Editorial

Do we still need to debate the merits of pleurectomy/decortication *vs.* extrapleural pneumonectomy for malignant pleural mesothelioma?

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Malignant pleural mesothelioma (MPM) causes laminar tumor growth in the visceral and parietal pleura, whose complete surgical resection is impossible (1). Since it is impossible to achieve microscopically complete resection in MPM, curative-intent surgery aims to achieve macroscopic complete resection (MCR) (2). Currently, two curative-intent surgical procedures are available for MPM: pleurectomy/decortication (P/D) and extrapleural pneumonectomy (EPP) (3). EPP involves *en bloc* resection of the lung, pleura, pericardium, and diaphragm, followed by soft tissue patch reconstruction. These structures may remain intact if the pericardium and/or diaphragm remain unaffected by the tumor. Whereas P/D is a lung-sparing surgery that only removes the parietal/visceral pleura. This procedure is defined as extended P/D when the diaphragm and/or pericardium are resected.

Although EPP is relatively standardized, P/D is highly variable and is emerging as the dominant extirpative procedure for MPM, globally (4). However, because of the lack of prospective randomized studies, the best technique among EPP and P/D for MPM tumor resection remains yet to be determined. Moreover, MPM has a poor track record for unsubstantiated claims for 'benefits' of surgery (5). To begin with, few surgeons believe that EPP and P/D are interchangeable, and a cross-sectional survey of thoracic surgeons with a special interest in MPM reported that EPP and extended P/D were favored by 90% and 68% of surgeons, respectively, for adequate cytoreduction (MCR), whereas only 23% of surgeons favored P/D alone (6).

Over the past decade, EPP was considered the only surgical procedure in patients with resectable MPM that achieved MCR and extended their survival if in TNM stage I as reported in the retrospective International Association for the Study of Lung Cancer (IASLC) database (7). Patients with stage I tumors resected by EPP had a median survival of 40 months, whereas patients managed by P/D had a median survival of 23 months (7). EPP has the following advantages over P/D: First, although complete microscopic resection is theoretically impossible in both EPP and P/D, EPP is the more extensive debulking surgery for MPM than P/D. Furthermore, visceral pleurectomy with P/D is more likely to leave residual tumor cells compared to EPP because the connection between the visceral pleura and lung parenchyma is usually tighter than that between the parietal pleura and chest wall (3). Second, high-dose radiotherapy to improve local control is more easily performed after EPP compared to P/D, as there is an empty cavity without the remaining lung parenchyma (8). The 17/04 SAKK randomized trial showed that radiotherapy was associated with a slightly better median locoregional relapse-free

survival (9.4 *vs.* 7.6 months) in post-EPP observation *vs.* adjuvant (minimum dose of 50 Gy with a daily fraction size of 1.8–2 Gy) group (9).

Despite these characteristics and advantages of EPP, in recent years, there has been a shift from EPP to P/D, in high-volume thoracic surgery centers around the world (10). A 20-year-long, single-institution study, by Klotz *et al.* in patients with MPM compared the overall survival (OS) between the trimodal EPP, extended P/D combined with hyperthermic intrathoracic chemotherapy (HITOC) and adjuvant chemotherapy (CTx), and CTx alone cohorts (1). The median OS of the extended P/D-HITOC cohort (38.1 months) was significantly longer than that of the EPP (24.0 months) and CTx (15.8 months) alone cohorts. Multivariate analysis also revealed that extended P/D-HITOC significantly improved OS. Perioperative morbidity was lower in the extended P/D-HITOC cohort than in the EPP cohort. The authors concluded that changing the surgical approach to a less radical lung-sparing technique, such as extended P/D-HITOC, may improve OS compared to trimodal EPP. A meta-analysis by Taioli *et al.* that included 24 distinct datasets and 1,512 patients treated with P/D and 1391 patients treated with EPP reported a significantly higher proportion of short-term deaths in the EPP group than in the P/D group (4.5% *vs.* 1.7%; P<0.05) (11). Furthermore, a systematic review by Cao *et al.* demonstrated a trend favoring P/D as it significantly lowered perioperative morbidity (27.9% *vs.* 62.0%, P<0.01), mortality outcomes (2.9% *vs.* 6.8%, P=0.02), and improved long-term survival (ranged between 13–29 *vs.* 12–22 months) in patients who underwent P/D compared with EPP (12).

