Multimodality Therapy in Patients With Primary Pericardial Mesothelioma

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ABSTRACT

Introduction: Primary pericardial mesothelioma (PPM) has no accepted standard-of-care treatment options with management and outcomes often extrapolated from diffuse pleural mesothelioma. Disease-specific research is needed to better define PPM. We report our institutional experience with PPM highlighting the potential role for multimodality therapy.

Methods: Patients with PPM diagnosed by a multidisciplinary team of medical oncologists, thoracic surgeons, thoracic pathologists, and radiologists between January 2011 and January 2022 were followed to February 2022. Clinicopathologic features and treatment outcomes were annotated. Overall survival (OS) was defined from the date of pathologic diagnosis.

Results: The median age at diagnosis of the 12 patients identified with having PPM was 51 (range: 21–71) years old. Most patients were of female sex (n = 8; 67%), 75% of the samples were epithelioid (n = 9), and 25% were non-epithelioid (two sarcomatoid and one biphasic). Most cases (92%, 11 of 12) had expression of at least two mesothelial markers on immunohistochemistry. The median OS of the cohort was 25.9 months. Five patients had an OS greater than 12 months; four of whom received pericardial radiation. Three of the patients who received radiation did so as part of a trimodality approach (surgical resection, adjuvant chemotherapy, and radiation); the OS for patients who received trimodality therapy was 70.3 months versus 8.2 months for those who did not.

Conclusions: PPM represents a distinct disease with no universally accepted treatment options. Our findings suggest that trimodality therapy may improve outcomes in selected patients with PPM.

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Keywords: Primary pericardial mesothelioma; Trimodality therapy; Multimodality therapy; Primary pericardial tumors

Introduction

Malignant mesotheliomas are unique diseases with distinct clinicopathologic features involving serosal surfaces, including the pleura, peritoneum, pericardium, and tunica vaginalis. Primary pericardial mesothelioma (PPM) is an understudied and clinically discrete disease representing less than 1% of mesotheliomas.\(^1,2\) Only approximately 100 cumulative cases have been published, many of which were diagnosed at autopsy.\(^1\) Radiologic findings with PPM can be nonspecific and results of cytologic evaluation by pericardiocentesis are often unrevealing; conclusive diagnostic evaluation often requires tissue sampling.\(^1,2\) Clinical outcomes remain unacceptably poor (median survival of 4–6 mo),\(^3\) and owing to diagnostic challenges and disease rarity, PPM has been historically harder to study than other mesotheliomas.

Currently, treatment options for PPM are extrapolated from the more often studied diffuse pleural mesotheliomas (DPMs). Although multimodality therapy consisting of chemotherapy, surgery, and radiation therapy for DPM remains a standard option for potentially resectable disease,\(^4,5\) the effectiveness of this approach in PPM is not well defined. With recent advances in our appreciation of the distinct clinicopathologic characteristics\(^6–9\) and disease-specific treatment options in DPM and malignant peritoneal mesothelioma,\(^10–12\) there is a need for detailed disease-specific research to better define PPM. Here, we report our institutional experience with PPM.

Materials and Methods

Patients with PPM evaluated at the Memorial Sloan Kettering Cancer Center (MSK) between January 2011 and January 2022 were identified and their cases annotated. PPM diagnosis was adjudicated by our multidisciplinary mesothelioma working group, consisting of thoracic surgeons, medical oncologists, pathologists, and radiologists, who integrated clinical documentation, radiology, and pathologic review. Immunohistochemistry was performed after clinically validated protocols with appropriate internal controls. Slides from cases with non-MSK biopsies and resections were formally reviewed by subspecialty thoracic pathologists at MSK when available. Patients were followed to February 2022, and clinicopathologic features and treatment outcomes were annotated. Overall survival (OS) was defined from the date of pathologic diagnosis. Survival analysis was performed using the Kaplan-Meier method in GraphPad Prism version 8 (GraphPad, San Diego, CA). For patients considered for trimodality therapy, operability and resectability were determined in collaboration between medical oncologists and thoracic surgeons with expertise in treating patients with mesothelioma. Dedicated thoracic imaging was performed with computed tomography or positron emission tomography scans to evaluate for extent of disease and potential involvement of adjacent structures. Cardiac magnetic resonance imaging was performed when needed to assess myocardial invasion, root of major vessel invasion, or specific cardiac chamber function. Standard-of-care intraoperative transesophageal echocardiogram was performed for monitoring during resections. The study was approved by the MSK Institutional Review Board and performed in accordance with the U.S. Common Rule.

