The Third Italian Consensus Conference for Malignant Pleural Mesothelioma: State of the art and recommendations

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http://dx.doi.org/10.1016/j.critrevonc.2016.05.004
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ARTICLE INFO

Article history:
Received 19 November 2015
Received in revised form 17 March 2016
Accepted 10 May 2016

Keywords:
Malignant Pleural Mesothelioma
Recommendations
Epidemiology
Diagnosis
Therapy
Supportive care
End of life

ABSTRACT

Malignant Pleural Mesothelioma (MPM) remains a relevant public health issue, and asbestos exposure is the most relevant risk factor. The incidence has considerably and constantly increased over the past two decades in the industrialized countries and is expected to peak in 2020–2025. In Italy, a standardized rate incidence in 2011 among men was 3.5 and 1.25 per 100,000 in men and women, respectively, and wide differences are noted among different geographic areas. The disease remains challenging in terms of diagnosis, staging and treatment and an optimal strategy has not yet been clearly defined. The Third Italian Multidisciplinary Consensus Conference on Malignant Pleural Mesothelioma was held in Bari (Italy) in January 30–31, 2015. This Consensus has provided updated recommendations on the MPM management for health institutions, clinicians and patients.

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1. Introduction

This paper reports about the state of the art and recommendations related to public health and surveillance issues, diagnostic and therapeutic aspects for Malignant Pleural Mesothelioma (MPM), based on the Third Italian Consensus Conference, held in Bari on January 29–30, 2015 and endorsed by the Associazione Italiana di Oncologia Medica (AIOM—Italian Association of Medical Oncology).

For further details about previous Italian consensus conferences on MPM, the readers should refer to previous papers published in 2011 (Pinto et al., 2011) and 2013 (Pinto et al., 2013).

2. Methods

The consensus conference adopted the GRADE methodology (http://www.gradeworkinggroup.org/) to design and build up the recommendations. In the planning phase, each panel (see Appendix A) defined relevant questions, chose the endpoints for each question and ranked their relevance. A methodological working 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 (Schünemann et al., 2008). These evidence profiles represented the basis for the panel discussion and recommendations. The GRADE approach was limited to questions relative to treatment 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 Tables 1 and 2 (electronically only).

3. Epidemiology, public health and surveillance evidence

In Italy in 2011 MPM incidence was 3.49 and 1.25 cases per 100,000 person/years in men and women respectively with 1428 (1035 in men and 393 in women) reported as incident cases (Anon, 2015). National incidence and mortality trends for MPM are starting to level off.

The Second Italian Consensus Conference on MPM adopted a mathematical model for the prediction of MPM incidence in humans after exposure to asbestos (Pinto et al., 2013). A recent pooled analysis (Reid et al., 2014) showed that, after about 45 years since first exposure, the trend in incidence and mortality increase is slowing down, although the same reduction is not observed for peritoneal MM. Further studies are appropriate.

For cumulative exposure in the dose-response relationships there are no changes compared to the statements of the Second Italian consensus Conference (Pinto et al., 2013).

The dose-response relationship may be used to assess the proportional causal weight of any distinct exposure period (Price and Ware, 2005; Mastrangelo et al., 2014). However, it is necessary to adopt assumptions about several key factors that in most instances are not precisely known, among others, the relative potency of the different types of asbestos, the exposure intensity, and the duration of the preclinical phases of MPM.

It is relevant to assess incidence in relation to long-term exposure patterns, which often consist of a complex temporal sequence of exposures, which are difficult to analyse separately untying the relative relevance of duration, intensity, and cumulative exposure (Lubin and Caporaso, 2006; Vlanderen et al., 2013; Richardson et al., 2012). Cumulative exposure is a summary exposure index, successfully used in several fields in cancer research (Thomas, 2013) but it does not allow to distinguish which of its components, duration or intensity, may possibly play a prominent role, neither it allows to establish whether the temporal sequence of exposures is important (Checkoway et al., 2004). Six different studies offered evidence that duration and intensity are independent determinants of MM occurrence.

Even if the analysis of latency is intuitively appealing, under the assumption of a shorter latency for the most exposed, it is misleading because the results are not dependent on the relationship between exposure and disease, but on the time boundaries of the
observation (Pike and Doll, 1965). Furthermore, in cohort studies, latency can be determined only for a minority of individuals at risk, due to the combined effect of censoring and competing mortality (Langholz et al., 1999). An increase in exposure causing an increase in incidence in the target population necessarily entails the acceleration of failure time (i.e. latency time), as the relationship between the increase in incidence and acceleration of failure time is mathematically determined (Berry, 2007); nevertheless and contrary to what intuition might suggest, the average latency is unaffected.1

Non-occupational exposure to asbestos is more difficult to detect than the occupational exposure, and its relative importance is likely to increase. In Italy incidence of MPM among women is very high, for both non-occupational (environmental and domestic) and occupational asbestos exposure. The Italian MPM incidence surveillance system documented that 10.2% of MPM cases are due to non-occupational exposure to asbestos (Registro Nazionale Mesoteliomi, 2012). The potential of sharing databases for case identification and for the assessment of exposure is crucial, and prompt and exhaustive implementation has been strongly recommended.

