

Biological and Clinical Aspects of Malignant Pleural Mesothelioma: Past, Present and Future Treatment Strategies

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ABSTRACT

Pleural mesothelioma is still increasing and its prognosis remains dismal. Trimodality therapy (surgery, chemo and radiotherapy) is the treatment that seems work better, even if there is no evidence if extrapleural pneumonectomy is more curative than pleurectomy/decortication so far. Chemotherapy will probably play a fundamental role in the next future and further randomized studies are necessary, but patients should see the benefits of participating in randomized and controlled trials.

Key words: Mesothelioma; Surgery; Chemotherapy

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INTRODUCTION

At present, we are witnessing an ever-increasing number of cases of malignant pleural mesothelioma (MPM), with poor prognoses. Asbestos is the principal carcinogen associated with MPM. Malignant mesotheliomas initially occur on the parietal pleural surface of the pleural mesothelium, and one possibility is that the asbestos fibers stick out from the surface of the lung and cause repeated cycles of scratching damage, inflammation and repair in the adjacent parietal pleura. Mesothelial cells normally facilitate the free movement of the pleural surfaces during respiration by enmeshing lubricating glycoproteins. These cells readily proliferate in response to injury and growth factors. Sequences of Simian Virus 40, a DNA virus, have been found in atypical mesothelial proliferations and there is some evidence that SV 40 may have been inadvertently transmitted to humans via injectable poliomyelitis vaccines 35 to 50 years ago. Its role remains unclear and unproven so far. In the initial phase of MPM, its symptoms generally go unnoticed, but as its dimensions increase, its symptomatology is typically that of a mass progressively occupying more and more space within the pleural cavity. In some cases the clinical presentation may worsen to the point of developing Tobias syndrome – a condition characterized by scoliosis and a retraction of the accordant hemithorax; or, alternatively, Pancoast syndrome, with an involvement of the brachial plexus and cervical sympathetic nerves. A pleural effusion occurs at the outset of nearly all cases (Figures 1, 2), while in a small percentage of cases (1%) the disease manifests itself with a spontaneous pneumothorax (Figure 3).

No matter how carefully selected the patients or how successfully they've undergone multimodal treatment (surgery, chemo and radiation therapy), controlling the disease remains a problem to be solved. Even when patients undergo a pleurectomy/decortication (P/D) or an extrapleural pneumonectomy (EPP), a progression of the disease remains inevitable.

The most significant histological subtypes are epithelioid (Figure 4), biphasic (Figure 5), sarcomatoid (Figure 6) and desmoplastic (Figure 7).

DISCUSSION

Mesothelioma surgery has evolved in order to obtain an ever-increasing oncological radicality, as, from the beginning, the surgical



Figure 1 Rx T: MPM pleural effusion (left).



Figure 2 Rx T: pleural mass (right) of MPM with effusion.



Figure 3 Rx T: MPM pneumothorax (left), 0.1% of cases.

debulking of the disease has proven to be extremely difficult. For this reason, from the point of view of a resective strategy, two surgical methods have developed: the pleurectomy/decortication (Figures 8, 9), conceptually derived from pleural empyema surgery; and the pleuropneumonectomy or so-called extrapleural pneumonectomy (Figures 10, 11), to which there are various associated protocols of CT and RT. Surgeons in favor of EPP believe it makes possible a complete macroscopic removal of the disease with acceptable risk of morbidity and mortality and facilitates the administration of postoperative RT at high doses with excellent local control.

Supporters of P/D believe that it provides adequate cytoreduction, particularly in patients at early stages of MPM (I and II), without the risk of morbidity and mortality that characterize EPP. They also believe that P/D plays an important role in the multimodal treatment when combined with intrapleural and/or systemic CT and intensity modulated radiation therapy (IMRT). Because the surgery, utilized singularly, whether P/D or EPP, has given disappointing results, in the same ways as CT and RT, the multimodal treatment strategy was developed. The innovation of multimodal treatment as a cure for MPM has been to adopt a combination of surgical resection and adjuvant therapy (chemo, radiation or both), as such a strategy represents a better therapeutic option for patients, even if only for a select group^[1,2]. There are two fundamental studies regarding multimodal treatment of MPM, one combining surgery with RT, the other with adjuvant CT.

