Clinics in Surgery

Review Article
Published: 24 Aug, 2020

The Askin-Rosai Tumor: A Clinicopathological Review

Adil Abdelhamed Abbas[1] and Hatim Qasim Almaghraby[2]*

[1]The Pediatric Hematology/Oncology Section, King Saud bin Abdulaziz University for Health Sciences, KSA

[2]Department of Laboratory Medicine, King Saud bin Abdulaziz University for Health Sciences, KSA

Abstract

The Askin-Rosai (A-R) tumor merely represents specific histopathological appearance of Malignant Round Blue Cell Tumor (MRBCT) originating in the bones or the soft tissues of the thoracic cavity. On light microscopy, the same histopathological appearance of A-R tumor has been termed Ewing Sarcoma (ES), Primitive Neuroectodermal Tumor (PNET), by various other authors. The immunophenotypic profile is similar. The chromosomal translocation t (11; 22) (q24; q12) resulting in the EWSR1-FLI1 fusion gene is detected in nearly 90% of cases of ES, PNET and A-R tumor. Therefore, A-R tumor, ES and PNET are currently regarded as one entity grouped together under the Ewing Family Tumors (EFT) and are treated in an exactly identical way. Nearly a quarter of patients develop metastasis in the lungs, bone or Bone Marrow (BM). Because of rarity of the A-R tumor, there are no separate treatment trials and the disease is treated within the contest of the EFT. Optimal treatment requires the use of adjuvant and new adjuvant Chemotherapy (CTR), radical surgical resection and/or involved field Radiotherapy (RT). Without CTR 90% of the patient relapse and die as a result of disease. Effective radical surgical resection was always complicated by the tumor size and local invasiveness. Compared to other EFT at other locations the overall prognosis of A-R tumor remains poor. Variable Overall Survival (OS) and Disease-Free Survival (DFS) at 5-years results were reported for localized disease (45% to 60% and 60% to 85% respectively). The OS for metastatic disease remains very poor at around 15% at 3-years. Little progress has been made in the treatment over the last 3 decades. Improved CTR regimens, surgical and RT delivery techniques and the use of newer targeted medications represent the hope for improving the outcomes. Literature review revealed the presence of large number of case reports and case series which indicates the rarity of this late childhood tumor, its aggressive nature. Larger randomized controlled trials are needed. In this review article we provided detailed account of this group of tumors and discuss the most recent advances used in the diagnosis and treatment.

Keywords: Askin-Rosay tumor; Chest wall; Ewing's sarcoma; Primitive neuroectodermal tumor

OPEN ACCESS

Correspondence:
Adil Abdelhamed Abbas, The Pediatric Hematology/Oncology Section, King Saud Bin Abdulaziz University for Health Sciences, Princess Nourah Oncology Centre, P.O. Box 9515, Jeddah 21423, KSA, Tel: +966566692401; E-mail: adilahabbas2000@yahoo.com.au

Received Date: *21 Jun 2020*
Accepted Date: *05 Aug 2020*
Published Date: *24 Aug 2020*

Citation:
Abbas AA, Almaghraby HQ. The Askin-Rosai Tumor: A Clinicopathological Review. Clin Surg. 2020; 5: 2914.

Introduction

Primary chest wall neoplasms in children and adolescents represent only 5% of all thoracic malignancies. Malignant tumors account for >50% and those include primary and secondary malignancies [1,2]. ES/PNET is a rare MRBCT of mesenchymal origin with a varying degree of neuronal differentiation. After Osteosarcoma (OSS) and Rhabdomyosarcoma (RMS), ES represent the third most common malignant chest wall tumor in children [2,3].

ES/PNET can affect the bone or soft tissue and is considered the most lethal of all bone sarcomas. Extraskeletal ES/PNET may originate in the various soft tissues including those of the thoraco-pulmonary regions including the lungs and the pericardium. ES/PNET tumor metastasis to other bones, BM and lungs in nearly 25% of patients [3-5].

ES was first described by James Ewing who in 1921 described a diffuse hemangioendothelioma of bone. The A-R tumor however was first described as a distinct clinical entity only in 1979 [6,7].

The A-R tumor merely represents specific histopathological appearance of a MRBCT originating in the structures of the thoraco-pulmonary region. The tumor has many features in common with ES and PNET. Histopathological differentiation between the A-R tumor and ES or PNET is difficult. On light microscopy, the same histopathological appearance of A-R tumor has been termed PNET, ES, malignant neuroepithelioma and peripheral Neuroblastoma (NBL) by various authors [7]. The Immunohistochemical profile is rather similar. In fact, the histopathological features of the A-R tumor described by Askin himself in his original article are regarded by most authors as very similar or indistinguishable from ES and PNET. The tumor in fact differs only in their degree of cellular

differentiation. The recently discovered chromosomal translocation t (11; 22) (q24; q12) resulting in the EWSR1-FLI1 fusion gene is detected in >90% of cases of ES, PNET and A-R tumor and is considered the whole mark of the diagnosis. Therefore, the A-R tumors, ES and PNET are currently regarded as one entity and grouped under the EFT and are treated in exactly similar way [3,8].