Recently issues related to airborne asbestos fibers in the environment have been raised. Information from Italian regions is scanty: a recent monitoring campaign conducted in the city of Modena showed an average concentration around 0.1 fibers/l, similar to the data reported in the International Agency for Research on Cancer (IARC) monograph n. 100 (IARC International Agency for Research on Cancer (IARC), 2012). WHO estimated that for a continuous exposure to 0.4–1 fiber/l (as measured with current methodology), a lifetime risk of MM would be from (4 to 10) × 100,000. Linear extrapolation to the 0.1 fiber/l (current background level) would correspond to lifelong excess in the order of one case (from 0.4 to 2.5) of MPM every 100,000 persons (World Health Organization Regional Office for Europe, 2000).

The presence of asbestos in water is becoming a matter of concern for a large part of the population, however there is no evidence of risk for pleural MM related to ingested fibers. Risk of exposure to airborne asbestos fibers because of the use of asbestos contaminated water can occur indoor and outdoor in circumstances when an important level (millions/l) of fibers in water is detected.

Epidemiological studies and case reports from ReNaM underlined the causal role of talc containing asbestos fibers (Finkelstein, 2012). The need for greater understanding of this material, its source, where and how it was used in Italy, was acknowledged, with priority for epidemiological studies.

Fibrous fluoro-edenite has been classified as carcinogenic to humans by IARC on the basis of sufficient evidence including MPM in humans. In Italy, exposure is known in the area of Biancavilla (Sicily); it was also detected in other volcanic areas in Japan. Silicon Carbide (SiC) whiskers were classified as probably carcinogenic to humans, in absence of human data but with clear evidence of MPM in experimental animals. The IARC Monograph considered different types of Carbon Nanotubes (CNT), of which a specific type (MWNT-7) was classified as ‘possibly carcinogenic’, while the classification could not be extended to other CNTs for lack of consistent data (Grosse et al., 2014).

The proportion of hereditary MPM cases in Italy is between 1.3 and 2.5%, considering only population-based surveys (Ascoli et al., 2007; Ascoli et al., 2014). In the population living or working in Wittenoom, MPM cases among relatives represented 7%, and a twofold increase of MPM risk for blood relatives of cases was estimated, after adjustment for asbestos exposure (de Klerk et al., 2013). The role of BAP1 germ-line mutations is limited to the cases occurring in familial aggregations corresponding to the BAP1 cancer syndrome, while it is negligible (at most 1.4%) for sporadic MPM cases (Betti et al., 2015).

Health surveillance programs aimed to workers formerly exposed to asbestos or occupations with potential asbestos exposure are defined according to current Italian laws [257/2006 and 81/2008]. So far, no diagnostic test has enough sensitivity and specificity high enough to be adopted for early diagnosis of MM in asymptomatic subjects. Health surveillance activity should provide also information on risks and on medical perspective, collect information on occupational history, especially regarding asbestos exposures, and provide counselling for smoking cessation.

Health surveillance programs of asbestos exposed workers should: (1) inform asbestos exposed subjects about their risk related to (present or past) asbestos exposures; (2) inform relatives of asbestos exposed subjects of their possible health risks; (3) Fully reconstruct occupational history, especially regarding asbestos exposures; (4) provide information about diagnostic tools, therapy and forensic medicine perspectives; (5) support claims for compensation; (6) give counseling on smoking cessation and on other relevant matters related to health and life style.

In Italy, a reliable estimate of the economic burden associated to mesothelioma, including medical care, insurance and fiscal costs, and human capital costs related to productivity loss, provided an estimate of 250,000 Euro per MM case (Iavicoli et al., 2014).

4. Diagnostic pathology and clinical laboratory

The differential diagnosis with both pleural benign asbestos-induced disease and pleural metastases from adenocarcinomas (mainly from lung, breast and kidney tumours) may represent a difficult task. It should always be kept in mind that metastatic tumours to the pleura greatly outnumber primary MPM (Smith and Colby, 2014).

The conventional light microscopy features of MPM are well established, especially in the epithelial variant, but MPM may show a broad spectrum of unusual morphologic appearances (Ordóñez, 2013a, 2012a,b,c; Churg et al., 2014) and a definitive diagnosis of MPM in individual cases may require information about clinical data and other malignancies. The diagnosis of MPM is mainly dependent on an adequate pleural sampling, in terms of both tissue quantity and quality. Thoracoscopy is considered the preferred biopsy technique, allowing multiple (a minimum of five biopsies is recommended), large and deep biopsies comprising soft tissues of the parietal pleura or the lung. Ultrasound-guided and computed-tomography-guided biopsies may have a high diagnostic yield (up to 90%) (Pinto et al., 2013; Scherpereeal et al., 2010; van Zandwijk et al., 2013).

Cytology cannot assess invasion into sub-pleural tissues or lung parenchyma, but careful examination of cytology findings (hypercellularity, three-dimensional morular/papillary structures, macronucleoli, cell cannibalism, multinucleated cells, squamoid cells, blebbing, intracytoplasmic vacuoles, monomorphic population of atypical cells, pink haze around cells) may consistently suggest a diagnosis of epithelial MPM (Kawai et al., 2014; Painel et al., 2013; Hjerpe et al., 2015; Henderson et al., 2013a). The diagnosis of sarcomatoid MPM on cytology is extremely difficult and often requires a cell-block and a close correlation with clinical data and imaging studies. In selected cases fulfilling the cytological criteria of malignancy and immunohistochemistry (IHC) evidence of mesothelial cell differentiation, a definitive diagnosis of MPM on pleural effusion can be performed.

