Abstract

The present perspective is a synthesis of 80 published investigations in the setting of different types of primitive neuroectodermal tumor (PNET), extra-skeletal Ewing’s sarcoma and Askin’s tumor of cardiac origin. We identified 80 investigations and reviewed the clinical presentation, diagnostic modalities, treatment strategies and outcomes. Clinical presentation, roentgenography, cross-sectional transthoracic and trans esophageal echocardiography, magnetic resonance imaging, positron emission tomography-computerized tomographic scan, pericardial biopsy, histopathology examination with special staining and cytogenetic analysis provided the diagnostic information and identified cardiac metastases to other organs.

In this review, we have attempted to address several concerning issues of late non-specific clinical presentation and late detection due to its rarity, issues of local recurrence, remote metastases, and role of surgery, adjuvant perioperative chemo radiotherapy, and cardiac transplantation in select instances. Due to delayed presentation and local disease progression, radical tumor excision entails severe cardiac damage. Perioperative chemo radiotherapy with aggressive surgical resection and concomitant salvage one and one-half ventricular repair or cardiac transplantation may be considered necessary in certain subset of patients. The overall reported mortality for patients diagnosed to have Ewing's sarcoma family of tumors (i.e. primary cardiac Ewing's sarcoma, Askin's tumor, cardiac PNET) is 23.1%. Knowledge of different types of Ewing’s sarcoma family of tumors (ESFTs) and their management protocol should contribute to the armamentarium of the cardiac surgeon and oncologists faced with these uncommon malignant neoplasms.
Introduction

The Ewing sarcoma family of tumors (ESFTs) is a group of rare malignancies arising from the migrating cells of the neural crest characteristically composed of small round cells arranged in cords and embedded in fibrous tissue. This group includes classic Ewing sarcoma of the bone, extra skeletal Ewing sarcoma (EES), peripheral primitive neuroectodermal tumors (PNETs) and Askin’s tumor. PNET was first described as a tumor of neural origin by Stout in 1918 [1]. The term EES was introduced in 1969 by Tefft and associates [2]. Ewing’s sarcoma family of tumors are aggressive type of tumors with a high incidence of local recurrence and distant metastases.

Primitive neuroectodermal tumors in general are rare and highly malignant small round cell tumors of undifferentiated neuroectodermal origin affecting bone and soft tissues [3]. They have been classified into 3 categories, namely central, autonomic, and peripheral PNETs. The first case report of myocardial PNET was in 1996 by Charney and colleagues [4].

A distinct clinic pathologic entity, proposed by Askin and associates in 1979, termed “malignant small round cell tumor” of the thoracopulmonary region has been reported in both children and young adults [5]. The tumor arises in the extra pulmonary tissues of the thoracic wall as well as in the pulmonary parenchyma. Although, the precise histogenesis of this entity has not been established, there is evidence to support its derivation from a primitive pluripotent cell expressing a neuroectodermal phenotype as confirmed by expression of cluster of differentiation (CD) 99, synaptophysin and CD 56 [5,6]. The universally accepted view is that these neoplasms are essentially the same entity showing various degrees of neuroectodermal differentiation, and Ewing’s sarcoma is considered to be the beginning, while PNET the end of the spectrum.

Clinical studies on cardiac ESFTs are limited and insufficient to generate evidence-based guidelines of diagnosis and warrant new insights into its management. The diagnosis and treatment of PNETs / Askin’s tumors remains a challenge for clinicians due to their rarity, absence of standard diagnostic and therapeutic guidelines, small-scale, single institutional clinical trials and late presentation. Till date, 13 cases of primary cardiac Ewing sarcoma family of tumors (ESFTs) and 11 cases of metastatic Ewing sarcoma to the heart have been reported [4-28].

Incidence

Primary cardiac tumors constitute only 0.001%-0.28% based upon data from autopsy series [29,30]. However, 80% of cardiac tumors which are clinically detected are metastatic. Available data from single-centre studies vary and the reported prevalence is between 3% and 28.7% [31-41].

Among the common primary tumors, atrial myxoma constitutes 70%-77% of cases [42,43]. The common primary malignant cardiac tumors include sarcomas, followed by lymphoma and mesothelioma [11,44]. The true incidence of PNET involving the myocardium or periocardium is unknown because it is extremely rare. Our extensive literature search revealed 13 cases of primary cardiac Ewing sarcoma family of tumors [4,7-18]. It is the most common type of sarcoma in the first 2 decades of life (Table 1) [45].

