-Jâhre). Due to the long latency of the disease and the lack of precise data on airborne fiber levels, the exact evaluation may be difficult, especially for people other than experienced occupational hygienists or occupational physicians.

Mineral analyses (MA) of biological samples (BAL, lung tissue) by light or electron microscopy can give information about the retained asbestos dose, mainly for amphiboles, which have a longer pulmonary biopersistence than chrysotile. Due to the long latency of MPM and the fact that MPM can be associated with low-dose exposures, MA will not always show high levels of asbestos fibers or bodies. They may however be useful in revealing high levels of fibers when exposure history is unknown or difficult to assess (e.g. indirect exposures). They may also identify specific environmental fibers (e.g. tremolite)[23].

Most MPM cases are linked to past occupational exposure, and MPM is recognised as an occupational disease in most, if not all, national worker's compensation schemes. MPM being generally a severe and fatal disease, the social security aspects are important for the patient and the relatives. As with other occupational cancers, mesotheliomas are under-reported. It is advisable to systematically assess the past exposure history of MPM patients according to the practices of the national worker's compensation or other relevant social security scheme[10].

Evidence

Evaluation of asbestos exposure in a patient with MPM can be made with different tools, mainly through specific occupational and environmental questionnaires.

Recommendation

- Evaluation of asbestos exposure (mainly through specific occupational and environmental questionnaires) is relevant and should be performed for social security and medico-legal purposes according to relevant national practices (grade 1A).

Statement

- Exposure assessment is also important in specific scientific purposes. However it has no therapeutic relevance and may be difficult to perform without the help of occupational hygienists or occupational physicians (experts' advice).

The above principles apply also for mineralogical analysis of biological samples (quantification of asbestos bodies or asbestos fibres in BAL fluid or lung tissue samples). Such mineralogical analyses are not required in the clinical management of mesothelioma.

4) Is there a rationale for MPM screening?

A screening programme is medically justified if the detection of the disease at an earlier stage improves the prognosis by more effective medical or surgical treatment. To date, according to the data available on MPM (prevalence, prognosis, treatment) and the performance (sensitivity, specificity) of potential screening methods, the medical efficacy of a large-scale screening is not established[4,5].

Low dose CT scan has not been proven to be an effective screening tool for the detection of early MPM: no single case of pleural mesothelioma was detected in a cohort of 1045 asbestos exposed workers[24]. PET scan and MRI are imaging techniques that are useful in the clinical management of malignant pleural diseases and in the differentiation of malignant from benign pleural disease, but are not available and/or applicable for screening purposes.

Biological markers (such as soluble mesothelin related peptides, SMRP, osteopontin) are currently studied[25]. Because of the sensitivity and specificity of available biological markers, and because of the prevalence of the disease, the number of false positive tests would be several times higher than true positive subjects identified if screening was proposed to all asbestos-exposed subjects. Therefore, biological markers cannot be presently proposed as screening tools[4,5]. A recent study assessed the value of serum SMRP as a screening test. In a prospective test in 538 individuals with an occupational exposure to asbestos, a low specificity and high number of false positive values were found[26]. No mesothelioma but one lung cancer and one suspected cardiac tumor were observed in this cohort, although 15 subjects (almost 3%) had elevated SMRP levels. This fact could result into a large number of patients would need to be followed-up, with expensive and possibly harmful investigations for many years[27]. Finally, there is no proof that early discovery of a MPM will cure the patient or even improve his or her survival for many months. The authors concluded that SMRP test should not be used for screening pending the results of ongoing large prospective studies that

not only examine its diagnostic accuracy but also the relationship between SMRP levels and survival-specific and disease-specific mortality[26].

Recommendations

- In the present knowledge, there is no place for screening of MPM (grade 1B).
- The usefulness of thoracic imaging and/or biological markers should be further evaluated in selected highly exposed populations included in voluntary surveillance protocols (grade 1B).

Diagnosis of malignant pleural mesothelioma (MPM)

A. From a Clinical point of view

1. Are there any diagnostic clinical criteria?

Recommendation

- The clinical manifestations of MPM are usually non specific and insidious and should not be used alone as diagnostic criteria, even in case of previous asbestos exposure (1A).

2. Are there any specific diagnostic imaging criteria?

Recommendations

- Chest X-ray usually shows a unilateral pleural effusion or thickening. Chest X-ray alone should not be used for the diagnosis of MPM[28] (1A)
- Chest CT scan is unsuitable for definitive diagnosis of MPM, but diffuse or nodular pleural thickening are suggestive of the disease[28,29] (1A)

Statements

- MRI is not relevant for the diagnosis of mesothelioma[29] (1B)
- PET scanning is currently not useful for the diagnosis of mesothelioma[29-31] (1C).

3. What is the role of thoracoscopy for the diagnosis?

When a mesothelioma is suspected on clinical or radiological data, thoracoscopy is the best method to obtain the diagnosis (see Pathology chapter below).

Recommendation

- It is recommended, except in case of preoperative contraindication or pleural symphysis, to perform thoracoscopy for the diagnosis of MPM (1A).

B. From a Pathological point of view

The accurate diagnosis of mesothelioma, a malignant tumour that arises from mesothelial cells that line the serosal cavities, is made on histopathological examination. However, diagnosis can be difficult because mesothelioma is a very heterogeneous cancer and this creates various misleading histopathological pitfalls. Moreover, the pleura is a common site for metastatic disease.

