



Second Italian Consensus Conference on Malignant Pleural Mesothelioma: State of the art and recommendations

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ABSTRACT

Malignant pleural mesothelioma (MPM) is a relevant public health issue. A large amount of data indicate a relationship between mesothelioma and asbestos exposure. MPM incidence has considerably and constantly increased over the past two decades in industrialized countries and is expected to peak in 2010–2020. In Italy, the standardized incidence rate in 2008 was 3.6 and 1.3 per 100,000 in men and women respectively, with wide differences from one region to another. The approach to this disease remains difficult and complex in terms of pathogenic mechanism, diagnosis, staging and treatment thus an optimal strategy has not yet been clearly defined. The Second Italian Multidisciplinary Consensus Conference on Malignant Pleural Mesothelioma was held in Turin (Italy) on November 24–25, 2011: recommendations on MPM management for public health institutions, clinicians and patients are presented in this report.

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Introduction

Malignant pleural mesothelioma (MPM) nowadays can no longer be considered an uncommon malignant disease, as the extensive use of asbestos since the 1950s has led to an important increase in both incidence and mortality rates. Incidence has considerably and constantly increased over the past two decades in the industrialized countries and is expected to peak in 2010–2020. The approach

to this disease remains difficult and complex in terms of diagnosis, staging and treatment and an optimal strategy has not yet been clearly defined. The First Italian Consensus Conference on Malignant Pleural Mesothelioma was held in Bologna (Italy) in 2008.¹

The Second Italian Multidisciplinary Consensus Conference on Malignant Pleural Mesothelioma was held in Turin (Italy) in November 2011 and endorsed by AIOM (Italian Association of Medical Oncology).

Methods

The consensus adopted the GRADE approach (<http://www.gradeworkinggroup.org/>) to design and build up the recom-

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mentations. In the planning phase, each panel defined some relevant questions, chose the endpoints and ranked their importance. The methodological group organized the electronic search, selected the relevant evidence according to the panel indications, produced summary of findings, tables and rated the quality of evidence according to GRADE.² These profiles represented the basis for the recommendation. The GRADE approach was limited to questions relative to efficacy comparisons. For questions related to diagnosis and epidemiology the approach remained the same as used in the previous consensus. The list of questions for discussion and consensus proposed to each panel of experts is reported in [supplementary Table 1](#).

Summary of epidemiology, public health and surveillance evidence

According to the Italian Registry of Malignant Mesothelioma (ReNaM), in 2008 MPM incidence was 3.6 cases per 100,000 person-years in men and 1.3 in women. Corresponding rates for peritoneal MM were 0.24 and 0.12 and 1422 incident cases of MM (all sites) were observed.³

In Italy median survival of MPM cases diagnosed in 1990–2001 was 9.8 months and less than 10% were alive after 3 years, similarly to other countries.^{4–6}

The occurrence of MPM showed an increasing trend in recent decades, steeper in industrialized countries, related to asbestos exposure and its temporal variation.^{7–10} In Italy analyses using different models agreed in predicting the epidemic peak. According to one model it is expected between 2010 and 2020, with about 1000 deaths per year¹¹, while on the basis of an alternative model, the peak should occur in 2012–2025 with a maximum of 800 deaths per year in males.⁸ The rate of increase is slowing down in countries that first started asbestos reduction policies or banned asbestos. This change is more evident in younger age classes that were less exposed.⁷

All asbestos types cause MM.^{12,13} Amphiboles are more potent in causing MM than chrysotile, but the magnitude of the difference between the two asbestos families is still debated.¹⁴

“Asbestiform minerals” include other naturally occurring fibrous minerals (e.g., erionite, fluoro-edenite and vermiculite) which share silica based framework and fibrous morphology with asbestos. They had no or limited use but some have been causally associated to MM in humans upon environmental exposure.^{12,13} Risk of MPM is increased after non-occupational exposure to asbestos and asbestiform mineral fibers.^{15,16} Non-occupational exposure is estimated to cause 8.3% of MPM in Italy.¹⁷ In the ReNaM case series, asbestos exposure was detected in 80.5% of cases with exposure assessment (93% in men diagnosed in the most recent years).¹⁸

IARC classified man made mineral fibers (MMMMF, amorphous materials produced in fibrous shape by extrusion or other artificial means) with various degrees of evidence of carcinogenicity.^{19,20} In epidemiological studies the exposure to ceramic fibers and glass-wool was not associated with MM, opposite to animal studies.^{20–25} For High Aspect Ratio Nanomaterials (HARNs), similarities between asbestos and carbon nanotubes were reported, but conflicting data were obtained in experimental studies.^{26–29}

Research on other causes of MPM focused on ionizing radiation and viruses. The studies on thorotrast and on subjects treated with ionizing radiation showed an increased risk of MM, both pleural and peritoneal, depending on the exposed body area.³⁰ However, such exposure explains a minimal proportion (1.7–4.7%) of MM cases occurring in Italy. Research no longer supports a causal association with SV40 infection.^{31,32}

Family clusters of MPM may suggest genetic predisposition but common asbestos exposure must be carefully investigated and family clusters only include 1.38% of all cases.^{33,34} Studies on genetic risk suggested association between MPM and polymorphisms of genes of DNA repair after oxidative stress: ORs were between 2 and 4, in addition to the asbestos induced risk.^{35,36} BAP1, an oncosuppressor gene, was investigated in two studies on MM.^{37,38}

Asbestos fibers (AF) act through different mechanisms.^{39–42} The main factors modeling MM risk include fiber type, size, exposure level and time.^{43–45} Our systematic review of the literature showed that risk of MM increased with cumulative dose and lung fiber burden, in agreement with previous reviews.^{46–50} The group acknowledged difficulties and possible errors in the estimation of cumulative dose, the importance of evaluating separately intensity and its time variation when possible, and that fiber burden at the sampling time may not represent accurately the lifelong burden relevant for the carcinogenic process.