The diagnosis of A-R tumor is sometimes very difficult as the clinical presentation may mimic other common pediatric disorders and malignancies [9].

The A-R tumor is a very aggressive malignancy and has the lowest patient survival rates of all primary musculoskeletal tumors. Because of the rarity of the tumor, there are no specific defined guidelines for management. Before the era of systemic CTR, over 90% of patients died from systemic metastases within 2 to 5 years of diagnosis. However, this has now completely changed and the A-R tumor is considered a potentially curable tumor. The introduction of aggressive CTR regimen in the early 1970's and treatment of patients within clinical trials has resulted in improved survivals. Modern treatment approaches involve the use of Combined Modality Therapy (CMT) with combination of radical surgical resection, adjuvant and new adjuvant CTR and involved field RT [10,11]. The overall prognosis remains poor and results are even inferior to EFT affecting other body sites with high relapse rates, low Event Free Survival (EFS) and OS. Improved CTR regimens, use of newer targeted medications and improved RT and surgical techniques may help to improve the outcomes [12,7]. In this review article we conducted wide literature search and went through large number of published case reports and case series to provide detailed review of A-R tumor and discuss the various clinical aspects of the disease in addition to the recent advances used in the diagnosis and treatment.

Epidemiology

The A-R tumor is rare and therefore the available epidemiology is likely to be unreliable. EFT in general, represents a small percentage (<1%) of all childhood and adolescent sarcomas. The international annual incidence rates average <2 cases of per million per year [3,13]. The disease prevalence was reported as 0.2 cases per million. The A-R tumor affect children of all ages but more commonly adolescents and young adults aged between 10 and 30 years. The main age at diagnosis is around 18 years. Few cases have been reported older adult and elderly patients. The tumor tends to behave more aggressively in older children with extensive local invasion and wide metastatic spread [5,14-17].

The A-R tumor affects males more than females with male to female ratio of 1.5:1. Although the original series published by Askin et al. in 1979 reported female predominance, later reports indicated male predominance. A-R tumors are generally more common in Caucasian than in other races. However, except for the rarity of A-R tumor in African Americans, there is no specific racial or ethnic predilection and no geographic variation in the incidence of this tumor [5,8,18].

Classification

The World Health Organization (WHO) sarcoma classification is a very useful tool and is considered an indispensable reference for most histopathologists. The Fourth edition of the WHO classification book (the blue book) was produced in February 2013. The book is a product of collaboration work of 159 authors from 24 countries. The WHO classification incorporated the recent changes especially the emerged genetic and pathogenic developments. Sarcomas were classified according to the tissue of origin (adipose tissue, muscle, bone, cartilages, etc.) and graded (benign, malignant, intermediate) as to the degree of local invasiveness and metastatic potentials. EFT (including the A-R tumor) were classified under the aggressive malignant group of sarcomas of uncertain differentiation together with tumors such as Synovial Sarcoma (SS), Clear Cell Sarcoma (CCS), Desmoplastic small round blue cell tumor, extra renal rhabdoid tumor and ES. The A-R tumor was classified by the WHO as ES/PNET/ organizing tumors of neuroectodermal, bone and soft tissue origin as a single entity [19-22].

Clinical Presentation

Symptoms and signs

The most common clinical presentation of A-R tumor is with palpable rapidly growing, tender mass overlying the anterior or anterio-lateral chest wall. Other presentations include chest pain, prolonged fever, cough, progressive dyspnoea, and hemoptysis. Rarer presentations include thoracic wall mass originating from rib, pleura or the mediastinum and expand inside the thoracic cavity causing mass effect on the lungs, trachea and the main blood vessels. A very rare presentation is with synchronous bilateral chest wall tumor masses. Patients may also present with a variety of constitutional symptoms such as fever, malaise, and anorexia and weight loss. Some patients may become no specifically ill for a period of time before the appearance of more specific symptoms. The A-R tumor is very aggressive and some cases especially those who present late run an accelerated course and die after short time despite therapy [11,18,21,23]. Parikh et al. reported 15 cases of A-R tumor treated at Tata Memorial Hospital in Mumbai, India over a period of 3 years (12 males and three females). The clinical presentations included chest wall swelling (14), chest pain (11), bone involvement (6), dyspnoea (4), fever (4), cough (1), weight loss (1), and hemoptysis (1). Patients received CMT according to different protocols. Of the 10 patients who have completed induction, 5 received Vincristine (VCR) and Cyclophosphamide (CPA), whereas the other 5 patients received more aggressive CTR. Complete Remission (CR) has been achieved in two and four of these patients, respectively. Unfortunately, one patient in each group developed local disease recurrence and died [7,18,24-26].