1 Note: C. Bianchi did not agree and expressed the following comment, sent during the revision of the report: “Claudio Bianchi believes that an inverse relationship exists between intensity of asbestos exposure and length of the latency period.”
Table 1

Proposal for immunohistochemistry investigation.

- An antibody battery consisting of two mesothelioma positive markers (always including calretinin) and two markers for the carcinoma phenotype (one being carcino-embryonic antigen [CEA]) should be performed.
- A second-run of antibodies useful for the differential diagnosis, always in the context of microscopic findings and clinical information, includes D2-40, WT1, CD5, MOC31 and TTF1 for the carcinoma phenotype.
- The above-mentioned markers are not entirely reliable for sarcomatoid mesothelioma: an initial investigation with combination of antibodies against cytokeratins is recommended, subsequently integrated by additional IHC markers such as calretinin, WT1 and D2-40.
- Immunonegativity for such markers does not exclude the diagnosis of MPM, since 30% present a "null" phenotype.

Table 2

Recommendations of the pathology and laboratory panel.

- At thoracoscopy, a minimum of five deep 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 cytologic diagnosis is always advisable, whenever possible.
- Intraoperative examination may be used in defining the adequacy of removed tumour tissue in the suspect of MPM, but does not provide information about the MPM subtype.
- Standardized report including subtyping of mesothelioma into epithelioid, sarcomatoid and biphasic is advisable.
- Immunohistochemical markers antibody panels are recommended for a more precise subtype classification (see Table 1).
- Mesothelin, fibulin-3 and other serum biomarkers (e.g., osteopontin) are still under evaluation in diagnosis, prognosis and monitoring MPM. Their use is not recommended in clinical practice.

According to the World Health Organization classification of pleural tumors (Churg et al., 2015), MPM is subdivided into three basic histological types: epithelioid, biphasic and sarcomatous.

MPM typically presents with lung encasement and relative sparing of the lung parenchyma, but pathologists should be aware of unusual presentations, including cases of MPM with absent or inconspicuous pleural involvement manifesting as metastatic disease in usual sites (e.g., skin, soft tissues) or mimicking interstitial lung diseases (Larsen et al., 2013).

IHC is the most helpful ancillary technique in integrating the diagnosis of MPM (Ordóñez, 2013b; Betta et al., 2012) and differentiating epithelioid MPM from pulmonary or extrapulmonary adenocarcinomas involving the pleura. IHC markers including calretinin, D2-40 (podoplanin antibody), Wilms' tumor-1 protein (WT-1), cytokeratins 5/6, mesothelin and thomboembolism are recommended. Negative IHC markers include carcinoembryonic antigen (CEA), BerEP4, MOC-31, claudin-4, CD155 (Henderson et al., 2013b; Lonardi et al., 2011; Jo et al., 2014). Napsin A and TTF-1, CDX2, PAX-8, apocrine markers and hormonal receptors allow differential diagnosis between pleural metastases and MPM (Table 1).

Variants of the BRCAl-associated protein 1 (BAP1), resulting in nuclear protein loss, were reported in hereditary and sporadic mesothelioma. In a recent study, BAP1 was expressed in all benign mesothelial tumors, whereas 139 out of 212 (66%) mesotheliomas were BAP1 negative, especially in epithelioid/biphasic compared with sarcomatoid/desmoplastic subtypes (69% vs 15%). In biopsies interpreted as reactive mesothelial proliferation, BAP1 loss was 100% predictive of malignancy, whereas only 3 out of 36 (8%) BAP1-positive cases progressed to mesothelioma. On cytology/cell blocks, benign mesothelial cells were invariably positive for BAP1, whereas 64% of mesotheliomas showed loss of protein. BAP1 immunostaining represents an excellent biomarker with an unprecedented specificity (100%) in the distinction between benign and malignant mesothelial proliferations (Cigognetti et al., 2015).

IHC plays a limited role for the diagnosis of sarcomatoid MPM (Ordóñez, 2013a; Scherpereel et al., 2010). Most of sarcomatoid MPM express pan-cytokeratins, vimentin and even markers of smooth muscle differentiation (e.g., smooth muscle actin), but mesothelial markers often fail to recognize mesothelial differentiation of sarcomatoid MPM or rather show a weak and focal expression, only. The most useful markers for sarcomatoid MPM include D2-40 and calretinin (Pinto et al., 2013; Ordóñez, 2013a; Scherpereel et al., 2010; Churg et al., 2015; Henderson et al., 2013b). The availability of clinical and imaging data and at least two pan-cytokeratins and two non-mesothelial markers is required to support a diagnosis of sarcomatoid MPM (Pinto et al., 2013; Ordóñez, 2013a; Scherpereel et al., 2010; Churg et al., 2015).

Soluble mesothelin-related peptide (SMRP), osteopontin and fibulin-3 have so far been proposed as promising MPM markers in both serum and pleural effusion fluid (Lao et al., 2014; Creaney et al., 2011; Hollevoet et al., 2011; Hollevoet et al., 2010; Luo et al., 2010; Wheatley-Price et al., 2010; Creaney et al., 2014a; Franceschini et al., 2014). However, their clinical application is characterized by low sensitivity, specificity and reproducibility, then requiring further validation before their application as diagnostic or screening tools (van Zandwijk et al., 2013; Kawai et al., 2014; Paintal et al., 2013; Hjerre et al., 2015; Henderson et al., 2013a; Churg et al., 2015; Larsen et al., 2013; Ordóñez, 2013b).