Memorial Sloan Kettering Cancer Center has conducted a prospective study in which patients have undergone EPP ($n = 54$) followed by RT at high doses (54 Gy) at the ipsilateral hemithorax. The adjuvant RT has been studied to improve local control after

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- **Diffuse Malignant Mesothelioma**
 - Epithelioid mesothelioma
 - Sarcomatoid mesothelioma
 - Desmoplastic mesothelioma
 - Biphasic mesothelioma
- **Localised Malignant mesothelioma**
 - Epithelioid mesothelioma
 - Sarcomatoid mesothelioma
 - Biphasic mesothelioma
- **Well-differentiated papillary mesothelioma**
- **Adenomatoid tumour**

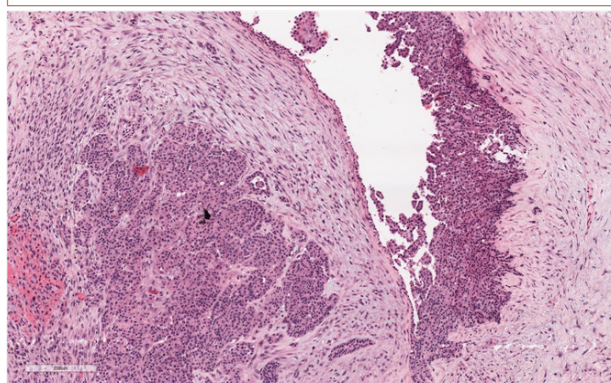


Figure 4 Hematoxylin - Eosin: Epithelioid Mesothelioma (by courtesy of Dr L. Delsedime Pathology, Univeristy of Turin, Italy).

