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**Teaching Case**

# Malignant Pericardial Mesothelioma Treated Using Volumetric Modulated Arc Therapy With a Simultaneous Integrated Boost

Cole Steber, MD,[a,][*] Joshua Farris, MD, PhD,[a] Ryan T. Hughes, MD,[a] Corbin A. Helis, MD,[a] Tawfeq Naal, MD,[b] Jung W. Kim-Shapiro, MD,[b] Travis Jacobson, PhD,[a] and Michael K. Farris, MD[a]

*Departments of [a]Radiation Oncology and [b]Pathology, Wake Forest School of Medicine, Winston Salem, North Carolina*

## Case Report

A 28-year-old woman with a past medical history significant for tobacco use (10 pack-years), anxiety, depression, morbid obesity, and bipolar disorder presented to the emergency department with new onset dyspnea with exertion or lying supine, as well as minimally productive cough. She was hemodynamically stable with an unremarkable physical examination. Chest radiograph demonstrated symmetrical interstitial and airspace opacities predominating in the bilateral lower lobes. Blood counts, metabolic panel, and liver function tests were unremarkable. Troponin was elevated at 0.128 and trended down to 0.105 at 6 hours and 0.054 at 18 hours. Electrocardiogram demonstrated sinus rhythm with possible left atrial enlargement with a prolonged QT interval and T wave abnormality. Computed tomography (CT) angiography of the chest demonstrated a bulky soft tissue mass centered in the left atrium, measuring 6.0 × 4.0 × 5.1 cm (Fig 1). Initial differential diagnosis included atrial myxoma, metastasis, or other primary cardiac neoplasm. Transthoracic echocardiogram revealed a normal left ventricular ejection fractions of 55% to 60%. The left atrium was mildly dilated and the atrial mass protruded into the left ventricle with partial obstruction of the mitral valve. Owing to body habitus, cardiac magnetic resonance imaging (MRI) could not be obtained.

She underwent left atrial mass resection with septal reconstruction using a bovine pericardial patch via a superior septal approach. Initial pathologic diagnosis was undifferentiated high-grade sarcoma based on high-grade histomorphology with nonlocalizing immunostaining pattern and lack of cytogenetic abnormalities of SYT and MDM2. Staging work-up with a contrast-enhanced CT of the chest/abdomen/pelvis showed no distant disease and resolution of the previously noted pulmonary edema. She then started adjuvant cyclophosphamide and Adriamycin. Further pathology review showed negative Sarcoma Targeted Gene Fusion Panel (performed at Mayo Clinic Laboratories). Immunohistochemistry strongly favored malignant mesothelioma based on positivity for various cytokeratins (keratin 5/6, keratin AE1/AE3, and keratin OSCAR) and mesothelial markers (WT-1, D2-40) (Fig 2). Consensus review determined mesothelioma was the best interpretation. Her adjuvant systemic regimen was altered to carboplatin and pemetrexed. She received 5 cycles and tolerated this well and was referred for consideration of adjuvant radiation therapy (RT).

Now, at 5 months after surgery and 1 month after completion of chemotherapy, we opted for restaging with a repeat CT angiography of the heart and a whole body positron emission tomography (PET) scan. Imaging revealed avid local tumor recurrence in the left atrium, at 3.2 × 2.2 × 2.8 cm (Fig 3A) and an additional small hypermetabolic para-aortic lymph node (Fig 3B). She otherwise had no evidence of distant disease. After multidisciplinary tumor board review, she was felt to be ineligible for further resection given the extent of her initial operation. The consensus recommendation was to proceed with definitive RT alone.