Hematologic and peripheral blood changes

The associated systemic inflammatory reaction results in variable degrees of anemia, leukocytosis, elevated Erythrocytic Sedimentation Rate (ESR) and other serum acute phase reactants such as the C-reactive protein, alkaline phosphatase and Neuron Specific Enolase (NSE). Peripheral blood smear examination often shows normocytic normochromic anemia however, it may sometimes show leucoerythroblastic blood picture. BM infiltration with A-R tumor cells may rarely result in moderate to severe degree of anemia, leucopenia and thrombocytopenia. The treating physician must put in mind that A-R tumor patients often show similar blood and biochemical findings to patients with other inflammatory conditions and that can sometimes lead to delay of the diagnosis. Elevated Lactate Dehydrogenase (LDH) enzyme level indicates malignant tumor cell proliferation and is associated with poor prognosis [9,27].

Radiological Diagnosis

On plain Chest Radiography (CXR) the A-R tumor typically

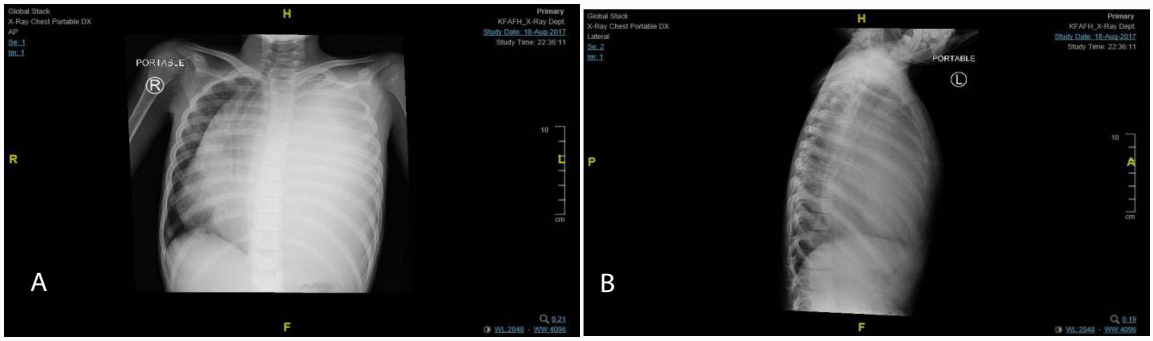

Figure 1A & 1B: CXR, anteroposterior (A) and lateral (B) views showing complete opacification of the left side of the chest cavity with a solid soft tissue mass causing mediastinal shift to the right side. No significant pleural effusion.

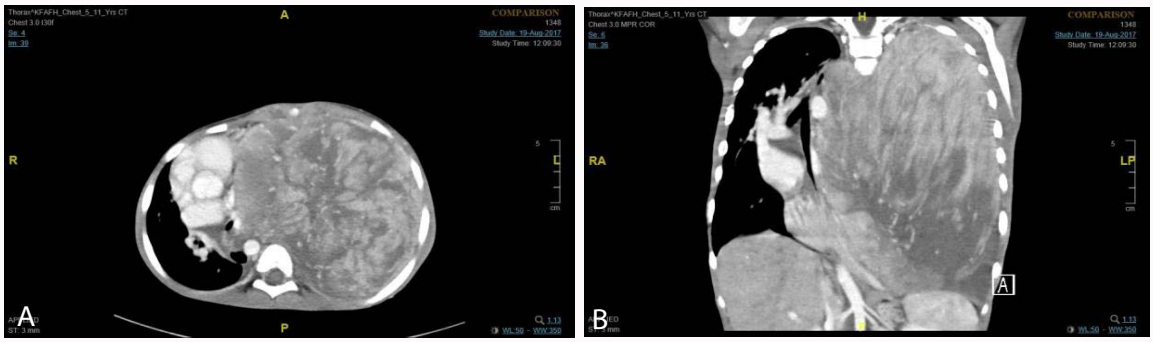

Figure 2A & 2B: CT scan, axial & coronal showing a large heterogeneous necrotic soft tissue mass occupying the whole left hemithorax. The lesion is encroaching into the middle and upper mediastinum and is inseparable from the mediastinal structures. Mild mass effect is seen over the left main bronchus. The left lung lower lobe shows some aeration and atelectasis. No evidence of pulmonary infiltration. The left second rib shows destructive expansion due to tumor infiltration. Noted is mild left side pleural effusion.

involve the periosteum and soft tissues of the thoracic wall, with extension into the pleura and pulmonary parenchyma. The CXR may show the intrathoracic, intraparenchymal mass with extrathoracic extension together with cortical rib bone destruction, lung lesions and fluid effusions (Figure 1A, 1B). The A-R tumor is better evaluated with cross-sectional imaging such as Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) scans. Most patients has localized but invasive disease. Extension into the intercostal muscles, pleura, lung tissue and pericardium with ipsilateral pleural effusion is common [26,28]. The CT scan is sensitive in detecting detailed anatomic involvement, lung tissue lesions, destruction of the bone cortex, liver and lung metastasis and calcification (Figure 2A, 2B). Tumor calcification and local or regional lymphadenopathy are however rarely seen. The CT scan is essential in assessing CTR response and disease recurrence. MRI often allows more accurate delineation and localization of the tumor and the extent of tissue invasion. MRI scan renders superior soft-tissue contrast and spatial resolution and is better for delineating the full extent of disease and the presence of BM involvement.