Incidence of MM after asbestos exposure increases proportionally to exposure multiplied by a power (3 or 4) of time since exposure (usually called latency). Time gives more weight to exposures that occurred early.^{46,48,51}

Recent reports analyzed alternative models either including a term for the reduction of AF burden with time^{52,53} or based on the two stages and clonal expansion model.^{54,55} The examined reports suggest a possible reduction of risk after exposure cessation but the evidence is still matter of debate.⁵⁶ Biopersistence in the lung is lower for chrysotile and for short fibers. Knowledge on the transportation of fibers into the pleural compartment and on the ratio between pulmonary and pleural concentration is still limited.⁵⁷

In terms of surveillance a MM registry (ReNaM) is active in Italy, and notification is compulsory (DPCM n. 308/2002). It is organized in Regional Operational Units – aimed at data collection – coordinated by ReNaM, where the national database is maintained and data are analyzed. The main source of data on exposures is personal interview, therefore early notification of cases is mandatory to collect accurate information. Notification of MM to the compensation board is compulsory, as for all occupational diseases.

Health surveillance of former asbestos workers should aim at providing assistance for enquiries on health or compensation issues, promoting a healthier life style and alerting on possible medical interventions.

MM diagnosis and treatment represents an important cost for the National Health Service.⁵⁸ Cost per case was estimated as € 15,000 in Scotland⁵⁹ and € 24,000 in Italy⁶⁰, for a total annual cost in Italy in the order of € 25 million. Recommendations from the epidemiology, public health and surveillance panel are summarized in [Table 1](#).

Summary of pathology and laboratory evidence

The current reference diagnostic method is mainly based on light microscopic examination of tissue samples stained with conventional hematoxylin–eosin and immunohistochemical stains. The pathological recognition of MPM may pose a difficult differential diagnosis with both pleural benign asbestos-induced disease, and pleural metastases of adenocarcinoma, generally from lung or breast. Metastatic cancers greatly outnumber MPM. The molec-

[†] Some of the above reported statements on the relationship between asbestos exposure and MM occurrence were not completely endorsed by one component of the panel, who commented: “The computation of cumulative dose as the product of dose by duration however is a gross simplification as the relevant time factor for MPM is the latency and not the duration and the effect of latency is orders of magnitude higher than that of dose. Nevertheless, MPM risk increases according to a measure that compounds two factors (dose and duration, the latter taken as a proxy of the latency). Both factors are associated to MM incidence. In conclusion, cumulative dose is a misleading metric and should be used only when data for distinguishing dose and time factors are not available.

Table 1

Recommendations from the panel epidemiology, public health and surveillance.

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- Notification of all cases to the local mesothelioma registry is compulsory, and early notification is mandatory for collecting accurate information on exposure.
 - Asbestos exposure should be always suspected. Occupational exposure is the most likely origin, but also non-occupational exposure should be investigated, in particular when occupational exposure is unlikely.
 - Exposure to asbestiform minerals or other fibrous materials should be investigated too, in particular when asbestos exposure is unlikely.
 - Notification of MM to the compensation board is compulsory, as for all occupational diseases.
 - Health surveillance in properly qualified and experienced health services is recommended as a form of support to exposed subjects, although no data exist on the screening benefit on disease occurrence and prognosis in this population group.
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Table 2

Proposed immunohistochemical panels.

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- Epithelioid/mixed MPM – The value of a first-line antibody battery is confirmed, consisting of two mesothelioma positive markers, always including calretinin (the antibody against human recombinant calretinin appears to give a superior discrimination with concurrent nuclear and cytoplasmic positivity), and two markers for the carcinoma phenotype (one being carcino embryonic antigen/CEA). The second-line antibodies are chosen in the light of the differential diagnosis considered on the microscopic ground and within the clinical context and include D2–40, WT1 and CK5 (the two omitted in the first-line investigation) for the mesothelial phenotype and BerEP4, CD15 (LeuM1), MOC31 and TTF1 for the carcinoma phenotype.
- Sarcomatoid MPM – The above-mentioned markers are not entirely reliable in sarcomatoid mesothelioma. The use of a broad spectrum cytokeratin is recommended as the first-line antibody, being one among calretinin, WT1 and D2–40 the optimal choice in the second-line battery. Negative immunostainings of such markers does not exclude the diagnosis of MPM, since a few of them feature a “null” phenotype.
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ular carcinogenesis of MPM is incompletely understood.^{61–73}

The conventional light microscopy features of MPM are well defined⁷² but a definitive histological diagnosis of MPM in a single case is often fraught with morphological pitfalls, because this tumour has phenotypic versatility and can mimic either benign pleural lesions or metastatic tumours affecting serosal membranes. It is important to define what is an adequate sample in terms of both tissue quantity and quality, which provides the pathologist with information enabling a confident and accurate diagnosis. It is agreed that thoracoscopy represents the best biopsy technique in that light and that a minimum of five biopsies are recommended for a representative sample, particularly in mixed subtype, whenever possible.^{1,61,62}

Cytology alone is a reliable diagnostic tool for experienced cytopathologists. However, tissue confirmation of the cytodiagnosis is always advisable, whenever possible.

