

Received date: Sep 14, 2019

Accepted date: Oct 14, 2019

Published date: Oct 19, 2019

***Corresponding author**

Dr. Ujjwal K. Chowdhury, Department of
Cardiothoracic and Vascular Surgery, Ansari
Nagar, New Delhi, INDIA, Tel: 91-11-26588700,
Email: ujjwalchowdhury@gmail.com

Review Article**Copyright**

© 2019 Chowdhury UK. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Keywords

Askin's tumor, Cardiopulmonary bypass, Cluster of differentiation 99, Effusive-constrictive pericarditis, Extra-skeletal Ewing's sarcoma, Fluorodeoxyglucose, Fluorescent in-situ hybridization, Immunohistochemical stain O13, Neuron-specific enolase, One and one-half ventricular repair, Peripheral neuroepithelioma, Primitive neuroectodermal tumor, Synaptophysin.

A Treatise on the Management of Primary Primitive Neuro ectodermal Tumor, Ewing's Sarcoma and Askin's Tumor of Cardiac Origin

Ujjwal Kumar Chowdhury^{1*}, Diplomate NB¹, Nikhil Bansal¹, Niwin George¹, Sukhjeet Singh¹, Lakshmi Kumari Sankhyan¹, Suruchi Hasija DM², Vasubabu Gudala¹, Prateek Vaswani¹

¹Departments of Cardiothoracic and Vascular Surgery, All India Institute of Medical Sciences, India

²Departments of Cardiothoracic and Cardiac Anesthesia, All India Institute of Medical Sciences, India

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 pericardium 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, ependyoblastoma, 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 histogenesis 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