Data reported so far do not prompt the immediate use of any new test (including methylation-specific real-time PCR analysis, oligonucleotide Array-Based CGH or micro-RNA) in the routine diagnostic setting (Creaney et al., 2014b; de Assis et al., 2014). Prospective studies are worth being carried out, to evaluate the reproducibility of data produced by different laboratories.

The role of BAP1 and NF2 in promoting sporadic and hereditary mesotheliomas has been investigated (Betta et al., 2012; Weber et al., 2014; Testa et al., 2011; Yoshikawa et al., 2012; Cheung et al., 2013). Next generation sequencing studies identified genetic variations clustered in the p53/DNA repair (TP53, SMACB1, and BAP1) and PI3K–AKT pathways (PGDFRA, KIT, KDR, HRAS, PIK3CA, STK11, and NF2) as the most commonly identified and validated (Ladanyi et al., 2012).

Finally, a standardization of the diagnosis of MPM on pathologic report is recommended in order to prevent misinterpretation of morphologic and IHC data among pathologists and clinicians. Recommendations from the pathology panel are summarized in Table 2.

5. Imaging and endoscopic assessment

5.1. Diagnostic imaging

Depending from the presence or absence of pleural effusion, its extent (localized or diffuse, unilateral or bilateral) and from the presence or absence of calcified lesions at the pleural level, the contribution of imaging may be significantly different. Imaging identifies pleural thickening, differentiate benign from malignant pleural thickening, and, if possible, contribute to the definition of etiology (Sureka et al., 2013).

Generally, in presence of non-conclusive findings at chest X-ray (CXR), particularly when pleural lesions are suspected, computed tomography (CT) is the recommended second-step study.

Ultrasound (US), including contrast-enhanced US (CEUS), may be sometimes useful in identifying pleural abnormalities. US may quantify pleural effusions and thickening. Discrete malignant nodules may be identified and evaluated on the basis of their vascularization (Sartori et al., 2013).
When CT-based diagnosis was compared with histological findings, CT scan demonstrated a sensitivity of 68% (95%CI 62–75%) and a specificity of 78% (95%CI 72–84%). A significant proportion of patients with pleural effusion had malignancy, despite a negative CT report. Therefore, in the case of a patient with undiagnosed pleural effusion, the decision to plan a pleural biopsy should not be based on CT alone (Hallifax et al., 2015).

The role of fluorodeoxyglucose positron emission tomography (FDG-PET) remains as reported in the previous consensus paper (Pinto et al., 2013).

There is no single modality to confirm MPM diagnosis prior to surgery, but so far available studies have shown that PET-CT is superior to FDG-PET, magnetic resonance imaging (MRI) and CT in terms of specificity and sensitivity in the detection of MPM (Zahid et al., 2011).

5.2. Invasive diagnosis compared to what was already discussed in the second Italian Consensus Conference, no new invasive diagnostic modalities have been implemented

In patients with pleural effusion, thoracentesis remains the first minimally invasive diagnostic maneuver; malignant effusions can be diagnosed by pleural fluid cytology in about 60% of cases. US-guidance improves the success rate and reduces complications, including pneumothorax (Hooper et al., 2010).

CT- or US-guided biopsy definitely replaced blind needle biopsy of pleural thickening or lesions clearly identified with imaging techniques (Maskell et al., 2003; Qureshi and Gleeson, 2006; Adams et al., 2001; Metintas et al., 2010a). A blind needle biopsy may be still considered only when the pleural cavity is inaccessible due to extensive pleural adhesion.

Thoracoscopy is the most reliable invasive technique to diagnose MPM with a diagnostic yield of over 90% (Churg et al., 2014; Boutin and Rey, 1993; Hansen et al., 1998; Galbis et al., 2011; Brims et al., 2012), allowing extensive sampling of the pleura and the subsequent pleurodesis. In the lack of studies comparing image-guided biopsy and thoracoscopy, the diagnostic choice is based on the clinical evaluation of each individual case (Metintas et al., 2010b).

The assessment through thoracoscopy of visceral pleura involvement is crucial to establish the extent of disease and to formulate a correct TNM classification (American Joint Committee on Cancer, 2010). The involvement of the parietal and diaphragmatic pleura or the visceral pleura, limited or extensive, has prognostic value (Kao et al., 2011).

Endobronchial ultrasound (EBUS) for nodal staging in MPM is a new promising technique with some advantages compared to mediastinoscopy (less complications, minimal trauma to peritracheal tissue, access to hilar lymph-nodes usually inaccessible to mediastinoscopy) with a similar accuracy. Esophageal endoscoposcopic ultrasound (EUS) is indicated when suspected nodes are identified on imaging studies at those sites which are not assessable by EBUS (Rice et al., 2009; Tournoy et al., 2008; Zielinski et al., 2010; Richards et al., 2010).

For staging purposes, CT may underestimate early chest wall invasion, diaphragmatic and peritoneal involvement, as for its well-known limitation in assessment of nodal disease, and MRI can be used to complement CT in detecting invasion of chest wall or mediastinum, or trans-diaphragmatic extension. PET/CT can accurately demonstrate intrathoracic and extrathoracic lymphadenopathy and metastatic disease (Truong et al., 2013a; Nickell et al., 2014; Basu et al., 2011; Erasmus et al., 2005).