Nuclear Tc99 bone scintigraphy (bone scan), in EFT demonstrates high Tc99 - Methylene Diphosphonate (MDP) uptake. In nearly all cases, blood flow, blood pool, and delayed static phase images show increased Tc99 uptake at primary bone and metastatic sites (Figure 3) [21,29,30]. Fluorine-18-fluorodeoxyglucose - Positron Emission Tomography (PET) scan is not routinely used to evaluate chest wall neoplasms. Although it has the potential to differentiate malignant from benign chest wall lesions, PET/CT scan have no much role in establishing the diagnosis. PET/CT scans primary functions is the evaluation of treatment response, and detection of recurrence. Ultrasonography (U/S) has a limited role in the evaluation and characterization of chest wall lesions; however, it can be used to guide biopsy. U/S scan however, has been shown to depict chest wall invasion by the tumor more accurately than the CT scan [2,16,21,28,30].

The typical CT and MRI findings in A-R tumor include large mass with invasion of the chest wall and pleura. Winer-Muram et al. from the St Jude Children's Research Hospital in Memphis, TN, USA, described the radiological findings of A-R tumor at presentation in 2 boys and 8 girls using CT and MRI scans. All tumors (100%) were large and heterogeneous on CT and T2 weighted MRI scans and appeared on one side of the chest only. Plural involvement was seen in 7 patients (70%) and severe rib destruction in five (50%). Seven tumors (70%) had increased signal intensity greater than that of skeletal muscles on T1 weighted MRI images. Seven tumors (70%) showed presence of extensive hemorrhage and necrosis. Extension of the tumor into the chest wall structures was detected in seven patients (70%) using MRI but only in four patients (40%) using CT scan. Muscle invasion was seen on seven patients (70%) on MRI. Lung metastasis was detected in four patients (40%) by CT scan but only in one patient (10%) using MRI scan. MRI scans were more accurate in detecting chest wall invasion whereas CT scan images were more determinant in detecting bone invasion and lung metastasis [31].

Histopathological Diagnosis

A-R tumors, ES and PNET share common histologic and molecular features and are currently regarded as one neoplastic entity, grouped under the EFT. Differentiation between EFT and

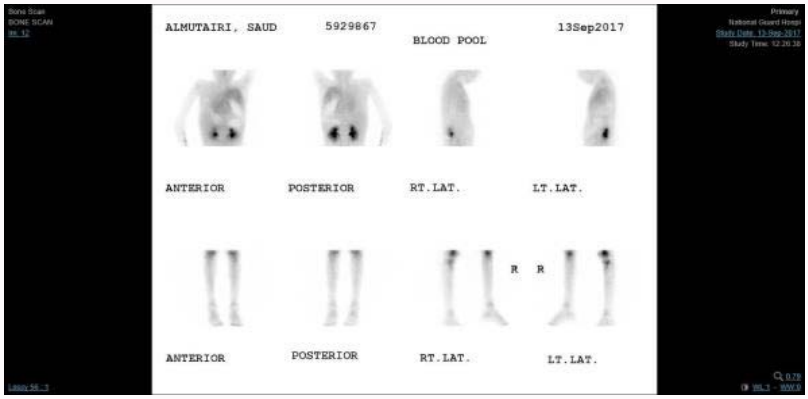

Figure 3: Tc. 99 Nuclear bone scintigraphy scan showing prominent pathological uptake is seen in the region of the left hemithorax and the whole mediastinum on both flow and blood pool phases consistent with the patient's known A - R tumor. Delayed whole body scan showed no evidence of other bone metastasis.

