

CLINICAL CASE CHALLENGES

Multimodality Treatment for Advanced Cervical Cancer With Isolated Metastasis to Interventricular Septum of the Heart



Ayelet Shapira-Daniels, MD,^a Daniela Katz, MD,^b Gal Aviel, MD,^a Amichay Meirovitz, MD,^c Dan Gilon, MD,^{d,e} Oz M. Shapira, MD^a

Cervical cancer is one of the most common malignancies in women worldwide (1). Approximately 90% are squamous cell carcinomas (SCC), whereas the rest are adenocarcinomas. Due to increased awareness and global early detection programs, most patients are diagnosed at an early stage. Lymphatic and hematogenous spread of the disease is uncommon and associated with a dismal prognosis, with one-half the patients dying within 6 months (1). Involvement of the heart is extremely rare (2–4). Only 38 cases were reported during the last 50 years, of whom only a handful had attempted complete (RO) resection (2–4). We report a patient with advanced stage SCC of the cervix and a single metastasis to the interventricular septum (IVS) discovered incidentally during comprehensive clinical staging. Multimodality treatment including chemotherapy, antivascular endothelial growth factor therapy, radiotherapy, and radical cardiac surgery resulted in exceptional survival.

CLINICAL CASE

A 40-year-old healthy White female presented with irregular vaginal bleeding 6 months after delivering her third child. Physical examination, pelvic ultrasound, magnetic resonance imaging (MRI), and computed tomography (CT) revealed a 6.4 × 4.3-cm invasive uterine cervical tumor and a lytic bone lesion in the right ileum. Total body ¹⁸F-fluorodeoxyglucose positron emission tomography (FDG-PET)/CT imaging (Figure 1) showed intense uptake of the tracer in the pelvic mass, the lytic bone lesion, and the IVS (standardized uptake values [SUV] = 7.0) corresponding to a single 2.4 × 1.6-cm tumor mass observed in the contrast-enhanced CT. Transthoracic echocardiography showed normal biventricular function (left ventricular ejection fraction [LVEF] of 55%), no valvular abnormalities, and an ill-defined solid mass. CT angiography of the heart showed a heterogeneous mass involving the mid-distal septum with delayed contrast enhancement. Cardiac MRI (CMR) characteristics of the mass included rapid gadolinium uptake in first-pass perfusion, delayed contrast enhancement, as well as isointense and hyperintense signals in T1-weighted and T2-weighted sequences, respectively. A biopsy of the cervical mass and the lytic bone lesion confirmed the diagnosis of metastatic poorly differentiated SCC. Biopsy of the cardiac mass was deemed unnecessary at this stage, given the bone metastasis and multimodality imaging of the heart findings that were highly suggestive of malignancy. The multidisciplinary cardiac tumor team comprising medical and radiation oncology, cardiology, radiology, and cardiothoracic surgery specialists recommended systemic cancer therapy. The patient received 18 courses of carboplatin and paclitaxel in combination with bevacizumab (Avastin, Genetech, South San Francisco, California) with complete resolution of the cervical tumor and the bone metastasis after 4 months of therapy. However, the cardiac metastasis decreased only slightly in size, and ¹⁸F-FDG-PET/CT imaging showed an

From the ^aDepartment of Cardiothoracic Surgery, Hadassah Hebrew University Medical Center, Jerusalem, Israel; ^bDepartment of Oncology, Shamir Medical Center, Beer Yaacov, Israel; ^cDepartment of Oncology, Hadassah Hebrew University Medical Center, Jerusalem, Israel; ^dDepartment of Cardiology, Hadassah Hebrew University Medical Center, Jerusalem, Israel; and the ^eDepartment of Cardiology, Shamir Medical Center, Beer Yaacov, Israel. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: CardioOncology* [author instructions page](#).

Manuscript received April 29, 2020; revised manuscript received June 8, 2020, accepted June 10, 2020.

**ABBREVIATIONS
AND ACRONYMS**

CMR = cardiac magnetic resonance imaging

CT = computed tomography

¹⁸F-FDG-PET = ¹⁸F-fluorodeoxyglucose positron emission tomography

IVS = interventricular septum

LVEF = left ventricular ejection fraction

SCC = squamous cell carcinoma

SUV = standard-uptake value

increase in tracer uptake intensity from 7.0 to 13.1 SUV. Given the patient's young age, excellent response to systemic therapy (excluding the heart), and lack of alternative effective therapy, we proceeded with surgical resection of the metastasis.

Surgery (**Figure 2**) was performed using normothermic cardiopulmonary bypass and cardioplegic arrest. The tumor was exposed via a longitudinal incision in the right ventricle parallel to the IVS, carefully preserving the left anterior descending coronary artery. A 6 × 5-cm elliptical portion of the septum including the tumor mass was excised, preserving the septal papillary muscle of the tricuspid valve. It was difficult to ascertain a clean margin in the posterior-basal septum area. The septum was reconstructed using a bovine pericardial patch sewn into the left ventricular aspect of the septum. The ventriculotomy was then closed and the patient weaned off cardiopulmonary bypass. Transesophageal echocardiography after separation from cardiopulmonary bypass showed mildly reduced LVEF (40%) secondary to asynchronous contraction and loss of septal contribution to global left ventricular function, as well as trace mitral regurgitation and mild tricuspid regurgitation.