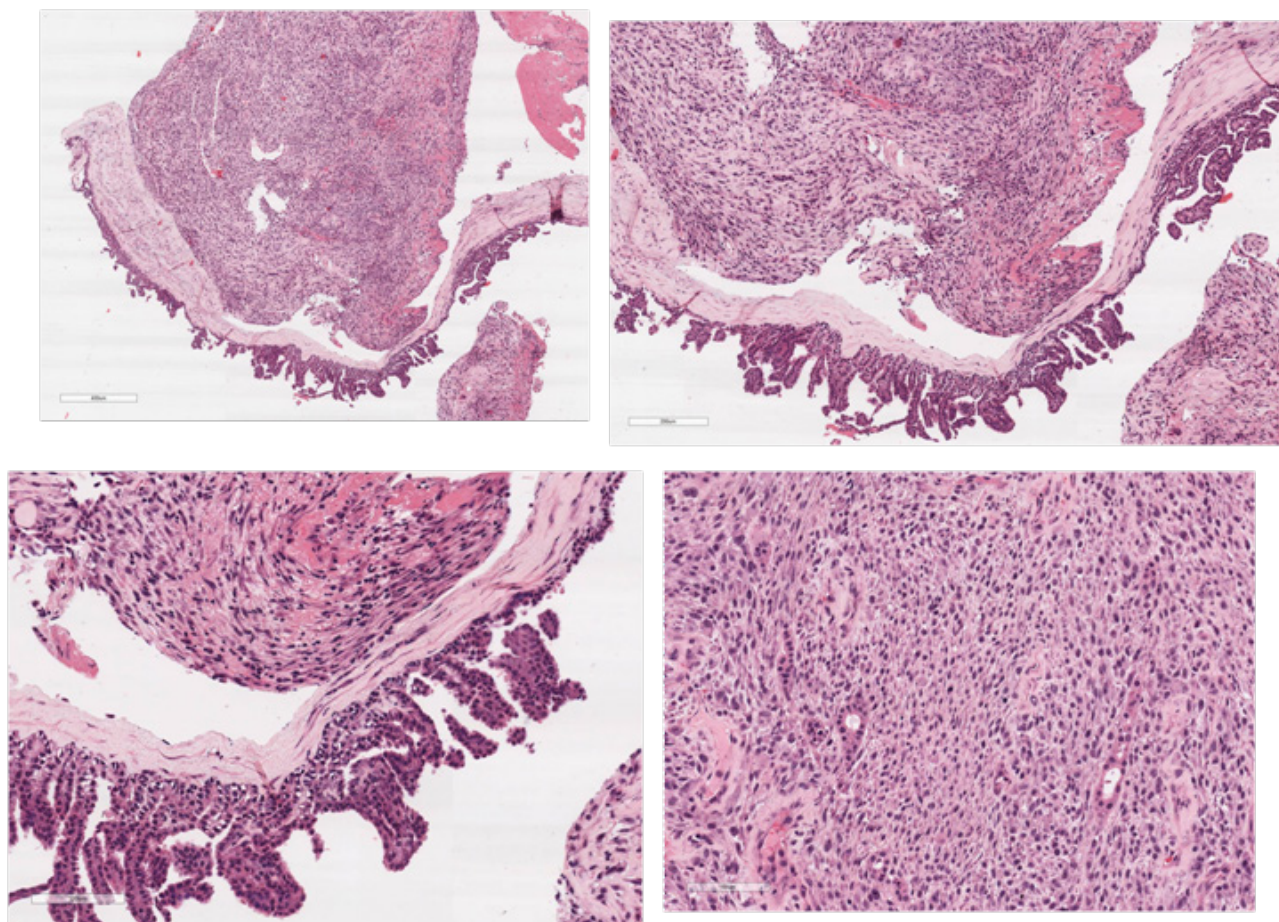


Figure 5 Hematoxylin - Eosin: Biphasic Mesothelioma (by courtesy of Dr L. Delsedime Pathology, University of Turin, Italy).