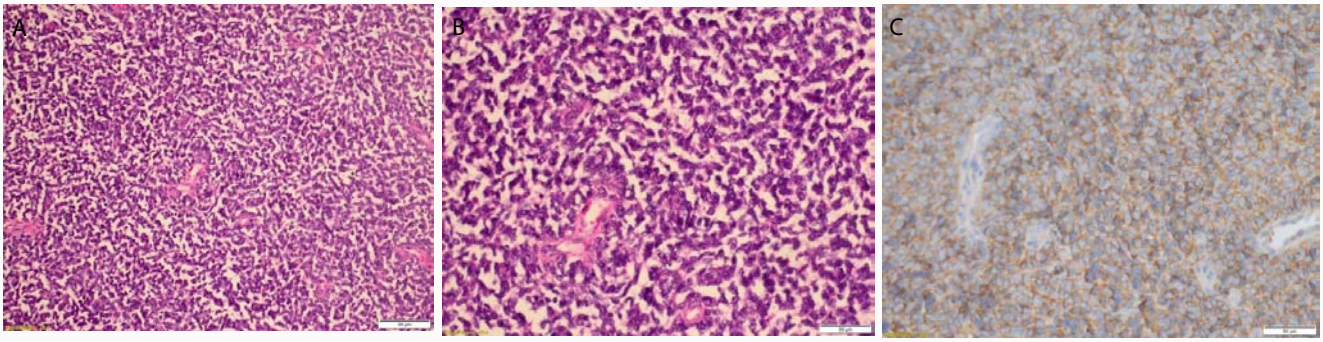

Figure 4A-4C: H&E-stained slides with increasing magnification (A&B) showing the neoplastic growth composed of sheets of small round uniform tumor cells, exhibiting round to oval nuclei, with scant amphophilic cytoplasm and few nucleoli. Large areas of hemorrhage are present in between the tumor cells as well as focal areas of necrosis and many mitotic figures (7/10 HPF). The target cells are positive for CD99 in a diffuse membranous pattern characteristic of A - R tumor (C).

other small MRBCT may be very difficult and requires familiarity with the specific histology and immunohistochemistry of the tumors. Fine Needle Aspiration (FNA) cytology may give a clue about the diagnosis however; true cut Core Tissue Biopsy (CTB) is always needed [30]. The gross macroscopic features of A-R tumor are somewhat variable. The biopsy specimen is often hemorrhagic, widely necrotic and has a tan - grayish appearance. Tumor size rarely exceeds 10 cm in the maximum diameter. The tumor tends to be solid but fragile, multi-lobular and soft in consistency. Calcification is rarely seen despite extensive necrosis. On microscopic examination, the histomorphological spectrum of the specimen ranges from classical to atypical ES and PNET and A-R tumor. Tumor samples show sheets of closely packed, monotonous small round cells arranged in a nested, sheet - like, or solid patterns with fibrous strands dividing them into irregular masses (maximum diameter 14 μm). Typically, the tumor cells show large nuclei, clear and distinct nuclear membrane and ill-defined pale scanty cytoplasm. The nuclei have frequent indentations, small hardly conspicuous, 1-3 nucleoli, variable mitotic activity and areas of necrosis and apoptosis which sometimes give variable biphasic appearance of dark and light cells (Figure 4A, 4B). In general EFT cells usually contain large amounts of glycogen. Diastase pre-digested Periodic Acid Schiff stain (DPAS) may stain the cytoplasmic glycogen positive. DPAS positivity was long considered against the diagnosis of EFT. However, many authors reported DPAS positivity in a significant proportion of their EFT patients. RMS and Lymphoblastic Lymphoma (LL), are excluded by attention to finer details like rosette formation and absence of rhabdomyoblasts [24,32-34].

The tumor stroma is rich in thin walled blood vessels. When associated with abundant necrotic ghost cells, this rich vascularity can be mistakenly interpreted as alveolar RMS or angiosarcoma. In approximately 15% of cases of EFT, the tumor is composed of small round cells arranged in sheets or lobules. The cytoplasm shows small hair-like neurofibrillary processes that coalesce in the center to form circumferential shapes called Homer-Wright Rosettes (HRR) making the diagnosis of PNET. Light microscopic findings of A-R tumor is characterized by a lobular pattern and richly cellular, monomorphic small round blue cells containing vesicular nucleus with coarse chromatin and finely granular quality (primitive "salt and pepper" nucleus) in addition to the pathognomonic HRR. Distinguishing ES from PNET from A-R tumor appears academic [8,32]. A study by Parham et al. from the Department of Pathology, St Jude Children's Research Hospital, Memphis, TN, USA, failed to demonstrate significant outcome differences between the different types of EFT [35].

Under the electron microscope, EFTs demonstrates uniform, densely packed undifferentiated tumor cells. The cytoplasmic is rich in glycogen but contains scarce organelles and occasional desmosome-like junctions. Frequently, the tumors show signs of neural differentiation such as the presence of dense cytoplasmic neurosecretory granules, dendritic processes, and microtubules [36,37].

Prior to the discovery of CD99 (MIC2) immunohisto marker, the diagnosis of EFT was one of exclusion using other stains. CD99

is encoded by the MIC2, a pseudo-autosomal gene, located on the short arm of the sex chromosomes that produces a protein located on the cell membrane called CD99. CD99 staining is >95% sensitive for EFT CD99 stain cells in a diffuse membranous pattern (Figure 4C). EFT including the A-R tumor are rarely negative for CD99. CD99 positivity however is not specific for EFT and may be rarely seen in other tumors such as LL, small cell carcinoma, RMS and desmoplastic small round cells tumor. NBL on the other hand is typically negative for CD99 [24,32].