S.No.	Authors	No. of patients	Age/Sex	Clinical presentation/ diagnosis	Treatment	Results
1.	Higgins JC et al, 1994 ⁷	1	13 years/ Male	Cardiac tamponade, pulsus paradoxus, pericardiocentesis- 450ml serosanguinous fluid aspirated, PAP 46/32 mmHg, CXR- enlarged cardiac silhouette, echocardiograph- large pericardial effusion,	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	Died, unable to wean from CPB, autopsy done, extraskelatal Ewing's sarcoma
2.	Paul S et al, 2007 ⁸	1	14 years/ Male	Cough, chest x-ray- large mediastinal mass, CT/ MRI- Mass invaded both atria, vena-cava, lung, CT-guided biopsy- Ewing's sarcoma, PNET,	Sarcoma based chemotherapy (18 weeks)- Vincristine, Ifosafamide, Doxorubicin (Adriamycin), Etoposide. Chemotherapy- 2 additional weeks- Vincristine, Doxorubicin, Ifosafamide. CPB- aortobicaval cannulation- Enblock resection of lower-third of SVC, free wall- right and left atrium, interatrial septum, right pneumonectomy, reconstruction of interatrial septum, right atrial free wall, SVC using bovine pericardium. Pericardium covered using porcine, submucosal tissue grafts (Cormatrix, Cardiovascular, Atlanta, GA). Adjuvant chemotherapy for 6 weeks postoperatively.	Discharge on day 14, sinus rhythm, histology- negative resection margins with 40% viable tumor
3.	Chowdhury UK et al, 2010 ⁹	1	4 years/ Male	14 kg, SOB- NYHA-IV, pulsus paradoxus, CXR- CTR 0.8, normal lung fields, ECG- RAD, RVH, ST-T changes, Echo- large mass obliterating RV cavity, LVEF 0.2, metastatic work-up, CT, MRI- negative	CPB- cardioplegia, massive sanguinous pericardial effusion, massive intracavitary mass obliterating RV cavity, interventricular septum, tricuspid chordopapillary apparatus. Unable to wean from CPB- salvage 1.5 VR, histopath- hyperchromatic nuclei, scanty cytoplasm, Rosettes present. Immunohistochemistry- strong cytoplasmic membrane positivity for CD 99 in the tumor cells	Died first postoperative day- intractable ventricular arrhythmias
4.	Charney DA et al, 1996 ⁴	1	63 years/ Male	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 workup- negative	Cardiac transplantation, post-transplant- cyclosporine, steroids, no additional chemotherapeutic drugs, Biopsy- immunohistochemical positivity for O13 (CD99), neuron specific enolase, Synaptophysin, Vimentin. Myocardial PNET	Survived
5.	Nwaejike N et al, 2012 ¹⁰	1	42 years/ Female	SOB- 6 weeks, 18 weeks back- delivered a healthy baby, Echo- 7 x 8 cm mass behind the heart, large pericardial effusion, normal LV function. Pericardial centesis 2.0 lit fluid, protein 36 g/dl, cytologic examination mesothelial cells, no malignancy. CT, MRI- 7x8 cm mass adherent to the posterior wall ventricle, IVC obstruction, solid encapsulated mass adherent to the first 2cm coronary sinus and posterior free wall of left atrium.	CPB- Vascular, non-homogenous mass, posterior wall of left atrium and coronary sinus excision, reconstruction of the coronary sinus using bovine pericardium. Histopath, immunostaining, focally positive, pancytokeratin MNF 116, diffuse staining for Vimentin, variable positivity for CD 99	Discharge on 6 th postoperative day. Follow up- well at 2 years
6.	Rajappa S et al, 2007 ¹¹	1	40 years/ Male	Acute coronary syndrome, ECG- anterior wall ST-T changes, CT- large, well-defined, exophytic mass 5.6 x 7 cm x 9 cm x 5.6 cm, anterior to heart, invading interventricular septum, ventricular myocardium, distal LAD encased by tumor mass, 90% obstruction	Thoracotomy- mass was inoperable, biopsy tumor- monomorphous blue cells, hyperchromatic nuclei, infiltrating, collagenous tissue, Immunohistochemistry- positive for CD99 Diagnosis- PNET Chemotherapy- Ifosphamide, etoposide, alternating with vincristine, doxorubicin, cyclophosphamide, 2 cycles chemotherapy	Repeat evaluation, 50% regression, symptom relief
7.	Besirli K et al, 2000 ¹²	1	31 years/ Male	Dyspnea, chest pain, sweating- 1 year, CXR- cardiomegaly, increased transverse diameter, Echo- mass, cystic lesion, septations compressing right atrium, pericardial effusion, CT- non-homogenous mass (11x8x9 cm) compressing SVC, pericardial effusion	Hemorrhagic, debfrrinated blood 1.5 ltr, Biopsy- Homer-Wright type rosettes, immunohistochemically- tumor cells, intensely positive for neuron specific enolase and MIC-2 gene product. Diagnosis- PNET	Follow-up at 17 months, alive, refused chemotherapy
8.	Kath R et al, 2000 ¹³	1	44 years/ Male	Gradually increasing SOB, Echo- large pericardial effusion 45 mm over right, 57 mm over the left ventricle, Pericardiocentesis- No atypical cells, CT-thorax- homogenous hypodense structure over LA, coronary angio and video assisted thoracoscopy, epicardial tumor of LA	CPB, round and solid tumor, 3 cm diameter at the tip of left atrial appendage, histochemistry, immunohistological stain, CD-99 and NSE +ve Diagnosis- PNET	
9.	Mohandas KM et al, 1992 ¹⁴	1	18 years/ Female	Generalized Anasarca, ascites, hepatomegaly, bilateral pleural effusion, unresolving pericardial effusion, tachycardia, CXR- cardiomegaly, 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	Hemorrhagic fluid, both pleural cavities, thickened pericardium- 5cm at places tightly encasing the heart and route of great vessels, histopathology- monotonous 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	Died shortly after diagnosis, before operative intervention

