

Pericardial Mesothelioma, a Disease for Brave Hearts



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In the past decade, there has been a steady, although slow, improvement in the treatment of mesothelioma, the rare tumor of the mesothelial surfaces caused by asbestos exposure. The advances were mostly driven by research in the field of pleural mesothelioma biology and treatment and, at a lesser extent, peritoneal mesothelioma,^{1,2} which is the second most frequent. Pericardial mesothelioma is an exceedingly rare entity. Its correlation with asbestos exposure is controversial; indeed, on one hand, some authors exclude any correlation,³ and, on the other hand, others report significant association with asbestos exposure,⁴ thus leaving the real pathogenic process uncertain.

According to the most recent epidemiologic data from the Italian Registry on Mesothelioma, one of the most accurate and comprehensive national registries in the world, pericardial mesothelioma has an incidence of 0.049/million/y in men and 0.023/million/year in women,⁴ whereas the estimated incidence of pericardial mesothelioma in the United States is 10 to 15 new cases per year.³

According to a definition borrowed from the field of sarcoma, pericardial mesothelioma could be defined as “ultra-rare” (i.e., incidence <1/million/y).⁵ The “ultra-rarity” entails major difficulties in conducting adequately powered, prospective studies together with major challenges in making correct diagnosis and in dissecting disease biology.

Given the complete absence of prospective evidence and specific clinical recommendations in this exceptional presentation, treatment generally follows that of pleural mesothelioma, often with unsatisfactory outcomes.

The recent article of Offin et al.⁶ in the *Journal of Thoracic Oncology* describes the largest retrospective monoinstitutional case series of patients with pericardial mesothelioma ever published to date. The series is composed of 12 patients, eight females and four males, treated in a period of 11 years, with a median age of 51 years, and none of the patients reported asbestos exposure. The median age at diagnosis, lower than that reported for the pleural counterpart, is in line with what was reported in the above-mentioned Italian Registry and Surveillance, Epidemiology, and End Results Program (SEER) database analysis (median age of 61 and 53 y, respectively). This observation along with the lack

of asbestos exposure might suggest a distinct biological entity with respect to pleural mesothelioma. Nonetheless, the relative frequency of histotypes (75% epithelioid and 25% nonepithelioid) is superimposable with the larger pleural mesothelioma series. Furthermore, the only Next Generation Sequencing (NGS) analysis reported reveals multiple alterations, including TP53, NF2, and CDKN2A, highly consistent with those described in pleural mesothelioma.^{2,7} Nevertheless, tumor heterogeneity of the epithelioid subtype has been recently discussed,² and the biological and molecular portraits may suggest the optimal treatment according to the clinical phenotype, also in this setting.

Two main points in the article deserve to be highlighted.

First, the median overall survival (OS) for the overall cohort was 25.9 months, which is numerically longer than the most recent OS data for pleural mesothelioma⁸ and sharply superior to the median OS of 2 to 6 months previously reported for pericardial mesothelioma.^{4,9,10}

Second, the patients with the longest survival were the three who underwent a trimodality treatment (e.g., surgery, adjuvant cisplatin plus pemetrexed, and adjuvant radiation therapy with different radiation therapy strategies): these patients had a far longer median OS than

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patients treated with systemic therapy only or lost to follow-up (70.3 versus 8.2 mo, hazard ratio = 0.19).

Although selection bias might underpin this result, we think that this finding is still notable, considering the difficulty of achieving a complete resection in pericardial tumors, even at highly experienced centers. Indeed, in the article by Offin et al.,⁶ all the patients who underwent surgery had macroscopic residual disease after resection (R2).

In the present series, trimodality treatment seemed to be associated with the best survival outcomes. This is consonant with published data in pleural mesothelioma^{11,12} and discordant with previous retrospective data analysis on pericardial mesothelioma suggesting that only systemic chemotherapy is associated with improved survival.¹⁰

As for pleural mesothelioma, the multidisciplinary team including all the specialists involved in the disease management has a core role in the selection of patients potentially amenable to multimodality treatment; the pericardial involvement adds complexity to the general management thus deserving the expertise of the cardiothoracic surgeon.

Indeed, in the article by Offin et al.,⁶ all the patients selected for trimodality therapy had prolonged disease control. Therefore, the multidisciplinary team could aid the selection of patients suitable for more “brave” and aggressive treatment. This issue acquires more and more relevance, considering that the specimen availability may help researchers to depict the main hallmarks of pericardial mesotheliomas.

As for all the ultra-rare cancers, high-quality evidence can only be built with extensive international collaboration of referral centers. A recent consensus article from the Connective Tissue Oncology Society¹³ recommends the collaboration among reference centers for ultra-rare sarcomas, to warrant the conduction of high-quality retrospective studies. In this context, “large” and well-documented retrospective evidence from referral centers, as this case series, may also widen the knowledge of the disease, building the basis for future investigations.

In conclusion, we think that a multidisciplinary team at the referral centers is the key for an optimal management for this disease. Furthermore, we believe that global collaborative efforts, including the largest number of referral centers, should be done. This will allow the generation of adequate evidence for the definition of clinical recommendations and constitute the basis to support new drug developments for pericardial mesothelioma.

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