The patient was CT simulated in the supine position using a wingboard and custom vacuum bag immobilization. Respiratory motion was accounted for using 4-dimensional (4D) CT. Radiation treatment was prescribed using volumetric modulated arc therapy (VMAT) with 54 Gy in 30 fractions at 1.8 Gy/fx to the entire left atrium and any areas that were touched by the initial preoperative mass, with a simultaneous integrated boost (SIB) of 60 Gy in 30 fractions at 2 Gy/fx to the gross tumor volume. An internal target volume (ITV) for the 54 Gy volume and for the boosted volume was created based on the motion of the left atrium and gross disease,
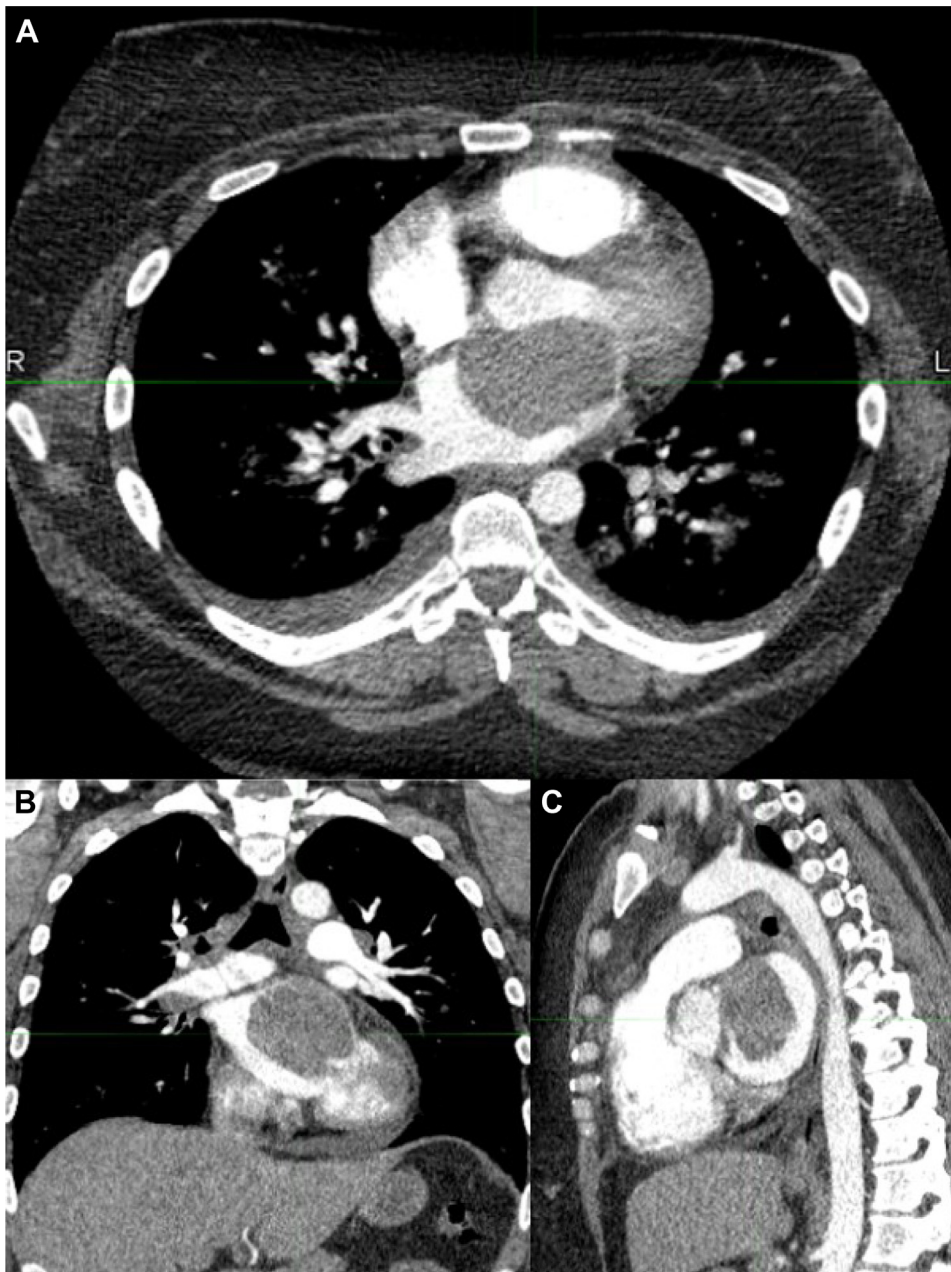