S.No.	Authors	No. of patients	Age/Sex	Clinical presentation/ diagnosis	Treatment	Results
10.	Chen W et al, 2018 ¹⁵	1	13 years/ Female	Dyspnoea, edema-both lower limbs- 2 weeks, Echo- 3.3x2.6x4.4 cm hypoechoic solid mass at the left coronary sulcus within the pericardial cavity, CT Chest- Large mass in the pericardial cavity with mild to moderate enhancement, metastatic work-up negative, pericardiocentesis-hemorrhagic fluid with neutrophilic and red cells	Pericardiectomy and removal of the mass, pathology 7x3x2.5 cm solitary well circumscribed mass, postoperative adjuvant chemotherapy. Pericardial mass (5 cm) which protruded into the pericardium cavity. Monotonous small round cells with scanty clear cytoplasm and brisk mitosis. Homer Wright rosettes. Immunophenotype- CD99, SYN, CD56, NSE positive, CK, CGA, LCA, Myo D1, CR negative. FISH showed a split signal pattern signifying rearrangement of EWRS-1	No evidence of disease at 8 months
11.	Azribi F et al, 2010 ¹⁶	1	51 years/ Male	Clinical evidence- cardiac tamponade, pericardiocentesis- 3 ltr hemorrhagic fluid, CT- large pericardial mass 64x60 mm, histology- cellular malignant tumor composed of small, blue, round, uniform cells with vesicular nuclei, scanty cytoplasm. Immunohistochemically, strong staining CD99. Tumors negative for cytokeratin, CK-7, CK-20, synaptophysin, chromogranin, CD 56, TTF-1, S-100 protein, myo D1, Desmin	Sternotomy-mass invading the entire pulmonary artery and upper areas of RV, LV. Unresectable tumor- pericardial window done. Tumor pericardium 81x78 mm. Rapidly growing extrasosseous Ewing's sarcoma of the pericardium. Chemotherapy- VIDE regimen (vincristine, doxorubicin, ifosfamide, plus mesna and etoposide) given for 28 days for six cycles - good response, further chemotherapy- back regimen (vincristine, dactinomycin, cyclophosphamide) for 28 days x 3 cycles - good response, surgical resection done. Post-surgery- further chemotherapy, VAC regimen	No recurrence at 24 months after diagnosis
12.	Fan C et al, 2017 ¹⁷	1	53 years/ Female	SOB- 2 weeks, massive pericardial effusion, pericardiocentesis - blood constituents present, no epithelial cells. CT- hypo-intense tumor mass extending from the LV, fused PET-CT imaging-hypermetabolic soft tissue mass (40 mm x 30 mm)- postero-inferior to LV, severe focal FDG activity	CPB- total tumor resection, LV wall defect repaired by "sand wich" method with 2 sheets of felt and 3-0 prolene cardiopulmonary bypass time, aortic cross clamp time 55 and 30 min respectively. Diagnosis- peripheral primitive, neuroectodermal tumor	No tumor recurrence during 24 months follow up.
13.	Dou X et al, 2013 ¹⁸	1	30 years/ Male	Unresolving pneumonia left lung along with painful swelling mass, left chest wall, no fever, hemoptysis, Horner's syndrome present, contract CT- large, heterogenous density compatible with areas of non-enhancing necrosis (15 x 22.5 cm), destroyed 2 nd rib, needle biopsy- small round cells with scant cytoplasm and stained positive for NSE, CD99 and vimentin. Diagnosis- Askin tumor	Chemoradiotherapy instead of surgery , vincristine, epirubicin, cisplatin (4 cycles), radiotherapy (1.8 Gy per fraction x 20 fractions) Refused further treatment	Doing well at the time of writing the manuscript with no evidence of metastases

1.5 VR: One and one-half ventricle repair; CPB: Cardiopulmonary bypass; CT: Computed tomography; CTR: Cardiothoracic ratio; CXR: Chest x-ray; ECG: Electrocardiogram; FDG: Fluoro-deoxyglucose; IVC: Inferior vena cava; LA: Left atrium; LAD: Left anterior descending coronary artery; LV: Left ventricle; LVEF: Left ventricular ejection fraction; MRI: Magnetic resonance imaging; NYHA: New York Heart Association; PAP: Pulmonary artery pressure; PET: Positron emission tomography; PNET: Primitive neuroectodermal tumor; RV: Right ventricle; SOB: Shortness of breath; SVC: Superior vena cava

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 younger patients [4,7-18]. In contrast to PNET of other sites which have male predominance, primary PNET of the pericardium appears to show a female preponderance. In contrast to secondary cardiac tumors, the primary ESFTs produce significant impairment of cardiac function.

The clinical presentation of cardiac PNET is dependent on tumor size, 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 age 10 to 20 years for Ewing's sarcoma. The EES variety is distributed equally across both genders and is also associated with poorer prognosis [7-18].