Patients and Methods

With these deficiencies in mind, we analyzed the published literature to identify the described instances of primary primitive cardiac PNET and evaluated clinical studies describing their clinical presentation, the surgical techniques, local recurrence, remote micrometastases, adjuvant chemoradiotherapy, immunotherapy and their outcomes. The search engines employed were Pubmed, MEDLINE, Google Scholar, Cochrane database and Embase. The search included literature in all languages.

This strategy yielded 86 investigations that provided best answer to these topics. With respect to drawing conclusions from the sum total of the peer reviewed published literature, we have synthesized all these features to outline the issues of concern, trends of various treatment strategies and have attempted to lay down guidelines for treatment of primary primitive cardiac ESFT [1-80].

Etiopathogenesis and progression of disease: The ESFT is malignant tumors of small undifferentiated neuroectodermal cells occurring both in CNS and in peripheral locations. In the CNS, they include medulloblastoma, pineoblastoma, ependymoblastoma, and CNS neuroblastoma. PNETs outside the CNS have been reported in bone, limbs, soft tissues of the back, abdomen, pancreas, gonads, kidney and breast [4-28]. Included in this category of ESFT outside the CNS are extraskeletal Ewing’s sarcoma (EES), Askin’s tumor, PNET of bone or soft tissues as they all share a common neural histiogenesis and tumor genetics [3-18]. The genetic hallmark of ESFT is the presence of chromosomal translocation t (11; 22) (q24; q12), which creates the EWS/FLI1 fusion gene and results in the expression of a chimeric protein. They have a common cell surface marker, CD99 (product of the MIC-2 gene) [65-70].

An Askin’s tumor is a soft tissue sarcoma belonging to the ESFTs localized in the thoracopulmonary region. This neoplasm usually arises from the soft tissue of the chest wall and sometimes in the lung [5]. Pathologically, an Askin tumor is a malignant small round cell tumor that is known to be derived from neuroectodermal cells due to their cytogenetic appearance [5,14,47,48,65-70]. There are numerous overlapping clinical and pathological characteristics and therapeutic approaches between Askin’s tumor/PNETs and Ewing sarcoma. Cardiac PNETs have poor prognosis and extensive metastases at presentation, warrant aggressive treatment with chemoradiotherapy and limited surgical option [7-18].

Askin and colleagues reported 77.7% mortality following diagnosis with a mean survival period of 8 months [5]. Contesso and associates reported 2- and 6-year survival rates of 38% and 14%, respectively [6]. The initial tumor volume (>100 ml), the histopathological response to initial chemotherapy and the presence of metastases at diagnosis were identified as major prognostic factors [49-51].

Table 1: Summary of the published investigations documenting the diagnosis and management of primary primitive neuro-ectodermal tumor, Ewing’s sarcoma and Askin’s tumor of cardiac origin

