



Spare the lung: surgical treatment approach for malignant pleural mesothelioma

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Comment on: Klotz LV, Hoffmann H, Shah R, *et al.* Multimodal therapy of epithelioid pleural mesothelioma: improved survival by changing the surgical treatment approach. *Transl Lung Cancer Res* 2022;11:2230-42.

Submitted Dec 26, 2022. Accepted for publication Jan 23, 2023. Published online Jan 29, 2023.

doi: 10.21037/tlcr-22-909

View this article at: <https://dx.doi.org/10.21037/tlcr-22-909>

In a recent study published on *Translational Lung Cancer Research*, Klotz and colleagues report the results of their retrospective analyses, where they compared treatment outcomes among patients diagnosed with epithelioid malignant pleural mesothelioma (MPM) (1). They compared survival of three patient cohorts: one was treated with an extrapleural pneumonectomy (EPP); one was treated with an extended pleurectomy/decortication (EPD) combined with hyperthermic intrathoracic chemoperfusion (HITOC) and adjuvant chemotherapy; and one was treated with chemotherapy alone. They demonstrated that the median overall survival (OS) was significantly longer in the EPD/HITOC cohort than in the EPP and chemotherapy cohorts. In addition, their multivariate analysis showed that EPD/HITOC was significantly associated with improved OS. Based on these findings, they concluded that a less radical lung-sparing surgery, EPD, should be performed in patients with epithelioid MPM.

MPM is strongly associated with past asbestos exposure, and its incidence has continued to increase in many developing countries. Surgical resection is applied to patients in the earlier stages of the disease. However, a tumor resection with wide microscopically negative margins is not feasible in MPM, due to the surrounding vital structures. The aim of a surgical resection for MPM is to remove the entire macroscopic tumor from the hemithorax. A macroscopic complete resection can be achieved with both an EPP and a PD. However, it remains controversial

which is the more appropriate procedure. Although an EPP was traditionally the technique of choice, perioperative mortality and morbidity were significantly lower with an EPD than with an EPP. A systematic review showed that OS was comparable between those treated with an EPP and those treated with an EPD (2). Those results were further supported in a meta-analysis (3). In addition, the EPP is generally more deleterious than an EPD, in terms of quality of life for the patient (4). Based on those reports, the recent European Society of Medical Oncology Clinical Practice Guidelines considered a lung-sparing EPD the first-choice surgical procedure (5). However, an EPP could also be offered to highly selected patients in high-volume centers. Due to the lack of a direct comparison between these two surgical modalities, the superiority of an EPD has not been established.

Klotz and colleagues analyzed the outcomes of patients with epithelioid MPM treated with a multimodal approach during the last 2 decades in a single high-volume center in Germany. They changed their surgical approach between 2012 and 2013, from an EPP-based multimodal treatment to an EPD/HITOC treatment. Many institutions around the world have similarly changed their surgical policies, based on a randomized feasibility study that compared EPP and no-EPP treatments (6).

In the Klotz study, the median OS of the EPD/HITOC, EPP, and chemotherapy cohorts were 38.1, 24.0, and 15.8 months, respectively. These median OS were

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consistent with those reported previously. Better survival was significantly associated with good performance status, a younger age, and negative lymph node status. The perioperative morbidity rate was significantly higher in the EPP cohort (36.2%) than in the EPD/HITOC cohort (18%). The strength of the study was that the results of different surgical approaches were compared in a high-volume institution. This real-world data might support a less radical lung-sparing technique as the first-choice surgical procedure for epithelioid MPM. It seems quite natural that survival was worst in the chemotherapy cohort, because those patients had unresectable, advanced disease.

Of note, the study by Klotz and colleagues had some limitations. The main limitations were the retrospective study design and the limited number of selected patients. Moreover, the EPD/HITOC cohort contained more patients and better performance status, compared to the EPP cohort. Second, as the authors described, due to the time difference, potential improvements in perioperative management and recent advancements in treating tumor recurrence might have influenced the improved OS in the EPD/HITOC cohort. Third, the role of an HITOC adjunct to surgery for MPM has not been established. The objective of the HITOC is to eradicate the remaining cancer cells. To date, improvements in recurrence-free survival and OS have been observed in a retrospective single-center analysis (7). However, the efficacy of HITOC has not been demonstrated in a prospective trial.

In the future, the lung-sparing EPD will be a standard surgical approach for resectable MPM, based on the above-mentioned retrospective studies, including the meta-analyses. The current report by Klotz and colleagues also supported the efficacy of EPD and demonstrated that it could maintain the patient's quality of life. Nevertheless, many problems remain to be resolved concerning the surgical approach for MPM. First, there is no clear evidence on the impact of EPD on extended OS in patients with MPM. The evidence may be provided by the MARS2 trial, which will prospectively compare the extent of survival improvement between EPD and non-surgical therapy (8). Another major outstanding issue is whether systemic chemotherapy should be delivered in a neoadjuvant or adjuvant setting. Some clues to this issue might come from a randomized phase II trial that aims to compare the effect of neoadjuvant and adjuvant chemotherapy in combination with surgery in MPM (9). Furthermore, the exact role of HITOC should be clarified in a prospective clinical trial.

We sincerely hope that, through prospective clinical

trials and grounded real-world data, an optimal clinical approach will be established for patients with MPM.

Acknowledgments

Funding: The author is supported by grants-in-aid from the Ministry of Health, Labor, and Welfare, Japan.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Translational Lung Cancer Research*. The article did not undergo external peer review.

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at <https://tldr.amegroups.com/article/view/10.21037/tlcr-22-909/coif>). The author reports grants and personal fees from ONO, Bristol-Meyers Squib, and personal fees from Chugai and Behringer Ingelheim.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Fujimoto N. Spare the lung: surgical treatment approach for malignant pleural mesothelioma. *Transl Lung Cancer Res* 2023;12(2):197-199. doi: 10.21037/tlcr-22-909