

# Treatment of mesothelioma: still a long way to go!

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Prognosis of patients with malignant pleural mesothelioma remains very poor. Single treatment modality is clearly not effective in improving disease-free and overall survival. For this reason combined modality therapy is intensively investigated. In the well-performed and timely systematic review by Cao and colleagues, results of trimodality therapy for mesothelioma consisting of neoadjuvant or adjuvant chemotherapy, extrapleural pneumonectomy and adjuvant radiotherapy, were evaluated (1). A total of 16 studies were included of which one was a randomized controlled trial, 5 were prospective studies and the others selected retrospective, observational studies. Although the results are inconsistent, the authors conclude that trimodality therapy for mesothelioma may offer acceptable perioperative outcomes and long-term survival in selected patients who are treated in specialized centers (1).

In mesothelioma many unresolved issues remain. As this is not a spherical tumor, precise staging is rather problematic (2). Determination of the T-factor is difficult and current imaging techniques do not allow for an accurate estimate of tumor extension although new 3D-techniques are being developed. Lymph node spread (N-status) is quite different from lung cancer. As the tumor is primarily located on the parietal pleura, mediastinal lymph nodes may be involved as the first lymph node stations, which does not really represent N2 disease as the hilar N1 nodes may not contain metastatic disease. Precise restaging after induction therapy is even more difficult and for this reason modified RECIST (Response Evaluation Criteria In Solid Tumors) criteria have been proposed (3).

Regarding surgical treatment of mesothelioma, several surgical procedures are available ranging from partial pleurectomy to extensive pleurectomy/decortication and extrapleural pneumonectomy. However, different definitions

have been used making comparison between surgical series difficult and unreliable. Recently, uniform definitions have been proposed by a working group of the International Association for the Study of Lung Cancer (IASLC) and these should be adhered to for correct interpretation of surgical results (4).

After the results of the randomized pilot study of the Mesothelioma and Radical Surgery (MARS) trial became available, the role of extensive surgery for mesothelioma has recently been questioned (5). Extrapleural pneumonectomy is a technically demanding procedure which can only be performed in patients with early stage disease and good performance status. On the other hand, it provides the most extensive debulking procedure which is currently available allowing adjuvant high-dose radiotherapy to the empty hemithorax. When combined with neoadjuvant chemotherapy this trimodality treatment has found to be feasible in centers with experience with mesothelioma surgery, but difficult to perform within predefined time limits as shown in a phase II feasibility trial of the European Organisation for Research and Treatment of Cancer (EORTC) (6).

To add to the controversy, the results of the retrospective database of the IASLC became available very recently (7). Patients who underwent extrapleural pneumonectomy for stage I disease had the most favorable outcome with a median survival time of 40 months compared to 23 months for those patients who had pleurectomy/decortication. So, further well-designed phase II and III trials are still required to determine the optimal trimodality therapy in mesothelioma. Hopefully, the prospective database currently set up by IASLC will collect a sufficiently high number of cases to perform a scientifically valid, in-depth analysis.

Although mesothelioma remains a dreadful disease, no definite recommendations can presently be made regarding the most effective surgical procedure which is tolerable for our patients within a multimodality setting, the best regimen and timing of trimodality therapy, and the possible role of targeted therapies. Joined international efforts are certainly required to determine optimal staging, restaging and therapy in order to improve overall survival. We are currently confronted with a sharp rise in incidence of mesothelioma cases (8). So, urgent action is needed as time is ticking away very fast...

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