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Authors</th>
<th>No. of patients</th>
<th>Age/Sex</th>
<th>Clinical presentation/ diagnosis</th>
<th>Treatment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Higgins JC et al, 1994&lt;sup&gt;†&lt;/sup&gt;</td>
<td>1</td>
<td>13 years/ Male</td>
<td>Cardiac tamponade; pulsus paradoxus; pericardiocectomy- 450ml serosanguinous fluid aspirated, IAP 46/32 mmHg, CXR- enlarged cardiac silhouette, echocardiograph- large pericardial effusion.</td>
<td>CPB, large tense sanguinous effusion, large biventricular cardiac tumor- 8 x 8 cm, diffuse pericardial seeding, no tumor in lungs / thorax, excision of the tumor mass</td>
<td>Died, unable to wean from CPB, autopsy done, extraskeletal Ewing’s sarcoma</td>
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<tr>
<td>2.</td>
<td>Paul S et al, 2007&lt;sup&gt;†&lt;/sup&gt;</td>
<td>1</td>
<td>14 years/ Male</td>
<td>Cough, chest x-ray- large mediastinal mass, CT- MRI- Mass invaded both aorta, vena-cava, lung, CT-guided biopsy- Ewing’s sarcoma, PNET,</td>
<td>Sanoma based chemotheraphy (11 weeks)- Vincristine, Ifosfamide, Doxorubicin (Adriamycin), Etoposide. Chemotherapy- 2 additional weeks- Vincristine, Doxorubicin, Ifosamide. CPB- aortobivial cainulation- Enblock resection of lower-third of SVC, free wall- left and right atrium, interatral septum, right pneumonectomy, reconstruction of internalia septum, right atrial free wall, SVC using bovine pericardium. Pericardium covered using porcine, submuscular tissue grafts (Cormatrix, Cardiovascular, Atlanta, GA). Adjuvant chemotherapy for 6 weeks postoperatively</td>
<td>Discharge on day 14, sinus rhythm, histology- negative resection margins with 40% viable tumor</td>
</tr>
<tr>
<td>3.</td>
<td>Chowdhury UK et al, 2010&lt;sup&gt;†&lt;/sup&gt;</td>
<td>1</td>
<td>4 years/ Male</td>
<td>SOB- 2 weeks, CXR- massive cardiomegaly, bilateral pleural effusion, Echocardiography- large mass cardiac apex, interventricular septum, CT scan- 5 cm heterogenous tumor, anterior RV wall, interventricular septum, metastatic work-up, CT, MRI- negative</td>
<td>Cardiac transplantation, post-autopsy- cyclesoprine, steroids, no additional chemotherapy drugs, Biopsy- immunohistochemically positive for O13 (CD99), neuron specific enolase, Synaptophysin. Vimentin. Myocardial PNET.</td>
<td>Died first postoperative day- intractable ventricular arhythmias</td>
</tr>
<tr>
<td>4.</td>
<td>Chamney DA et al, 1996&lt;sup&gt;†&lt;/sup&gt;</td>
<td>1</td>
<td>63 years/ Male</td>
<td>SOB- 6 weeks, CXR- large mass cardiac apex, interventricular septum, CT scan- 5 cm heterogenous tumor, anterior RV wall, interventricular septum, metastatic work-up, negative</td>
<td>CPB- cardiologia; massive tensional pericardial effusion, massive intracavity mass obliterating RV cavity, interventricular septum, tricupid chordopathy apparutus. Unable to wean from CPB: salvage 1.5 VR, histopath- hyperchromatic nuclei, scanty cytoplasm, Rosettes present. Immunohistochemistry- strong cytologic membrane positivity for CD 99 in the tumor cells</td>
<td>Discharge on 6&lt;sup&gt;th&lt;/sup&gt; postoperative day. Follow-up- well at 2 years</td>
</tr>
<tr>
<td>5.</td>
<td>Nwaejike N et al, 2012&lt;sup&gt;†&lt;/sup&gt;</td>
<td>1</td>
<td>42 years/ Female</td>
<td>Acute coronary syndrome, ECG- anterior wall ST-T changes, CT- large, well-defined, exophytic mass 5.6 x 7 x 9 cm x 5.6 cm, anterior to heart, invading interventricular septum, ventricular myocardium, distal LAD encased by tumor mass, 90% obstruction</td>
<td>Thoracotomy: mass was inoperable, biopsy tumor- mononuclear morphous blue cells, hyperchromatic nuclei, infiltrating, collagenous tissue. Immunohistochemistry- positive for CD99. Diagnosis- PNET. Chemotherapy- Ifosphamide, etoposide, alternating with vincristine, doxorubicin, cyclophosphamide, 2 cycles chemotherapy.</td>
