Editorial

Treatment of malignant pleural mesothelioma: lessons learned and quo vadis?

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Macroscopic complete resection (MCR) is the goal of surgery and seems to have the most significant effect on survival in patients undergoing surgery-directed multimodality treatment (MMT) for malignant pleural mesothelioma (MPM) (1). For the authors, it is not questionable that Dr. David J. Sugarbaker and his team had, have and will have a significant impact on the term MCR and the surgery-directed MMT, respectively. Therefore, the authors read with great interest the recently published article on the new concepts in the treatment of MPM by Dr. David J. Sugarbaker *et al.* (2). Most respectfully, we take the opportunity to add some thoughts and comments on that topic.

Paradigm shift

Extrapleural pneumonectomy (EPP) has historically been considered as the standard surgical approach for MPM (3). The rationale of EPP was based on the philosophy of achieving "wider negative" margins in the pre-era of MMT options. In a survey of opinions and beliefs among 802 thoracic surgeons, EPP was believed to be more effective than pleurectomy/decortication (PD) (4). However, conceptually both EPP and RP share a similar risk of "oncological failure": doubtful negative resection margins. Lung tissue, mediastinal organs and vessels, parietal and visceral pleura, as well as chest wall line up next to each other within few millimeters. It is doubtful whether a pneumonectomy leads to wider negative margins in most of the cases. Recurrence of disease occurs locally and distantly irrespective of the aggressiveness of surgery. Nonetheless, various international guidelines had advocated EPP for many decades (5,6).

But introducing more effective chemotherapy (7) resulted in survival that was more favorable after P/D compared to EPP at the beginning of the 90ies (8). More and more studies showed promising results whenever PD was the surgical treatment of choice (9-11). Surgical techniques and intraoperative additive treatments were developed resulting in improved overall survival and patients-reported outcomes like preserved pulmonary function and quality of life (11-16). A meta-analysis proved at least non-inferiority for PD compared to EPP with regard to various outcome measures (17). More and more centers previously advocating EPP have implemented PD as surgical treatment of choice in the interim (18-20).

In the recent guideline from North America, the NCCN panel declared both EPP and PD as reasonable surgical options to achieve MCR (21). On the other side, EPP has been abandoned in most European countries after publication of the very conflictive results of the MARS feasibility trial (22). Furthermore, extension of the surgical procedure from P/D to EPP in stages III and IV patients have not shown to lead to superior survival (9). The surgical

landscape seems to evolve and a European guideline suggested that EPP should be performed only within clinical trials (23). A paradigm shift from aggressive EPP towards PD has occurred.

Patient selection

The precise role of each component in the MMT of MPM is unanswered. Nonetheless, long-term survival might be achieved only in patients undergoing surgery-based MMT protocols. A few years ago, the "SMART approach" (Induction radiotherapy followed by EPP) showed very promising long-term survival in the feasibility study (24). The cumulative 3-year survival was 84% in the first 25 patients after a follow-up of 23 months. Median survival was not reached. In the follow-up analysis, median survival was 28.3 months in a cohort of 90 patients (25). One interpretation of these developments might be the fact that very highly selected patients might profit most from different MMT approaches. However, the outcomes might be less enthusiastic whenever patients are included less selectively in MMT protocols. Thus, patient selection for the right treatment of MPM is the key component for success.

Future perspectives

There is a latency between asbestos exposure and the diagnosis of MPM up to 40 years (26). Nonetheless, screening using low-dose computed tomography on asbestos exposed workers has not been proven to be efficient (27). Similarly, patients with mesothelioma might have higher amount of serum biomarkers like mesothelin, osteopontin and fibulin-3, but no blood test has yet been accepted as standard of care (28-30). Since germline BAP1 mutations may also play a role in the development of MPM (31), "prophylactic treatment" might have a role in high-risk patients to avoid this dismal disease. Thus, prevention and early detection of the disease should be the focus of future research projects.

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Footnote

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

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