**Figure 1**    Computed tomography angiography chest imaging at diagnosis, before any therapy in axial (A), coronal (B), and sagittal (C) slices.
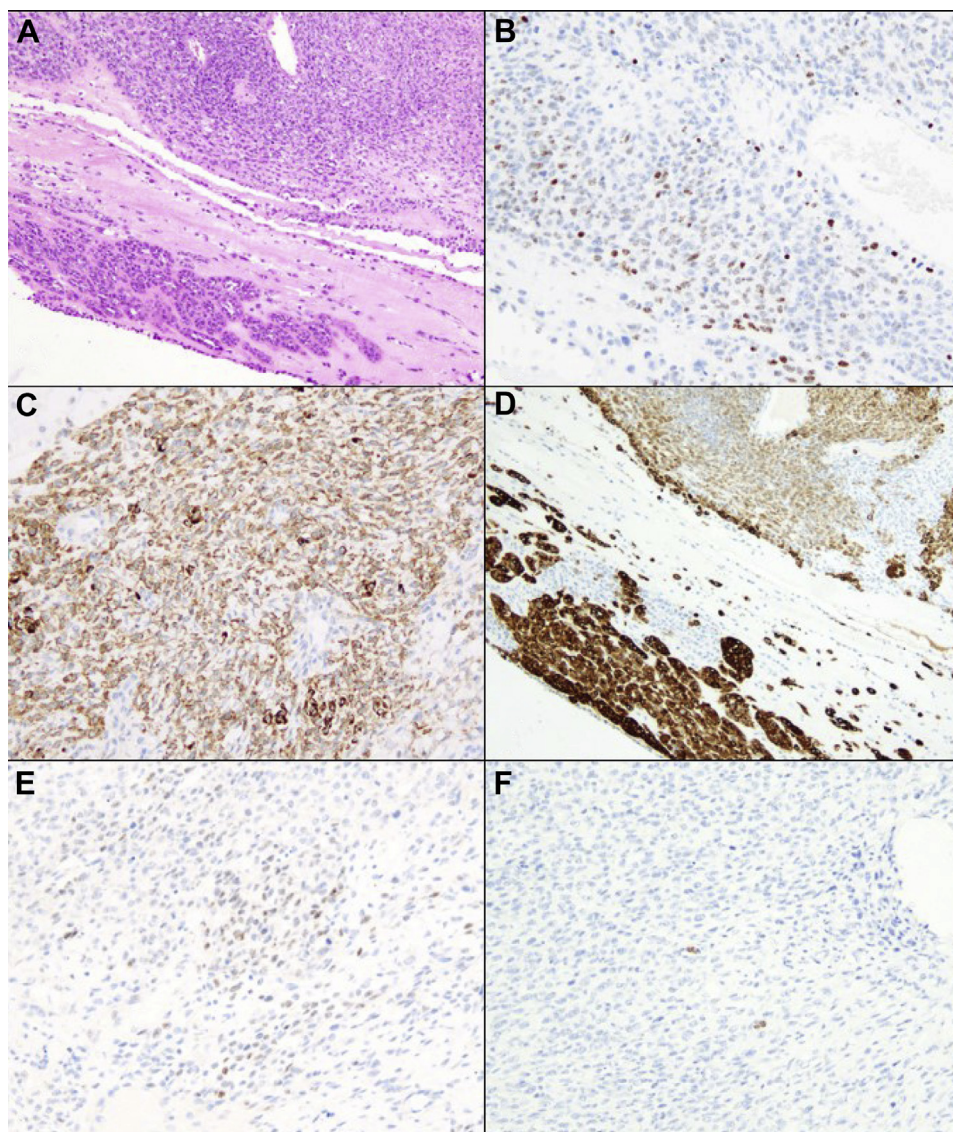
**Figure 2**    Malignant pericardial mesothelioma showing epithelioid and sarcomatous features (A). By immunohistochemistry staining, the neoplastic cells were positive for GATA3 (B), keratin AE1/AE3 (C), CK5/6 (D), and WT-1 (E). They were negative for polyclonal CEA (F).

respectively, on the 4D CT images. To limit the volume of irradiated heart, no clinical target volume was used, and a planning target volume was created with a 5 mm expansion from the respective ITVs. We used daily cone beam CT for image guidance.