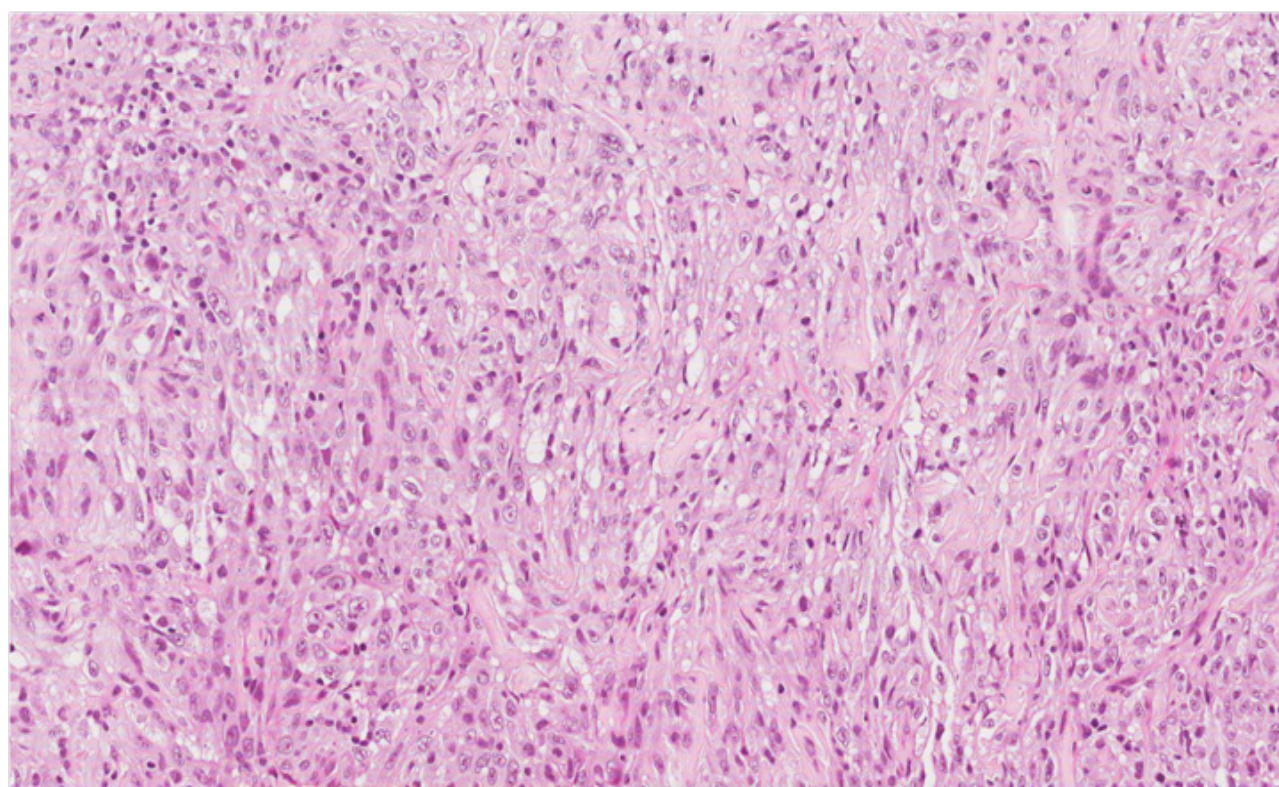


Figure 6 Hematoxylin - Eosin: Sarcomatoid Mesothelioma (by courtesy of Dr L. Delsedime Pathology, University of Turin, Italy).

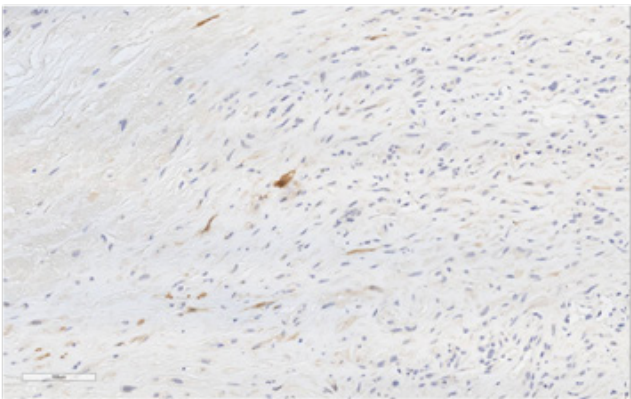
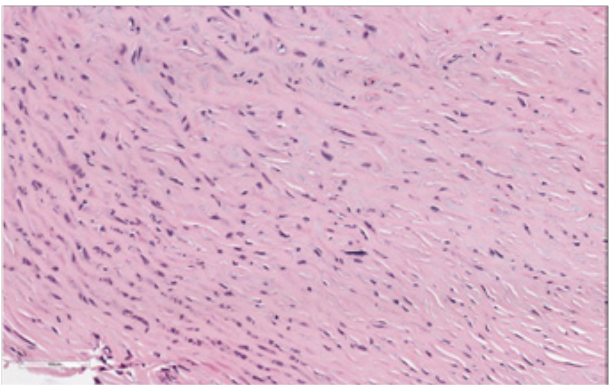
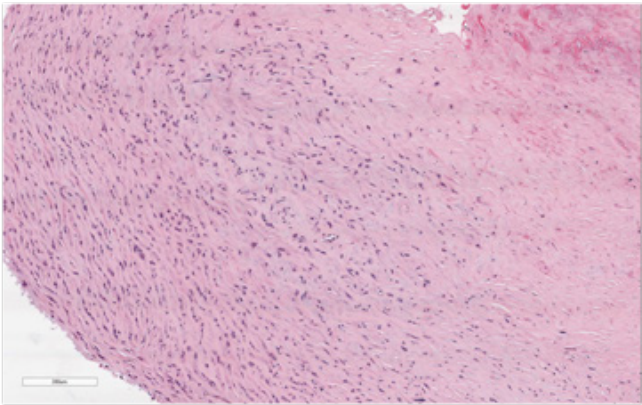
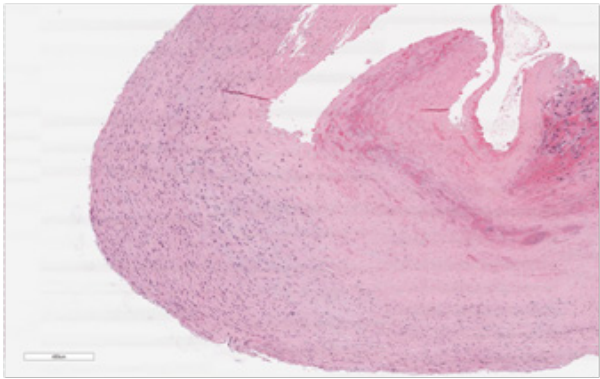


Figure 7 Hematoxylin-Eosin: Desmoid Mesothelioma, Calretinin right low (by courtesy of Dr L. Delsedime, Pathology, University of Turin, Italy).