In case with either no tissue available or unsuitable scanty tissue material, the microscopic evaluation of an adequate cellular effusion can be of diagnostic value, preferably with additional immunocytochemical characterisation, when the clinical and instrumental context of a given patient is appropriate.^{1,61,63}

MPM is generally divided into three basic histological subtypes: epithelioid, biphasic and sarcomatous. The majority of MPM are epithelial (>50%) and patients with this subtype are generally thought to experience a somewhat longer survival than do patients with the other subtypes. However, a great variety of histological patterns exists within such three basic histological types.

Immunohistochemistry has been recognized as having the most practical utility, distinguishing epithelioid MPM from peripheral adenocarcinomas involving the pleura.

The immunohistochemical markers should be chosen based on the differential diagnosis generated by the cyto-morphologic findings, as well as the clinical features, site (pleural, peritoneal, or pericardial), age and gender. These panels, however, are continuously changing as a result of the identification of new markers and the publication of new information regarding the value of individual markers. In Table 2 the proposed immunohistochemical panels are separately considered whether the morphological subtype of MPM is epithelioid/mixed or sarcomatoid.

The optimal blood biomarker on the one side should differentiate MPM from both benign pleural conditions as well as pleural metastases, and on the other reflect disease stage and even predict tumor development in asbestos-exposed subjects. Soluble mesothelin-related peptide (SMRP) and osteopontin have so far been proposed as promising MPM markers in both serum and pleural effusion fluid. Both molecules have also a potential role as prognostic markers, but their clinical application requires further validation.^{64–68}

Data reported so far do not prompt the immediate use of any new test (including for example methylation-specific real-time PCR analysis or oligonucleotide Array-Based CGH or micro-RNA) in the routine diagnostic setting. Prospective studies are worth being carried out to evaluate the reproducibility of results so far produced by different laboratories.

In the light of the expanding role of targeted therapies for MPM patients, it is recommended an accurate storage of archival material in order to secure the feasibility of additional investigation at a later time with regard to the determination of gene or protein expression of markers of susceptibility or response to specific therapeutic agents.⁶⁹ Recommendations from the pathology panel are summarized in Table 3.

Table 3

Recommendations of the pathology committee.

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- Thoracoscopy represents the best biopsy technique and a minimum of five biopsies are recommended, whenever possible.
 - Cytology alone is a reliable diagnostic tool for experienced cytopathologists, preferably with additional immunocytochemical characterisation. However, tissue confirmation of the cytodiagnosis is always advisable, whenever possible.
 - Regarding immunohistochemical markers antibody panels need to be separately considered whether the tumour subtype of MPM is epithelioid/mixed or sarcomatoid.
 - Epithelioid/mixed MPM: two mesothelioma positive markers, always including calretinin and two markers for the carcinoma phenotype, one being carcino embryonic antigen (CEA).
 - Sarcomatoid MPM: the use of a broad spectrum cytokeratin is recommended as the first-line antibody, being one among calretinin, WT1 and D2–40 the optimal choice in the second-line battery.
 - Mesothelin and other serum biomarkers (e.g. osteopontin) are currently under evaluation in diagnosis, prognosis and monitoring MPM.
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Summary of imaging and endoscopic assessment evidence

Non-invasive diagnostic procedures

The sole chest-X ray finding of the pleural plaques does not require additional investigations, whereas recurrent unilateral pleural effusion not related to any known etiology should be further characterized by contrast-enhanced computed tomography (CT). However, CT underestimates early chest wall invasion, peritoneal involvement, and has well-known limitations in nodal metastatic evaluation. Magnetic resonance imaging (MRI) is superior to CT, both in the differentiation of malignant from benign pleural disease and in the assessment of chest wall and diaphragmatic involvement. Fluorodeoxyglucose positron emission tomography (FDG-PET) is a useful tool for the differentiation of benign from malignant lesions, for staging, and for monitoring response to therapy. PET-CT is superior to other imaging modalities in detecting more extensive disease involvement and identifying unsuspected occult distant metastases. PET-CT scanning may be very useful for N staging, especially due to its high negative predictive value which may save patients unnecessary invasive diagnostic procedures such as mediastinoscopy.

Both the number of the CT detectors and the CT acquisition protocol are important factors for MPM diagnosis. The latest CT technology (>32 detector rows) allows thin-section volumetric acquisitions providing an isotropic data set, which can be rearranged in any plane. As a result, these multiplanar reconstructions allow to easily evaluate the presence of very limited pleural thickening. The CT scanning delay should be also set at 60 s to optimize the maximum pleural uptake.^{74–91}

There are no recent comparative data related to accuracy for T staging between CT and MRI. By using one detector row CT scanner, CT correctly stage T parameter in up to 60% of cases, thus understaging more often the local disease extent as compared to MRI. However, such a gap between CT and MRI has been increasingly reduced. The multi-slice CT allows an adequate diagnostic assessment in most cases. The CT assessment of the chest wall, diaphragm or pericardium invasion has greatly improved largely due to the thin-section multiplanar imaging. On the other hand, new MRI sequences such as ultra fast GE T1 isotropic 3D and ultra fast SE T2 single shot have also respectively improved the evaluation of both chest wall invasion and the pleural effusion.^{1,85,86}

Ultrasound tool can be very useful in identifying pleural abnormalities. Pleural effusions and thickening can be readily appreciated by ultrasound and discrete malignant nodules may be seen.