Several studies indicated PET/CT for nodal staging, with superior sensitivity, specificity and accuracy than other imaging techniques (Rice et al., 2009; Flores et al., 2003). However, PET/CT has a well known limitation in the assessment of lymphnodal micrometastatic disease (Sørensen et al., 2008). Consequently, a surgical staging is recommended (mediastinoscopy, EBUS, EUS-FNA and laparoscopy), especially for candidates to multimodal treatment (Truong et al., 2013b).

The measurement of tumor thickness on CT scan is the current standard in the assessment of response to therapy. However, inter-observer variability represents an issue. Alternative CT-based tumor response criteria, such as direct measurement of tumor volume changes, have been suggested as a surrogate for tumor response (Armato et al., 2013). Computer-aided detection (CAD) protocols, using dedicated software or other automated methods for volumetric evaluation of the response to therapy, have been proposed (Frauenfelder et al., 2011; Labby et al., 2013a; Labby et al., 2013b). PET parameters that measure tumor activity and functional tumor volume were suggested as indicators of patient prognosis (Armato et al., 2013).

So far, 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, remains the standard for the assessment of the therapeutic response of MPM. (Byrne and Nowak, 2004)

6. Surgery

6.1. Role of surgery in diagnosis

If feasible, thoracoscopy is recommended for diagnostic purposes. Multiple biopsies of both normal and seemingly abnormal pleura, including sub-pleural tissue, are recommended to minimize false negative results (Churg et al., 2014). Even if the diagnostic performance of uniportal thoracoscopic pleural biopsy is not equivalent to that of an open biopsy (Greillier et al., 2007; Bueno et al., 2004; Attanoos and Gibbs, 2008), thoracoscopy is preferable because of the increased risk of tumor implantation in the chest wall and the higher morbidity rate of open surgery (Churg et al., 2004).

Mediastinoscopy or laparoscopy are recommended for those patients with mediastinal nodal involvement or abdominal disease extension, respectively, that would preclude surgical consideration.

6.2. Treatment of malignant pleural effusion

Pleural drainage reduces pleural effusion, dyspnea, chest pain or persistent cough in patients who demonstrate a trapped lung on chest X-ray. The timing for chest tube insertion after unsuccessful pleural drainage is dictated by: (a) presence of the above mentioned symptoms associated to a time to recurrence shorter than 10 days; (b) contraindications to more invasive procedures or general anesthesia; (c) 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 into the pleural cavity, as talc slurry under local anesthesia.

Alternatively, patients who tolerate general anesthesia can undergo thoracoscopy and talc insufflation under direct vision, which ensures a thorough distribution of the agent. This technique is also recommended in patients who are candidates for extended pleurectomy/decortication (P/D) and extra-pleural pneumonectomy (EPP) because pleural adhesion facilitates subsequent extrapleural dissection while minimizing the chance for tumor dissemination. Contraindication to talc poudrage is the trapped lung syndrome and, in this cases, VATS pleurectomy has been advocated (Waller et al., 1995; Halstead et al., 2005; Martin-Ucar et al., 2001; Nakas et al., 2008).
Table 3

Recommendations of the surgical panel.

- A multidisciplinary team including surgeons, medical oncologists, respiratory physicians, radiologists and radiation oncologists is recommended to define the best treatment strategy in each individual patient.
- The two procedures with curative intent are extrapleural pneumonectomy (EPP) and extended pleurectomy/decortication (P/D).
- These surgical procedures should be performed in clinically and functionally selected patients with pre-treatment stages I and II, and selected stage III, preferably in the context of clinical studies. A priority goal of research is to identify the correct surgical contribution and type of intervention, in order to uniform procedures and results.
- Surgical procedures performed with curative intent should be reserved to referral thoracic surgical centers with dedicated expertise.

6.3. Resectable disease

Consensus was also obtained about thorough evaluation of the performance status and the cardiopulmonary reserve of surgical candidates as well as for the need of a correct definition of the surgical interventions, in the attempt to uniform procedures and results (Rice et al., 2011 Aug). EPP and extended P/D may be considered in stages I, II and selected (NO) stage III MPM, without distant spreading. If deemed good surgical candidates, patients should receive surgical resection (P/D or EPP), adjuvant radiation therapy (hemithoracic external beam or intensity modulated radiation therapy), and either neoadjuvant or adjuvant chemotherapy (cisplatin-pemetrexed for 4 cycles). The optimal precise sequence of treatments within thetrimodality is unclear, and should be decided upon by a multidisciplinary consensus for each individual patient (Gomez and Tsao, 2014).

Even if randomized clinical trials comparing the two surgical approaches are lacking (Treasure et al., 2014), recent studies suggest that extended P/D has lower mortality, less complications than EPP and comparable survival rates (Flores Pass and Seshan et al., 2008; Lang-Lazdunski et al., 2012). In 2015, a meta-analysis including 1,512 patients treated with P/D and 1,391 treated with EPP (Taioli et al., 2015) showed that perioperative 30-day mortality was significantly higher after EPP than after P/D. These results were confirmed by another meta-analysis (Cao et al., 2014).