<td>Survived</td>
</tr>
<tr>
<td>6.</td>
<td>Rajappa S et al, 2007&lt;sup&gt;†&lt;/sup&gt;</td>
<td>1</td>
<td>40 years/ Male</td>
<td>Acute coronary syndrome, ECG- anterior wall ST-T changes, CT- large, well-defined, exophytic mass 5.6 x 7 x 9 cm x 5.6 cm, anterior to heart, invading interventricular septum, ventricular myocardium, distal LAD encased by tumor mass, 90% obstruction</td>
<td>Thoracotomy: mass was inoperable, biopsy tumor- mononuclear morphous blue cells, hyperchromatic nuclei, infiltrating, collagenous tissue. Immunohistochemistry- positive for CD99. Diagnosis- PNET. Chemotherapy- Ifosphamide, etoposide, alternating with vincristine, doxorubicin, cyclophosphamide, 2 cycles chemotherapy.</td>
<td>Thoracotomy: mass was inoperable, biopsy tumor- mononuclear morphous blue cells, hyperchromatic nuclei, infiltrating, collagenous tissue. Immunohistochemistry- positive for CD99. Diagnosis- PNET. Chemotherapy- Ifosphamide, etoposide, alternating with vincristine, doxorubicin, cyclophosphamide, 2 cycles chemotherapy.</td>
</tr>
<tr>
<td>7.</td>
<td>Besriti K et al, 2000&lt;sup&gt;†&lt;/sup&gt;</td>
<td>1</td>
<td>31 years/ Male</td>
<td>Dyspnea; chest pain; sweating; 1 year; CXR- cardiomegaly, increased transverse diameter, Echo- mass, cystic lesions, septations compressing right atrium, pericardial effusion, CT- non-homogenous mass (11x9x8 cm) compressing SVC, pericardial effusion</td>
<td>Hemorrhagic, debridement blood 1.5 ltr, Biopsy- Homer-Wright type rossettes, immunohistochemically- tumor cells, intensely positive for neuron specific enolase and MIC-2 gene product. Diagnosis- PNET. Follow-up at 17 months, alive, refused chemotherapy</td>
<td>Follow-up at 17 months, alive, refused chemotherapy</td>
</tr>
<tr>
<td>8.</td>
<td>Kath R et al, 2000&lt;sup&gt;†&lt;/sup&gt;</td>
<td>1</td>
<td>44 years/ Male</td>
<td>Gradually increasing SOB, Echo- large pericardial effusion 45 mm over right, 57 mm over the left ventricle, Pericardiocectomy- No atypical cells, CT-thorax- homogenous hypodense structure over LA, coronary angio and video asstened thoracotomy, epicardial tumor of LA.</td>
<td>CPB, round and solid tumor, 3 cm diameter at the tip of left atrial appendage, histschemistry, immunohistochemical stain, CD-99 and NSE +ve. Diagnosis- PNET.</td>
<td>Died shortly after diagnosis, before operative intervention</td>
</tr>
<tr>
<td>9.</td>
<td>Mohandas KM et al, 1992&lt;sup&gt;†&lt;/sup&gt;</td>
<td>1</td>
<td>18 years/ Female</td>
<td>Generalized Khasard, acanthoses, Hepatomegaly- bilateral pleural effusion, unresolved pericardial effusion, thactychia-Cardio- cardiacomagaly, bilateral pleural effusion, pericardial centesis, no malignant cells, repeated aspirations, Echo- generalized thickening pericardium, obliteration pericardial cavity, encapsulation of the heart, CT- massive pericardial effusion, bilateral pleural effusion, collapse, left upper lobe, effusive-constrictive pericarditis.</td>
<td>Hemorrhagic fluid, both pleural cavities, thicken pericardium 5cm at places tightly encasing the heart and route of great vessels, histopathology- mononuclear small round cells without mitosis or necrosis infiltrating the myocardial fibres and pulmonary hila. Immunohistochemical stain for cytokeratin, leucocyte common antigen, epithelial membrane antigen, vimentin negative. Diagnosis- malignant small cell tumor in childhood of thoraco-pulmonary region (Askin-Rosai) tumor.</td>
<td>Died shortly after diagnosis, before operative intervention</td>
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</tbody>
</table>

