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CORRESPONDENCE

An Inconvenient Truth Concerning Surgery for Mesothelioma

TO THE EDITOR: A recently published ASCO clinical practice guideline discussed the treatment of malignant pleural mesothelioma.[1] The authors are commended for their efforts in producing a guideline in this important area. The ASCO guideline methodology states that to return a "strong" recommendation, there should be high confidence that the recommendation reflects best practice. This should be based on: (1) strong evidence for a true net effect (eg, benefits exceed harm); (2) consistent results, with no or minor exceptions; (3) minor or no concerns about study quality; and/or (4) the extent of the Expert Panelists' agreement.

On the basis of these criteria, we do not believe that the following "strong" recommendations in the guideline regarding surgical cytoreduction with extrapleural pneumonectomy (EPP) or pleurectomy/decortication (P/D) reflect the published literature: "In selected patients with early-stage disease, it is strongly recommended that a maximal surgical cytoreduction should be performed"[1] and "maximal surgical cytoreduction involves either EPP or lung-sparing options (P/D, extended P/D)."[1]

The authors assert that this recommendation is supported by the published literature. The evidence quoted, however, is limited to case series[2,3] from which, as retrospective, nonrandomized data, only limited conclusions can be drawn. In one referenced series, Bovolato et al[3] reported that a modest benefit was observed with surgery combined with systemic therapy.[3] This conclusion was based, however, on a retrospective comparison of overall survival (OS) between patients treated medically, with chemotherapy or best supportive care, and those treated surgically with P/D or EPP.[3] Unsurprisingly, there was significant heterogeneity between the groups in this study. The researchers acknowledged that when their analyses were restricted to patients with good prognostic factors (as would usually be the case for surgical patients) there was no statistically significant difference in OS between study groups. The review by Sharif et al,[2] quoted in the guideline, concluded that EPP provides no benefit for symptom control or OS compared with supportive care. The Mesothelioma and Radical Surgery (MARS) feasibility trial remains the only randomized study conducted in this field.[4] It is surprising that it is not referenced in the relevant section of the guideline. MARS attempted a head-to-head comparison of surgery (EPP) versus no surgery but was terminated after the 50-patient feasibility phase because of the high morbidity associated with EPP and better survival in the nonsurgical arm.[4] Survival was significantly better in the comparator arm, even though three patients in the comparator arm elected to have EPP off trial at another center and were therefore exposed to the risk of harm from EPP. It is mystifying how the guideline group can conclude that there is strong evidence to recommend surgery with EPP for this patient group.

Similarly, there are no randomized controlled trials demonstrating a benefit for P/D or extended P/D for mesothelioma. Given the significant morbidity associated with radical mesothelioma surgery and the absence of any proven benefit, in our opinion, it would have been more appropriate for the guideline authors to conclude that if surgery in any form were to be contemplated for a patient with mesothelioma, it should take place in the context of a properly conducted randomized controlled trial.

The patent lack of high-quality surgical evidence has, in fact, resulted in the funding of a large randomized controlled trial in the United Kingdom. MARS 2 (ClinicalTrials.gov identifier: NCT02040272) randomly assigns patients to EPD or no surgery, in combination with pemetrexed/cisplatin chemotherapy, to address the currently unanswered question regarding the role of EPD in malignant pleural mesothelioma management. It is currently recruiting well, and we await these important results with interest.

Finally, we would also like to draw the authors' attention to their recommendation that the optimal management of symptomatic pleural effusions in mesothelioma includes video-assisted thoracoscopic surgery (VATS) decortication and pleurodesis. This is one area where there is strong randomized controlled data comparing VATS-partial pleurectomy (VATS-PP) with talc pleurodesis. The Meso-VATS trial, published in *The Lancet Oncology* in 2014, demonstrated that VATS-PP offered no survival benefit at 12 months over talc poudrage/slurry and was associated with more complications and a longer hospital stay.[5] Despite acknowledging this information in their literature review, the authors recommend that VATS-PP be offered as an option for management of pleural effusion.

Surgery for mesothelioma, whether with radical or palliative intent, has been shown in well-conducted randomized controlled trials to confer no benefit in overall survival or quality of life. Although this truth may be inconvenient for providers of such surgery, it deserves greater recognition in the guideline recommendations of an organization with the worldwide reputation and influence of ASCO.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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