Macroscopic aspect of mesothelioma may vary during its natural history, so that it is depends upon the time mesothelioma is first observed. As pleural mesotheliomas progress their gross appearance becomes more suggestive of MPM to some extent, although other malignant tumours may have a pseudomesotheliomatous aspect (thymomas, carcinomas, lymphomas, angiosarcomas, etc.). The microscopic characteristics of MPM are well defined in the new international classification of pleural tumours[32]. However, this tumour has varied and deceptive appearance in a high percentage of cases and may resemble benign pleural lesions or metastatic lesions, which are much more common than mesothelioma in the general population. Thus the most frequent metastatic pleural tumours are from lung or breast carcinoma whose morphology can be mistaken for mesothelioma on standard sections stained with haematoxylin-eosin-saffron (in 7-15% and 7-11% respectively). Diagnostic problems also occur with frequent benign inflammatory or reactive lesions of the pleura that may occur in patients about the same age as in MPM (pleural effusion during cardiac failure, collagen disease, pneumonia, digestive disease such as cirrhosis, etc). These lesions are often secondary and lead to atypical mesothelial hyperplasia which can result into diagnostic error. In a validation exercise carried out in France by the Pathology Group for Assistance in the Diagnosis of Mesothelioma ("Mesopath"), within the context of the National Program of Mesothelioma Survey (1998-2007), such errors represent 13% of initially-diagnosed cases[10].

1. Which specimens for which clinical presentation?

As pleural effusion is usually the first clinical sign of MPM, cytology is often the first diagnostic examination to be carried out.

Recommendations

- It is not recommended to make a diagnosis of mesothelioma based on cytology alone because of the high risk of diagnostic error (1B)

- It is recommended that a cytologic suspicion of mesothelioma be followed by tissue confirmation (1B)
- Disease recurrence and metastases can be ascertained on cytology alone. This recommendation is in agreement with the one proposed by the International Mesothelioma Panel (1B).

Diagnosis of mesothelioma from fine needle biopsies (Abrams or Castelain needles) is associated with the same problems as cytology. A conclusive diagnosis can only be made if the material is representative of the tumour, in sufficient quantity to allow immunohistochemical characterisation and in the context of appropriate clinical, radiological and/or surgical findings.

Recommendations

- Thoracoscopy should be preferred for diagnostic investigation, allowing complete visual examination of the pleura, multiple, deep and large biopsies (preferably including fat and/or muscle to assess tumour invasion) and providing a diagnosis in more than 90% of cases (1A)
- Fine needle biopsies are not primarily recommended for the diagnosis of mesothelioma because they are associated with low sensitivity (around 30%) (1A).
- It is recommended to take biopsies of both normal and seemingly abnormal pleura (1C).
- It is not recommended to make a diagnosis of MPM solely on frozen tissue sections (1B).

2. What classification should be used?

Recommendation

- It is recommended that the WHO 2004 classification[32] be used for mesothelial tumours (1A). This provides a comparative basis for diagnosis, prognosis and patient management. An updated classification from the IMIG is expected in 2009.

3. Should a complementary immunohistochemical examination be carried out in addition to morphological examination? Which immunohistochemical markers and how many antibodies should be used for which histological variants?

Recommendation

- It is recommended that a diagnosis of MPM always be based on immunohistochemical examination (1A).

The International Mesothelioma Panel has put forward various recommendations. The immunohistochemical approach is depending on whether the tumour subtype of mesothelioma is epithelioid or sarcomatoid.

Recommendations

- To separate epithelioid mesothelioma from adenocarcinoma, it is recommended to use two markers with positive diagnostic value for mesothelioma (nuclear markers such as anti-calretinin and anti-WT1 or the membrane marker anti-EMA, or for epithelioid mesothelioma, anti-CK5/6, antiD2-40 (podoplanin), anti-mesothelin, etc…) and two markers with negative diagnostic value (anti-Ber-EP4, a membrane marker; anti-TTF1, a nuclear marker; monoclonal anti-CEA, anti-B72-3, anti-MOC-31, anti-ER/PR, anti-EMA, cytoplasmic staining) to validate the diagnosis (1A). Among the various sources of antibodies, it is mandatory to use those presenting at minimum 60 to 70% sensitivity. It is not recommended to use anti-CK7/anti CK20 to make the diagnosis of mesothelioma (1A). The antibodies requirements are summarized in Table 1.
- To separate sarcomatoid mesothelioma from squamous and transitional cell carcinoma (Table 2), it is recommended to use two broad-spectrum anti-cytokeratin antibodies; negative immunostaining with a single antibody does not exclude the diagnosis (1C), and two markers with negative predictive value (such as anti-CD34 and anti-BCL2, anti-desmin, anti-S100) to confirm the diagnosis (1A).

With regard to atypical mesothelial hyperplasia (superficial mesothelial proliferations), there are currently no commercially available immunohistochemical markers that identify the benign or malignant nature of the cells observed.

4. Should electron microscopic examination and molecular biology be performed?

Recommendation

- Electron microscopy and molecular biology should not be carried out routinely to confirm the diagnosis of mesothelioma (1A)

Statement

- There are no diagnostic or therapeutic reasons for freezing pleural tumour tissue (1A).

5. Should the advice of an expert panel be sought faced with a suspicion of MPM?

Recommendation

- An independent expert panel should be asked to confirm the diagnosis particularly in clinical trials, or in any case where there is doubt about the diagnosis (1B).

Table 1. Immunohistochemistry to separate epithelioid mesothelioma from adenocarcinoma.

Antibody	Current value	mesothelioma	% of positivity	adenocarcinoma	% of positivity
Mesothelioma					
Calretinin	Essential	Positive (nuclear and cytoplasmic)	80 –100%	Usually negative	5-10% cytoplasmic positivity of lung adenocarcinoma
Keratin CK5/6	Useful	Positive (cytoplasmic)	60 –100%	Usually negative	2-10%,focal positivity
WT-1	Useful	Positive (nuclear)	43-93%	Lung adenocarcinoma are negative	0%
EMA	Useful	Positive (membranous)	60-100%	Positive (cytoplasmic)	70-100%
Podoplanin	Useful	Positive (membranous)	80-100%	Usually negative	7% focal positivity
Lung adenocarcinoma					
CEA monoclonal	Very useful	Almost invariably negative	0%	Positive (cytoplasmic)	50-90%
CD15	Useful	Never expressed in mesothelioma	0%	Positive (membranous)	50-70% focally positive
Ber-EP4	Very useful	Positive or negative (membranous)	Up to 20% car be focally positive	Positive (membranous)	95-100%
TTF-1	Very useful	Never expressed	0%	Positive (nuclear)	70-85% of lung adénocarcinoma
B72.3	Very useful	Rarely positive	< 1%	Positive (cytoplasmic)	70-85% of lung adénocarcinoma
Breast carcinoma					
ER	Very useful	Never expressed in mesothelioma	0%	+ nuclear staining	~ 70%

Table 2. Immunohistochemistry for separating sarcomatoid mesothelioma from squamous and transitional cell carcinoma.