A particularly challenging task on histomorphology is differentiating EFT from LL. Even on immunohistochemistry there is a degree of overlap as CD99 positivity and FLI1 gene rearrangement has been reported in some cases of LL. Although Leucocyte Common Antigen (LCA) is a more specific marker to LL however, even LCA often fails to solve the puzzle. Only Terminal deoxynucleotidyl Transferase (TdT) which is typically positive in LL can confidently differentiate between the two tumors [38].

EFT is commonly immunoreactive for one or more of the neural markers such as S-100, synaptophysin, CD57, and NSE. EFT may also express occasional positivity for epithelial markers and this positivity may represent a major diagnostic pitfall in the unexperienced hand. Folpe et al. reported that 25% of ES's can demonstrate immunohistochemical positivity for CK AE 1.3, while some others reported positivity in 20% of cases for CK AE 1.3 or CAM 5.2 [32]. The A-R tumor has many histopathologic features in common with other EFT but is characterized by the presence of neurosecretory granules and microtubules on electron microscopy in about 67% of cases. These features help to distinguish it from SS, Liposarcoma (LS) and Undifferentiated Sarcoma (USS). The A-R tumor however can be diagnosed with great certainty based on the microscopic soft tissue parenchymal orientation and the positive staining for CD99, NSE and chromogranin and negativity for Periodic Acid Schiff (PAS) (seen in nearly 80% of cases), in addition to the absence of the dimorphic light and dark cellular pattern and the punched out clear cytoplasmic vacuoles. In many occasions however the true nature of the tumor cannot be precisely determined [22,24,39,40].

Spread of A-R tumor into the BM is clearly caused by hematogenous spread. The BM is often widely infiltrated with the disease but rather in patchy manner. The BM aspiration specimen stained with Leishman or Hematoxylin and Eosin (H&E) may reveal the large, non-hematopoietic, sarcoma cells with hyperchromatic nuclei, high nuclear-cytoplasmic ration, diffuse chromatin pattern, abundant pale blue cytoplasm and coalescing vacuoles. Trephine BM biopsy is generally more sensitive in detecting BM infiltration and may show sheets of mononuclear sarcoma cell arranged in clusters and strongly positive for CD99. The EWS/ETS - oncogene fusion transcripts can be detected in up to 95% of cases and provide tumor-specific diagnostic marker. Using the very sensitive Polymerase Chain Reaction (PCR) or Fluorescent *in situ* Hybridization (FISH) technique minimal amounts of tumor cells contaminating BM can be identified. Nearly 25% of patients with localized EFT have such minimal BM infiltration. However, the significance of detection of this minimal amount of BM involvement remains controversial [41-43].

Cytogenetic and Molecular Features

There are no known genetic syndromes that predispose to the development of any of the EFT. A meta-analysis involving TP53 point mutations in primary, metastatic and relapsed EFT revealed that

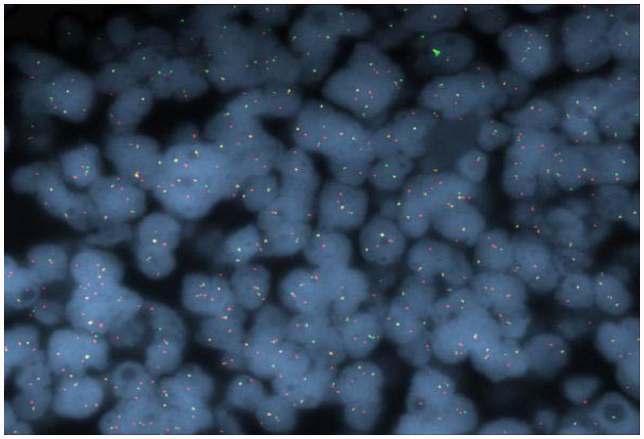

Figure 5: FISH probe of tissue biopsy showing EWSR1 gene rearrangement (22q12). A positive result is indicated by the presence of nucleoli with separated red and green signals or isolate 5' red signals confirming the diagnosis of EFT.

TP53 mutations are detected in only 10% of cases. Across all other sarcomas, EFT was associated with the lowest frequencies of TP53 mutation [44,45].

Molecular gene aberrations are common in EFT including A-R tumor. Molecular studies can be performed using PCR and FISH (Figure 5). These studies can luckily be done on fresh, frozen or even paraffin-embedded tumor tissue. The most frequent translocation in EFT is t (11; 22) (q24; q12), detected in nearly 90% of cases and is considered the whole mark of the diagnosis. This translocation results in fusion of the 3' end of the FLI-1 on chromosome 11q24 with the 5' end of the EWSR1 gene on chromosome 22q12 (EWSR1-FLI1). This translocation causes continuous activation of an onco-protein located in the FLI-1 gene domain, which is capable of DNA binding and subsequent malignant transformation in another 10% of EFT patients, the EWS-ERG gene fusion caused by t (21; 22) (q22; q12) is observed. Very few EFT patients may express the EWS-ETV1 fusion gene caused t (7; 22) (q22; q12) [46,47].