According to the CT findings, the subsequent diagnostic workup may be summarized as follows:

- (1) gross irregular pleural masses (with or without pleural effusion) should be further investigated by US or CT guided-biopsy;
- (2) limited irregular pleural thickening (with or without pleural effusion) may be evaluated by PET-CT scanning;
- (3) recurrent pleural effusion without any visible abnormality at CT scan should be directly investigated by thoracotomy.

In terms of the assessment of the therapeutic response despite the use of uni-dimensional measurements, application of the RECIST criteria is not straightforward. More recently, the use of modified RECIST criteria, which take into account the irregular morphology of the tumor (by measuring tumor thickness perpendicular to the chest wall or mediastinum in two sites at three different levels on the CT scan), the assessment has slightly improved. Specifically, the use of computer assisted diagnosis (CAD) software may provide semi-automated volumetric measurements of the tumor which have been proved to anticipate the clinically evident

disease progression, although further studies are needed to establish their utility. Advanced nuclear medicine techniques based on the use of a new semi-automated parameter – the total glycolytic volume (TGV) – is very promising as it takes into account of both volume and glycolytic activity of the MPM. Dynamic contrast enhanced (DCE) MRI through the assessment of the enhancement profiles might provide complementary as well as relevant information in addition to the volumetric changes. In the future, this experimental technique could allow also a biological characterization of the MPM.^{1,75,87–91}

Invasive instrumental diagnosis

As at the time of the 2008 Consensus¹, the critical role of invasive instrumental diagnosis in MPM is still confirmed in guidelines since published.^{92–94} However, the small number and the characteristics of studies do not allow the grading of evidence.

In general no newly established tools for MPM diagnosis have been introduced for the last 4 years except endoscopic ultrasound-guided lymph nodes needle aspiration as a possible alternative to mediastinoscopy.

Blind pleural biopsy with needles such as Abram's or Cope's needles has been in use for many years but its low diagnostic yield and not infrequent possible complications make it less reliable than other pleural biopsy techniques nowadays available.⁹⁵ Recently CT or ultrasound (US)-guided biopsy techniques became preferred because a higher diagnostic yield (70–80%) than blind needle biopsy, especially in pleural thickenings or lesions clearly visible with imaging techniques.^{96–99} They are particularly indicated when the pleural cavity is inaccessible due to extensive pleural adhesion. No comparative studies of CT vs. US are available; the advantages of US are the lack of radiation and real-time images while those of CT are the possibility to sample areas difficult to access with US such as retrocostal or paravertebral areas. Thoracoscopy is still^{92,100–103} today the most reliable invasive technique to diagnose MPM with a diagnostic yield of over 90%. The major indication is the presence of pleural effusion allowing the extensive sampling of the pleura and a therapeutic approach through pleurodesis. In the absence of studies comparing image-guided biopsy and thoracoscopy the choice of the diagnostic choice in each individual case is based on the clinical evaluation.⁹⁹

The evaluation at thoracoscopy of visceral pleura involvement is crucial to establish the extension of the disease and to formulate a correct TNM classification.¹⁰⁴ The sole involvement of the parietal and diaphragmatic pleura or the visceral pleura, and on whether visceral involvement is limited or extensive are associated with prognostic value.¹⁰⁵

The use of endobronchial ultrasound (EBUS) for nodal staging in MPM is a new but promising technique with some advantages compared to mediastinoscopy (less complications, minimal trauma to peritracheal tissue, possibility to reach hilar nodes usually inaccessible to mediastinoscopy) with a similar accuracy. Esophageal endoscopic ultrasound (EUS) is indicated when suspected nodes are identified on imaging studies at those sites which are not assessable by EBUS.^{106–109} Recommendations from the imaging and endoscopic assessment panel are summarized in Table 4.

Summary of chemotherapy evidence

First-line chemotherapy

Approximately 85–90% of patients with MPM present with locally advanced unresectable disease at diagnosis and such patients rely on palliative treatment. The response rate and survival are generally greater for combinations than for single-agent regimens,

Table 4
Recommendations of the diagnostic committee.

Non-invasive procedures

- Chest X-ray remains the primary imaging modality for patients with suspected MPM and the sole CXR finding of the pleural plaques does not require additional investigations.
- The multi-slice CT allows an adequate diagnostic assessment in most cases.
- CT has major limitations in MPM evaluation and MRI is superior to CT, both in the differentiation of malignant from benign pleural disease and in the assessment of chest wall and diaphragmatic involvement. However, latest multidetector technologies allows to get more precise information even with CT.
- FDG-PET is useful for the differentiation of benign from malignant lesions, for staging, and for monitoring response to therapy. PET-CT scanning may be very useful for N staging, especially due to its high negative predictive value.
- Modified RECIST criteria remains the response evaluation validated system, but its application is not straightforward.
- Promising results are coming from different tools such as: the use of computer assisted diagnosis (CAD) software; nuclear medicine technique; dynamic contrast enhanced (DCE) MRI.