In the case of discordance between CT and FDG-PET findings in assessing the nodal status, a thorough preoperative exploration of the mediastinum is recommended (Sugarbaker et al., 2014). Cervical mediastinoscopy and endoscopic procedures (EBUS and EUS) may be considered (alone or in combination) to detect nodal metastases otherwise inaccessible to mediastinoscopy (Nakas et al., 2012).

Recommendations from the surgery panel are summarized in Table 3.

7. Radiotherapy

7.1. Radiotherapy for port-site prophylaxis

Three randomized trials have been conducted to evaluate the efficacy of prophylactic irradiation in terms of tract-metastases-free survival. An initial study (Boutin et al., 1995) was positive, even if with some criticisms due to the limited number of enrolled patients and the high rate of port-site failure in patients not receiving radiotherapy (20%). More recently, two randomized trials (Bydder et al., 2004; O’Rourke et al., 2007) did not detect any benefit. Globally considered, the quality of these studies is modest, with quality assessment, according to GRADE criteria, negatively influenced by imprecision. Currently, there is no convincing evidence in offering systematically radiotherapy for port-site prophylaxis. An ongoing UK study (SMART trial) is looking at the best time to give radiotherapy to prevent mesothelioma spreading after a procedure to the chest wall.

7.2. Adjuvant radiotherapy

There are no randomized data to support adjuvant post-EPP radiotherapy, but historical comparison suggests that radiotherapy at the total dose of 54 Gy could be associated with a significant reduction in local failure (11% compared to previous values in the range of 30–40% with radiation doses below 50 Gy) (Rusch et al., 2001).

Initial data with intensity modulated radiotherapy (IMRT), due to its planning capability in treating a very irregularly shaped PTV (planning target volume) and in reducing dose to organs at risk (liver, heart, kidney, lung) were highly encouraging, with local control rates around 90% (Forster et al., 2003). However, severe toxicity was relevant compared to classical 3D-conformal radiotherapy, including deaths from radiation pneumonitis, even if dosimetric predictors of radiation injury were below the normally accepted constraints (i.e., V20 < 20%). With the use of strict 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 (Rice et al., 2007). Despite the lack of randomized studies comparing 3D-Conformal RT and IMRT after EPP, IMRT (mainly volumetric IMRT) is currently preferred, since it allows a more conformal irradiation of the affected hemithorax. A Swiss prospective phase II randomized trial (SAKK17/04, NCT00334594) (Stahel et al., 2014) evaluated the role of hemithoracic RT after neo-adjuvant chemotherapy and EPP. The primary endpoint of 1-year increase in loco-regional relapse-free survival was not met. Few retrospective clinical data are available about radiotherapy as adjuvant treatment after P/D. The treatment volume in hemithoracic pleural irradiation should include all the pleural space (CTV defined as the entire hemithorax including the parietal and visceral pleura, the entire diaphragm and involved ipsilateral hilar lymphnode stations, without inclusion of the fissures, with optimal imaging for target definition still to be defined). However, even with the modern radiation techniques, it would be difficult to adequately spare the lung itself, with the risk of a severe radiation pneumonitis.

Preliminary experiences of lung sparing hemithoracic pleural IMRT have been presented (Rosenzweig et al., 2012; Minatel et al., 2014; Chance et al., 2015) and showed potentially promising results for both efficacy and safety (with a 20% rate of severe pneumonitis).

7.3. Palliative radiotherapy

Retrospective analyses indicated a clinical benefit in terms of symptom control in about 50% of patients treated with palliative radiotherapy. Chest infiltrating tumor masses causing pain represent the main indication. In this setting, there are few prospective trials (Bissett et al., 1991; Lindén et al., 1996; MacLeod et al., 2015) and hypofractionated schedules are generally used (dose/fraction in the range 3–5 Gy), with total doses from 20 to 40 Gy. Pain control is achieved more frequently with fractions larger than 3 Gy; the median duration of pain relief is generally satisfactory. Palliative irradiation is not effective in the treatment of dyspnea secondary to pleural effusion or mediastinal invasion. The very wide fields often required to palliate symptoms may cause significant acute toxicity, mainly fatigue; therefore, prospective studies with adequate clinical endpoints, including quality of life, are needed. The efficacy of palliative radiotherapy cannot be evaluated according to GRADE methodology and criteria, because there are no comparative trials.
Table 4

Recommendations of the radiotherapy panel.

4.1 Radiotherapy for port-site prophylaxis
- Systematic adjuvant irradiation of thoracic tracts is not routinely indicated.
- Radiotherapy as a part of a multimodality approach
- The most appropriate timing of delivering radiotherapy should be discussed upfront in a multidisciplinary board.
- For patients with resectable MPM, who undergo EPP (after neo-adjuvant chemotherapy), adjuvant radiotherapy can be recommended for “highly selected patients” (good performance status, epitheliod histology, female), to improve local control.
- RT should be considered only for patients who meet the following criteria: ECOG PS ≤ 1, FEV1 > 80% and good functional pulmonary status, adequate renal function, absence of contralateral chest disease
- 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 may be considered in centers with an adequate experience in this field and in the context of clinical trials. Radiation exposure of the remaining lung should be strictly limited, given the high risk of fatal pneumonitis when strict limits are not applied (see text).
  - The clinical target volume (CTV) for post-EPP RT should encompass the entire pleural surfaces and the surgical bed of the whole hemothorax, 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 and single institution assessment.
- Adjuvant irradiation after P/D (lung sparing hemothoracic pleural IMRT) is usually not recommended, but may be considered with caution and under strict dose limits of organs at risk, only in the context of prospective clinical trials.