The pathogenetic similarities between EFT of bone and those of soft tissue are mainly attributed to the fact that both harbor the same translocation t (11; 22). There are no clear phenotypic differences between the cases associated with EWSR1-FLI1 and those associated with EWS-ERG gene fusions [8,48,49].

Molecular testing is important in suspected cases of A-R tumors were the classic EFT translocations are not detected. Exclusion of other common sarcoma may help in confirming diagnosis [45,49,50].

Diagnosis

Radiologic features is A-R tumor are distinctive. Plain radiographs, CT and MRI scan often show the large aggressive infiltrative tumor that involve the chest wall, extend into the thoracic cavity and occupies one side of the thoracic cavity. The tumor most commonly originates from the inner side of one of the ribs or the pleura but some originates in the lung. The final diagnosis however, still requires histopathological examination. FNA from the tumor itself or the surrounding pleural fluid may give a clue as to the small round blue cell nature of the tumor. CT scan or U/S guided true cut CTB is often enough to make a solid histopathological diagnosis using conventional morphological and immunophenotypic tests. Open tumor biopsy is seldom performed to obtain adequate material

for proper histopathological and molecular examination [32,39,51].

The light microscopic findings of A-R tumor is characterized by the presence of distinctive cellular cytoplasm and nuclear chromatin giving the primitive "salt and pepper" nuclear appearance, in addition to the presence of the pathognomonic HRR. A-R tumor immunocytochemical profile includes positivity for CD99, chromogranin and NSE and negativity for PAS. The membranous pattern of CD99 positivity is important as CD99 cytoplasmic pattern positivity can be seen in the small cell variant of SS. A small fraction of embryonal RMS patients may show CD99 positivity as well. Therefore, positivity for a second neural marker such as S-100 or synaptophysin and negativity for muscle markers is necessary to exclude RMS. Confirmatory molecular testing using PCR and FISH tests has become standard of care and carries great accuracy however, it is not yet available for use in many laboratories [8,30,32,39].

Differential Diagnosis

The A-R tumor presents a specific clinical presentation in a specific patient's age group. The radiological features are very conspicuous and one can easily suspect the diagnosis. However, the A-R tumor may sometimes pose a big diagnostic challenge as the clinical presentation often mimic other common pediatric disorders, such as Osteomyelitis (OM), empyema, lymphoma, hydatid cyst and tuberculosis. Establishing the correct diagnosis is therefore imperative both for directing treatment and predicting prognosis so as proper counseling is given [30,52,53]. The A-R tumor needs to be differentiated from some other malignant tumors; embryonal RMS, NBL ganglioneuroblastoma and LL, Condition such as OSS, Fibrosarcoma (FS), Epithelial Sarcoma (ESS) and USS. These tumors often show similar imaging features to A-R tumor. The presence of large soft tissue component associated with the bone lesions or a pathological bone fracture is characteristic of all malignant sarcomas. Associated lung, bone, BM or liver metastasis may also occur in all sarcomas. Non-malignant causes such as OM often present diagnostic challenge and are difficult to differentiate from EFT especially in smaller children. Metastatic bone lesions should be seriously considered in the differential diagnosis and the possibility of a primary tumor elsewhere explored. CTB followed by careful histopathological, cytogenetic and molecular testing is therefore the only ways to differentiate between these conditions and establish the correct diagnosis [52,54,55].

Metastatic Disease

When diagnosed, the A-R tumor is commonly localized to the site of origin in the thoracic cavity. The A-R tumor is classified a high-grade sarcoma. In addition to its tendency for local deep tissue invasiveness, the tumor commonly metastasizes to regional and distant sites. Disease metastasis is diagnosed in nearly 25% of patients. Metastatic disease is more commonly seen in older patients and those with large tumor size, common sites of metastasis are the lung (50%), bone (25%), BM (15%) and liver (5%). Metastasis can occur in any bone but metastasis to the vertebra, pelvis and scapula is more common. In few occasions, the patient may have metastatic disease in more than one organ at the same time [51].

Little progress has been made in the treatment of EFT over the last 30 years particularly for those with metastatic disease. The interval compression strategy which was very successful in treating localized tumors had not shown any success in patients with metastasis. The addition of IFO and ETO to the CTR cycles or intensification with High Dose (HD) CTR and Hematopoietic Stem Cell (HSC) support has not improved outcomes of patients with metastatic (except for selected patients with isolated lung relapse) [44,56,57].

BM metastasis is not common in A-R tumor. BM involvement indicates advanced stage disease and carries poor prognosis. In many occasions, the presence is BM infiltration indicates largely resistant and incurable disease. However, BM infiltration does not mean rapidly fatal disease as several patients live with the disease for many years after the diagnosis. Spread of the disease into the BM is clearly caused by hematogenous spread. The BM is often widely infiltrated with the disease but in rather patchy manner. Peripheral blood changes reflecting heavy BM involvement may occur but is not common [41-43].