Antibody	Current value	mesothelioma	% of positivity	Squamous and transitional cell carcinoma	% of positivity

Mesothelioma					
Calretinin	Useful	Positive (strong nuclear and cytoplasmic)	80 –100%	Usually cytoplasmic positivity	5-40%
Keratin CK5/6	Not useful	Positive (cytoplasmic)	60 –100%	Cytoplasmic positivity	100%
WT-1	Very Useful	Positive (nuclear)	43-93%	negative	0%
Squamous cell carcinoma					
p63	Very useful	Almost always negative	0%	Positive (nuclear)	~100%
Ber-EP4	Useful	Positive or negative	Up to 20% are positive	Positive (cytoplasmic)	80-100%
MOC 31	Useful	Positive or negative (focal membranous staining)	2-10%	Positive (membranous)	97-100%

Staging, pre-therapeutic investigations and prognostic factors

1. Which staging classification is used?

Staging describes the anatomical extent of a tumour. There are at least 5 staging systems available in pleural mesothelioma, the latest one devised by members of the International Mesothelioma Interest Group and approved by the Union International Contre le Cancer (UICC) (summarized in Table 2 in Annex – online material)[33]. The main drawback of the classifications is the inaccuracy in describing T- and N-extent by current imaging techniques. Because of this, an international panel of experts could not agree on a common staging classification in pleural mesothelioma and strongly advocated the development of a new robust and uniform clinical staging system that should be prospectively validated, TNM-based, and include the existing surgical-pathological staging systems.

Recommendation

- In the absence of a uniform, robust and validated staging system, the experts advocate the use of the most recent TNM-based UICC-classification[33] (1C).

2. What are the minimal pretreatment staging examinations?

The following assumptions were made by the experts' panel: (a) an optimal pretreatment assessment protocol should be simple and widely applicable, sequential and logical, not unnecessarily invasive and identify candidates for proper treatment; (b) the functional and psychological suitability of individual patients for different forms of therapy should be assessed separately (i.e. cardiac and/or pulmonary function); (c) a profound assessment of asbestos exposure should be made in every patient at presentation and recorded in the medical file.

Evidence

The pretreatment assessment is empirically split into three steps, which are to some degree overlapping[34]. Whether a patient goes through all three steps depends strongly on the results of the procedures and the consequences for the choice of treatment with radical or palliative intent only.

Step I is to be considered in all patients at presentation or diagnosis (Table 3). Step II is to be considered in patients being candidate for any kind of active treatment (Table 4). Step III is the final process of patient selection for combined modality or radical locoregional treatment (Table 5). It is the opinion of the experts that this last situation will be only the case in a

minority of patients with pleural mesothelioma. This is reflected in the paucity of evidence, reflecting different institutional practice. Among the investigations to be considered are mediastinoscopy, MRI of the chest, Video Assisted Thoracoscopy (VATS), E(B)US-FNA, FDG-PET-scan and laparoscopy. In the absence of comparative trials no formal advice regarding their respective efficacy can be given.

The experts further agree on that in patients proceeding to step II or higher: (a) a diagnosis of mesothelioma should be confidently established, preferably on a biopsy specimen with adequate immunohistochemistry and subtyping; (b) the interval within which the pre-treatment assessment has to be finalised should be as short as possible; (c) recent (<1 month old) imaging studies should be available prior to invasive procedures. Further research should be done done with regard to the comparative efficacy of different intrathoracic techniques (mediastinoscopy, VATS, EUS-FNA) and the value of the newer ones (PET-CT, EBUS-FNA).

Recommendation

- A three step pre-treatment assessment is recommended based on empirical observation, good clinical practice and the fact that the treatment intent differs between patients (1C).

3. Which prognostic factors are of importance?

Prognostic factors are pre-treatment clinical or biological characteristics of patient or tumour which impact on the outcome, regardless of the treatment installed.

Evidence

Several prognostic factors have been described in large multicenter series and have been independently validated[35]. Among these, the Surveillance, Epidemiology and End Results (SEER) Program review is a landmark retrospective series of 1475 patients with histologically confirmed mesothelioma and showing that age, gender, tumour stage, treatment and geographic area of residence were important prognostic factors[36]. A number of factors - performance status, stage, weight loss - are common to other tumours; others like age and gender have not been confirmed in all series. Symptoms and quality of life are increasingly being investigated as prognostic factors. Non-epitheloid subtype is consistedly associated with a poorer prognosis. Of the numerous biological factors studied, low hemoglobin level, high LDH, high white blood cell and high thrombocyte count have been repeatedly associated with a poor prognosis. New serum biomarkers with potential prognosis significance (e.g. soluble mesothelin and osteopontin) are currently under investigation [37-39]. Based on these various

factors, three prognostic scores have been developed and prospectively validated: the CALGB and the EORTC prognostic scoring system (Table 6)[40,41]. The latter was later adapted according to the results of the multivariate analysis of prognostic factors of a large randomised chemotherapy trial in good performance patients[42,43].