She tolerated treatment well. Her only acute toxicities per Common Terminology Criteria for Adverse Events v5.0 were grade 2 esophagitis and grade 1 fatigue. At 1 month after completion of her RT, she did experience occasional feelings of dizziness but otherwise had no complaints. Repeat cardiac CT imaging demonstrated an interval increase in the size of the left atrial mass to 4.3 × 4.3 × 2.4 cm (Fig 4). After further multidisciplinary review she was started on gemcitabine and cisplatin. PET imaging, completed after 3 cycles of chemotherapy and

approximately 3 months after completion of RT, revealed resolution of hypermetabolic uptake at the left atrium. Cardiac CT imaging demonstrated only slight enlargement of the mass with dimensions of 4.7 × 4.2 × 4.0 cm. She is now being further evaluated for possible surgical resection by an oncologic cardiothoracic specialist.

## Discussion/Literature Review

Malignant involvement of the heart is known to be rare, as shown in previous autopsy series.[1,2] Secondary tumor involvement is the most common form of malignant cardiac neoplasms, as reported after 12,485 autopsies: the incidence of secondary heart tumors was
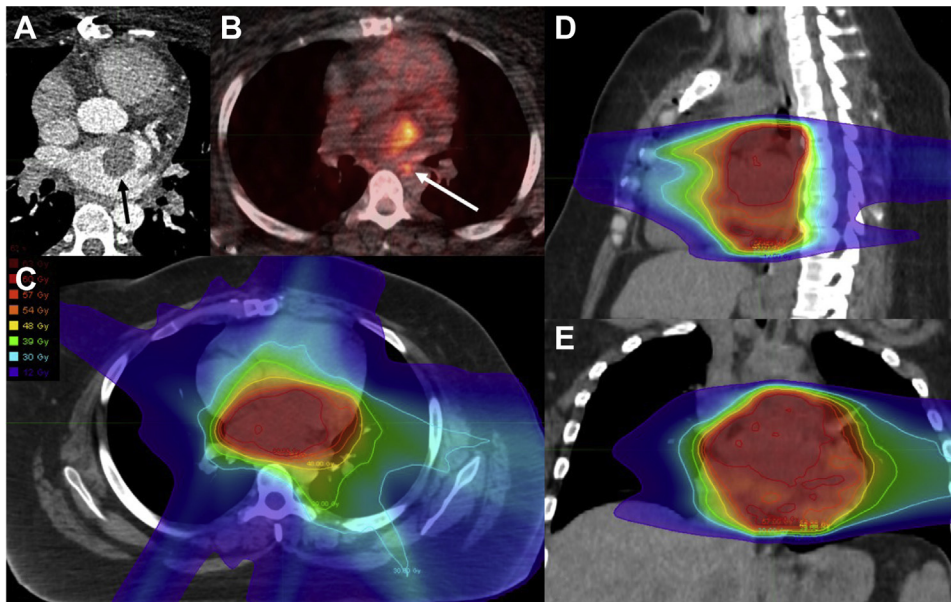
**Figure 3** Cardiac computed tomography with contrast showing evidence of recurrence after R1 surgical resection and completion of x6 total cycles of systemic therapy (black arrow) (A). Positron emission tomography/computed tomography showing recurrent left atrial mass and posterior adjacent hypermetabolic lymph node (white arrow) (B). Radiation treatment planning images in the axial (C), sagittal (D), and coronal (E) slices.



**Figure 4** Cardiac computed tomography with contrast showing progression 1 month after radiation therapy.

1.23% and 0.056% for primary heart tumors.[1] Malignant mesothelioma represents a neoplasm arising from the mesothelial surfaces of the pleura, peritoneum, pericardium, or tunica vaginalis. The majority of cases involve the pleura. Malignant pericardial mesothelioma (MPcM) comprises no more than 1% of all mesothelioma cases.[3] A large autopsy series of 500,000 cases showed the incidence of MPcM to be 0.0022%.[2] Diagnosis is difficult and is often not confirmed until late in the disease course as the presenting clinical signs and symptoms are frequently nonspecific.[4] A large review of published cases found that 92% of patients were symptomatic upon presentation.[5] Common symptoms included dyspnea, peripheral edema, chest pain, cough, and fatigue. In this same study of the tumors diagnosed premortem, the most common methods of diagnosing this tumor were via pericardiectomy, pericardial biopsy, and pericardial mass resection, in descending order.[5] There are 3 subtypes of mesothelioma and include epithelial, sarcomatoid, and biphasic histologic subtypes.[6] The most common subtype is epithelial, which also has the best prognosis.[7]

