Perspective on malignant pleural mesothelioma diagnosis and treatment

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Malignant pleural mesothelioma (MPM) is an aggressive solid malignancy with dismal prognosis. The majority of newly diagnosed MPM patients present with advanced (IMIG/UICC stage IV) disease and are therefore treated with chemotherapy and supportive measures. The median survival of this group of patients ranges from 12 months with chemotherapy to 7 months with supportive care (1,2). Nonetheless, for a selected group of patients that present with a locally advanced disease (IMIG/UICC stage I–III), a personally tailored multimodality therapeutic (MMT) protocol comprising of cyto-reductive surgery and chemotherapy with or without radio-therapy may be the best therapeutic option. Although MMT is also associated with high rates of morbidity and mortality, it remains the sole option to significantly extend the survival of patients that physically and clinically qualify for this aggressive treatment strategy (3-8).

The ESMO clinical practice guidelines for diagnosis, treatment, and follow-up of MPM dovetail with two other recently published guideline sets: the first published under the auspices of the Asbestos Diseases Research Institute (ADRI) in Australia and the second under the sponsorship of the National Comprehensive Cancer Network (NCCN) in the United States. These guidelines have the important mission of helping clinicians to better pursue the diagnosis of MPM and of making the most appropriate recommendation for a treatment plan based on each patient’s disease characteristics (9,10) (NCCN mesothelioma guidelines). We congratulate the ESMO guideline authors for performing a comprehensive literature review and for their insightful contribution of personal knowledge and experience to this report. However, reading through the ESMO guidelines from the perspective of a surgical team, we feel that some of the recommendations that the guidelines offer regarding the diagnosis and staging of MPM and regarding the role of cyto-reductive surgery in MMT for MPM are somewhat vague and incomplete. Thus, we discuss our approach to these issues in the following paragraphs.

Diagnosis and staging of MPM

The ESMO guidelines highlight the importance and complexity of reaching a conclusive histo-pathological diagnosis of MPM as well as of accurately determining disease stage. However, the exact technique and considerations of pre cyto-reductive surgery invasive diagnostics are not fully described.

For initial diagnosis, the ESMO guidelines recommend using CT scanning of the thorax (Data Level II, Recommendation Class A) and for pathological diagnosis, the guidelines state that: “larger and directly targeted biopsy samples facilitate definitive diagnosis. Surgical-type samples are preferred for diagnosis” (Data Level IV, Recommendation Class A). Recommendations for staging are as follows:

- The use of MRI is only recommended in special situations when tumor delineation is necessary (Data Level II, Recommendation Class B);
- The use of PET scanning is limited and can be used for localization of tumor sites, distant metastases, or early response to treatment, as part of a study protocol.
Role for cyto-reductive surgery based MMT for MPM

The ESMO guidelines correctly highlight the pros and cons of radical surgery for MPM. They acknowledge the extended survival benefits that surgery-based MMT protocols may offer (annotating series and studies that reported median survival ranges of 12.8 to 46.9 months) and also discuss the high morbidity and mortality rates associated with these treatments (annotating series and studies that reported on post op mortality rates ranging from 0% to 19%). The guidelines make the following recommendations:

- (Surgery) To be part of a multimodality treatment, preferably as part of a study (Data Level II, Recommendation Class A);
- (Surgery) To perform a macroscopic complete resection by means of P/D or EPP (Data Level III, Recommendation Class C).

Although we concur with these recommendations, we do not find them clear enough with regards to defining the exact aim of surgery for MMP and to determining the optimal setting for such surgeries to be performed. Instead, we highlight a 2012 standpoint published by the International Mesothelioma Interest Group (IMIG) which more thoroughly discusses and summarizes these issues (13).

To recap, the IMIG recommendations regarding the role of cyto-reductive surgery in the treatment of MMP are as follows:

- Surgical macroscopic complete resection and control of micrometastatic disease play a vital role in the MMT of MPM, as is the case for other solid malignancies;
- Surgical cytoreduction is indicated when macroscopic complete resection is deemed achievable;
- The type of surgery (EPP or P/D) depends on clinical factors and on individual surgical judgment and expertise;
- Only surgeons who achieve morbidity and mortality within the scope of the literature should perform surgery for MPM.

These recommendations were based in part on preliminary analysis of the IASLC database that has shown three major findings. First, “for MPM patients’ survival was significantly different according to whether the surgical procedure was performed with curative versus palliative intent (median survival 18 vs. 12 months)”. Second: “among all patients undergoing curative-intent surgery those who had additional treatment, either chemotherapy or radiation or both had a significantly better outcome (median survivals of 20 vs. 11 months)”. Third: when “prognostic groups defined by the type of curative-intent procedure performed (EPP vs. P/D) were examined in relationship to tumor
stage, stage I tumors resected by EPP were associated with a median survival of 40 months whereas those managed by P/D had a median survival of 23 months. No differences in survival between EPP and P/D were identified in patients with higher-stage disease (12).

Notably, in line with the IMIG statement, the ADRI and NCCN guidelines also make more exact recommendations regarding the role cytoreductive surgery in the MMT of MMP than do the ESMO guidelines. Specifically, the ADRI guidelines states that:

- Radical surgical approaches should be restricted to institutions with significant surgical experience and high volume of cases (Recommendation Grade B);
- Extensive cytoreductive surgery should only be used as part of multimodality treatment (Recommendation Grade B).

The NCCN guidelines state that:

- Surgical resection should be performed on carefully evaluated patients by board-certified thoracic surgeons with experience in managing MPM;
- The goal of surgery is complete gross cyto-reduction of the tumor;
- For early disease (confined to the pleural envelope, no N2 lymph node involvement) with favorable histology (epithelioid), P/D should be the first option. EPP may be considered in select patients for complete gross cyto-reduction.

Taken together, we consider the IMIG statement coupled with the ADRI and NCCN recommendations important since they highlight that cytoreductive surgery, as part of MMT protocol, should be performed in cases where macroscopic complete resection is deemed achievable. They also highlight the importance of having this operation performed in centers with excellent surgical outcomes. In terms of the optimal surgical approach (EPP vs. P/D), Takuwa and Hasegawa have recently reviewed the literature and concluded that there is no clear-cut evidence to favor EPP over P/D or vise versa (14). We agree with their view and with the IMIG statement and believe that given the complexity and the high rates of morbidity and mortality associated with MMT for MPM, there is no substitute for a highly experienced surgeon and for a competent multidisciplinary medical team in order to optimize clinical outcomes.

In summary, in this commentary we addressed key issues in the surgical treatment of MPM. We highlight the importance of determining an accurate pre-operative stage of disease by pursuing an extensive and invasive staging protocol and emphasize the significance of achieving complete surgical macroscopic resection as part of a MMT protocols for MPM (15,16).

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Footnote

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