Recommendations

- Performance status of the patient and histopathological subtype are currently the only prognostic factors of clinical importance that may routinely be used in the management of patients with malignant mesothelioma (2A)
- Other parameters with prognostic capacity as age, gender, stage, presence or absence of certain symptoms and hematological factors should be recorded at baseline and reported in clinical trials (2A).

Table 3 : parameters to be considered in all patients at presentation/diagnosis

Investigations	**Including**	**Confirmatory tests**
Demographics	Gender and age, asbestos exposure	
Clinical history	Performance status, comorbidities, presence/absence of chest pain, dyspnea, change in body weight or BMI*	As appropriate
Physical examination	Presence or absence of "shrinking hemithorax", cutaneous nodules...	As appropriate
Radiological investigations	Chest X-ray: PA/lateral	Chest X-ray: in-/expiration, pre-/post drainage of pleural fluid
Blood tests	Hemoglobin, leukocytes, platelets, basic biochemistry	

*BMI: Body Mass Index

Table 4: investigations performed in patients likely to receive any kind of active

treatment		
Investigations	**Including**	**Confirmatory tests**
Primary tumour	Adequate biopsy for histology confirmation	
CT scan of chest and upper abdomen	Spiral technique, with iv contrast, including at least level of both kidneys after drainage of pleural fluid	
Pulmonary function tests	Forced Vital Capacity (FVC), Forced Expiratory Volume 1 sec (FEV1)	
Bone scan	Not routine, to be considered on clinical suspicion only	CT/MRI to confirm dubious findings
Brain CT/MRI		

Table 5: investigations to be considered in patients candidate for surgery or multimodal treatment			
Area	**Investigation**	**Comment**	**Confirmatory tests**
Pulmonary function tests	DLCO in addition to FVC and FEV1	Assessment similar to the one for lung cancer	Lung scintigraphy probably performed as for any pulmectomy
Primary tumour	Adequate biopsy for histological subtyping		
Diaphragm	CT-scan or MRI		
Extra-thoracic, to exclude "occult" M1	FDG-PET/CT		Biopsy of suspected extrathoracic lesions
	Laparoscopy	According to institutional practice	
Mediastinum, excluding T4, N2/3 involvement	Cervical mediastinoscopy		
	VATS, contralateral VATS		
	MRI of the chest, Gadolinium enhanced		
	E(B)US-FNA	Investigational	

Table 6: prognostic scoring systems in malignant mesothelioma			
	Parameter	Good prognostic group	Poor prognostic group
CALGB (n= 337)[40]	Performance status	Good	Poor
	Age	<75 y	≥75 y
	Chest pain	Absent	Present
	Platelet count	<400 x 10^{12}/l	≥ 400 x 10^{12}/l
	LDH	<500 IU/l	≥ 500 IU/l
EORTC (n=204)[41]	Performance status	0	1-2
	Histological subtype	Epitheloid	Non-epitheloid
	Gender	Female	Male
	Certainty of diagnosis	Definite	Possible
	WBC count	<8.3 x 109/l	≥ 8.3 x 10^{9}/l
EORTC (n=250)[42]°	Stage	I-II	III-IV
	Histology	Epitheloid	Non-epitheloid
	Interval since diagnosis	<50 days	≥ 50 days
	Platelet count	< 350 x 10^{12}/l	≥350 x 10^{12}/l
	Hemoglobin difference*	<1	>1
	Pain	Absent	Present
	Appetite loss	Absent	Present

°: Performance status 0-1 was an inclusion criterium for this series.

*: Difference between actual value and 16 g/dl in male and 14 g/dl in female

Treatment of Malignant Pleural Mesothelioma (MPM)

A. Surgery for MPM

1. What is the evidence for debulking decortication/pleurectomy for symptom control?

Debulking pleurectomy/decortication can be defined as significant but incomplete macroscopic clearance of pleural tumour. The objective of the operation is to relieve an entrapped lung by removing the visceral tumour cortex. Removal of the parietal tumour cortex may relieve a restrictive ventilatory deficit and reduce chest wall pain. The operative procedure may be performed by either open thoracotomy or closed video assisted thoracoscopic surgery (VATS).

Evidence: there is limited evidence supporting debulking surgery. There is at present an absence of randomized trials, but a national study is ongoing in United Kingdom supported by the NCRI comparing VATS debulking with chemical pleurodesis (MesoVATS). There are a small series of retrospective studies which provide low grade evidence for debulking pleurectomy[44-47]. The associated morbidity of thoracotomy may diminish the benefits[48], however there is limited but emerging evidence that VATS can provide good symptom control and may have a beneficial effect on survival[46].

Recommendations

- Pleurectomy/decortication should not be proposed in 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)
- The VATS approach is to be preferred (1C).

2. What is the evidence for radical surgery in MPM?

Radical surgery may be defined as an attempt to remove all macroscopic tumour from the hemithorax. These objectives are usually achieved by extrapleural pneumonectomy (EPP) with en-bloc resection of pleura, lung, pericardium and diaphragm and systematic nodal dissection.

Evidence: there is limited evidence for the efficacy of radical surgery for mesothelioma. Among resected mesothelioma patients, the only published long-term survivors have undergone radical surgery (EPP) as part of a multimodality program[49-51]. There have been a number of subsequent prospective and retrospective series which have all demonstrated a

similar median survival of 20 - 24 months[49-51]. Operative mortality has fallen to an acceptable level of around 5% in experienced centres[51] but morbidity remains high at around 50%.

Recommendation

- Radical surgery (EPP) should be performed only in clinical trials, in specialized centers, as a part of multimodal treatment (see this chapter below)

B. Radiotherapy in MPM

1. What is the role of 'palliative' radiotherapy aimed at pain relief?

Recommendation

- Palliative radiotherapy aimed at pain relief may be considered in cases of painful chest wall infiltration or nodules (2C).