Results

A total of 12 patients were identified after radiologic, clinical, and pathologic confirmation of PPM. During their disease course, eight patients had extrapericardial involvement of their PPM (pleural involvement, thoracic adenopathy, or both); no patient had evidence of extra-thoracic metastatic disease during the study period. Relative to DPM,\(^13\) patients with PPM tended to be younger (median age 51 y; range: 21–71 y), more often of female sex (n = 8; 67%), and reported less smoking history or known classical occupational asbestos exposure (Table 1).

Epithelioid histology predominated (75%; n = 9) with only 25% (n = 3) of cases having nonepithelioid histology (Supplementary Table 1). Tumors from all but one patient expressed at least two mesothelial markers. The tumor from patient 10 was negative for WT1, concurring the diagnosis of mesothelioma. Next-generation sequencing (MSK-IMPACT)\(^14\) was performed on the tissue from one patient’s (patient 3) tumor and noted multiple alterations, including in TP53, NF2, and CDKN2 (Supplementary Table 2). No other patient had adequate material available and gave consent before death for genomic testing.

Seven patients received therapy with platinum and pemetrexed; the other five patients either died before treatment initiation or were lost to follow-up (n = 3). Patients 3 and 4, both of whom previously received six cycles of platinum/pemetrexed with a clinically assessed partial response, went on to receive immunotherapy with ipilimumab and nivolumab at progression for 2.3 and 6.0 months, respectively. Five patients (patients 1–5) survived longer than 12 months; of these, four (patients 1, 2, 3, and 5) received pericardial radiation therapy. Of the five total patients who received pericardial radiation therapy, none experienced documented
Supplementary Fig. 1). Patient 1 had a 3.6-year interval pericardial radiation, totaling 5400 cGy in 30 fractions and pemetrexed for four cycles, followed by artery, and left phrenic nerve) and adjuvant cisplatin [R2] owing to proximity to the aortic root, pulmonary went a pericardiectomy (macroscopic residual disease intensity-modulated radiation therapy. Patient 1 under-\textsuperscript{--} \textsuperscript{rm} \textsuperscript{tive} sequential radiation therapy to a total dose of 6000 cGy in 30 fractions (Supplementary Fig. 1); as of last follow-up, the patient had no evidence of recurrent cancer (3.3 y from the completion of radiation). Patients 1 and 2 had improved survival compared with the overall cohort with an OS of 70.3 and 48.6 months (ongoing), respectively (Fig. 1). Patient 5 underwent treatment at an outside facility, including pericardiectomy (R2 reportedly with extensive right atrial involvement and no clear tumor planes intraoperatively on frozen pathologic assessment), four cycles of adjuvant cisplatin and pemetrexed, and postoperative radiation (4500 cGy in 25 fractions). Patient 5 was alive and without recurrence at last point of contact (OS of 14.7 mo). Median OS for pa-\textsuperscript{tients who received trimodality therapy was 70.3 months versus 8.2 months for those who did not (hazard ratio = 0.14, 95% confidence interval: 0.02–0.89, \textit{p} < 0.05; Supplementary Fig. 2).

Discussion

A substantial difficulty exists in establishing treatment protocols for patients with PPM owing to its rarity and a paucity of disease-specific research. Although multimodality therapy is well established in potentially operable and resectable DPM,\textsuperscript{4,5} the role of this approach is not established in PPM. We described improved outcomes in three patients who underwent trimodality therapy compared with those who did not. Furthermore, although this cohort is numerically small, for a disease entity with only approximately 100 published cases, this series highlights the potential importance of trimodality therapy for patients with PPM.