Domen *et al.* explained the reasons why EPP could not significantly improve survival compared with P/D as follows (13): first, EPP has disadvantages such as severe deterioration of postoperative cardiopulmonary function and quality of life (QoL) and poor tolerance to chemotherapy in cases of recurrence. A single-center study by Rena *et al.* (n=77) showed that patients who underwent EPP had a higher postoperative complication rate, worse long-term QoL, and shorter residual lifetime after disease recurrence than those who underwent P/D (14). Second, patients who undergo P/D have more post-recurrence treatment options than those who undergo EPP. Moreover, post-recurrence survival was longer in patients who underwent P/D than in patients who underwent EPP. Similarly, in our single institution study, in 57 patients who developed recurrence after P/D, the 1-year post-recurrence survival rate was 59.5% (median, 14.4 months), and 43 patients (75.4%) underwent post-recurrence treatment (15). Whereas in 39 patients who developed recurrence after EPP, the 1-year post-recurrence survival rate was 40.0% (median, 6.5 months), and 21 patients (53.8%) underwent post-recurrence treatment (16).

Recently, immune checkpoint inhibitors for MPM have received considerable attention (17). We have reported on the efficacy and safety of nivolumab treatment in patients with recurrent MPM after curative intent surgery (18). Maintaining a good QoL in patients with recurrent MPM improves tolerance to post-recurrence treatment, which is vital for OS (15). Third, the patients who undergo P/D have a better cardiopulmonary reserve; therefore, they better tolerate postoperative non-oncological disorders such as pneumonia and cardiovascular disease than those who undergo EPP (2). Fourth, the P/D technique has improved acceptable MCR, which makes it a preferred method (19).

These findings are in agreement with Klotz's report (1). The current practice at the Hyogo Medical University in Japan is to perform P/D, the least invasive surgical procedure to achieve MCR (20). The intraoperative conversion from P/D to EPP should be considered only if MCR is achieved upon extrapleural dissection of the parietal pleura. Furthermore, the mediastinum, chest wall, and diaphragm should also achieve an MCR. In this context, MCR was achieved only in cases that underwent EPP, as mandated, because of an extensive tumor invasion to the pulmonary parenchyma or decortication failure (20). A shift from EPP to P/D, as the preferred surgical technique, is already known to most pulmonologists and thoracic surgeons; therefore, it is beneficial to debate the merits of EPP *vs.* P/D.

The critical issue is whether to convert to EPP or complete P/D as R2 resection in cases of an unexpected diffuse tumor invasion to the pulmonary parenchyma during P/D operation. In cases of visceral pleurectomy, we occasionally encounter diffuse tumor invasion of the pulmonary parenchyma, wherein conversion from P/D to EPP is required. In such cases, two alternatives are available. The first procedure involves conversion to EPP to achieve MCR and the second procedure involves performing a partial pleurectomy with R2 resection. We have reported the outcomes of conversion from P/D to EPP for MPM in 9.9% (18/181) of the patients with P/D intention (21). Extensive tumor invasion into the pulmonary parenchyma was the most common reason for the conversion. OS (median, 29.2 *vs.* 57.0 months, P<0.01) and progression-

free survival (median, 15.3 *vs.* 23.2 months, P<0.01) were significantly shorter in patients with conversion to EPP than in those with P/D, which can be attributed to the fact that the patients in the conversion to the EPP group had a more advanced stage (21).

In contrast, Lang-Lazdunski *et al.* reported no survival advantage after EPP (22). However, this could be because they chose the second procedure and performed partial pleurectomy with R2 resection without converting to EPP when MCR could not be achieved with P/D. As a result, of 102 patients who underwent P/D, 57 (55.7%) had MCR with a median OS of 32.0 months. Among those who achieved MCR, the median OS was 45.0 months for R1 resection *vs.* 17.4 months for R2 resection (P=0.001) (20). However, our study outcomes of conversion to EPP (21) were similar to those reported by Lang-Lazdunski *et al.* (22). In cases of conversion to EPP, when MPM recurs on the contralateral side, there is no reserve, and their demise may be hastened because of reduced lung reserve. It should be studied whether partial pleurectomy with R2 resection and two intact lungs serves the patients better and results in longer survival than conversion to EPP with no residual tumor and only one lung. Lymph node disease may also be strongly associated with outcomes (23). The increase in EPP-associated postoperative mortality and loss of lung function raises the question of the additional benefit of conversion to EPP in lymph node-positive disease (23). An intraoperative pathological assessment of lymph nodes is recommended to ensure that MCR can be achieved before considering conversion to EPP. Ripley concluded that if the lymph nodes are negative and MCR can only be achieved with EPP, then proceeding with the EPP may be beneficial. Further research is needed to determine whether to convert to EPP or complete P/D as R2 resection in cases of unexpected diffuse tumor invasion to the pulmonary parenchyma during P/D.

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