2. What is the role of radiotherapy in the prevention of parietal seeding along the drainage channels?

Boutin and al previously suggested that an irradiation with 3 x 7 Gy for three consecutive days, in the four weeks following drainage or thoracoscopy, should be performed to prevent subcutaneous metastasis developing along drainage channels or thoracocentis tracts[52]. However, a recent randomised trial was published comparing immediate drain site radiotherapy 21 Gy in three fractions to best supportive care in 61 pts treated between 1998 and 2004, with no difference in terms of tract metastatic recurrence between the 2 arms [53,54]. The authors concluded that prophylactic drain site radiotherapy in MPM did not reduce the incidence of tumour seeding as indicated by previous studies. They came to the same conclusion as the Cochrane Overview[55]. Suboptimal techniques of radiotherapy may explain the discrepancy of these results, and should certainly be an issue.

Recommendation

- The value of prophylactic radiotherapy is questionable. Therefore the experts were not able to draw any recommendation.

3. What is the role of post-operative radiotherapy?

Data from the literature are limited and come from retrospective studies.

Recommendations

- Radiotherapy should not be performed after pleurectomy or decortication (1A).

- Post-operative irradiation after EPP should only be proposed in clinical trials, in specialized centers, as a part of multimodal treatment (see this chapter) (1A).

In the absence of Phase III randomised trials, the establishment of a prospective controlled study evaluating the efficacy and tolerability of adjuvant radiotherapy post-EPP (minimum dose of 50 Gy with daily fraction size of 1.8 to 2 Gy) is recommended (1C). A randomized multicenter European study is ongoing to answer this question (SAKK study). Retrospective studies seem to show a radiation dose effect that should be further studied with conformal radiation technique. In the study published by Rush and al, who used 54 Gy hemithorax radiation as adjuvant therapy after EPP, the local recurrence rate was 13%, with a 4% local-only recurrence rate, whereas in the study published by Baldini et al, there was a 50% local recurrence rate, with a 13% local-only rate, after trimodality therapy[50,56]. The ability to cover fully all the areas at risk, limited by the surrounding normal structures (heart and liver, particularly), the total dose given and radiotherapy technique contribute to explain these discrepancies.

4. What is the place for intensity-modulated radiotherapy (IMRT) in malignant pleural mesothelioma (MPM) after EPP?

Preliminary results of IMRT in the adjuvant setting after EPP seemed particularly promising as they could provide good local control and protect organs at risk such as heart or liver. However, severe pulmonary toxicity has been reported in recent studies so that it should not be recommended outside of clinical trials; six out of 13 patients developped fatal pneumonitis[57].

Derived from these recent retrospective studies, so as to predict the risk of pneumonitis, the following pulmonary dosimetric values (V20, V5 and Mean Lung Dose) should be specified. The V20 (volume of both lung minus the PTV) should be less than 15%, and the mean lung dose or MLD should be less than 10 Gy. These dosimetric constraints can be used for conformal radiotherapy as well, dose-volume histograms (DVH) of all target volumes (CTV and PTV) and of all critical organs (contralateral lung, cardiac volume, spinal cord, oesophagus, liver, right and left kidney) should be clearly stated.

Statement

- Further studies are needed to establish better the role of radiotherapy. Recent studies have underlined the importance of radiotherapy technique both in terms of local control and toxicity.

Recommendation

- It is therefore recommended to carry out this radiotherapy only in specialised centres (advice of experts).

C. Chemotherapy of MPM

The methodology used to answer the following questions was previously described[4,58]. The recommendations were based on (a) the on-line recommendations from the Cancer Care Ontario (www.cancercare.on.can) entitled « The use of chemotherapy in patients with advanced MPM »; (b) the literature review with meta-analysis published in 2002 by T. Berghmans et al[59], updated in 2003[60], completed by the articles published after these reviews until January 2009; and (c) the French recommendations on chemotherapy in MPM published by the French Speaking Society for Chest Medicine (SPLF)[4,58].

1) Has the benefit of chemotherapy been demonstrated?

Currently, only one randomised study assessed the efficacy of chemotherapy versus placebo in malignant mesothelioma. Results were presented at the ASCO and ECCO 2007[61]. No survival difference was observed between both arms, excepted for a trend favouring the vinorelbine sub-group. It must be pointed that, according to the results of randomised studies (see further) and the systematic review[59,60], the choice of comparative chemotherapy was probably not adequate. Also, the study was prematurely stopped due to the limited number of inclusions. Indirectly, the randomised studies performed by Vogelzang et al[62] and van Meerbeeck et al[42] suggested that a polychemotherapy including cisplatin and an antifolate, pemetrexed or raltitrexed, could increase survival if we consider that cisplatin monotherapy is equivalent to a therapeutic abstention. Indeed, median survival rates observed with the combinations of cisplatin-pemetrexed (12.1 months) or cisplatin-raltitrexed (11.4 months) were largely above those usually reported in the literature (7 to 9 months). The statistically significant difference in comparison with the cisplatin monotherapy arm (9.3 and 8.8 months) was an indirect argument suggesting a beneficial effect of chemotherapy. However, no published study has compared cisplatin monotherapy to palliative care only.

Table 3 (Annex – online material) summarises the data concerning chemotherapy in randomised (5 trials) and non randomised studies. In first line, two randomised phase III trials are available[42,62]. They demonstrated the superiority of a combination of cisplatin and pemetrexed or raltitrexed over cisplatin monotherapy, both for response rates and survival, although cisplatin alone should not be considered as a standard treatment. It is important to

note the role of folic acid and vitamin B12 supplementation to reduce the haematological toxicity of pemetrexed. Other cisplatin-based combinations produced interesting response rates, as observed in the meta-analysis of phase II studies[59,60], around 25-30% for the following associations cisplatin plus etoposide, cisplatin plus doxorubicin, cisplatin plus gemcitabine, cisplatin plus interferon, oxaliplatin plus raltitrexed (or gemcitabine or vinorelbine) and methotrexate. The combinations cisplatin-pemetrexed or cisplatin-raltitrexed could act as reference arms in further randomised trials. The inclusion of patients in good general condition in clinical trials remains ethically justified.