4.3 Radiotherapy for symptom palliation
- A role for palliative hypofractionated radiotherapy (daily doses of 3–5 Gy) for the control of secondary chest pain is proven. However, a careful clinical evaluation is mandatory in every single patient, especially considering that such treatments may be associated with acute toxicities.

Recommendations from the radiotherapy panel are summarized in Table 4.

8. Chemotherapy

8.1. First-line chemotherapy

The role of chemotherapy in MPM, as well as the optimal timing of chemotherapy, have been reviewed by Fennell et al. (Fennell et al., 2008) and in the previous consensus paper (Pinto et al., 2013).

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 cycles) showed a small, not significant increase in overall survival with chemotherapy (Muers et al., 2008). The evidence profile of GRADE applied to this randomized trial suggests a moderate quality of information regarding both efficacy and safety.

Platinum-based doublet containing a third-generation antifolate (pemetrexed or raltitrexed) is the front-line standard of care (Vogelzang et al., 2003; Van Meerbeeck et al., 2005). The evidence profile of GRADE applied to randomized trials conducted in the front-line setting suggests a high quality of information regarding both efficacy and safety. The pemetrexed-containing combination is supported by a greater amount and quality of clinical information (Muers et al., 2008).

Pemetrexed can be safely administered in combination with carboplatin, with efficacy comparable to cisplatin-pemetrexed (Santoro et al., 2008). The combination of carboplatin and pemetrexed could be an alternative treatment option for patients who are not candidates to cisplatin-based therapy. On the other hand, in patients unfit for platinum-based chemotherapy, the use of single agent vinorelbine as first-line therapy could be considered, although the consensus panel was not unanimous, due to the limited evidence supporting this treatment (Fennell et al., 2008).

A better knowledge of major molecular pathways involved in MPM biology has lead to the identification of potential new therapeutic targets (Stahel et al., 2015). A randomized phase II trial testing the addition of the anti-VEGF antibody bevacizumab versus placebo to gemcitabine-cisplatin reported no significant difference, neither in terms of progression-free survival nor in overall survival (Kindler et al., 2012). The randomized phase II MAPS (Mesothelioma Avastin plus Pemetrexed-cisplatin Study), evaluating the addition of bevacizumab to pemetrexed-cisplatin, met its phase II its primary end point (Zalcman et al., 2010). Data presented at the American Society of Clinical Oncology annual meeting in 2015 from the phase III study, conducted in 448 patients, demonstrated a 2.7–month improvement in median survival, mirrored by a 2.1-month benefit in median PFS (Zalcman et al., 2015). In a phase II, single-arm study testing the addition of amautuximab, an anti-mesothelin monoclonal antibody, to pemetrexed and cisplatin, the experimental combination was well tolerated and associated with an objective response rate of 40%. Although PFS was not significantly different from historical controls, a promising median OS of 14.8 months was observed (Hassan et al., 2014).

There are no data about the optimal duration of chemotherapy in patients with MPM. In the current practice, chemotherapy is administered for a median of 4–6 cycles, unless progression or severe toxicity occurs. Although a small study has shown that continuation of pemetrexed alone after induction with cisplatin and pemetrexed is feasible (van den Bogaert et al., 2006), there are no randomized trials supporting the efficacy of the maintenance approach. A randomized study testing the efficacy of switch maintenance with thalidomide versus no further treatment showed no survival improvement (Buikhuizen et al., 2013). A phase II randomized study of continuous maintenance with pemetrexed (Anon., 2016a), and another one testing the switch maintenance strategy with the folic acid kinase inhibitor defactinib are ongoing (Anon., 2016b).

In elderly patients, with the warning of a greater hematologic toxicity, the efficacy of platinum and pemetrexed is comparable to what observed in younger patients (Ceresoli et al., 2008). GRADE methodology was not adopted for the issue of treatment of elderly patients, because of the lack of randomized trials comparing active treatment versus best supportive care specifically in elderly patients, and particularly for subjects older than 75 years. However, the Consensus panel agreed that elderly patients with good performance status and without clinically relevant comorbidities might be candidate to chemotherapy (Ceresoli et al., 2014).

8.2. Second-line chemotherapy

The role of second-line chemotherapy was evaluated in a randomized phase III trial comparing pemetrexed plus best supportive care (BSC) versus BSC alone in patients previously treated with a first-line regimen not including pemetrexed. The study enrolled 243 patients, and showed a statistically significant increase in objective response rate, disease control rate and time to progression for pemetrexed, but without significant benefit in overall survival (Jassem et al., 2008). There are no approved agents for second-line treatment of MPM patients, and this remains a disease setting to test new agents. Consequently, patients should be encouraged to participate in clinical trials. When a clinical trial is not available, single-agent chemotherapy could be considered for fit patients, although the panel was not unanimous about this issue. Best supportive care remains a valid option (Ceresoli, 2014).
Several published and ongoing clinical investigations are exploring the potential benefit of targeted therapies in second line but so far there is no positive evidence. (Ceresoli, 2014). In a large phase III trial, conducted in 661 patients with previously treated MPM, the histone deacetylase inhibitor vorinostat failed to show any benefit (Krug et al., 2015). Following initial evidence from a small phase II trial (Calabro et al., 2013), a randomized double-blind, placebo-controlled phase III trial of the anti-CTLA4 antibody tremelimumab has been performed, but results are still pending (Anon, 2016c). Several immune-checkpoint inhibitors are currently under evaluation in this setting. In a phase Ib study, the anti-PD1 antibody pembrolizumab was well tolerated, and provided evidence of antitumor activity in patients with advanced PD-L1+ MPM (Alley et al., 2015).