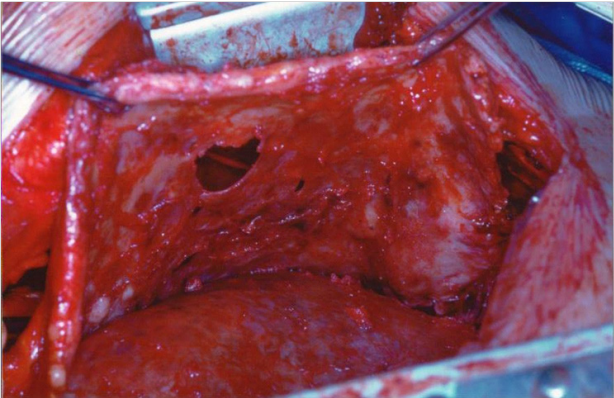


Figure 8 Pleurectomy/Decortication.

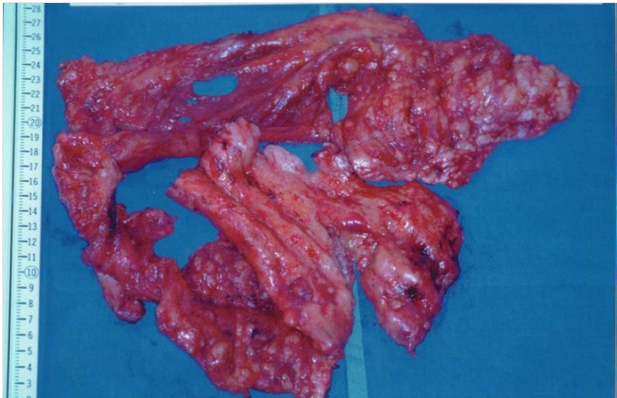


Figure 9 Pleurectomy/Decortication..

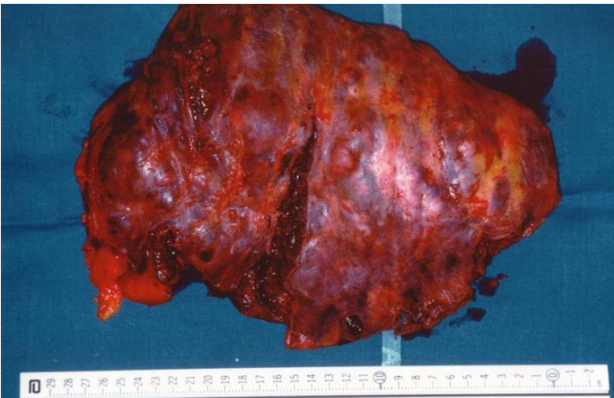


Figure 10 Pleuropneumonectomy.

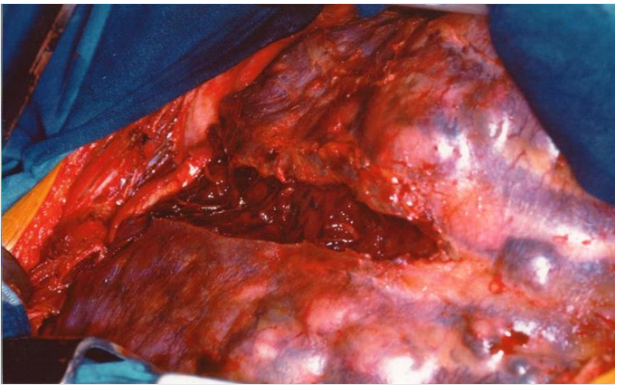
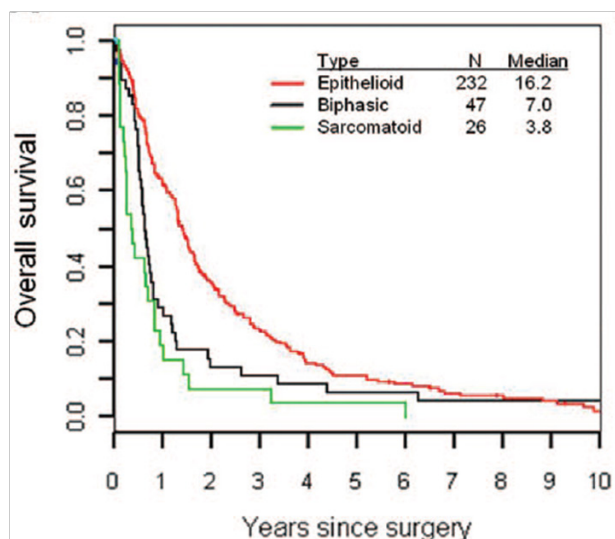