After failure of first-line chemotherapy, no randomised study demonstrated the impact of second-line treatment on survival or quality of life. Indirect data extracted from the follow-up of a first-line randomised trial[63] suggested that second-line chemotherapy after cisplatin-pemetrexed could increase survival in comparison with symptomatic treatment alone. These data need confirmation in a randomised study. The available data on this topic are rare (6 phase II studies[64-69] and do not allow to propose a particular chemotherapy schedule. It is recommended to include patients in good general condition in clinical studies, this approach being ethically acceptable.

First line combination chemotherapy including cisplatin and pemetrexed or raltitrexed demonstrated greater activity than cisplatin alone in phase III trials (level 1), with higher response rates and improved survival. However, in the BTS study, there was no survival advantage of chemotherapy (vinorelbine alone or MVP) over best supportive care alone (level 2). Other studies, including potentially active combination like cisplatin plus gemcitabine or etoposide or doxorubicin, could be conducted (versus BSC or cisplatin/pemetrexed or raltitrexed) (expert opinion). The role of non-platinum regimens remains to be elucidated (level 2). No randomised study has demonstrated the benefit of second-line chemotherapy on survival (except on survival without disease progression in a phase III study by Jassem et al[70]) or quality of life after failure of primary chemotherapy.

Recommendations

- Every patient should receive at least best supportive care (1A).
- 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). Alternatively, patients could be included in first and second-line clinical trials.

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

2) When should chemotherapy be started? For how long should chemotherapy be continued?

There is a shortage of available arguments in the literature on the most appropriate timing to administer chemotherapy: increase in overall survival in patients with adequate general condition in two randomised phase III trials[42,62]; (b) better theoretical efficacy of a chemotherapy on small tumour volume[71-73]; (c) a small size randomised trial compared, in patients with controlled symptoms during at least 4 weeks, immediate chemotherapy versus delayed treatment at the time of symptoms progression. The duration before symptomatic progression (25 weeks versus 11 weeks) and survival (median 14 months versus 10 months; 1-year 66% versus 36%) were prolonged in case of immediate chemotherapy without reaching formal statistical significance (p = 0,1)[74].

There are no data allowing to definitively answering the question of the optimal duration of chemotherapy. In Vogelzang's study[62], 53% of patients in the cisplatin-pemetrexed arm received 6 cycles (from 1 to 12 cycles, more than 8 cycles in 5%). In van Meerbeeck's study[42], the median number of cisplatin -raltitrexed cycles was 5 (from 1 to 10 cycles). We do not have data on the potential advantage to deliver more than 6 cycles in patients with stable disease. By analogy with NSCLC, it is recommended to stop chemotherapy in case of progression, grade 3-4 toxicity or toxic cumulative doses, and to stop chemotherapy after 6 cycles in stable or responding patients. Experimental treatments, including biological therapies, must be discontinued according to the pre-specified experimental protocol. There are no data on the value of maintenance treatment with chemotherapy or immunomodulators.

Recommendations

- 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 (1A), or following up to six cycles in patients who respond or are stable (2C).

3) What cytotoxic drugs are effective as second-line treatment?

Several publications are specifically dealing with second-line chemotherapy[64-70,75,76]. Other articles are difficult to interpret because assessing patients both in first and second-line. They were not considered for this review. Chemotherapies consisting in doxorubicin, doxorubicin plus cyclophosphamide, oxaliplatin-raltitrexed or ZD 0473 (platinum analogue) appeared ineffective. Some interesting response rates were noted with pemetrexed alone[69], the combination of carboplatin and pemetrexed[69] and of cisplatin, irinotecan and mitomycine C[68]. Nevertheless, pemetrexed was compared in a phase III randomised trial versus best supportive care. It showed an improvement in response rate and time to progression but failed to show any survival benefit[70]. Since vinorelbine has shown first line activity, it might be a reasonable choice in second line. A recent small study on 63 patients reported a 16% rate of responses and median survival of 9.6 months in this setting[76]. Thus, no drug has been validated in second line chemotherapy, and patients in a good performance status should rather be proposed to enter in clinical trials.

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 (2C).
- In other cases, inclusion of the patients in clinical trials is encouraged (2C).

4) What is the role of biotherapies in the treatment of MPM?

Results of studies assessing the efficacy of drugs modulating the activity of the immune system or having a "specific" action on the tumour (targeted therapies) are summarized in Table 3 (Annex – online material).

Immunomodulators

Interferons and interleukins are the principal drugs being tested in the treatment of malignant mesothelioma. Dose, method of administration (intrapleural, sub-cutaneous, intramuscular, intravenous), type of drug and disease stage varied from one study to another, so that results interpretation must be cautiously performed. Monotherapy with interferons or interleukin-2 seemed not effective and is not recommended outside of a clinical trial.

Interesting preliminary results were observed after administration of *Mycobacterium vaccae* in a limited number of patients. This needs to be confirmed before recommend the use of this treatment. Ranpirnase has not demonstrated its effectiveness.

Targeted therapies

Some biological targeted therapies are effective in lung, colon and breast cancers. Few studies are available in malignant mesothelioma. The principal drugs currently tested are the following.

Thalidomide (anti-angiogenic drug): among 40 patients treated in a phase I/II, 11 presented with stable disease during more than 6 months, with median survival of 230 days; however, these results do not allow classifying thalidomide as an active drug[77]. Bevacizumab (monoclonal antibody directed against VEGF) : a phase II randomised study compared cisplatin plus gemcitabine with or without bevacizumab. The addition of bevacizumab did not result into improved response rate (25% versus 22%) nor survival (MST 15.6 months versus 14.7 months; p = 0.91)[78]. Gefitinib : in a phase II study including 42 patients receiving gefitinib 500 mg p.o. every day, only two objective responses were documented; the authors concluded to the absence of activity of gefitinib in this indication[79]. Imatinib : it demonstrated no activity in a published phase II[80] and in 2 studies presented at the ASCO meeting[81,82]. Erlotinib: no objective response was observed in a phase II study among 33 patients with measurable disease[83].