Re-treatment with pemetrexed may be a potential second-line option in patients with MPM achieving a durable (>6 months) disease control with first-line pemetrexed-based chemotherapy (Ceresoli et al., 2011; Bearz et al., 2012; Zucali et al., 2012). However, there is no evidence from controlled clinical trials supporting this strategy and further prospective evaluation is needed. Recommendations from the chemotherapy panel are summarized in Table 5.

### 9. Continuity of care, pain management, psycho-social and legal issues

For the population at risk, psychological support should be planned and provided by psychologists with specific expertise (Ceresoli et al., 2011; Bearz et al., 2012; Zucali et al., 2012; Granieri et al., 2013; Grattan et al., 2011; O’Leary and Covell, 2002; Palinkas, 2012; Boardman et al., 2008; Downey and Willigen, 2005; Drescher et al., 2014). It should be directed to individuals or groups and aimed to obtain a realistic consciousness of the risk in its effective dimension, to favor a coexistence with it, to contain anguish and to reduce an inappropriate use of the social health care services (Bearz et al., 2012; Grattan et al., 2011; Barnes et al., 2002; Couch and Coles, 2011; Crighton et al., 2003; Foster and Goldstein, 2007; Guglielmucci et al., 2014).

For MPM patients, a multidisciplinary approach, involving a psychologist specialized in taking care of cancer patients and their families, is recommended. The psychological intervention is part of the communicative-relational process during the entire course of the disease, from the knowledge of the clinical condition to the selection of therapies (or the refusal of treatment) and to decisions related to the end of life (Guglielmucci et al., 2014; Baum, 1993; British Lung Foundation, 2013; Glik, 2007).

Adequate support should be provided to relatives or any subject close to the patient. In any case, their involvement should respect the patient’s will (Granieri et al., 2013; British Lung Foundation, 2007).

In order to secure the access of the patients to welfare and social security benefits, the physician in charge must comply to all his legal duties related to certifications in every case of diagnosed or suspect occupational disease (report under Italian DPR No 1124 of 1965 and subsequent amendments; certification – with the consent of the interested person – of occupational disease for the access to worker compensation benefits: legal duty to report).

Every health facility must adopt information policies (such as dedicated information desks, brochures) useful for the acquisition, by the patient, of full knowledge of his rights (insurance, welfare and any other right) and regarding the due legal procedures.

Oncology units should define and establish the most suitable organizational model, in order to ensure proper approach to patients needing palliative care (Partridge et al., 2014).

Considering the characteristics of this specific type of cancer and the limited life expectancy, it is recommended a multidisciplinary approach since diagnosis, with the presence of a physician expert in palliative care for the control of symptoms, in order to ensure the best quality of life to patients (Hui et al., 2015; Anon, 2016d; Cherny et al., 2010; Smith et al., 2012).

### Future areas of research

Unfortunately, the efficacy of current therapies is very limited, and the overall prognosis remains quite poor. In order to improve survival of MPM patients, effective strategy of early diagnosis and effective treatment strategies are highly needed. Unlike other cancers, MPM has not been well characterized in many aspects. Therefore, it is quite relevant to identify biomarkers of early disease, to better understand tumor biology, to develop novel diagnostic approaches as well as new treatment options, such as immunotherapy and targeted therapies directed against genomic abnormalities. A summary of future areas of research is summarized in Table 6.

### Appendix A.

### Contributors

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

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Table 6
Future areas of research.

- Integration of genomics, transcriptomics and proteomic information or identification of new targets in mesothelioma
- Blood-based biomarkers of early disease
- Evaluation of the role of BAP1 in germ-line and sporadic mesothelioma
- Evaluation of the role of functional imaging in diagnosis and in planning radiotherapy treatment
- Improvement in the assessment of response to therapies
- TNM staging of mesothelioma
- Evaluation of the role of extended pleurectomy/decortication versus no pleurectomy/decortication
- Evaluation of the role of pleurectomy plus chemotherapy in advanced disease
- Evaluation of the role of intrapleural criotherapy and photodynamic therapy
- Evaluation of trimodality and combined modality approaches in early stage mesothelioma
- Evaluation of risks and benefit of intensity modulated radiation therapy
- Evaluation of the role of prophylactic traits irradiation
- Identification of optimal treatment strategies in the elderly
- Evaluation of the role of early palliative care
- Evaluation of the efficacy of anti-angiogenic agents
- Evaluation of the efficacy of anti-mesothelin monoclonal antibodies alone and in combination with toxins and cytotoxic agents
- Evaluation of the efficacy of immune checkpoint inhibitors
- Evaluation of dendritic cell immunotherapy
- Evaluation of allogeneic tumor cell vaccine
- Evaluation of gene therapy

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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.critrevonc.2016.05.004.

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