Invasive procedures

- Blind pleural biopsy today should no longer be used for the diagnosis of MPM if other techniques are available.
- Image-guided (CT or US) pleural biopsy allows direct sampling of areas of nodularity or thickening with a high diagnostic yield. It is indicated when the lesions are visible with CT or US and in particular in absence of pleural effusion.
- To diagnose MPM and evaluate intrapleural extension of the tumour, thoracoscopy is the best method in presence of pleural effusion. Moreover, it allows the prevention of fluid recurrence through pleurodesis.
- The invasive staging of mediastinal nodes should be performed in patients to be treated by extrapleural pneumonectomy (EPP) when imaging techniques (PET in particular) suggest an extension to mediastinal lymph nodes. The consensus on this point was not unanimous.
- Laparoscopy has to be performed in patients candidates for extra-pleural pleuropneumectomy (EPP), after careful evaluation of imaging techniques (CT or MR) results, if transdiaphragmatic extension of tumour to the peritoneum (T4) cannot be excluded. The consensus on this point was not unanimous.

for platinum-containing regimens than for non-platinum-containing combinations and also for those regimens containing anti-folate rather than other molecules.

The only available randomized clinical trial comparing active symptom control (ASC) alone versus ASC in combination with chemotherapy (mitomycin, vinblastine and cisplatin for 4 cycles or single agent vinorelbine weekly for 12) showed a non-significant increase in median survival with chemotherapy; Although these results are disappointing as a whole, it should be noted that none of the chemotherapy regimens used in the study can be considered as standard options for MPM treatment and that the low statistical power could be another factor contributing to the observed lack of chemotherapy efficacy.¹¹⁰ The evidence profile of GRADE applied to this randomized trial suggested a moderate quality of information regarding efficacy and safety.

Data from two randomized trials have provided evidence to suggest that a platinum-based doublet containing a third-generation antifolate (pemetrexed or raltitrexed) is superior to platinum alone in terms of overall survival with improvement in symptoms and no deleterious effects on quality of life.^{111,112} Currently the combination of cisplatin and pemetrexed is widely used for the systemic treatment of MPM and it was unanimously considered by the panel as the gold standard for the first-line therapy of young patients with good PS and no co-morbidities. Raltitrexed in combination with cisplatin has been recently granted approval by AIFA (Agenzia Italiana per il Farmaco) for the treatment of this disease. The evidence profile of GRADE applied to these randomized trials suggested a moderate quality of information regarding efficacy and safety.

Data about the replacement of cisplatin with carboplatin are mainly from an expanded access program¹¹³ showing that pemetrexed can also be safely administered in combination with carboplatin with efficacy outcomes similar to cisplatin-pemetrexed. Even if a formal comparison is lacking based on relatively large numbers of treated patients the combination of carboplatin and pemetrexed may be considered as an alternative treatment option for patients who are not candidates for cisplatin-based therapy.

With the exception of a greater hematologic toxicity, in elderly patients the efficacy of platinum and pemetrexed is comparable to that observed in younger patients.^{113,114} GRADE criteria was not adopted because of the lack of comparative randomized trials comparing active treatment versus best supportive care in elderly patients.

Gemcitabine in combination with cisplatin or carboplatin has also been reported to be effective, with responses in 20–47% of patients, and well tolerated although no comparative randomized studies are available.

A better knowledge of major molecular pathways involved in MPM has lead to the identification of potential new targets for the systemic treatment of this disease and several agents have been tested (or are currently under evaluation) in first line setting. Unfortunately, many drugs that showed activity in preclinical models have demonstrated no activity in MPM patients. Recent examples include the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors, gefitinib and erlotinib, and the platelet-derived growth factor (PDGF) inhibitor, imatinib.

A randomized phase II trial of gemcitabine–cisplatin with the anti-VEGF antibody bevacizumab or placebo reported no difference in terms of efficacy.¹¹⁵ The ongoing randomized phase II/III MAPS (Mesothelioma Avastin plus Pemetrexed-cisplatin Study) study, which evaluates the addition of bevacizumab to pemetrexed–cisplatin met its phase II primary end point and is now enrolling in the phase III portion of the study.¹¹⁶

The optimal timing of chemotherapy treatment has only been addressed by a small study in which 43 patients with a good performance status and symptomatically stable at the time of diagnosis were randomized to receive either immediate or delayed chemotherapy. The immediate use of chemotherapy provided an extended period of symptom control and a trend to survival advantage (14 versus 10 months).

There are no data to support optimal chemotherapy duration in MPM. In current practice, chemotherapy treatment is administered for a median of 4–6 cycles, unless progression or severe toxicity occurs. An observational study compared maintenance pemetrexed versus no maintenance therapy. The study showed that the maintenance approach is feasible. However, this was not a randomized trial and, consequently, not powered to evaluate the efficacy of the maintenance approach. In addition the GRADE criteria showed a very poor quality of information regarding efficacy and safety.

Second-line chemotherapy

The role of second-line chemotherapy has been evaluated in a prospective, randomized phase III trial comparing pemetrexed versus best supportive care (BSC) in patients previously treated with a first line regimen not including pemetrexed having overall survival (OS) as a primary end point. The study enrolled 243 patients and

Table 5
Recommendations of the chemotherapy committee.

