

Surgical controversies in mesothelioma: MesoVATS addresses the role of surgical debulking

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Abstract: Contemporary multi-modality treatment of malignant mesothelioma remains challenging. The merits of surgical resection and the particular extent of resection continue to be debated topics. To date few randomized surgical trials have been completed to address many lingering issues concerning surgery in mesothelioma. Recently, the MesoVATS trial shows us that a minimally invasive thoracoscopic procedure for curative resection in mesothelioma is of limited benefit. Results of ongoing clinical trials are awaited.

Keywords: Mesothelioma; pleurectomy; VATS

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Malignant pleural mesothelioma (MPM) is a fatal malignancy with a diverse clinical spectrum inadequately captured by our current staging system(s) (1) and that remains poorly understood at the molecular level (2). Current treatment for this disease is comprised of multi-modality interventions, including surgical resection. Over the past 12 years or so, no significant reduction of mortality has been newly discovered other than therapy with anti-folate drugs improving survival in randomized control trials by a median of 12 weeks (3,4). The role and extent of curative intent surgery remains controversial since well-conducted, definitive trials have been difficult to execute and complete.

Recently, Rintoul and colleagues conducted only the second randomized surgical trial in mesothelioma, the MesoVATS study (5) appearing in the *Lancet*. The rationale for this trial was based largely on single institution, non-randomized studies that indicated video-assisted thoracoscopic partial pleurectomy (VAT-PP) seemed to improve symptom control compared against extra-pleural pneumonectomy (EPP) (6), and possibly increased survival compared with biopsy alone (7). The extent of tumor extirpation achieved with VAT-PP is a debulking only, to remove tumor from the parietal pleural and visceral pleura to re-expand the lung as much as practical. They compared

VAT-PP to talc pleurodesis palliation in 196 patients with suspected MPM randomly assigned, of whom 175 had a confirmed diagnosis of MPM were analyzed (87 VAT-PP vs. 88 talc). Their power analysis indicated they would need 90 patients per group. Patients were enrolled between 2003 and 2012.

Intention-to-treat results showed that VAT-PP conferred no survival benefit over talc pleurodesis at 12 months, the primary endpoint. Overall survival at 1 year was 52% (95% CI, 41-62%) in the VAT-PP cohort and 57% (95% CI, 46-66%) in the talc cohort [hazard ratio 1.04 (95% CI, 0.76-1.42); P=0.81]. Secondary outcomes were also assessed including resolution of pleural effusion, quality of life, lung function, exercise tolerance, surgical complications, and economic costs.

There are some significant caveats to this multi-institutional study, however, which required nearly 10 years to accrue enough patients. During this period, clinical practices worldwide evolved from those used in this study. For example, positron-emission tomography (PET) and/or magnetic resonance imaging (MRI) became commonly used in clinical staging, and VATS talc poudrage was preferred over talc slurry via chest tube. These various changes in combination with some patients withdrawing from the study affected the final numbers of patients available for

data reporting. In the comparator cohort receiving only talc as palliation, 35 of 72 (48%) patients were pleurodesed via chest tube and 34 of 73 (47%) patients were pleurodesed via a VATS approach. At 12 months, complete secondary outcome data were available for only 34 of 87 (39%) patients in the VAT-PP cohort compared to 37 of 88 (42%) patients in the talc cohort. The cost analysis was based on 98 patients who entered the study since 2009. Thus, the interpretations of this study are derived from subsets of enrolled patients, so some caution is needed when applying this data.

The most interesting finding(s), perhaps, from this study reveal the natural course of MPM in a modern patient cohort. The median overall survival in the palliative talc pleurodesis cohort was 13.5 months. This survival result was in the context of a typical, unselected MPM population recruited into this study. In total, 78% of patients who got randomized with a confirmed diagnosis of MPM were found to harbor an IMIG stage of III or IV and most had an ECOG performance status of 1. This result corroborates our commonly held notion of MPM patients usually presenting with advanced disease.

Not surprisingly, the median overall survival of 13.1 months for the VAT-PP cohort of MesoVATS is similar to the overall survival range of 7 to 14 months in the meta-analysis by Cao and colleagues (8) who reviewed 14 observational studies and case series of partial pleurectomy in MPM. VAT-PP is not a useful procedure to improve overall survival in the treatment of MPM as demonstrated by this study. The confounders in this study limit any further, wider extrapolations of the results. In MesoVATS, after their surgical procedure, visible tumor was often remaining on the pericardium and central diaphragm while no routine nodal sampling was performed.

In North America and other regions, partial pleurectomy, described in this study as VAT-PP, is not offered to MPM patients as a curative intent surgical procedure in the context of contemporary multi-modality treatment (www.nccn.org). It is unknown about the popularity of VAT-PP as a surgical technique in MPM. For lung sparing resections of MPM, surgeons adhere to the principal of removing all gross, macroscopic disease in the pleural space and of consistent, systematic mediastinal nodal sampling. Usually a thoracotomy is required for this more challenging type of dissection. If needed, the diaphragm and pericardium can be resected/reconstructed simultaneously (i.e., extended pleurectomy/decortication or e-P/D). A recent meta-analysis (9) of radical resections for MPM in selected

patients who underwent e-P/D had lower perioperative morbidity and mortality with similar, or even superior, long-term survival compared to EPP, in the context of multi-modality therapy.

In summary, MesoVATS has demonstrated that thoracoscopic debulking (VAT-PP) does not improve survival for MPM. What still remains unanswered is whether more aggressive local intervention may improve outcome. The precise role of EPP remains unsettled, even with the completion of a feasibility study of radical surgery in MPM (10). Results of the MARS-2 trial are awaited, wherein they will investigate the role of e-P/D added to standard induction chemotherapy and randomly compared with chemotherapy only (www.clinicaltrials.gov). Also, the Lung Cancer Group of the European Organization for Research and Treatment of Cancer will conduct a randomized phase II trial in patients with early-stage MPM randomizing between four cycles of neoadjuvant chemotherapy followed by P/D or P/D followed by four cycles of the same chemotherapy given in adjuvant setting (10).

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Footnote

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