Editorial

Malignant pleural mesothelioma: key determinants in tailoring the right treatment for the right patient

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Multimodality treatments for malignant pleural mesothelioma

Malignant pleural mesothelioma (MPM) is an aggressive solid malignancy with a dismal prognosis. Data from the International Association for the Study of Lung Cancer (IASLC) mesothelioma staging project, which is based on the records of both operable and non-operable MPM patients, indicates a median overall survival of 21, 19, 14 and 10 months for MPM patients with stage I, II, III and IV disease, respectively (1). Unfortunately, at diagnosis, the majority of MPM patients present with extensive disease and impaired functional status. They are, therefore, considered inoperable and are referred to chemotherapy-based treatment. Previously, the median survival of such patients was considered to be around 12 months. However, more recent trials with modern chemotherapy regiments indicate a median survival of up to 18 months for this group of patients (2-4). In contrast, the minority of MPM patients that present with localized disease and a preserved functional status are often considered candidates for a cytoreductive surgery-based multimodality treatment (MMT). Remarkably, this therapeutic approach has been previously shown to yield prolonged survival—median survival range of 30 up to 51 months—in highly selected subgroups of patients (5-8). Consequently, the various guidelines for the treatment of MPM [published by either the National Comprehensive Cancer Network (NCCN) in the United States (NCCN Mesothelioma Guidelines, www.nccn.org), the Asbestos Diseases Research Institute (ADRI) in Australia, or the European Society for Medical Oncology (ESMO)] have all recommended that cytoreductive surgery as part of a MMT treatment protocol will be considered for patients with potentially resectable MPM (9,10). A key question with respect to this general recommendation is how to design the right therapeutic protocol and the right type of surgery for the right patient? Or in other words, what are the essential components of an MMT protocol and who are the patients that would benefit most from this approach?

To further elaborate on these topic, we begin with a short review of the key findings in the recent publication "Extended Pleurectomy-Decortication-Based Treatment for Advanced Stage Epithelial Mesothelioma Yielding a Median Survival of Nearly Three Years" by Dr. Friedberg and colleagues (11). Next, we briefly review the results of some other key studies that have also evaluated the efficacy of cytoreductive surgery-based MMT protocols in MPM. Finally, we call attention to fundamental concepts that in our opinion help tailor the right surgery-based MMT treatment to the right patient. In this regard, we also discuss the concept of macroscopic complete resection (MCR) in light of the recent IASLC proposals for changes in the MPM staging system (1,12,13).

In their recent work, Friedberg and colleagues have assessed the long-term outcomes of ninety MPM patients,

treated with a MMT protocol consisting of extended pleurectomy and decortication (EPD) with intraoperative photodynamic therapy (PDT) and adjuvant pemetrexed based chemotherapy. They focused their analysis on 73 patients with histologically confirmed epithelioid mesothelioma (17 out of the 90 patients in the initial cohort were excluded from analysis because postoperatively they were histologically confirmed to have biphasic mesothelioma). The median follow up time was 5.3 years. MCR was achieved in all 73 patients. In addition, 100% of patients received PDT and 92% also received adjuvant chemotherapy. The 30- and 90-day mortality was 3% and 4% respectively. Dr. Friedberg and colleagues reported that 89% of patients had an American Joint Commission on Cancer (AJCC, 7th edition) stage III/IV disease, with 69% of the patients having positive N2 nodes (according to AJCC 7th edition). The median tumor volume that was measured in a representative subgroup of patients was 550 mL. The authors highlight that the median overall and disease-free survival for the entire seventy-three patient cohort was 3 and 1.2 years, respectively. They further specify that for the 19 patients without lymph node metastasis (74% AJCC stage III/IV median tumor volume 325 mL), the median overall and disease-free survival was 7.3 and 2.3 years, respectively. Conversely, it was 2.2 and 0.8 years, respectively for patients with lymph node metastasis (median tumor volume 675 mL). The authors further indicated that all the 17 that were excluded from the analysis (all of whom were histologically confirmed to have biphasic mesothelioma) survived for less than a year after surgery. The authors conclude that a lung-sparing complex surgery-based treatment plan that yields prolonged overall survival could be safely executed in a selected group of MPM patients (epithelioid histology) presenting with advanced disease (11). We acknowledge the authors for analyzing and publishing this comprehensive dataset. Furthermore, we congratulate Dr. Friedberg and his team for the prolonged median survival that they report.