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]. Studies of chest radiograph revealed abnormal findings including cardiomegaly, signs of heart failure, pleural and pericardial effusion, pulmonary consolidation and abnormalities in cardiac contour [53,54]. Echocardiography defines tumor location, growth pattern and pleuro-pericardial effusion [54].

Multidetector CT with ECG gating and magnetic resonance imaging (MRI) play an important role in the characterization of the mass, location, extent and assessment of the extra-cardiac spread [56-61]. Cardiac MRI, with and without gadolinium contrast, is useful to differentiate benign and malignant tumors and to delineate the extent, viability, and vascular invasion of the mass, which is necessary to determine the feasibility of surgical excision.

The combination of 18F-FDG PET and CT technology has revolutionized imaging by fusing functional and anatomic criteria for the staging of most tumors, thus allowing accurate anatomic

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 neurosecretory 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 immunochemical staining, pseudorosette formation on light microscopy, neurosecretory granules on electron microscopy, and presence of a balanced reciprocal translocation $t(11;22)$ in 85% of cases causing alteration of the pluripotent 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 extraosseous 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 ifosfamide to debulk the tumor [8]. Since there were no metastases on bone scan, abdominal CT and PET-CT, the patient underwent en bloc 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 neoadjuvant 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 28.5% in the patients with PNET of the chest wall in the CESS 81 study to 8.6% 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-fluorouracil (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