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Demographics and clinical presentation: Primary cardiac malignancies present a clinical dilemma. They are unusual and remain asymptomatic until they become large enough to cause signs and symptoms. The ages of patients in the published literature ranged between 13 and 51 years (average 27.3 years) with a predilection for male predominance, primary PNET of the pericardium appears between 13 and 51 years (average 27.3 years) with a predilection for male predominance, primary PNET of the pericardium appears. Both intramyocardial and intracavitary tumors cause cardiac dysrhythmias due to irritation and direct infiltration of conduction tissue [53]. Common ECG abnormalities include atrial fibrillation (16%) and ventricular tachycardia (7%) [37]. A large pericardial effusion may cause electrical alternans. The role of imaging is to identify the primary tumor, its invasion into the surrounding structures and metastatic foci [55-58].

Multidetector CT with ECG gating and magnetic resonance is imaging (MRI) play an important role in the characterization of the mass, location, rate of growth, involvement of pericardium, myocardium, valves, coronary arteries or invasion of adjacent mediastinal structure by the malignant mass. The clinical presentation accordingly differ and includes congestive right or left heart failure, arrhythmias, myocardial ischemia, thromboembolism, pericardial effusion and cardiac tamponade [3,11,52,53].

The EES differs from its skeletal counterpart in several respects. The average age at diagnosis of EES is 22 to 30 years in contrast to the EES variety is distributed equally across both genders and is also associated with poorer prognosis [7-18].
localization of cancer spread and providing the ability to differentiate between tumor and blood thrombus. In clinical practice, even though there is no recommendation regarding the use of PET-CT in this tumor, there is a trend to using it routinely for initial staging, detection of recurrence, and follow-up [61-64]. It is difficult to arrive at a definitive diagnosis prior to surgery based on imaging features alone; hence endomyocardial biopsy or pericardiocentesis is required for definitive diagnosis.

Histopathologic and cytogenetic criteria for diagnosis: Ewing’s sarcoma is difficult to differentiate from PNET due to similar anatomic locations, overlapping light microscopic appearance, cell biology, cytogenetics and wide age range at presentation. Pericardioscopy allows direct visualization of the pericardial space and pericardiocentesis for relieving cardiac tamponade or CT-guided pericardial biopsy demonstrates cytological diagnosis in more than 90% of cases of pericardial PNET [4-19].

Microscopic examination of the resected mass or specimen is the gold standard examination and shows diffuse sheets of round cells separated by fibrous tissue with or without Homer-Wright pseudorosettes. These round cells show strong CD-99 membrane positivity, and positive neural markers including S-100 protein, neuron specific enolase (NSE), synaptophysin, chromogranin, negative staining for cytokeratin, actin, desmin, myoglobin, and leucocyte common antigen [5-18]. Characteristic cytogenetic abnormality is reciprocal translocations: t (11;22) or t (21; 22) [65].

Primitive neuroectodermal tumors can be differentiated from Ewing sarcoma by its neuroectodermal granules on electron microscopic examination [65-68]. The antigen patterns in staining for neuron specific enolase and periodic acid-Schiff place the PNET histopathologically between Ewing sarcoma and neuroblastoma. Criteria for morphological diagnosis of malignant PNET include positive NSE immunohistochemical staining, pseudorosette formation on light microscopy, neuroectodermal granules on electron microscopy, and presence of a balanced reciprocal translocation t (11;22) in 85% of cases causing alteration of the pleuripotent neural crest cells [65-69].

Enzinger and Weiss’ criteria for the differentiation of the two include at least 2 neuronal markers, light microscopic rosettes, or ultrastructural evidence of neural differentiation for diagnosis of PNET over extrasosseous Ewing’s sarcoma [69].

Results

Despite increased awareness and improved diagnostic techniques, clinical manifestations of primary malignancies of the heart and pericardium are so variable that their discovery may still be incidental during surgery or autopsy [4,7-18].

The optimal treatment of cardiac ESFT remains to be determined [69-75]. Due to rarity of the disease, relevant studies are mostly small-scale in the form of case reports, case series and single-institution clinical trials. Till date, there have been no evidence-based studies on whether postoperative radiotherapy and/or chemotherapy benefits ESFT.

Early diagnosis and radical excisions are extremely important for good long-term outcome of primary cardiac ESFT. Unfortunately, most patients succumbed to progressive cardiac failure or distant metastases [69-77].

Due to delayed presentation, and local disease progression, radical tumor excision entails severe cardiac damage. Therefore, some investigators have performed orthotopic cardiac transplantation in the setting of unresectable but locally aggressive tumors involving only the heart in the absence of distant metastases [4].

There have been several reports of surgical excision of Ewing’s sarcoma with cardiac metastases [20-22,26-28]. The overall reported mortality for patients diagnosed to have ESFT (i.e. primary cardiac Ewing’s sarcoma, Askin’s tumor, cardiac PNET) is 23.1% (Table 1) [4-18]. Among the reported cases, one patient with pericardial Askin’s tumor died before any surgical intervention. One patient with cardiac Ewing’s sarcoma expired intraoperatively after attempted surgical resection; one patient died in hospital after undergoing palliative surgical excision and 1.5 VR [4-18].