Recommendation

- Immunomodulating agents, targeted biotherapies and vaccines should not be used in the treatment of MPM outside clinical trials (1C).

5) What assessment criteria should be used to determine the efficacy of chemotherapy in MPM?

The activity of a treatment can be assessed on clinical criteria (symptoms control and quality of life), imaging criteria (CT-scan, positron emission tomography or PET), survival criteria (time to progression, overall survival). The evaluation of response by thoracoscopy was never reported.

a) Imaging evaluation criteria of tumour response

Response evaluation criteria are varying from one study to another and not always reported. The systematic practice of a referential CT-scan after pleural symphysis and before beginning chemotherapy was not mandatory, distorting response evaluation. The timing for evaluation is also lacking most of the time.

Today, it can be considered that standard chest X-ray is not a valuable method to assess response to chemotherapy (see chapter on diagnosis).

There are different methods for objective response assessment depending on the type of criteria, WHO (product of 2 perpendicular measures) or RECIST (one dimension measure).

None of these methods is adapted to malignant mesothelioma whom development is essentially circumferential, on the gross pleural surface[84]. It is currently proposed modified "RECIST criteria" (measure of the short diameter perpendicular to the chest wall court) [84-86].

b) Tumour response evaluation according to PET criteria

Differentiating tumour tissue from post-chemotherapy scar lesions is difficult with CT-scan. PET allows assessment of both tumour sizes and captation intensity. The combination of PET and CT-scan, both examinations performed on the patient in the same position, allows a better correlation of these two techniques. The contribution of this new imaging modality in response evaluation needs yet to be validated. For clinical trials, in absence of standardisation in response evaluation with PET in malignant mesothelioma, the use of PET response criteria proposed by the EORTC[87] can be considered (Table 4 in Annex – online material).

c) Survival

Overall survival is the only valuable criteria to assess the effectiveness of chemotherapy in therapeutic protocols.

d) Quality of life

It is recommended to take into account quality of life and symptoms control to evaluate the clinical benefit (efficacy/tolerance) in disease of poor prognosis and for which the survival impact of the treatment is not clearly demonstrated or marginal. No particular score to assess quality of life is specifically recommended excepted the modified version of the Lung Cancer Symptom Scale (LCSS) adapted to patients presenting with malignant mesothelioma[88].

Recommendations

- For assessment and follow-up of MPM, chest CT-scan is recommended. If a patient has had pleurodesis, a chest CT-scan should be performed again before the start of chemotherapy in order to better evaluate the response to treatment (1B).
- The modified RECIST criteria are the preferred method of measuring response to treatment (1B).

PET-scan and biological markers are still under investigation for the evaluation of response to treatment in MPM.

D. Combined Modality approach

The following criteria are considered for possible extra-pleural pneumonectomy (EPP) indications:

1. biopsy proven malignant pleural mesothelioma of non-sarcomatoid cell type
2. clinical and/or pathological stage T1-3, N0-1, M0 (*)

3. patient fit for pneumonectomy by virtue of sufficient respiratory reserve and lacking other co-morbidity e.g. cardiovascular
4. patient fit to receive neoadjuvant/adjuvant chemotherapy
5. patient fit to receive adjuvant radical hemithorax irradiation
6. EORTC and CALGB scores (Table 6) may be calculated in patients to support EPP indication. But the value of the scores to define a "favourable prognosis" group should be validated in a prospective clinical trial.

(*) It should be noted that some centers include patients with N2 disease in their study although N2 disease has a worse overall survival.

1. What is the rationale behind the multi-modality approach?

Older literature indicates that surgery alone for MPM is not curative since no oncological resection margins can be obtained. The pleural lining, especially on the pericardium and mediastinum cannot be resected with a 1-2 cm margin. Therefore all surgical procedures are considered R1 resections[50]. This observation is therefore the rationale for combined therapy *(Level of evidence: Strong/low quality evidence).*

The use of radiation therapy to the full hemi-thorax is limited by critical organs such as contralateral lung, liver and heart most particularly but also spinal cord and oesophagus. Therefore it is difficult to administer a total dose more than 54 Gy to such a large volume, so that sophisticated treatment techniques, oriented by surgeon's and pathologist's findings, are needed.[89,90] *(Level of evidence: Strong/low quality evidence).*

2. ***Which patient is suitable for this approach?***

Due to the extent of surgery and combination treatment, patients need to undergo a thorough work-up before embarking on any multi-modality treatment. Until 2004, most combined treatments have focussed on surgery followed by radiation therapy since active chemotherapy regimens were not available. For potential patients the work-up should consist of at least:

a) physical examination: shrinkage of the afflicted hemi-thorax is considered a sign of advanced disease. No signs of growth through the ribs or in the abdomen
b) pulmonary function tests: post pneumonectomy values should be sufficient for normal daily life functioning
c) adequate cardiac reserve with the absence of elevated pulmonary pressure or rhythm disorders *(Level of evidence: Weak/moderate quality evidence)*

d) radiological examinations to rule out spread of the disease beyond the rib cage; through the diaphragm; contra-lateral extension and multiple node involvement *(Level of evidence: Weak/moderate quality evidence)*
e) Histological examination; the best results have been obtained with MPM of the epithelial type *(Level of evidence: Weak/high quality evidence)*
f) Gender: there are no solid data that there is a difference in response to treatment between the different sexes[91] *(Level of evidence: Strong/low quality evidence).*