1. Stout AP. A tumor of the ulnar nerve. *Proc N.Y. Pathol. SOC.* 1918; 18: 2-11.
2. Tefft M, Fernandez C, Newton W, Soule E, and Moon T. Round cell tumors: Ewing's vs. rhabdomyosarcoma. *Int J Radial Oncol Biol Phys.* 1977; 2: 26-27.
3. Jürgens H, Bier V, Harms D, Beck J, Brandeis W, Etspüler G, et al. Malignant peripheral neuroectodermal tumors. A retrospective analysis of 42 patients. *Cancer.* 1988; 61: 349-357.
4. Charney DA, Charney JM, Ghali VS, Teplitz C. Primitive neuroectodermal tumor of the myocardium: a case report, review of the literature, immunohistochemical, and ultrastructural study. *Hum Pathol.* 1996; 27: 1365-1369.
5. Askin FB, Rosai J, Sibley RK, Dehner LP, McAlister WH. Malignant small cell tumor of the thoracopulmonary region in childhood: A distinctive clinicopathologic entity of uncertain histogenesis. *Cancer* 1979; 43: 2438-2451.
6. Contesso G, Llombart-Bosch A, Terrier P, Peydro-Olaya A, Henry-Amar M, Oberlin O, et al. Does malignant small round cell tumor of the thoracopulmonary region (Askin tumor) constitute a clinicopathologic entity? An analysis of 30 cases with immunohistochemical and electron microscopic support treated at the Institute Gustave Roussy. *Cancer* 1992; 69: 1012-1020.
7. Higgins JC, Katzman PJ, Yeager SB, Dickerman JD, Leavitt BJ, Tischler MD, et al. Extraskelatal Ewing's sarcoma of primary cardiac origin. *Pediatr Cardiol.* 1994; 15: 207-208.
8. Paul S, Ramanathan T, Cohen DM, Lebenthal A, Zellos L, Aranki SF, et al. Primary ewing sarcoma invading the heart: Reaction and reconstruction. *J Thorac Cardiovasc Surg* 2007; 133: 1667-1669.
9. Chowdhury UK, Saxena A, Ray R, Sheil A, Reddy SM, Agarwal S, Mittal C. Salvage one and one-half ventricular repair and resection of Ewing's sarcoma of cardiac origin. *Hellenic J Cardiol* 2010; 51: 71-73.
10. Nwaejike N, Rassl D, Ford H, Large SR. Primitive neuroectodermal tumor of the heart. *Ann Thorac Surg* 2012; 93: 27-29.
11. Rajappa S, Gundeti S, Varadpande L, Bethune N, Rao S, Digumarti R. Cardiac primitive neuroectodermal tumor presenting as acute coronary syndrome. *J Clin Oncol* 2007; 25: 449-451.
12. Besirli K, Arslan C, Tuzun H, Oz B. The primitive neuroectodermal tumor of the heart. *European Journal of Cardiothoracic Surgery* 2000; 18: 619-621.
13. Kath R, Krack A, Schneider C, Katenkamp D, Hoffken K. Cardiac manifestations of peripheral primitive neuroectodermal tumor (pPNET): a rare case. *Dtsch Med Wochenschr.* 2000; 125: 1192-1194.
14. K. M. Mohandas, R. F. Chinoy, N. H. Merchant, R. G. Lotliker, P. B. Desai. Malignant small cell tumor (Askin-Rosai) of the pericardium. *Postgrad Med J.* 1992; 68: 140-142.
15. Zhenwei Chen, Rongming Chen, Chising Ng, Hongqi Shi. Primary pericardial primitive neuroectodermal tumor: A case report and review of literature. *Int J Clin Exp Pathol.* 2018; 11: 2155-2159.
16. Azribi F, Razak AR, Bough G, Lee D, Rowe D, Bown N et al. Extrasosseous pericardial Ewing's sarcoma. *J Clin Oncol.* 2010; 28 : e48-e50.
17. Fan C, Kong D, Tan C, Yang J. Isolated cardiac peripheral primitive neuroectodermal tumor: A case report. *Cancer Biol Ther.* 2017; 18 : 4-7.
18. Xue Dou, Hongjiang Yan, Renben Wang. Treatment of an Askin tumor: A case report and review of literature. *Oncol Lett.* 2013; 6: 985-989.
19. Cláudio Ribeiro da Cunha, Paulo César Santos, Daniel Oliveira de Conti, Fernando A. Atik. Ewing's sarcoma presenting as an isolated intra-cardiac mass. *Eur J Cardiothorac Surg.* 2012; 41: 1398.
20. Kurt R, Kaya H, Beton O, Yucel H, Tekin G. Left atrial metastasis of Ewing's sarcoma mimicking atrial myxoma. *Türk Kardiyol Dem Ars.* 2016; 44: 88.
21. Pamukcu B, Bilge AK, Meric M, Atilgan D. Metastatic Ewing's sarcoma involving the right ventricle. *Türk Kardiyol Dem Ars.* 2008; 36: 546-548.
22. Sturmberg JP, Meyer H, Körfer R, Matthies W, Thies WR, Schauer A, et al. Ewing's sarcoma metastasizing from the right pelvis via the inferior vena cava into the heart: diagnosis and successful surgical treatment. *Pediatr Cardiol.* 1988; 9: 127-129.
23. Raafat J, Brown JA, Oster MW. Metastatic Ewing sarcoma to the heart simulating Adriamycin cardiotoxicity. *Med Pediatr Oncol* 1978; 5: 51-54.
24. Janssen DP, Van de Kaa CA, Noyez L, Van Haelst UJ, Lacquet LK. A solitary metastasis in the heart from Ewing's sarcoma. *Eur J Cardiothorac Surg.* 1994; 8: 51-53.
25. Wilson KS, Nyssen J, Alexander S. Ewing sarcoma: phalangeal primary with fatal cardiac metastases. *Med Pediatr Oncol* 1979; 7: 361-364.
26. Bae SJ, Hwang JH, Nam BD, Kim HJ, Kim KU, Kim DW, Choi IH. Multiple Ewing Sarcoma/Primitive Neuroectodermal Tumors in the Mediastinum: A Case Report and Literature Review. *Medicine* 2016; 95: e2725.
27. Naseri E, Eralp B, Oztek I. Emergency management of severe right ventricular inflow obstruction secondary to a metastatic cardiac tumor. *Ann Thorac Surg.* 2005; 79: 709-711.
28. Abbas Agaimy, Johannes Rösch, Michael Weyand, Thomas Strecker. Primary and metastatic cardiac sarcomas: a 12-year experience at a German heart center. *Int J Clin Exp Pathol.* 2012; 5: 928-938.
29. Mc Allister HA Jr. Primary tumors of the heart and pericardium. *Pathol Annu* 1979; 14: 325-355.
30. Stanisław Ostrowski, Anna Marcinkiewicz, Anna Kośmider, Ryszard Jaszewski. Sarcomas of the heart as a difficult interdisciplinary problem. *Arch Med Sci.* 2014; 10: 135-148.
31. Barreiro M, Renilla A, Jimenez JM, Martin M, Al Musa T, Garcia L, et al. Primary cardiac tumors: 32 years of experience from a Spanish tertiary surgical center. *Cardiovasc Pathol.* 2013; 22: 424-427.