There is no consensus on the optimal treatment of MPcM. Treatment modalities that have been reported include surgical resection of the mass and/or pericardium, chemotherapy, RT, or multimodality therapy. A recent review suggested that there was a benefit to resection of pericardial masses, but not necessarily for pericardiectomy.[5] When tumors are localized, the surgical goal should be complete resection as this has been shown to provide excellent local control and long-term survival.[8] MPcM often presents as a diffuse mass, which frequently makes complete oncologic resection unachievable without significant morbidity. In such cases, the goal of surgery is often palliative and includes pericardiectomy to relieve constrictive symptoms.[9]

Systemic therapy options are varied, but phase III data from treatment of malignant pleural mesothelioma have suggested the efficacy of first line platinum-based regimens in combination with pemetrexed.[10] In a large review of cases of MPcM, patients who received multimodality therapy compared with single modality therapy had improved overall survival (OS) (median 16 months vs 4.5 months).[5] In that report, 44% of patients received chemotherapy.[5] Of those who received chemotherapy, particularly with platinum in combination with pemetrexed, there was evidence of survival benefit with median survival of 18 months versus 0.5 months. Combined with reports of response to combination platinum-pemetrexed chemotherapy in the metastatic setting, there is likely a benefit in the unresectable and adjuvant setting.[11,12] Future systemic options for MPcM will likely include immunotherapies, which are currently undergoing investigation in the setting of salvage therapy for pleural mesothelioma (NCT02054806).[13] One such completed study examined 125 patients with pleural mesothelioma with progression after first or second line therapy and randomized them to anti-programmed cell death 1 nivolumab monotherapy or nivolumab plus cytotoxic T-lymphocyte-associated protein 4 ipilimumab combination therapy.[14] Twelve-week disease control was found in 40% in the monotherapy group and 52% of the combination therapy group and without unexpected toxicity. Another emerging treatment approach is the use of chimeric antigen receptor T-cell therapy, and there is a current phase I study investigating mesothelin-targeted T cells administered intrapleurally (NCT02414269).[15]

Owing to disease rarity, the role of RT in the management of MPcM is unclear. In the setting of resectable malignant pleural mesothelioma, postoperative RT provides improved local control after extrapleural pneumonectomy.[16] For localized MPcM, 1 case report described treating gross disease involving the pericardium near the large vessels to 58 Gy.[17] Temporary control was obtained, though progression occurred 7 months after treatment and the patient died after 18 months. Another case described a patient who had undergone partial resection and was treated with intermittent chemotherapy for 3 years.[18] After localized disease progression the patient underwent 3-dimensional conformal RT to a dose of 64 Gy covering the gross disease. At 50 months from the completion of RT, there was no evidence of progression of disease. In the current case, we used VMAT with a SIB to treat gross disease to 60 Gy and the larger volume of the left atrium and associated pericardium to 54 Gy.

In MPcM, a disease with a median survival of 6 to 12 months postdiagnosis, the potential cardiac toxicities of RT are often less concerning than local disease progression, but cannot be completely ignored. There are limited reports of long-term survivors. In this disease the target is often within the cardiac tissues, and careful delineation of treatment volumes becomes necessary to limit acute and subacute toxicity. We used heart constraints extrapolated from the Radiation Therapy Oncology Group 0617 and a subsequent analysis of dosimetric parameters, understanding that these constraints were designed for tumors that were not within the heart itself.[19,20] For the heart minus ITV, V60 was 0.84%, V50 was 11.38%, mean heart dose was 27.01 Gy, and max heart dose was 61.68 Gy. Although radiation-induced cardiac toxicity is a concern, recent reports of ablative radiation to the heart for refractory ventricular arrhythmias have demonstrated that discrete lesions in and around the heart can likely tolerate larger doses of radiation.[21] Unfortunately, in this case the patient's body habitus made it impossible to obtain a cardiac MRI. Altogether, we felt that tumor size, location, and lack of cardiac MRI limited our ability to safely treat this lesion with stereotactic body RT techniques.