Remarkably, three contemporary studies that have also evaluated the role of EPD based MMT for MPM have reported on median survival times that corroborate well with the findings of Dr. Friedberg and colleagues (median survival range of 30–33 months) (6,11,14,15). Specifically, in 2011 Schirren and colleagues reported the outcomes of thirty-five MPM patients who were treated with a therapeutic protocol consisting of EPD followed by 4 cycles of chemotherapy and prophylactic radiotherapy. They reported an overall median survival of 30 months. In a multivariate analysis, they found that advanced stages III/IV (19/35), nodal metastases (5/35), non-epithelial histology (8/35) and macroscopic incomplete resections (17/35 patient) were associated with reduced survival. 33/35 of patients in this study received all three components of the MMT protocol. Notably. patients that had MCR achieved a mean survival of 43.3 months (6). In 2014, Trovo and colleagues reported the results of an EPD + high dose radiation therapy + chemotherapy protocol in twenty MPM patients. The median overall survival was 33 months. Stage III/IV was found in 12/20 of patients, lymph node metastasis (N1/N2) was present in 3/20 of patients, epithelioid histology in 18/20 of patients and MCR was achieved in 17/20 of patients. Further, 19/20 patients received chemotherapy and 20/20 received radiation as scheduled (14). More recently, Lang-Lazdunski and colleagues have reported the results of EPD + hyperthermic pleural lavage with povidone-iodine + prophylactic radiotherapy and systemic chemotherapy in a series of one hundred and two patients. In this series, the overall median survival was 32 months. Stage III/IV was found in 71/102 of patients, lymph node metastasis (N1/N2) were present in 34/102 of patients, epithelioid histology was confirmed in 73/102 of patients and MCR was achieved in 57/102 of patients. All patients received the prophylactic radiation and 96/102 also received chemotherapy. Most notably, patients in this series who had either epithelial histology or MCR survived significantly longer—median survival of 35 and 45 months, respectively (15). As a whole, these studies support the recognition that patients with epithelial histology that present with a limited lymph node metastatic burden can obtain prolonged survival if MCR is achieved in surgery and if MMT is indeed pursued.

Review of studies that looked at the efficacy of extra pleural pneumonectomy (EPP) based MMT protocols for the treatment of MPM draw a pretty similar picture. To illustrate, in a retrospective series that reviewed the characteristics of MPM patients who had EPP and survived longer than three years, our team has identified epithelioid histology to be significantly more common in long-term survivors (16). Furthermore, in a recent trial, we have examined the association between lymph node status and survival among five hundred and twenty nine patients with epithelioid MPM who had EPP. We reported that the outcome by pathologic lymph node status (N, number of patients, median overall survival) was N0: 224, 26 months; N1: 118, 17 months; N2: 181, 13 months; N3: 5, 7 months (17). Finally, when considering the benefits of achieving MCR and of adhering to the entire treatment plan, four trials from the past years reinforce the recognition

that MCR is a fundamental contributor to life extension. Nonetheless, they raise concerns regarding the feasibility of completing a trimodality treatment plan in a substantial portion of patients that undergo EPP. In particular, studies by Krug *et al.* and Hasegawa *et al.* have indicated that extended survival (median survival range, 29–39 months) is achieved in patients that complete the entire treatment protocol (18,19), while studies by De-Perrot *et al.* and Stahel *et al.* have not shown clear survival benefits for completion of the third component of the EPP-based MMT protocol (either chemotherapy or radiation) (7,20). The contradictory finding of these studies may stem in part from their design, in part from the distinct protocols that were used to deliver radiotherapy, and in part from the morbidity and mortality that was associated with EEP in each of the studies. Nonetheless, and similarly to studies which focused on EPD-based protocols, all studies indicate that MCR should be perused and that both epithelial histology and negative nodes serve as favorable prognostic markers.

Taken as a whole, we would like to use these EPD/EPP-based MMT studies to highlight the following fundamentals/concepts.

Tumor histology and node status predict long term survival

Patients that present with epithelioid histology and have negative lymph nodes appear to benefit the most from EPD/EPP based MMT. We therefore, consider these patients to be the best candidates for cytoreductive surgery-based MMT.

Completion of the entire MMT protocol may improve long-term survival

The vast majority of patients participating in the EPD-based trials as well as those that achieved prolonged survival in the EPP-based trials have all completed the entire MMT protocol. This suggests that if tolerated, adherence to all components of the MMT protocol is an important factor in pursuing prolonged survival.