32. Thiene G, Basso C, Rizzo S. Cardiac tumors: classification and epidemiology. In: Basso C, Valente M, Thiene G, Edn. *Cardiac Tumor Pathology*. New York, NY: Springer Science+Business Media. 2013; 23-30.
33. Thierry Carrel, Gabor Erdős, Balthasar Eberle, Lars Englberger, Jean-Pierre Pfammatter, Jürg Schmidli, et al. Surgical treatment of cardiac tumors- an overview and presentation of interesting cases. *Cardiovasc Med*. 2011; 14: 242-257.
34. Kumar N, Agarwal S, Ahuja A, Das P, Airon B, Ray R. Spectrum of cardiac tumors excluding myxoma: experience of a tertiary center with review of the literature. *Pathol Res Pract*. 2011; 207: 769-774.
35. Patel J, Sheppard M. Pathological study of primary cardiac and pericardial tumors in a specialist UK centre: surgical and autopsy series. *Cardiovasc Pathol*. 2010; 19: 343-352.
36. Matebele M, Peters P, Mundy J, Shah P. Cardiac tumors in adults: surgical management and follow-up of 19 patients in an Australian tertiary hospital. *Interact Cardiovasc Thorac Surg*. 2010; 10: 892-895.
37. Elbardissi A, Dearani A, Daly R, Mullany CJ, Puga FJ, Schaff HV, et al. Survival after resection of primary cardiac tumors: a 48-year experience. *Circulation*. 2008; 118: 7-15.
38. Yu K, Liu Y, Wang H, Hu S, Long C. Epidemiological and pathological characteristics of cardiac tumors: a clinical study of 242 cases. *Interact Cardiovasc Thorac Surg*. 2007; 6: 636-639.
39. Bossert T, Gummert JF, Battellini R, Walther T, Falk V, Mohr FW, et al. Surgical experience with 77 primary cardiac tumors. *Interact Cardiovasc Thorac Surg*. 2005; 4: 311-315.
40. Agarwal V, Agarwal S, Srivastava AK, Kapoor S. Primary cardiac tumors: surgical experience and follow up. *Indian Heart J*. 2003; 55: 632-636.
41. Grande A, Ragni T, Viganò M. Primary cardiac tumors: a clinical experience of 12 years. *Tex Heart Inst J*. 1993; 20: 223-230.
42. Basso C, Valente M, Poletti A, Casarotto D, Thiene G. Surgical pathology of primary cardiac and pericardial tumors. *Eur. J. Cardiothorac. Surg*. 1997; 12: 730-737.
43. Grier HE, Krailo MD, Tarbell NJ, Link MP, Fryer CJ, Pritchard DJ, et al. Addition of ifosfamide and etoposide to standard chemotherapy for Ewing's sarcoma and primitive neuroectodermal tumor of bone. *N Engl J Med*. 2003; 348: 694-701.
44. Chai Y, Huang L, Yue L. Peripheral primitive neuroectodermal tumor of left ventricular wall origin: a rare case. *Acta Cardiol*. 2007; 62: 523-524.
45. Purkayastha A, Pathak A, Sharma N, Viswanath S, Dutta V. Primitive neuroectodermal tumor of lungs in adults: a rare series of three cases treated with upfront chemo-radiation. *Transl Lung Cancer Res*. 2016; 5: 350-355.
46. Mikami Y, Nakajima M, Hashimoto H, Irei I, Matsushima T, Kawabata S and Manabe T. Primary pulmonary primitive neuroectodermal tumor (PNET). A case report. *Pathol Res Pract*. 2001; 197: 113-119.
47. Fink M, Salisbury J and Gishen P. Askin tumor: three case histories and a review of the literature. *Eur J Radiol*. 1992; 14: 178-180.
48. de Alava E, Gerald WL. Molecular biology of the Ewing's sarcoma/ primitive neuroectodermal tumor family. *J Clin Oncol*. 2000; 18: 204-213.
49. Takanami I, Imamura T, Naruke M and Kodaira S. Long-term survival after repeated resections of Askin tumor recurrences. *Eur J Cardiothorac Surg*. 1998; 13: 313-315.
50. Sauer R, Jürgens H, Burgers JM, Dunst J, Hawicek R and Michaelis J. Prognostic factors in the treatment of Ewing's sarcoma. The Ewing's Sarcoma Study Group of the German Society of Paediatric Oncology CESS 81. *Radiother Oncol*. 1987; 10: 101-110.
51. La TH, Meyers PA, Wexler LH, Alektiar KM, Healey JH, Boland P J, et al. Radiation therapy for Ewing's sarcoma: results from Memorial Sloan-Kettering in the modern era. *Int J Radiat Oncol Biol Phys*. 2006; 64: 544-550.