Gross pathology clearly demonstrated the tumor. However, tumor histology revealed areas of interstitial fibrosis, necrosis, and areas of inflammation, and there was no evidence of a viable tumor in the entire specimen. Because the pathological report was consistent with no active disease in the heart and a follow-up ¹⁸F-FDG PET/CT after surgery confirmed complete response of all tumor sites, the multidisciplinary team recommendation was to proceed with therapy with curative intent. Shortly after surgery, the patient received 50 Gy of external beam irradiation to the pelvis boosted by 27.5 Gy of vaginal brachytherapy.

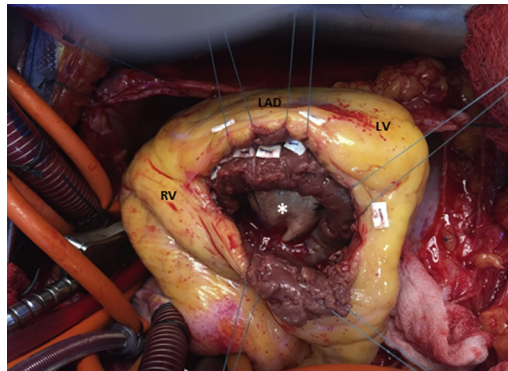
The patient recovered uneventfully, returned to New York Heart Association functional class I, and continued clinical and imaging follow-up at 3- to 4-month intervals. Repeat ¹⁸F-FDG PET/CT showed complete resolution of the malignancy. Two years after surgery, CMR and ¹⁸F-FDG PET/CT were highly suggestive of local cardiac recurrence showing a 1.6-cm mass in the posterior-basal IVS. The ¹⁸F-FDG PET/CT tracer avidity increased from 0 to 4.7 and up to 13 SUV within a few months. Echocardiographic assessment of the septum was suboptimal, possibly due to post-operative changes and the presence of patch. Transesophageal echocardiography-guided endomyocardial biopsy was negative for tumor. Nevertheless, systemic treatment using the same combination of carboplatin, paclitaxel, and bevacizumab (Avastin, Genentech, South San Francisco, California) was resumed. Forty-five months after initial diagnosis, the patient was in New York Heart Association functional class I to II. CMR showed a slight decrease in the IVS mass size to 1.4 cm. The pathological avidity in FDG-PET decreased to 5 SUV. There were no other systemic or pelvic new findings.

FIGURE 1 Pre-Operative Imaging



Pre-operative ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography scan showing a 2.4 × 1.6-cm tumor mass in the interventricular septum with intense uptake of the tracer (standard-uptake value = 7.0). LV = left ventricle; RV = right ventricle.

FIGURE 2 Surgery



Near-complete resection of the interventricular septum via a right ventriculotomy parallel to the interventricular septum. Reconstruction of the septum using a bovine pericardial patch (**asterisk**) sewn into the left ventricular side of the septum. LAD = left anterior descending coronary artery; other abbreviations as in [Figure 1](#).

DISCUSSION

The incidence of secondary metastatic tumors to the heart is 22 to 132 times more common than primary malignant tumors, and estimated to be in the range of 0.7% to 3.5% at autopsy series in the general population, and up to 14.0% in patients with known malignancies (5,6). The incidence of cardiac metastases has increased over the past decades, likely due to improved life expectancy of oncological patients and advances in diagnosis (5,6). The most common primary malignancies metastasizing to the heart include lung cancer, breast cancer, malignant melanoma, germ cell tumors, and hematological malignancies (5-7).

The most frequent mode of metastatic spread of SCC of the cervix is via the lymphatics to the para-iliac and para-aortic lymph nodes (1). Hematogenous spread is unusual and most commonly involves the lungs, bone, liver, and brain (1). Cardiac metastases from cervical cancer are exceedingly rare (2-4). The vast majority of cases have involved the right heart, presumably due to hematogenous spread of cervical cancer to the inferior vena cava via the uterine veins, coupled with filtration of tumor cells by the lungs.

Patients with cardiac metastases from cervical cancer present with a myriad of symptoms that depend on tumor location and size, leading to heart failure, arrhythmias, or tamponade (2-4). Many cases were diagnosed postmortem. Antemortem diagnosis was usually achieved by multimodality imaging including transthoracic and transesophageal echocardiography, CT angiography of the heart, CMR, and ^{18}F -FDG PET/CT (2-7). Tissue diagnosis should be pursued for prognostic implications and optimizing treatment, but may not be feasible. Our patient had no symptoms related to the cardiac metastasis. The tumor was discovered by ^{18}F -FDG PET/CT during the process of initial clinical staging of the disease. ^{18}F -FDG PET/CT is a particularly useful imaging modality in this setting. Together with CMR for detailed tumor characterization, these imaging modalities provide a comprehensive assessment of disease status that is essential for optimal shared decision making (6,7).