Intraoperative therapeutics to enhance loco-regional disease control should be incorporated in to MMT protocols

Classical MMT protocols are based on three modalities. These key components include: (I) cytoreductive surgery to achieve MCR; (II) adjuvant/neo-adjuvant chemotherapy; and (III) adjuvant/neo-adjuvant radiotherapy. Notably, as illustrated in the works of Dr. Friedberg and Dr. Lang-Lazdunski, as well as in previous publications by our group, these classical MMT protocols may be augmented by the addition of an intraoperative component to enhance loco-regional disease control (PDT or hyperthermic pleural lavage with povidone-iodine or hyperthermic intraoperative chemotherapy). Our own experience is with the incorporation of intraoperative heated chemotherapy into our EPP and EPD cases. We have shown that the addition of heated chemotherapy was generally safe and well tolerated and that it was specifically beneficial for patients who either did not receive radiation or who had N1 or N2 positive lymph nodes (5). Taken together, these experiences suggest that incorporating intraoperative therapies as a fourth dimension to the more conventional trimodality therapeutic protocols is desired.

MCR is a fundamental component of any MMT

Patients in which MCR was achieved, whether by EPD or EPP, had significantly prolonged survival. While a comprehensive discussion about the optimal surgical approach to achieve MCR in MPM is beyond the scope of this editorial, we do stress that EPD is associated with reduced morbidity and mortality compared to EPP and furthermore, that it is more likely to permit completion of the entire treatment protocol. Nonetheless, EPP—rather than EPD—is still considered the most extensive cytoreductive surgery and is most likely to permit MCR in patients with high tumor burden (21-23). As a concept, we emphasize that achieving MCR while limiting surgery associated morbidity and mortality are the prime goals of the surgical part of the MMT.

The new mesothelioma staging system—T and N disease denominators and disease stage *vs.* disease burden as indicators of the potential to achieve MCR

T- denominator

Data collected for the IASLC new mesothelioma staging system indicates that tumor thickness (as a simplified surrogate of tumor volume or tumor burden) and nodular or rindlike morphology were significantly associated with survival. Interestingly, the current database further suggests that tumor thickness is also significantly associated with lymph node metastatic burden. In particular, patients with tumor maximal thickness of less than 5.1 mm had a 14% risk of nodal metastases, whereas this risk rose to 38% in patients with tumors of maximal thickness greater than

5.1 mm (P<0.0001). Similarly, tumor thickness cutpoints (based on three-level summation) of less than 13 mm, 13 to 60 mm, and more than 60 mm were associated with nodal metastases in 14%, 37%, and 47% of cases (P<0.0001) (12,13). These findings, which also corroborate well with previous observations by our team as well as with the tumor volume associated survival reported by Dr. Friedberg in his recent manuscript, indicate that it is important to measure the tumor volume/thickness as part of the routine evaluation of mesothelioma patients (11,24).

N-denominator

The manuscripts that precede the new IASLC mesothelioma staging system highlight the recommendation to unite N1 and N2 lymph node station into a new N1 definition. This recommendation is based on the similar overall survival recorded in patients with either N1 or N2 disease (12,13). And yet, as previously shown by our team (17), lymph node related data also suggests that patients that have both N1 and N2 disease have significantly worse survival compared to those with either N1 or N2 (13). Therefore, an emerging concept that arises from these findings is that in MPM, the N1 lymph node metastatic burden or the number of distinct anatomic locations (lymph node in stations 2 to 14, pericardial, peridiaphragmatic, intercostal, retrocrural and internal mammary chain) with positive N1 lymph nodes may predict survival. Consequently, it is important to try and evaluate not only the N denominator but also the lymph node metastatic burden in every MPM patient.

New staging

In the new staging system, patients that present with tumors that qualify for T1 or T2 T-denominator and to N1 N-denominator will be staged as stage II rather than stage III in the previous system. Furthermore, according to the new staging system patients with stage II disease will have a median survival of 19 months compared to 14 months for patients in stage III disease. In the previous system, stage III patients had a median survival of 17.8 months. This example illustrates how the new staging system helps better evaluate the prognosis of patients that were previously determined to have stage III disease.

When viewed as a whole, these considerations promote the concept that in addition to evaluating mesothelioma by determining disease stage per se, it is also important to record the overall burden of disease as manifested by tumor volume and/or lymph node metastatic burden and/or number of distinct anatomic locations with positive N1 lymph nodes. Given that these parameters are emerging (tumor volume) or are likely to become (number of involved lymph nodes) important prognostic markers, we recommend that an effort is made to routinely evaluate and record them both preoperatively and postoperatively. Novel understandings that may stem from this data may help surgeons determine whether MCR is likely achievable and thus guide their decisions of recommending surgery and of choosing the right surgical technique (EPD *vs.* EPP) for the right patient.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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