52. Perchinsky MJ, Lichtenstein SV, Tyers GF. Primary cardiac tumors: Forty years' experience with 71 patients. *Cancer*. 1997; 79: 1809-1815.
53. Grebenc ML, Rosado de Christenson ML, Burke AP, Green CE, Galvin JR. Primary cardiac and pericardial neoplasms: radiologic-pathologic correlation. *Radiographics*. 2000; 20: 1073-1103.
54. Agaimy A, Rosch J, Weyand M, Strecker T. Primary and metastatic cardiac sarcomas: a 12-year experience at a German heart center. *Int J Clin Exp Pathol*. 2012; 5: 928-938.
55. O'Donnell DH, Abbara S, Chaithiraphan V, Yared K, Killeen RP, Cury RC, et al. Cardiac tumors: optimal cardiac MR sequences and spectrum of imaging appearances. *Am J Roentgenol*. 2009; 193: 377-387.
56. Hoey E, Ganeshan A, Nader K, Randhawa K, Watkin R. Cardiac neoplasms and pseudotumors: imaging findings on multidetector CT angiography. *Diagn Interv Radiol*. 2012; 18: 67-77.
57. Araoz PA, Eklund HE, Welch TJ, Breen JF. CT and MR imaging of primary cardiac malignancies. *Radiographics*. 1999; 19: 1421-1434.
58. Sparrow PJ, Kurian JB, Jones TR, Mohan US. MR imaging of cardiac tumors. *Radiographics*. 2005; 25: 1255-1276.
59. Buckley O, Madan R, Kwong R, Frank J R, Andeta Hunsaker. Cardiac masses part 2: key imaging features for diagnosis and surgical planning. *Am J Roentgenol*. 2011; 197: 842-851.
60. Puppala S, Hoey ET, Mankad K, Wood AM. Primary cardiac angiosarcoma arising from the interatrial septum: magnetic resonance imaging appearances. *Br J Radiol*. 2010; 83: 230-234.
61. Coccia P, Ruggiero A, Rufini V, Maurizi P, Attina G, Marano R, et al. Cardiac metastases of Ewing sarcoma detected by 18F-FDG PET/CT. *J Pediatr Hematol Oncol*. 2012; 34: 236-238.
62. Franzius C, Daldrop-Link HE, Sciuk J, Rummeny EJ, Bielack S, Jurgens H, et al. FDG-PET for detection of pulmonary metastases from malignant primary bone tumors: comparison with spiral CT. *Ann Oncol*. 2001; 12: 479-486.
63. Gerth HU, Juergens KU, Gerss J, Schober O, Franzius C, Dirksen U. Significant benefit of multimodal imaging: PET/CT compared with PET alone in staging and follow-up of patients with Ewing tumors. *J Nucl Med*. 2007; 48: 1932-1939.
64. Rahbar K, Seifarth H, Schöffers M, Stegger I, Hoffmeier A, Spieker T, et al. Differentiation of malignant and benign cardiac tumors using 18 F-FDG PET/CT. *J Nucl Med*. 2012; 53: 856-863.
65. Szuhai K, Ijszenga M, de Jong D, Karseladze A, Tanke HJ, Hogendoorn PC. The NFATc2 gene is involved in a novel cloned translocation in a Ewing sarcoma variant that couples its function in immunology to oncology. *Clin Cancer Res*. 2009; 15: 2259-2268.
66. Tsokos M, Alaggio RD, Dehner LP, Dickman PS. Ewing sarcoma/ peripheral primitive neuroectodermal tumor and related tumors. *Pediatr Dev Pathol*. 2012; 15: 108-126.
67. Ohno T, Ouchida M, Lee L, Gatalica Z, Rao VN, Reddy ES. The EWS gene, involved in Ewing family of tumors, malignant melanoma of soft parts and desmoplastic small round cell tumors, codes for an RNA binding protein with novel regulatory domains. *Oncogene*. 1994; 9: 3087-3097.
68. Delattre O, Zucman J, Melot T, Garau XS, Zucker JM, Lenoir GM, et al. The Ewing family of tumors- a subgroup small-round-cell tumors defined by specific chimeric transcripts. *N Engl J Med*. 1994; 331: 294-299.
69. Enzinger FM, Weiss SW. Primitive neuroectodermal tumors and related lesions, in Enzinger FM, Weiss SW (eds). *Soft Tissue Tumors* (eds 3). St Louis, MO, Mosby, 1995, pp 929-964.
70. Kushner BH, Hajdu SI, Gulati SC, Erlanson RA, Exelby PR, Liebermann PH. Extracranial primitive neuroectodermal tumors. The Memorial Sloan-Kettering Cancer Center experience. *Cancer*. 1991; 67: 1825-1829.
71. Christiansen S, Semik M, Dockhorn-Dworniczak B, Rotker J, Thomas M, Schmidt C, et al. Diagnosis, treatment and outcome of patients with Askin-tumors. *Thorac Cardiovasc Surg*. 2000; 48: 311-315.