Figure 11 Pleuropneumonectomy.



From Journal of Thoracic Oncology, volume 6, Number 5, May 2011.

EPP, particularly for high doses of radiation which can be applied without risk of pneumonia. This therapeutic strategy has resulted in a dramatic reduction in local recurrence prolonging survival in patients at advanced stages of the disease. The median survival has been 33.8 months for stages I and II, and 10 months for stages III and IV.

The intervention of EPP followed by adjuvant CT has been studied at Brigham and Women's Hospital in 183 patients with MPM. The perioperative mortality equaled 3.8%. Among the remaining 176 patients, 38% survived 2 years, 15% survived 5 years, and the median survival was 19 months.

In fact, at the moment the most appropriate treatment for MPM is considered to be the trimodality protocol, which consists of surgery following chemotherapy and radiation therapy. Regarding this it must be noted that in a study by Sugarbaker published in 1999, it was made clear that patients with MPM who had undergone EPP followed by CT and RT could survive for a longer period. In particular, among the stage I subgroup with the epithelial histotype, negative margins of resection and lack of lymph node involvement registered a survival rate of 68% for 2 years, and 46% for 5 years^[3,4].

However, the decision to select between an EPP or P/D is still mostly based on the preference of the surgeon rather than conclusive scientific evidence, since there is not enough significant statistical data for either regarding survival rates^[5-8].

In fact, to justify the choice of surgical procedure, some studies focus on the importance of two "end points", which are the rate of progression and the type of relapse. However, these "end points" have not always proven to be very accurate parameters for carrying out follow ups, because definitions regarding the "progression of diseases" aren't always clear, and relapses haven't always been studied in homogenous ways. Therefore, estimations of how the disease will progress tend to differ considerably from estimations related to 5-year survival.

Rush and Pass (2008) showed that patients with MPM at stages I and II presented a survival of 19 months when having undergone an EPP and of 23 months with a P/D: the study in question, like other analogous studies, emphasized the similitudes of the outcome after an EPP or P/D for MPM in a multicentre trial, and doesn't allow for a clear understanding of which of the two procedures are preferable, as the typically diffuse spread of MPM throughout the chest renders debulking particularly difficult in either cases.

More recently the general concept of trimodality therapy for

mesothelioma has generated the idea of neoadjuvant CT as a strategy for treatment. This new concept of neoadjuvant CT in MPM has been extrapolated by results obtained in patients with stage IIIA NSCLC. In fact, the use of neoadjuvant CT in stage IIIA NSCLC has made major pulmonary resections possible with acceptable risk of morbidity and mortality^[9].

This strategy has been evaluated in at least 6 studies:

1. In 2002, the French group for thoracic pathology reported a median survival of 23 months for patients with MPM treated with neoadjuvant CT with cisplatin and gemcitabine, EPP and postoperative RT. These results were much superior to the group of patients with MPM treated with EPP followed by adjuvant CT and RT, where the median survival was only 13 months^[10].

2. In 2003, De Perrot, Ginsberg and Payne presented a study in which it was reported a median survival of 74% during a year with an operative mortality of 6% for MPM patients treated with neoadjuvant CT followed by surgery (EPP) and postoperative RT^[11].