3. ***What is the best combination?***

There is a body of literature that deals with the combination of surgical resection followed by radiation therapy. The procedures vary with regard to the extent of resection (removal of the complete diaphragm, pericardium, placement of patches etc). Recently the bi-modality approach has been extended with pre or per-operative chemotherapy: two studies have been performed using platinum with an anti-folate (pemetrexed). One has been presented as a poster[92] while the EORTC study 08031 is being analyzed[93]. Some reports have been made on the use of per- and post-operative chemotherapy combined with hyperthermia. This approach however is not tested in a multi-centre fashion[94-96]. All surgical combination therapies that included EPP can only be performed at the cost of additional morbidity (up to 70%) and a mortality rate in specialized centres that should be less than 7% *(Level of evidence: Strong/low quality evidence).*

Currently national groups are considering the question whether there is any advantage at all of this tri-modality treatment. Recently a Swiss study tested the effect of induction chemotherapy followed by EPP and limited radiation to high-risk sites in 61 patients. Of the 45 patients who had an EPP, the survival was 23 months compared to 19.8 months for the whole group[51] *(Level of evidence: Strong/low quality evidence).*

In conclusion, there are limited and weak data available on the best combination treatment.

Recommendation

- Patients who are considered candidates for this multimodal approach should be included in a prospective randomised trial in specialized centers.

E. Control of symptoms in MPM

Mesothelioma has a high symptom burden: a study of 53 patients with mesothelioma receiving chemotherapy with cisplatin and gemcitabine revealed that their mean scores on the EORTC quality of life questionnaire exceeded reference scores in lung cancer in the following areas: fatigue, dyspnoea, pain, insomnia, cough and anorexia[97]. This chapter is confined to discussion of symptoms frequently experienced by patients with mesothelioma. A retrospective randomised notes review demonstrated the common symptoms in mesothelioma as summarized in Table 5 (Annex – online material).

1. Management of pain

a) How is pain in MPM evaluated?

Pain in mesothelioma is frequently complex due to a combination of nociceptive, neuropathic and inflammatory factors[98].

- Use of a visual analogue pain assessment tool improves cancer pain management (1C)
- If the patient has cognitive impairment due to pain or advanced disease, pain may be assessed using a behavioural assessment tool such as the Doloplus scale (1C)

b) What is the general principle of treatment of pain in MPM?

Recommendations

- Pain control in mesothelioma should follow the principles of cancer pain management (1C).
- However, due to the complex nature of pain in mesothelioma, adjunct analgesia may frequently be required in addition to opiates. In cases of refractory pain unresponsive to the usual measures, a specialist pain management or specialist palliative medicine opinion should be sought (1C).
- Occasionally neuroablative techniques may be required, depending on specialist advice, and with careful consideration of the risks and benefits (2C).
- Palliative radiotherapy may be proposed and effective in treating pain due to tumour nodules (2C)

2. ***Management of dyspnoea***

a) Is repeated pleural aspiration justified?

Recommendations

- This should be avoidable if pleurodesis is performed early in the disease and before effusions have become loculated and/or the lung has become fixed and unable to expand fully (1C).

- Repeated aspiration or indwelling chest drain may occasionally be the most practical way to manage recurrent effusions in very frail patients (2C).

b) What is the place of pleurodesis?

Recommendation

- Pleurodesis is useful in preventing recurrent effusions. Sterile talc is preferred to other agents (1A).

c) When should talc pleurodesis be performed?

Recommendation

- Pleurodesis is most effective when performed early in the disease process (1C) but it should not be performed before sufficient tissue for diagnosis has been obtained (1A).

d) Are other treatments of value in the management of dyspnoea?

Recommendations

- Low dose oral morphine may be useful in reducing the sensation of dyspnoea and thus also reducing associated anxiety (1A).
- Oxygen may be helpful but should not be used unless there is evidence of reduced oxygen saturation (1C).

e) Can other measures be used to alleviate dyspnoea?

A simple fan that creates a cool stream of air across the face may reduce the sensation of dyspnoea via the trigeminal nerve. Self-help breathlessness management techniques, designed to increase patients' sense of mastery over their breathlessness, have been shown to be effective in lung cancer but the work has not be conducted specifically in mesothelioma[99].

3. Management of other physical symptoms

This is a brief account of simple measures used to palliate common symptoms (advice of experts). Further information should be sought from expert texts on palliative medicine.

Statements

- Cough may respond to cough suppressants such as codeine linctus or pholcodine. It is important to exclude or treat co-morbidities such as chest infection or cardiac failure.
- Anorexia, weight loss, and fatigue constitute the anorexia/cachexia syndrome common to many malignant conditions. Attention to high-energy, small volume, frequent meals, treatment of oral candida if present, and avoidance of dehydration and constipation may help.

- Sweating may improve with avoidance of restrictive clothing, use of a fan, and medication such as cimetidine.
- Dysphagia may be due to oral candida or from external compression of the oesophagus due to tumour. Candida responds to treatment with oral fluconazole. Stenting of the oesophagus may be effective in reducing dysphagia due to external compression.
- Ascites usually develops due to tumour extension through the diaphragm into the peritoneal cavity. Paracentesis may reduce discomfort due to large volume ascities but may need to be repeated.
- Constipation results from inactivity, poor oral intake and as an inevitable consequence of opiates. Laxatives should be prescribed proactively and taken regularly. This sign may suggest a tumour extension through the diaphragm into the peritoneal cavity.
- Vomiting may occur as a side effect of chemotherapy and responds to anti-emetics. It may also be a side-effect of opiate analgesics and changing to an alternative may be successful.

4. Management of psychological distress

Patients with mesothelioma may exhibit anger, depression or stoicism and resigned acceptance. Reports from specific mesothelioma telephone help-lines demonstrate that patients and their families request accurate information about the illness, treatment options, state benefits and medico-legal issues.

Recommendation

- Support may be offered by specialist nurses, psychological or psychiatric services and asbestos support groups (1C).

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