One patient with primary cardiac Ewing’s sarcoma expired intraoperatively after attempted surgical resection. The second patient had primary Ewing’s sarcoma invading both atria, superior vena cava (SVC) and right pulmonary parenchyma. The patient received 18 weeks of vincristine, ifosfamide, doxorubicin and etoposide, followed by 2 weeks of vincristine, doxorubicin and isotosamide to debulk the tumor [8]. Since there were no metastases on bone scan, abdominal CT and PET-CT, the patient underwent embloc resection of lower-third of the SVC, the free wall of the right and left atrium, interatrial septum and concomitant right pneumonectomy.

The defect in the right atrium was repaired using a glutaraldehyde-treated pericardial patch and the SVC was reconstructed with a bovine pericardial tube. Final pathologic examination revealed negative resection margins with 40% viable tumor. The patient received adjuvant chemoradiation therapy for 6 weeks postoperatively and was discharged home (Table 1) [8].

In 2010, we reported another 4-year old boy with primary Ewing’s sarcoma obliterating the entire RV cavity undergoing resection of the tumor mass, RV endoatriectomy and salvage one and one-half ventricular repair (1.5 VR). The patient died on first postoperative day due to intractable ventricular arrhythmias. In this instance, a dysfunctional, and dilated RV was an indication for 1.5 VR (Table 1).

In 2010, Azirbi and associates reported one case of rapidly growing pericardial Ewing’s sarcoma invading the entire pulmonary artery, and upper areas of right and left ventricle. Due to extensive local spread, the patient underwent 6 cycles of chemotherapy using VIDE regimen (vincristine, dactinomycin, cyclophosphamide). Each cycle lasted for 28 days. After achieving good response, 3 more cycles were repeated with VAC regimen (vincristine, doxorubicin, ifosfamide, plus mesna and etoposide) followed by palliative surgical resection. There was no recurrence till 24 months after diagnosis (Table 1) [16].
Literature documents 4 cases of pericardial PNET (Askin’s tumor). One patient underwent palliative surgical resection (pericardiectomy) with adjuvant chemotherapy. One patient underwent sarcoma-based chemoradiotherapy due to unresectable tumor mass. One patient refused chemotherapy, and one patient died before surgery [12-15].

Among 5 reported patients of cardiac PNET, 4 patients underwent palliative surgical resection with adjuvant chemotherapy. One patient underwent successful cardiac transplantation. All patients were alive at the time of reporting [4,10-18].

Discussion

Improvements in diagnostic technology have increased the referrals for surgical management. Chest radiography frequently demonstrated cardiomegaly. Although echocardiography is the investigation of choice for initial evaluation and is sensitive in predicting the etiology of most intracavitary cardiac masses, it is less reliable in determining the nature of intramural or extra-myocardial lesions. CT and MRI are complementary to each other in determining the presence, site, and nature of a cardiac mass, in predicting extracardiac extension of the tumor and in establishing the amount of myocardial and great vessel involvement.

Due to rarity of ESFT of cardiac origin, and inadequate data in the published literature, there is no uniform management protocol. Management options usually reflect extrapolation from experience treating Ewing’s sarcoma of skeletal origin or PNET and mandates a multidisciplinary approach. It is generally accepted in ESFT, a combination of adjuvant chemotherapy and immunotherapy is necessary due to propensity of micro metastatic disease [14-18].

The aim of treatment of ESFTs is to control local disease and distant metastases. A tumor free resection margin is associated with an improved outcome following surgery. The use of radiotherapy as an adjuvant therapy is decided by the histologic response to chemotherapy. Published results have documented superior results of local control and decreased distant relapse in patients administered neoadjuvant chemotherapy followed by radical surgical resection compared with the results in patients undergoing primary surgery followed by chemotherapy and/or radiotherapy [4-18].

Numerous researchers have reported satisfactory results of preoperative chemotherapy for reduction of tumor size followed by surgery. The results from MSKCC study demonstrated that postoperative radiotherapy was an effective modality for local control in patients without metastases and chemotherapy combined with irradiation in multiple metastatic settings [70-73]. The prevailing treatment of an ESFT is a combination of neo-adjuvant chemotherapy, radical surgical resection, adjuvant chemotherapy and radiotherapy to obtain a longer relapse-free survival [71-74].