72. Schuck A, Hofmann J, Rübe C, Hillmann A, Ahrens S, Paulussen M, et al. Radiotherapy in Ewing's sarcoma and PNET of the chest wall: results of the trials of CESS 81, CESS 86, and ECESS 92. *Int J Radiat Oncol Biol Phys.* 1998; 42: 1001-1006.
73. Schuck A, Ahrens S, Konarzewska A, paulussen M, Frohlich B, Konemann S, et al. Hemithorax irradiation for Ewing tumors of the chest wall. *Int J Radiat Oncol Biol Phys.* 2002; 54: 830-838.
74. Nakajima Y, Koizumi K, Hirata T, Hirai K, Fukushima M, Yamagishi S, et al: Long-term survival of Askin tumor for 10 years with 2 relapses. *Ann Thorac Cardiovasc. Surg.* 2006; 12: 137-140.
75. Eralp Y, Bavbek S, Başaran M, kaytan, Esra MD, Yaman, et al. Prognostic factors and survival in late adolescent and adult patients with small round cell tumors. *Am J Clin Oncol.* 2002; 25: 418-424.
76. Cañizares MA, Arnau A and Cantó A: Askin's tumor of the chest wall with early metastasis. *Arch Bronconeumol.* 2001; 37: 215-216.
77. Sauer R, Jürgens H, Burgers JM, Dunst J, Hawlicek R and Michaelis J: Prognostic factors in the treatment of Ewing's sarcoma. The Ewing's Sarcoma Study Group of the German Society of Paediatric Oncology CESS 81. *Radiother Oncol.* 1987; 10: 101-110.
78. Yeste L, Sierra A, Cañon R, Aristu J and Torre W: Successful use of intraoperative radiotherapy for local control of an Askin's tumor recurrence. *J Cardiovasc Surg (Torino).* 2001; 42: 143-145.
79. Nesbit ME Jr, Gehan EA, Burgert EO Jr, Vietti T J, Cangir A, Tefft M, et al. Multimodal therapy for the management of primary, nonmetastatic Ewing's sarcoma of bone: a long-term follow-up of the First Intergroup study. *J Clin Oncol.* 1990; 8: 1664-1674.
80. Burdach S, Jürgens H, Peters C, Nurnberger W, Mauz-Korholz C, korholz D, et al. Myeloablative radiochemotherapy and hematopoietic stem-cell rescue in poor-prognosis Ewing's sarcoma. *J Clin Oncol.* 1993; 11: 1482-1488.