A recent study of cardiac toxicity after dose-escalation RT trials in stage III non-small cell lung cancer included 112 patients.[22] They found 23% had 1 or more symptomatic events at a median of 26 months with 2 patients experiencing acute pericarditis. Patients had an increasing risk for events with higher heart mean doses as shown with competing risk-adjusted event rates at 2 years for 3 differing dose groups: <10 Gy, 10 to 20 Gy, or ≥20 Gy, with 4%, 7%, and 21% event rates, respectfully. Arrhythmias, effusions, and myocardial infarctions were the most common initial adverse events. A subsequent dosimetric analysis of Radiation Therapy Oncology Group 0617 showed on multivariate analysis (MVA) the heart V50 was associated with worse OS.[20] When patients were stratified by heart V50 greater than or less than 25%, the 1 year OS rates were 70.2% versus 46.8%, and the 2-year OS rates were 45.9% versus 26.7%.

Studies of long-term survivors of Hodgkin lymphoma using older radiation techniques and lower beam energies showed significant risks for acute pericarditis when treating the whole pericardium.[23] One large study suggested that for women who had undergone RT for breast cancer, the rate of coronary events had a relative increase of 7.4% per Gy above their baseline risk when accounting for mean dose to the heart.[24] Valvular dysfunction appears to be a less common event after irradiation and has a latent period of 10 to 20 years.[25,26] However, when it does occur, it is progressive and may require valve replacement. A recent dosimetric analysis has shown that not all heart tissues are created equally in terms of dose exposure and survival outcomes in patients receiving RT for lung cancer.[27] This study showed that when the heart is divided into substructures, the right atrium, right coronary artery, and ascending aorta maximum dose were found to have the greatest effect on survival, with a maximum equivalent dose in 2 Gy per fraction of 23 Gy as a possible dose limit to these structures. Although cardiac constraints are important, in this particular setting

the risks of exceeding cardiac constraints should be weighed against the potential physiological consequences of progressive disease in the atrium.

Although surgical resection remains the mainstay of therapy for MPcM, given the severe consequences of a local or marginal failure, the integration of RT into the management as a way of improving local control is attractive. Radiation volumes and doses for this disease have not been standardized. In the setting of unresectable gross disease, positive margins at surgical resection, or local recurrence after surgical resection, radiation dose escalation may provide increased rates of response. The use of modern radiation therapy planning techniques such as intensity modulated RT or VMAT with SIB can create highly conformal dose distributions that enable dose escalation to a target volume while limiting the dose to surrounding organs at risk to acceptable levels. A study involving malignant pleural mesothelioma investigated dose escalation using SIB to PET-positive areas of disease to 62.5 Gy.[28] Median time to local relapse was improved in those patients receiving the escalated dose from 8 to 17 months. A follow-up report compared patients with progressive pleural mesothelioma who were treated with intensity modulated RT with/without SIB with the same target dose as before.[29] They found that OS and cancer-specific survival were higher with SIB if the gross tumor volume based on PET volume was not greater than 205 cc. Although PET-based volumes have limited spatial resolution and are unlikely to be feasible for the majority of MPcM, emerging technologies such as 4D-MRI and MRI-guided linear accelerators may be able to provide more precise target delineation and localization, allowing for further dose escalation, as is currently being investigated in locally advanced pancreatic adenocarcinoma (NCT03621644).[30]

The ideal sequencing of adjuvant chemotherapy and RT is not yet clear. Although concurrent chemoradiotherapy is generally not given for pleural mesothelioma because of the high baseline risk of radiation-induced lung toxicity, concurrent cisplatin, pemetrexed, and RT have been shown to be safe and effective in the treatment of locally advanced nonsmall cell lung cancer.[31] With the more limited volumes in MPcM compared with pleural mesothelioma, this may be a feasible strategy, particularly in the setting of gross unresectable disease. In the case presented here, systemic therapy was started first, soon after surgery. By the time radiation oncology was consulted, her mass had grown back to nearly half of its original size. The benefits of RT in this setting may have been more significant if used while disease was still microscopic.

## Conclusions

Currently, multimodality therapy with surgery, systemic therapy, and RT is likely to provide the best durable control for malignant pericardial mesothelioma. Rates of distant failure are high, and delays to starting systemic therapy are suboptimal. Consideration of concurrent chemoradiation or incorporation of a short course of more hypofractionated adjuvant RT over 15 to 20 fractions just before chemotherapy or newer systemic therapies such as immunotherapy or targeted therapies should be further investigated, as local failure may increase risk of death.

## Acknowledgments

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