Perspective on malignant pleural mesothelioma diagnosis and treatment

Ori Wald, David J. Sugarbaker

Division of General Thoracic Surgery, Michael E. DeBakey Department of General Surgery, Baylor College of Medicine, Houston, TX, USA

Correspondence to: David J. Sugarbaker, MD. Professor and Chief, Division of General Thoracic Surgery, Michael E. DeBakey Department of General Surgery, Director, Lung Institute, Baylor College of Medicine, Olga Keith Wiess Chair in Surgery, Baylor College of Medicine, Houston, TX, USA. Email: david.sugarbaker@bcm.edu.

Submitted Feb 26, 2016. Accepted for publication Mar 07, 2016.
doi: 10.21037/atm.2016.03.17
View this article at: http://dx.doi.org/10.21037/atm.2016.03.17

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 MMP and regarding the role of cyto-reductive surgery in MMT for MMP 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

(Data Level III, Recommendation Class B);
- (Surgery) To obtain diagnostic samples of tumor tissue and to stage the patient (Data Level II, Recommendation Class A).

The ADRI guidelines are more specific about the pre cyto-reductive surgery invasive diagnostics test that should be performed and offers more detailed recommendations for the staging of potential surgical candidates. Specifically:

- Mediastinoscopy is recommended as an additional staging procedure for patients being considered for radical surgery in order to exclude N2 level nodal disease or to confirm pathological involvement where imaging is equivocal (Recommendation Grade B);
- Bilateral thoracoscopy and laparoscopy with peritoneal lavage may identify additional M1 disease or sarcomatoid histology and taking the potential morbidity associated with radical surgery into account extended (surgical) staging should be considered for all patients with MPM before resection (Recommendation Grade B).

In line with the ADRI guidelines, in our practice, we perform an extensive staging assessment in any patient who is a potential surgical candidate. The imaging modalities that we use are CT scan and MRI of the chest to assess the extent of thoracic disease and PET-CT scan to assess for distant metastasis. The invasive tests that we perform include a mediastinoscopy, a thoracoscopy and a laparoscopy. We obtained biopsies from lymph nodes in the mediastinum and from the thorax and peritoneum according to intraoperative findings. If the peritoneum is clear to eye inspection, we perform random biopsies and also wash the peritoneum for cytology. These procedures are done in a single OR session, and pathological analysis of the tissue samples is completed within 5 to 7 days. Once all data is obtained, disease stage is determined and a decision regarding cyto-reductive surgery is made. The rational behind our aggressive staging approach is the high rate of pathological upstaging among surgically treated patients and the high rates of recurrence in the abdomen and mediastinum that were reported for patients with stage III and IV disease relative to stage I–II (11,12). Thus, we anticipate that thorough pre-operative staging will enhance the detection of occult disease spread to the mediastinum and peritoneum and will help improve patient selection for surgery.

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 cyto-reductive 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 these 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).

Acknowledgements

None.

Footnote

Provenance: This is a Guest Perspective commissioned by Licun Wu, MD (Latner Thoracic Surgery Research Laboratories and Division of Thoracic Surgery, Toronto General Hospital, University Health Network, University of Toronto, Toronto, Canada).
Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Merritt N, Blewett CJ, Miller JD, et al. Survival after conservative (palliative) management of pleural malignant mesothelioma. J Surg Oncol 2001;78:171-4.
2. Vogelzang NJ, Rusthoven JJ, Symanowski J, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol 2003;21:2636-44.
3. Cho BC, Feld R, Leighl N, et al. A feasibility study evaluating Surgery for Mesothelioma After Radiation Therapy: the "SMART" approach for resectable malignant pleural mesothelioma. J Thorac Oncol 2014;9:397-402.
4. de Perrot M, Feld R, Cho BC, et al. Trimodality therapy with induction chemotherapy followed by extrapleural pneumonectomy and adjuvant high-dose hemithoracic radiation for malignant pleural mesothelioma. J Clin Oncol 2009;27:1413-8.
5. Gomez DR, Hong DS, Allen PK, et al. Patterns of failure, toxicity, and survival after extrapleural pneumonectomy and hemithoracic intensity-modulated radiation therapy for malignant pleural mesothelioma. J Thorac Oncol 2013;8:238-45.
6. Hasegawa S, Okada M, Tanaka F, et al. Trimodality strategy for treating malignant pleural mesothelioma: results of a feasibility study of induction pemetrexed plus cisplatin followed by extrapleural pneumonectomy and postoperative hemithoracic radiation (Japan Mesothelioma Interest Group 0601 Trial). Int J Clin Oncol 2015. [Epub ahead of print].

7. Krug LM, Pass HI, Rusch VW, et al. Multicenter phase II trial of neoadjuvant pemetrexed plus cisplatin followed by extrapleural pneumonectomy and radiation for malignant pleural mesothelioma. J Clin Oncol 2009;27:3007-13.
8. Van Schil PE, Baas P, Gaafar R, et al. Trimodality therapy for malignant pleural mesothelioma: results from an EORTC phase II multicentre trial. Eur Respir J 2010;36:1362-9.
9. Baas P, Fennell D, Kerr KM, et al. Malignant pleural mesothelioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015;26 Suppl 5:v31-9.
10. van Zandwijk N, Clarke C, Henderson D, et al. Guidelines for the diagnosis and treatment of malignant pleural mesothelioma. J Thorac Dis 2013;5:E254-307.
11. Baldini EH, Richards WG, Gill RR, et al. Updated patterns of failure after multimodality therapy for malignant pleural mesothelioma. J Thorac Cardiovasc Surg 2015;149:1374-81.
12. Rusch VW, Giroux D, Kennedy C, et al. Initial analysis of the international association for the study of lung cancer mesothelioma database. J Thorac Oncol 2012;7:1631-9.
13. Rusch V, Baldini EH, Bueno R, et al. The role of surgical cytoreduction in the treatment of malignant pleural mesothelioma: meeting summary of the International Mesothelioma Interest Group Congress, September 11-14, 2012, Boston, Mass. J Thorac Cardiovasc Surg 2013;145:909-10.
14. Takuwa T, Hasegawa S. Current surgical strategies for malignant pleural mesothelioma. Surg Today 2015. [Epub ahead of print].
15. Sugarbaker DJ, Flores RM, Jaklitsch MT, et al. Resection margins, extrapleural nodal status, and cell type determine postoperative long-term survival in trimodality therapy of malignant pleural mesothelioma: results in 183 patients. J Thorac Cardiovasc Surg 1999;117:54-63; discussion 63-5.
16. Sugarbaker DJ, Wolf AS. Surgery for malignant pleural mesothelioma. Expert Rev Respir Med 2010;4:363-72.

Cite this article as: Wald O, Sugarbaker DJ. Perspective on malignant pleural mesothelioma diagnosis and treatment. Ann Transl Med 2016;4(6):120. doi: 10.21037/atm.2016.03.17

