AB015. Diagnosis staging mesothelioma/role of neoadjuvant/adjuvant therapy

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Background: Mesothelioma is an asbestos-associated, male predominance, long latency period and occupational etiology malignant disease arising from the mesothelial cells of the pleurae in whose histogenesis all three germ layers are represented. That explains the de-differentiation of mesothelioma into epithelial and sarcomatoid. Despite more knowledge on histology, tumor biology and staging, there is still a relevant discrepancy between clinical and pathologic staging resulting in difficult prediction of prognosis and treatment outcome, making treatment allocation more challenging than in most other malignancies. The cause-effect relationship between inhalational exposure to asbestos and development of mesothelioma has been well documented in medical literature by several reports considering population at-risk not only for its occupational status (i.e., production of asbestos sheets, brake and clutch linings, construction/demolition work, dock and ship yard workers, electricians, plumbers, launderers) but also for its para-occupational status (para exposure via a relative or partner, living in the vicinity of an asbestos factory and environmental exposure). Despite the apparent dose-response relationship between asbestos exposure and the development of mesothelioma, there is no threshold of cumulative exposure below which there is no risk for future disease development. There is a prolonged latency (30–50 years) between exposure and the expression of malignant mesothelioma. Consequently, despite efforts to control asbestos exposure by environmental regulatory bodies commencing several decades ago, a global epidemic of deaths from mesothelioma is currently being experienced. The diagnosis of MPM is often delayed as a result of the non-specific nature of symptoms, which are followed by a swift and dismal clinical course. Several staging systems have been published, none of which optimally stratifies disease stage with survival. The American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) adopted a tumour, node and metastasis (TNM) model. In the last TNM revision, the eighth edition [2016] clinical and pathological T1a and T1b were combined into a single T1 classification. Clinical and pN1 and pN2 categories were collapsed into a single N category comprising ipsilateral, intrathoracic nodal metastases (N1). Nodes previously categorised as N3 were reclassified as N2. M category remained unchanged. Although the eighth edition aims to better predict survival in surgically and non-surgically treated patients with MPM, both parameters, T and N stage, are difficult to assess clinically and in particular the discrimination between T2 and T3 (infiltration of chest wall) is almost impossible. In general the clinical staging based on CT-scan, PET/CT scan, or MRI has a poor correlation with pathological staging.

Methods: The Guidelines of the European Respiratory Society and the European Society of Thoracic Surgeon strongly recommend a multiple and full thickness pleural biopsies from different locations by VATS in order to obtain enough material for multiple analyses which in the era of genomic medicine is the only warranty. Furthermore, thoracoscopic talc poudrage pleurodesis should be offered for fluid control, but also for improved dissection during tumor resection at a later time point in patients with I–IIIA stage disease. General oncological surgical principles such as microscopically free resection margins including a security distance cannot be achieved in mesothelioma for given anatomical circumstances. Therefore macroscopic complete resection (EPP=extrapleural pneumonectomy, EPD = extended pleurectomy and decortication, or P/D = pleurectomy/decortication) should be embedded into multimodality concepts. In the last decade a transition from EPP to P/D took place in most centers, because increasing evidence of similar OS, much lower mortality (2.5 fold), lower short-term mortality, better quality of life, and the shift in demographics of mesothelioma patients with increasingly elder patients.

Results: The literature and the existing evidence provide us only one RCT: the mesothelioma and radical surgery (MARS) which assessed the feasibility to randomize patients to undergo EPP or not performed in 12 UK hospitals. Out of 112 patients, 50 were randomized: 24 to EPP and 26 to non-EPP; 33 patients were excluded for disease progression, 5 patients were deemed inoperable and 19 patients refused surgery. Perioperative EPP-associated intend to treat mortality was 19% and also the actual mortality of 10.5%

was high in comparison to most EPP series of literature (30-day mortality up to 11.8%). In general presentation as 90-day mortality data would be much more representative and looking closer to available data of 90-day mortality the range goes up to 13.5%. The hazard ratio for overall survival between the EPP and non-EPP groups was 1.9 (95% CI: 0.92–3.93; exact P=0.082), median survival was 14.4 months (range: 5.3–18.7 months) for the EPP group and 19.5 months (13.4 months to time not yet reached) for the non-EPP group. It has been concluded by authors that the data, although limited, suggested that radical surgery (EPP) within tri-modal therapy offered no benefit and possibly harmed patients. The use of hemithoracic radiotherapy did not show significant survival benefit according to the results of a recent randomized, international, multicenter phase II trial (Stahel RA *et al.*, *Lancet Oncol* 2015). On the contrary the SMART protocol with induction radiotherapy followed by EPP showed very promising cumulative OS (58% at 3 years) (Cho BC *et al.*, *J Thorac Oncol* 2014).

Conclusions: EPP does not improve survival when added to treatment with chemoradiotherapy. EPD may result in lower perioperative mortality than EPP and should be offered in a clinical trial. The role of EPD in good prognosis patients should be examined further in clinical trials, which should include robust measurement of quality of life. Currently the MARS 2 trial is accruing patients, comparing EPD *vs.* P/D. Furthermore the results of ongoing trials assessing further modalities such as immunotherapy or targeted therapy might be a promising extension in the multimodality treatment panel for mesothelioma in adjunct to surgery.

Keywords: Mesothelioma; neoadjuvant therapy; talc poudrage; extrapleural pneumonectomy; pleurectomy/decortication

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