<p><i>First-line</i></p> <ul style="list-style-type: none"> –Consensus was reached in recommending chemotherapy with third generation antifolate-platinum (cisplatin or carboplatin) combination for patients with advanced MPM and good PS. –For elderly patients, with a PS = 0 or 1, without significant (uncontrolled) comorbidities, with no signs and symptoms (or few) related to the disease, a chemotherapy treatment can be considered. –Chemotherapy should be started as soon as possible following the diagnosis and administered for a maximum of 4–6 courses, without a maintenance approach. <p><i>Second-line</i></p> <ul style="list-style-type: none"> –For patients with rapidly declining PS, older age or significant co-morbidities, the use of supportive care measures alone was considered appropriate in this setting. –For patients with good PS without comorbidities and not-elderly, a chemotherapy treatment with pemetrexed if not given in first line, and gemcitabine or vinorelbine for those pretreated with pemetrexed, can be considered. –For those patients with a time to progression equal or higher than 6 months, a re-challenge with first line chemotherapy regimen/pemetrexed may be considered a treatment opportunity.
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showed a statistically significant increase in objective response rate, disease control rate and time to progression for pemetrexed but a lack of overall survival benefit likely to be due to a significant imbalance in PSC between the two arms.¹¹⁷ The Evidence profile of GRADE applied to this randomized trial suggested a moderate quality of information regarding efficacy and safety.

Similarly to front-line there are ongoing clinical investigations in the attempt of getting benefit from a targeted therapy in unresectable MPM. In a large phase III trial in 661 patients with previously-treated, unresectable MPM vorinostat, an histone deacetylase inhibitor, failed to extend overall survival without any difference in response rate, forced vital capacity or dyspnea score.

Re-treatment with pemetrexed-based chemotherapy (PBC) has been explored in few trials, mainly retrospectively and in a limited number of patients. Re-treatment with PBC seems to be a potential option in the second-line setting in patients with MPM achieving a durable disease control with an induction containing the same drug^{118–120}, but further evaluation in prospective trials is needed. Recommendations from the chemotherapy panel are summarized in Table 5.

Summary of surgical evidence

Previous Italian Expert Opinions¹ focused on the need for correct staging definition of malignant pleural mesothelioma (MPM), identifying ITMIG T1a-b and T2 as potential subsets amenable to surgery with an intent to cure. Thoracoscopy represents the diagnostic modality which enables the surgeon to fully understand the feasibility of a pleural vs pleuro-pulmonary resection.^{121–145} In fact, laparoscopy and mediastinoscopy are used for those patients with a mediastinal nodal or abdominal disease extension which would preclude surgical consideration.

Consensus was also obtained as to the need for thorough evaluation of the performance status and the cardiopulmonary reserve of surgical candidates. In particular, the clinical recommendations were to investigate these patients, especially those amenable to extrapleuro-pneumonectomy (EPP), according to the same protocols used for lung cancer surgical patients. These included routine assessment of DLCO, ventilation-perfusion scans and blood gas analysis in those patients with borderline or uncertain spirometry in order to outline the predict postoperative lung function. Refer to the previously released guidelines for minimal requirements for EPP. Conversely, patients with reduced cardiopulmonary function could still be selected for pleurectomy/decortication (P/D) either with a palliative or curative intent.

Pleural drainage serves the purpose to reduce pleural effusion and dyspnea, chest pain or persistent cough in patients who may demonstrate a trapped lung on chest X-ray. The timing for chest tube insertion after ineffective thoracenteses is dictated by the

presence of the above mentioned symptoms associated to a time to recurrence less than 10 days, contraindications to more invasive procedures or general anesthesia and the radiographic demonstration of a trapped lung syndrome. With a chest tube in place, talc poudrage can be performed by injecting a pulverized, natural hydrated magnesium silicate with the approximate chemical formula of $Mg_3(Si_2O_5)_2(OH)$ into the pleural cavity as talc slurry. The latter procedure is feasible also under local anesthesia. The aim is to induce chemical pleurodesis which is most effective in patients whose lungs maintain the ability to fully re-expand after the evacuation of pleural effusion. Moreover, the need to relieve symptoms and a short time to recurrence of the effusion represent additional indications for talc poudrage. As a consequence, patients with trapped lung syndrome and candidates to P/D are not amenable to this procedure.

Alternatively, patients who can tolerate general anesthesia can be subjected to thoracoscopy and talc insufflation under direct vision which ensures an thorough distribution of the pleurodetic agent. This technique is recommended also in EPP candidates since the talc powder may induce coalescence of the visceral and parietal pleural folds thus obliterating the pleural space and facilitating extrapleural dissection with an en-bloc removal of the pleuro-pulmonary specimen while minimizing the chance for tumor dissemination. In the event of a thoracoscopic exploration in a patient with MPM, some caveats need be observed, including the resection of the thoracoscopic port site to avoid local recurrences if major surgery is contemplated. The location of the thoracoscopic site strategically placed along the line of a subsequent thoracotomy becomes of paramount importance.