Our findings were generally consistent with those of a previous pooled analysis by McGehee et al.,\textsuperscript{1} which included patients treated for the disease and those identified at autopsy. McGehee et al.\textsuperscript{1} noted a relatively young patient population with less reported smoking and asbestos exposure but with male predominance. The association of classical asbestos exposures with PPM is less well defined than in DPM; further prospective annotation is needed to explore this finding. On the basis of these findings, the site of origin may influence the demographics of mesotheliomas\textsuperscript{8,13}; the biological underpinnings of this finding have yet to be understood.

We noted numerically improved OS compared with historical reports,\textsuperscript{3} mostly driven by patients who received trimodality therapy. McGehee et al.\textsuperscript{1} also noted improved outcomes with bimodality or trimodality therapy (8% of patients) versus patients who received unimodality treatment (16.0 versus 4.5 mo, respectively; hazard ratio = 0.45, 95% confidence interval: 0.23–0.90). Details on the extent of the surgical resections, toxicity secondary to radiation as monitored by routine transthoracic echocardiography or cardiac magnetic resonance imaging at the discretion of the treating team. Of patients with prospective follow-up, 67% (six of nine) died during the study interval. Median OS of the 12-patient cohort was 25.9 months with a median follow-up of 20.5 months (range: 0 d–70.3 mo).

Three patients (patients 1, 2, and 5) underwent trimodality therapy consisting of surgical resection, adjuvant chemotherapy, and sequential adjuvant intensity-modulated radiation therapy. Patient 1 under-\textsuperscript{went a pericardiectomy (macroscopic residual disease [R2] owing to proximity to the aortic root, pulmonary artery, and left phrenic nerve) and adjuvant cisplatin and pemetrexed for four cycles, followed by pericardial radiation, totaling 5400 cGy in 30 fractions (Supplementary Fig. 1). Patient 1 had a 3.6-year interval from the conclusion of radiation until disease recurrence. Patient 2 had a radical resection of a dominant pericardial mass (R2 owing to extensive involvement of the pulmonary artery, aorta, and superior vena cava), followed by adjuvant cisplatin, pemetrexed, and bevacizumab for four cycles (first cycle with cisplatin and pemetrexed alone), and definitive sequential radiation therapy to a total dose of 6000 cGy in 30 fractions (Supplementary Fig. 1); as of last follow-up, the patient had no evidence of recurrent cancer (3.3 y from the completion of radiation). Patients 1 and 2 had improved survival compared with the overall cohort with an OS of 70.3 and 48.6 months (ongoing), respectively (Fig. 1). Patient 5 underwent treatment at an outside facility, including pericardiectomy (R2 reportedly with extensive right atrial involvement and no clear tumor planes intraoperatively on frozen pathologic assessment), four cycles of adjuvant cisplatin and pemetrexed, and postoperative radiation (4500 cGy in 25 fractions). Patient 5 was alive and without recurrence at last point of contact (OS of 14.7 mo). Median OS for pa-

### Table 1. Clinicopathologic Characteristic of Patients With Primary Pericardial Mesothelioma

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>( n = 12 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age at diagnosis (range)</td>
<td>51 (21–71)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>4 (33)</td>
</tr>
<tr>
<td>Female</td>
<td>8 (67)</td>
</tr>
<tr>
<td>Smoking history, n (%)</td>
<td></td>
</tr>
<tr>
<td>Ever smoker,</td>
<td>4 (33)</td>
</tr>
<tr>
<td>Never smoker</td>
<td>6 (55)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (17)</td>
</tr>
<tr>
<td>Self-reported classical occupational asbestos exposure, n (%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0 (0)</td>
</tr>
<tr>
<td>No</td>
<td>6 (50)</td>
</tr>
<tr>
<td>Unreported/unknown</td>
<td>6 (50)</td>
</tr>
<tr>
<td>Histology, n (%)</td>
<td></td>
</tr>
<tr>
<td>Epithelioid</td>
<td>9 (75)</td>
</tr>
<tr>
<td>Biphasic</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Sarcomatoid</td>
<td>2 (17)</td>
</tr>
<tr>
<td>Extrapericardial sites of disease,\textsuperscript{a} n (%)</td>
<td>8 (67)</td>
</tr>
<tr>
<td>Pleura, n</td>
<td>4</td>
</tr>
<tr>
<td>Thoracic adenopathy, n</td>
<td>8</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
</tr>
<tr>
<td>Surgical resection, n (%)</td>
<td>5 (45)</td>
</tr>
<tr>
<td>Radiation therapy,\textsuperscript{b} n (%)</td>
<td>5 (42)</td>
</tr>
<tr>
<td>Infusional therapies, n (%)</td>
<td>7 (58)</td>
</tr>
<tr>
<td>Platinum/pemetrexed, n</td>
<td>7</td>
</tr>
<tr>
<td>Immunotherapy,\textsuperscript{c} n</td>
<td>2</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Extrapericardial involvement was determined on the basis of physician review of imaging and/or pathologic confirmation at the time of pericardial biopsy/resection. No patient had extrathoracic disease.

