Editorial Commentary

Malignant pleural mesothelioma: between pragmatism and hope

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Although malignant pleural mesothelioma (MPM) is a rare tumor, it is among one the most discussed tumor in the industrial world. Mesothelioma represents 0.3% of all number of deaths for cancer in the recent GLOBOCAN study (1). The incidence is projected to increase in the next two decades, and the reported dismal 5-year survival rate of less than 5% makes MPM one of the deathliest worldwide tumor (2,3). Some Scientists suggest that the asbestos promotes a chronic pleural inflammatory that after years stimulates the development of a malignant mesothelioma in up to 5% of exposed individuals (4).

Patients but also physicians/surgeons are sometimes found lost in the numerous confusing articles on MPM which can be easily taken from internet. Certainly, the source from where the information have been extrapolated is of paramount importance to obtain reliable scientific data on survival and quality of life (5-10), and this should be taken in consideration by the "modern" patient who goes in internet to take information about his/her surgeon and proposed treatment. Nevertheless, although the modern patient is becoming more and more exigent, the mesothelioma patient's dream, isn't about which kind of treatment will be used, but about simpler pursuits: patients want undergo to the treatment, surgical or non-surgical, which gives them long term survival, and good quality of life.

In the modern real-life it is usual to find patients with MPM who are conducting a battle between the desire to live (hope) and the cruelty given by the large amount of data available on internet saying that the survival is poor (pragmatism) (11). For surgeons and oncologists, although at a different level of sadness, things are similar as we experience the contrast between the scientific evidence that surgery or other treatment does not "cure" MPM but in the same time we feel uncomfortable to deny hope to our patients.

So, what is the right thing to do? My personal opinion is that that a more profound dialogue is necessary to understand the pragmatism and hope in MPM in such a way to know where the scale should hang.

Pragmatism

The pragmatism arises from the data published in the literature and the daily life of our patients.

Regarding the former. After almost 16 years when it was suggested about the necessity to perform prospective randomized trials (RCT) for mesothelioma to clarify the results of the surgical treatment, things changed a little, but changed. In fact, since then few surgical RCTs on MPM have been published. The first was the well-known MARS trial. The study was performed in 50 patients who were randomly assigned: 24 to extrapleural pneumonectomy (EPP) and 26 to no EPP. Median survival was 14.4 months for the EPP group and 19.5 months for the no EPP group. The authors concluded that, "although limited, radical surgery in the form of EPP within trimodal therapy offers no benefit and possibly harms patients". Although the study included limited numbers and was extensively criticized, we must be in debt of the MARS trial (12) because it arises to the surgical community doubts about the exaggerated use of extrapleural pneumonectomy.

Moreover, the other RCT is the MESO-VATS trial (13). One hundred seventy-five patients underwent 88 to talc

pleurodesis and 87 to VATS-Pleurectomy/decortications (VATS-pp). The study showed that overall survival at 1 year was similar (52% in the VAT-PP group and 57% in the talc pleurodesis group) (P=0.81) but median hospital stay was longer for those who received VATS-pp (7 versus 3 days, P<0.0001). The authors concluded that for MPM "less is better".

Nevertheless, guidelines still recommend that at initial stage surgery could be either EPP or pleurectomy/decortication, and it should be part of a multimodal treatment (14-16). In my opinion it sounds wise that because the rarity of MPM and the unproved better surgical long-term result (17,18), EPP should be performed only in highly specialized centers and, as suggested, within a clinical trial (19).

Regarding the latter, the daily life of our patients. We already know that modern patients often use the web to identify the "best" surgeon and the "most innovative" treatment, but we sadly also know that except in rare occasions, which confirm the rule, worldwide patients and their families live the same terrible experience: survival remains poor.

Hope

Having treated many patients with MPM my personal feeling is that, hope, not false hope, is necessary (20). Although the pragmatism due to the dismal survival could stimulate the negative sentiment of sadness, a bright door towards the future must remain open to stimulate a new generation of scientists and surgeons to continue to think differently across the surgical and oncological spectrum (21-25).

Hope does not belong to those "physician/surgeons" who declare for new "miraculous" treatments only on the basis of their own experience, tumor stage, histology and performance status (pleurectomy, EPP, hyperthermic Intrathoracic Chemotherapy HITHOC, immunotherapy, chemotherapy, multimodal treatment etc.), and not on proved cure. All surgical centers with interest in mesothelioma should undertake or participate in an RCT before a decision to operate a patient with MPM is taken. For example, in 2013 as we have seen many patients (2) and there was no consensus of what it could have been the best surgical treatment for MPM, we decided to initiate a small pilot study comparing Debulking Surgery and vs talc pleurodesis alone (26). The study rationale is that because pleurectomy/decortication is not expected to achieve an R0 resection the addition of HITHOC at the end of the surgical procedure could achieve a "sterile" operative thoracic field and therefore could prolong survival. Nevertheless, the results of MARS2 trial (27) and other non-surgical trials could carry more hope (28).

The hope, but not false hope, need to be maintained "alive" in patients suffering of MPM, and the recent concept of integrating specialization and the individualization of surgery including immune checkpoint inhibitors, immunotherapies, targeted therapies, or novel drugs being investigated in malignant pleural mesothelioma, could permit the best long-term survival in the future. Perhaps in the future the individualized treatments (tailored) will permit to obtain better long-term survival overcoming the "cold" TNM stage where all human being are classified according to the stage of the disease without taking in consideration different important factors as genes and mood (positive *vs.* depressed) (29). Just to make an example, two patients at the same stage of the disease (T2N0M0) have a different mood: one is depressed while the other is optimistic (different genes!!!). Should they undergo the same treatment? perhaps the depressed patient should undergo PD while the positive patient should undergo EPP.

Conclusions

What it should be the right approach with a patient suffering of MPM? Be pragmatic saying that there is nothing to do, and suggest talc pleurodesis? or be positive with the doors always open to hope and new opportunities?

Although we can speculate that denying hope to a patient with MPM could have a strong impact on his/her survival because the possible development of immunodepression, it is evident that the same negative result could be obtained if false hope is given; for example, the promise of long-term survival after an extrapleural pneumonectomy (30,31).

My personal experience with many patients with MPM teaches that pragmatism and hope should both be taken in serious consideration, and are equally important (*Figure 1*). During consultation, although there is no doubt that we must be pragmatic, we should always end the clinical discussion with our patients administering a pill of humanity which includes the positive attitude to inform the patient about the possible "hope" which can only arrive from the participation in well designed new studies and trials.

In conclusion, patients with mesothelioma need special attention and expertise. Expertise could be found in those Units where pragmatism and hope are not enemies but are

Figure 1 Tip the balance in malignant pleural mesothelioma.

equally important, especially when hope is built on the solid ground of pragmatism.

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