Curative surgical procedures are aimed at attaining R0 resections with tumor-free margins. The reaching of the macroscopic complete resection (MCR) is an objective of this surgery. In the previously published guidelines, a statement regarding the need for multimodality regimens including surgery was clearly made. In medically and functionally suitable patients, EPP was considered in stages I, II and selected (N0) stage III MPM, without distant spreading nor pericardial effusion. In this setting, FDG-PET is crucial to rule out extrathoracic disease. Nevertheless, the jury is still out on whether to consider the involvement of the inner surface of the pericardium without concomitant effusion as amenable to radical surgery. Likewise, the contraindication to radical surgery due to N+ disease warrants careful staging to identify patients who may benefit from EPP. Accordingly, surgical exploration of the mediastinum is deemed mandatory prior to radical surgery especially as restaging procedure in the context of a multimodal treatment strategy. The recently published guidelines^{92,144–148} also advocated the resort to P/D for stage I MPM with curative intent. When compared to EPP, no statistically significant differences emerged as to overall and progression-free survival rates. In spite of similar recurrence rates, the pattern of recurrence differs based on the type of operation. In fact, while P/D patients tend to recur

Table 6
Recommendations of the surgical committee.

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- Surgeons, medical oncologists, respiratory physicians, radiologists and radiation oncologists should set up a workgroup to establish the best treatment strategy.
 - Radical pleurectomy/decortication (P/D) is intended as a lung sparing pleural resection with radical intent leaving no macroscopic residual disease. Conversely, subtotal P/D consists of a non radical P/D.
 - P/D should be performed in patients with stage I and II provided that a lung sparing pleural resection with radical intent leaving no macroscopic residual disease.
 - Chemotherapy should be part of a multimodal treatment in P/D.
 - Extrapleural pneumonectomy (EPP) should be performed in clinically and functionally selected patients with pre-treatment stages I and II, preferably in the setting of clinical studies.
 - EPP should be included in a multimodality treatment regimen administered with an intention to cure. Chemotherapy should be administered either in the pre- or post-operative setting.
 - Surgical procedures performed with an intention to cure should be reserved to referral thoracic surgical centers with dedicated expertise.
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locally, EPP patients demonstrate distant relapse of the disease. However, several factors may affect the interpretation of the surgical results, namely the inclusion of patients with heterogeneous stages in the EPP series whereas patients with more advanced age and borderline cardiorespiratory function are more often found in the P/D series. It has been rightfully emphasized that P/D patients end up being also subjected to adjuvant radiotherapy with the attendant lung morbidity.^{92,144–149}

The surgical panel concluded recommending EPP to achieve adequate local control of MPM, whereas P/D was suggested for patients with minimal, early stage disease. Also, it was suggested that P/D could be used for patients with less optimal functional profile compared to EPP candidates or, as a palliative procedure, for stages II and III and in the event of a trapped lung syndrome.

P/D in suitable surgical candidates with pre-treatment clinical stages I and II should be offered in the setting of a prospective, randomized trial comparing extrapleural pneumonectomy (EPP) to P/D as part of multimodality treatment.

Given the lack of definitive data and the difficulties of outlining a standard surgical approach for MPM, the panel indicated the need for multidisciplinary integration of expertise and concentration of the surgical activities on few qualified surgical centers dedicated to the cure of this disease. Recommendations from the surgical panel are summarized in Table 6.

Summary of radiotherapy evidence

Radiotherapy is widely used in the treatment of patients with MPM, as an integral part of trimodality therapy for early stage disease, in the prophylaxis of port-site recurrence and in the palliative setting.^{150,151} In spite of these possible different clinical indications, there is limited evidence regarding the precise role of radiotherapy.

Comparative studies in MPM investigating radiotherapy versus no-radiotherapy intervention as control arm are available only for prophylactic radiotherapy of tract sites. Three randomized trials have been conducted to evaluate efficacy of irradiation in terms of tract-metastases-free survival.^{152–154} The 2 most recent randomized trials did not show any benefit for adjuvant irradiation, with a moderate risk of port-site failure in the range of 10% without radiotherapy.

Drain sites were generally treated with adequate margins, using photons or electrons, and with hypofractionated schedules (e.g., 21 Gy in three fractions).^{155–157}

It has to be noted that globally the quality of these comparative studies is really moderate, with quality assessment, according to GRADE criteria, conditioned in a negative way mainly by imprecision.

There is no convincing supporting evidence in offering systematically radiotherapy for port-site prophylaxis, taking also into account that this kind of local recurrence likely represents only one event in the general progression of the disease, with its prevention

having no effect on the survival of patients or the natural history of the disease.

Retrospective analysis report a clinical benefit in about 50% of patients treated with symptomatic radiotherapy.^{155–157} The presence of chest infiltrating tumor masses causing pain is the most frequent indication for palliative treatment. There are only two prospective trials focusing on the assessment of the role of radiotherapy in palliation.^{158,159} Hypofractionated schedules are generally used (dose/fraction in the range 3–5 Gy), with total doses from 30 to 40 Gy. Acceptable pain control is achieved more frequently with fraction size larger than 4 Gy; the median duration of pain relief is generally satisfactory considering the short median survival for such patients (duration of pain control indicated by the available data sufficient to last most of the remaining life). Palliative irradiation does not seem to be so effective in the treatment of dyspnoea secondary to pleural effusions or mediastinal invasion. The very wide fields often required to palliate symptoms in mesothelioma patients may cause significant acute toxicity, mainly fatigue; therefore, prospective studies showing improved pain control and tolerable side effects are still required.

Analysis of the literature according to GRADE methodology and criteria did not find any comparative study addressing palliative radiotherapy.