Surgery: The basic premise for treatment of primary cardiac ESFTs is aggressive surgical resection regardless of tumor size to debulk the tumor mass and relieve pathway obstruction [70]. Patients requiring aggressive surgical resection of the tumor mass may be subjected to salvage one and one-half ventricular repair. In the absence of distal metastases in the setting of unresectable but locally aggressive tumors involving only the heart, cardiac transplantation may be the surgical treatment of choice. Adjuvant chemoradiotherapy may be helpful to palliate symptoms and minimize local recurrence.

Radiotherapy: The role of radiotherapy is to achieve a satisfactory control of the primary disease as well as an adjuvant therapy prior to or following resection. External-beam radiotherapy constitutes an alternative treatment strategy in patients whose pathological complete response rates are low, indicating a high risk of local relapse. The results from the Memorial Sloan-Kettering study demonstrated that radiotherapy was an effective modality for local control, particularly for patients without metastases [70].

The implementation of three dimensional conformal radiotherapy and intensity-modulated radiotherapy, including meticulous delineation of planning target volumes treatment planning and accurate execution, result in reduction of local failure rate from an unacceptable 25.5% in the patients with PNET of the chest wall in the CESS 81 study to 6.1% in the CESS 86 study [72].

In Cooperative Ewing’s Sarcoma Studies (CESS) 81 and 86 and European Intergroup Cooperative Ewing’s Sarcoma Study (EICESS) 92, radiotherapy was used in ~87% of patients as a pre- or post-operative adjuvant therapy or as radical radiotherapy for unresectable tumors [72,73]. Based on these studies, Schuck and associates concluded that irradiation alone or post-operative irradiation as local therapy had satisfactory outcomes in local control and patient survival [72,73]. Currently, the dose for adjuvant radiotherapy is usually between 20 and 60 Gy in patients with PNETs of the chest wall. In general, radiotherapy should be individualized in younger patients due to radiation-induced chest wall deformities, pulmonary fibrosis, and cardiomyopathy.

Chemotherapy: Based on the grouping of ESFT into the same WHO classification in 2002, the therapeutic guidelines of both diseases are similar. Chemotherapy is the first choice for the treatment of Ewing sarcoma, and the subsequent combination of surgery and radiation constitute the standard therapy [79]. Preoperative chemotherapy reduces the risk of intraoperative tumor rupture and tumor cell dissemination, increases the possibility of tumor free margin resection, and enhances the probability of postoperative function preservation [76-79].

Askin’s tumor/PNETs are highly sensitive to chemotherapy. Due to the characteristic high recurrence rates and the high likelihood of metastases of this disease, systemic chemotherapy should be prompt even though the disease is organ-confined [46,69,76-78]. Several chemotherapy regimen have been effectively used for ESFTs. These regimens include VIDE (vincristine, doxorubicin, ifosfamide, plus mesna and etoposide), VAC (vincristine, dactinomycin, cyclophosphamide) and a combination of DDP and 5-fluourouracil (5-FU) [76-79]. Grier and colleagues reported that adding IFM and etoposide to the standard therapy (VACA) significantly improved the outcomes for patients with non-metastatic ESFTs involving the bone [43]. For high-risk patients, EICESS 92 protocol is recommended [72].
Autologous bone marrow transplantation: During episodes of chemotherapy induced bone marrow suppression, granulocyte-colony stimulating factor has been successfully used by some investigators. Although controversial, autologous bone marrow transplantation and hematopoietic stem cell rescue have been used with variable success [79,80].

Conclusions

On the basis of the published literature including ours enunciated in the manuscript we conclude that the presence of a pericardial or asymmetric myocardial mass on echocardiography and MRI in the absence of a definite etiology warrants an early pericardial/ endomyocardial biopsy for establishing histologic diagnosis. Immunophenotypic and molecular studies are complementary investigative modalities in arriving at an accurate diagnosis of Ewing's sarcoma family of tumors.

Non-mutilative surgical treatment with negative resection margins, aggressive combination chemotherapy and postoperative radiotherapy are essential to achieve the best chance of cure in this rare group of diseases. Decision-making for one and one-half ventricular repair and cardiac transplantation should be done preoperatively, so as to reduce the cardiopulmonary bypass time and myocardial ischemia.

Multimodality therapy for Ewing's sarcoma family of tumors through a multidisciplinary approach involving thoracic and cardiac surgeons and oncologists is essential for a good outcome. A wider appreciation of this entity is warranted.

References