The median survival of patients diagnosed with cardiac metastasis from cervical cancer is 4 months (0 to 13 months) (2-4). The management of these patients should be individualized and discussed within a dedicated multidisciplinary tumor heart team (5-7). A multimodality treatment strategy including chemoradiation, biological therapy, and surgery is necessary to prolong survival and maintain quality of life. In this regard, in a prospective randomized trial, bevacizumab has been shown to improve survival when added to the commonly used platinum-paclitaxel and topotecan-paclitaxel chemotherapy regimens (8). Of note, treatment with bevacizumab has been shown to be associated with increased incidence of adverse cardiovascular side-effects such as uncontrolled hypertension, thromboembolism, cardiac ischemia, and heart failure (8). The decrease in LVEF in our patient occurred immediately after resection and remained stable, and our patient did not have severe cardiac limitations during follow-up. Her low LVEF was readily managed with cardiac medications.

Surgical resection should be considered for isolated cardiac metastasis in patients with favorable response to initial therapy and in whom complete resection is deemed feasible (2-7). Our patient had excellent response of the disease in the cervix and of the single pelvic bone metastasis with no evidence of new disease, with the exception of the cardiac metastasis, which remained metabolically active. This is not an infrequent clinical phenomenon in patients with primary or secondary malignant tumors of the heart (7), presumably due to differential response of the tumor to cancer therapy in different tissue environments (9). Given the patient's young age, good functional status, imaging suggesting feasibility of complete resection, as well as lack of an alternative effective treatment, we proceeded with surgery followed by intensive chemoradiation and bevacizumab with curative intent. Although the pathological examination in our case did not reveal residual tumor in the tissue specimen, surgical resection had an important impact on the design of her concurrent therapy and prognosis. The local recurrence supports the presence of tumor and findings of the pre-operative ¹⁸F-FDG PET/CT, highlighting the potential for false-negative tumor histological examinations following neoadjuvant chemotherapy (10). The radiological evidence of local recurrence in the area of slim resection margins—the basal-posterior septum—underscores the technical challenge of achieving complete R0 resection with clean margins when treating primary or secondary malignant tumors of the heart (6,7).

In summary, cardiac metastases from cervical cancer should be included in the differential diagnosis of secondary malignant tumors of the heart. We believe that the patient-specific, multimodality management with curative intent strategized and delivered by an experienced and dedicated multidisciplinary team was key to achieving exceptional survival in our patient.

ADDRESS FOR CORRESPONDENCE: Dr. Oz M. Shapira, Department of Cardiothoracic Surgery, Hadassah Hebrew University Medical Center, POB 12000, Ein-Kerem, Jerusalem 91120, Israel. E-mail: ozshapira@hadassah.org.il. Twitter: [@AyeletDaniels](https://twitter.com/AyeletDaniels).

REFERENCES

- Li Haoran, Wu X, Cheng Xi. Advances in diagnosis and treatment of metastatic cervical cancer. *J Gynecol Oncol* 2016;27:e43.
- Sasidharan A, Hande V, Mahantshetty U, Shrivastava SK. Cardiac metastasis in cervical cancer. *BJR Case Rep* 2016;2:20150300.
- Passi N, Zhang S, Cho SH. A rare case of cardiac metastatic mass. 2018. American College of Cardiology. Available at: <https://www.acc.org/membership/person?id=0AB4C17C-3059-45D3-8A26-38219F20D313>. Accessed April 11, 2020.
- Yang M, Yang L, Wang L, et al. Case report of cardiac metastasis from cervical squamous carcinoma and its literature review. *Gynecol Obst Case Report* 2018;4:1-7.
- Goldberg AD, Blankstein R, Padera RF. Tumors metastatic to the heart. *Circulation* 2013;128:1790-4.
- Tyebally S, Chen D, Bhattacharyya S, et al. Cardiac tumors: JACC CardioOncology state-of-the-art review. *J Am Coll Cardiol CardioOnc* 2020;2:293-311.
- Yanagawa B, Mazine A, Chan EY, et al. Surgery for tumors of the heart. *Semin Thorac Surg* 2018;30:385-97.
- Tewari KS, Sill MW, Long HJ III, et al. Improved survival with bevacizumab in advanced cervical cancer. *N Engl J Med* 2014;370:734-43.
- Alsaggar M, Yao Q, Cai H, Liu D. Differential growth and responsiveness to cancer therapy of tumor cells in different environments. *Clin Exp Metastasis* 2016;33:115-24.
- Provenzano E, Vallier AL, Champ R, et al. A central review of histopathology reports after breast cancer neoadjuvant chemotherapy in the neo-tango trial. *Br J Cancer* 2013;108:866-72.

KEY WORDS cardiac mass, cervical cancer, heart metastasis, multidisciplinary team, multimodality treatment