Trimodality therapy with curative intent has been attempted for over 30 years, even if the role of radiotherapy in MPM for a long time was generally considered secondary.^{160–163} Aggressive surgery alone does not improve survival and the association with chemotherapy does not reduce the incidence of local relapse, still remaining the most typical modality of failure.^{155,164} Since local disease control remains the major problem, adjuvant post-operative irradiation has a strong rationale.

No randomized data have so far been produced to support a role for adjuvant post-EPP radiotherapy, but an increase in total dose to 54 Gy was associated with a significant reduction in local failure (11% compared to previous higher values in the range of 30–40% with radiation doses below 50 Gy).^{150,162,163}

Patients are candidate for adjuvant post-EPP irradiation of the hemithorax if they have good performance status, pulmonary function and kidney function. The most appropriate timing of delivering radiotherapy (i.e., after surgical intervention, with or without chemotherapy) as well as recommendations regarding radiation therapy should be discussed in a multidisciplinary team, including radiation oncologists, surgeons, medical oncologists, diagnostic imaging specialists and pulmonologists.

Further attempts to improve local control with radiotherapy after EPP have focused on intensity modulated radiotherapy (IMRT), due to the planning capability of such a technique in treating a very irregularly shaped PTV and in reducing dose to organs at risk (liver, heart, kidneys, remaining lung).^{165–167} Initial reports were highly encouraging, with local control rates around 90%.^{151,166,168} However, severe toxicity is an important issue compared to classical 3D-conformal radiotherapy, with some patients died from radiation pneumonitis as a consequence of radiation

Table 7

Recommendations of the radiotherapy committee.

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- Systematic adjuvant irradiation of thoracic tracts is not routinely indicated nowadays, unless evidence of benefit will be shown in larger trials.
 - The panel confirms the possible positive role of palliative hypofractionated radiotherapy (daily doses of 4 Gy more efficacious than fractions of less than 4 Gy) in providing relief from chest pain associated with mesothelioma.
 - For patients with resectable MPM, who undergo EPP, adjuvant radiotherapy can be recommended for those with good performance status to improve local control. RT should be considered only for patients who meet the following criteria: ECOG S ≤1, FEV1 >80% and good functional pulmonary status, adequate renal function (perfusional renal scan confirming good function of contralateral kidney), absence of disease in contralateral chest.
 - The most appropriate timing of delivering radiotherapy and chemotherapy should be discussed upfront in a multidisciplinary board, including radiation oncologists.
 - Dose of radiation for adjuvant treatment following EPP should be 50–54 Gy in 1.8–2 Gy daily fractions, with 60 Gy delivered to macroscopic residual tumors if any.
 - IMRT is a promising treatment technique that allows a more conformal high-dose radiotherapy and improved coverage to the hemithorax. IMRT should only be used in centers with an adequate experience in this field or on clinical protocols.
 - Special attention should be paid to reduce radiation exposure of the remaining lung, as the risk of fatal pneumonitis with IMRT is excessively high when strict limits are not applied (V20 < 10%; mean lung dose kept as low as possible, preferably <8.5 Gy; low dose volumes minimized, with V5 < 60%).
 - The clinical tumor volume (CTV) for post-EPP RT should encompass the entire pleural surface (entire surgical bed of the whole hemithorax), and any potential sites with microscopic residual disease.
 - The gross tumor volume (GTV) should include any grossly visible tumor, with surgical clips indicative of gross residual tumor.
 - Elective nodal irradiation (regional nodes) is not recommended.
 - The planning target volume (PTV) should consider target motion and daily set-up errors, with margins of expansion dependent on single patient's and single institution's evaluations.
 - Adjuvant irradiation after P/D is usually not recommended, but may be considered with extreme caution and under strict dose limits of organs at risk only in the context of prospective clinical protocols approved by Ethical Committees.
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exposure of the remaining lung, even if with dosimetric predictors of radiation injury below the normally accepted constraints (i.e., V₂₀ < 20%).^{169,170} Considering also the possibility of an underlying undiagnosed asbestos-related interstitial lung disease, radiation exposure of the remaining lung has to be strictly limited with IMRT, for which spread of low doses to larger volumes represent a potential concern.^{1,150,167,170} With the use of safer dose constraints for lung exposure (V₂₀ < 10%, mean lung dose <8.5 Gy), more recent experiences of IMRT after EPP did not report unexpected excessive toxicity.

In spite of the lack of prospective phase III randomized studies comparing 3D-CRT and IMRT after EPP, IMRT in its various technical possibilities is generally preferred nowadays, since it allows a more conformal high-dose RT and improved coverage to the hemithorax at risk, provided the use of strict limits to minimize radiation exposure of the contralateral lung.^{167,171}

Very few retrospective clinical data are currently available regarding the use of radiotherapy as adjuvant treatment after P/D. Of course, since the treatment volume should include all the pleural space, including pulmonary fissures (MPM often spreads through pulmonary fissures), even with modern irradiation techniques it would be difficult to spare the lung itself.^{139,162,172,173} The risk related to a potentially lethal radiation pneumonitis could be really significant. Recommendations from the radiotherapy panel are summarized in Table 7.

Contributors

The following epidemiologists, public health and occupational physicians, pathologists, radiologists, pneumologists, nuclear medicine physicians, surgeons, medical oncologists and radiation oncologists have taken part in the Second Italian Consensus Conference of Malignant Pleural Mesothelioma.

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Conflict of Interest

Disclose any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations that could inappropriately influence their work.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.ctrv.2012.11.004>.

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