\textsuperscript{b}Defined as postoperative and/or definitive dose pericardial irradiation.

\textsuperscript{c}Two patients received ipilimumab and nivolumab.
chemotherapy regimen used, and radiation delivered were not provided. A notable potential confounder to the improved OS observed with trimodality therapy is that these patients, by definition, had to be medically operable and potentially resectable. Although not statistically conclusive due to the small sample size owing to the rarity of the disease, these findings suggest that surgery, adjuvant chemotherapy, and radiation delivered as in DPM may meaningfully improve survival in select patients and should be considered as an option in patients well enough for a multimodality approach.

PPM represents a diagnostically enigmatic entity with nonspecific symptoms and pericardial effusion cytologic evaluations that are often not definitive. As many as 75% of PPM cases are diagnosed at autopsy, and a multidisciplinary team consisting of medical oncologists, surgeons, pathologists, and radiologists is needed to accurately diagnose the disease. In our series, all patients were diagnosed by pericardial biopsy, pericardiocentesis, or both. Although a diagnosis of mesothelioma can be pathologically confirmed by rigorous morphologic and immunohistochemical assessment, there are no morphologic or immunophenotypic features specific for site of origin of mesothelioma (pericardial versus pleural or peritoneal). Integration of clinical and radiologic data is required to determine site of origin requiring a rigorous interdisciplinary review of cases to properly diagnose PPM given distinct epidemiologic and survival outcomes. Rigorous delineation of the site of origin better allows us to understand disease-specific prognostic, predictive, and treatment implications for patients with PPM. Furthermore, although the predictive and prognostic roles of histologic subtyping and genomic sequencing in DPM have been well established, there is a paucity of literature for PPM. Prospective next-generation sequencing (somatic and inherited), immunohistochemistry (e.g., PD-L1, BAP1, WT1, VISTA), and detailed histologic assessment of PPM are warranted with a goal of further refinement of our understanding of the disease and potential correlations with patient outcomes.

In conclusion, despite advances in our understanding of the biology and treatment options for patients with DPM and malignant peritoneal mesothelioma, there is a dearth of guidance for management of PPM. Our findings suggest that first-line trimodality therapy may result in the best long-term outcomes in selected patients well enough for an aggressive multimodality approach. Future confirmation of these findings and evaluation of pathologic and genomic differences between PPM and other disease entities are warranted to provide insight into possible biomarkers of interest.

CRediT Authorship Contribution Statement

Michael Offin: Conceptualization, Methodology, Formal analysis, Investigation, Writing—original draft, Writing—review and editing, Visualization, Supervision, Project administration.

Dilanka L. De Silva: Conceptualization, Methodology, Formal analysis, Investigation, Writing—original draft, Writing—review and editing, Visualization.

Jennifer L. Sauter: Conceptualization, Methodology, Formal analysis, Investigation, Writing—review and editing, Visualization.

Jacklynn V. Egger: Formal analysis, Investigation, Writing—review and editing, Visualization.

Ellen Yorke: Investigation, Writing—review and editing, Visualization.

Prasad S. Adusumilli: Conceptualization, Writing—review and editing.

Andreas Rimner: Conceptualization, Writing—review and editing, Visualization.

Valerie W. Rusch: Conceptualization, Writing—review and editing.

Marjorie G. Zauderer: Conceptualization, Methodology, Writing—review and editing, Supervision, Project administration.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the Journal of
References