3. In 2009, De Perrot, Feld, *et al* reported the experience of a single center with neoadjuvant CT followed by EPP and postoperative RT at high doses: the median survival for patients was 59 months using trimodality therapy, completed without mediastinal lymph node involvement. It has once again been confirmed how the N2 disease remains an important negative prognostic factor for survival^[12].

4. In 2007, Lucchi, Chella, *et al* presented a phase II study of a single centre centered on the following treatment: preoperative intracavitary IL-2, P/D, epidoxorubicin + post-operative intracavitary IL-2, adjuvant radiation therapy, cisplatin+gemcitabine for systemic therapy and s.c. longterm IL-2.

The median survival was 26 months (31 and 21 months for stages II and III respectively)^[13].

5. In 2009, Krug, Pass and Rush reported their experience with pemetrexed + cisplatin + EPP + adjuvant RT on 77 patients affected by MPM. The survival median was 29.1 months, and at 2 years they recorded a survival rate equaling 61.2%. The univariate analysis for subgroups of patients showed that the radiological response, and no other factor, was associated to an increase in survival. It was therefore once again confirmed what previous studies had already shown, which is that even when treatment is homogenous, only a subgroup of patients benefit with a long survival^[14].

6. From October 2005 to November 2008 in the MARS study 112 patients with MPM were registered. Out of them 50 were randomly assigned to EPP (24 pts) or to no EPP (26 pts). 83 out of 112 pts received CT before intervention. The findings were that there is no significative difference between the survival of the EPP group (median survival of 14.4 months) and the no EPP group (median survival of 19.5 months) and that there is no benefit to EPP within trimodality therapy over chemotherapy alone for survival or quality of life^[15].

However it is a well-established fact that in the treatment of MPM the most encouraging results have been obtained with the improvement of CT protocols, more than with surgery. In fact, EPP or P/D have only proved to be useful in the macroscopic removal of the disease. In regard to chemotherapy in MPM, only since 2000 have new molecules been used that are capable of working efficaciously with this disease. The results of a large, randomized trial presented in 2002 at the meeting of the American Society of Clinical Oncology and later published (Vogelzang, Rusthoven) brought into consideration the idea of combining pemetrexed (folate antimetabolites) + cisplatin, whereas initially that of gemcitabine + cisplatin was considered to be the most effective combination for MPM. In fact, the response in MPM to cisplatin and gemcitabine had

been estimated between 16 and 47 %^[16-18]. However, based on the most recent findings^[19,20], pemetrexed + cisplatin have since become the standard regimen for the first-line treatment of MPM. In fact, using this protocol, large clinical studies of phase III have shown a response rate of 41%, a median survival of 12.1 months and a rate of progression of 5.7 months. Regarding the cardiopulmonary function, the spread of the disease, and the possibility of macroscopically performing a radical resection, the fundamental importance of an accurate selection of patients has also been reconfirmed^[21]. To improve patient selection and to individuate high-response patients to chemotherapy, studies into gene expression profiling have also been undertaken^[22], though their findings are not yet conclusive.

The crucial point in MPM treatment, however, seems to be in the selection of patients, so much so that it can delineate the idea of a prognostic score of long-term survival for MPM patients who've undergone surgery. In fact, out of a recent multicenter analysis^[23] there emerged proof that a young age, a lack of exposure to asbestos, an epithelioid histology, and a low number of metastatic lymph nodes from all removed lymph nodes are all factors associated to better survival after EPP. Moreover multivariate analysis showed that nuclear atypia and mitotic count were independent prognostic factors so that it has been reported that nuclear grading is a strong predictor of survival in epithelioid diffuse malignant pleural mesothelioma^[24].

Knowledge about the biology of MPM, however, is not yet conclusive, and the estimation that a spike in illnesses will occur after 2015^[25,26], will favor a concentration of new cases of MPM at highly specialized centers. Only then can large case studies be evaluated and advancements in the necessary randomized studies be made.

Patient with MPM need to receive all the necessary information about their disease, so that they can decide which treatment on a clinical-evidence basis, and hopefully see the benefits of participating in randomized and controlled trials^[27,28].

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