Staging Systems

To decide the best method for treating A-R tumor, the exact stage of the disease must be known. The A-R tumor in general is typically classified as either localized or metastatic. The tumor is designated "localized" if it only affects the site of origin or directly extends into the surrounding bone, pleura, muscles and tendons. In localized disease, all imaging studies (CT, MRI, PET, Bone scan) in addition to the BM biopsy show no evidence of disease. EFT is designated metastatic when the radiological tests show evidence of disease spread beyond the site of origin. Even when all imaging studies are negative, nearly all patient have some degree of micrometastasis hence the use of CTR is essential.

The formal and commonly used staging system for EFT is the American Joint Committee on Cancer (AJCC) system for classification of bone cancers. There is no specific staging system for A-R tumor however; soft tissue sarcomas including EFT are staged using the TNMG staging system.

The AJCC system classifies the tumor as localized and metastatic and describes the tumor grade using key letters (T, N, M, G).

- T: describes the size of the primary tumor and whether it appears in other areas of the bone.
- N: describes the extent of spread to regional LN's.
- M: indicates whether the tumor has metastasized to other organs of the body such as the lungs, other bones or BM.
- G: describes the grade of the tumor. Low-grade tumor cells look more like normal cells and are less likely to metastasize, while high-grade tumor cells look more aggressive. (All EFT tumors are of high-grade).

The tumor grade is determined using the French Fédération Nationale des Centres de Lutte Contre Le Cancer (FNCLCC) grading system, and is based on 3 factors:

- Differentiation: Sarcoma cells are scored from 1 to 3, A score of 1 is given when the sarcoma cell look close to normal tissue cells. A score of 3 is given when the sarcoma cells look very abnormal and aggressive based on other histopathological criteria (see below).
- Mitotic figure count: The number of sarcoma cell seen actively dividing under the light microscope are given a score from 1 to 3.
- Tumor necrosis: The percentage of the tumor made up of dying necrotic cells is given a score from 0 to 2 [58-61].

Treatment Strategies

Because of rarity of the A-R tumor, there are no separate specific treatment trials for the disease. The disease is treated within the contest of the EFT as skeletal or extraskeletal disease. The best treatment approach for A-R tumor is with the use of CMT; a combination of neoadjuvant CTR, radical surgical resection and/or RT and adjuvant CTR. Several studies have confirmed that aggressive therapy in most occasions is translated into a longer Relapse Free Survival (RFS). When the intent of treatment is curative as in all cases of localized and some cases of metastatic disease, local control measures must be applied, otherwise, the patient chances for long term survival is severely jeopardized. Without the use of radical surgery, RT or both, relapse of the tumor is inevitable. Based on the available data, surgery, in general remains the preferred method of local control over RT [62]. The size of A-R tumor and its invasion into the surrounding vital tissue often precludes effective surgical resection however even partial surgical resection supplemented with adjuvant RT seem to give better DFS. Surgical resection alone or in combination with RT can offer cure, however, more than a third of the patients still relapse. The duration of survival following the first relapse (without active therapy) is <1 year. Second line CTR, second surgery and RT may prolong survival after relapse but cure is not common [63,64].

Chemotherapy (CTR)

Over the last few decades, the use of CTR for treatment of EFT has evolved from the use of single agents into the use of very effective multiagent combinations. VCR, Actinomycin D (ACD) and CPM were initially used. Subsequently Doxorubicin (DOX) and Etoposide (ETO) were added to the treatment protocol. Nowadays, most centers use CMT and start with neoadjuvant CTR to eradicate systemic disease spread and help reduce the tumor size and invasiveness. All patients then receive adjuvant CTR following the application of local control measures such as surgery, RT or both [8,63]. Veronesi et al. summarized the benefits of using neoadjuvant CTR treatment in EFT and indicated that the use of intensive neoadjuvant CTR resulted in reduction of the intraoperative risk of tumor rupture and dissemination and made complete surgical resection much easier. Surgical resection following neoadjuvant CTR allowed negative margins in 71%, compared to 37% of patients who did not receive neoadjuvant CTR. In addition, neoadjuvant CTR before surgery allows assessment of the tumor response in the resected specimens, which has valuable prognostic significance. Patients with good CTR response with tumor necrosis exceeding 90% has a documented better DFS [65].

Current CTR protocols for treatment of EFT include different combinations of six medications {DOX, CPM, VCR, ACD, Ifosfamide (IFO), ETO}. The Intergroup ES study-1 (IESS-1), conducted in the early 1990's has shown that the addition of DOX to VCR, ACD and CPA have significantly improved survival. Patient with localized disease treated with VAC and DOX had a 5-year EFS of 60% [66]. The IESS-II study that was conducted a short time afterwards have shown that in patients with localized EFT, the use of a dose intensified VAC and DOX regime was associated with a higher 5-year EFS (68%) compared to patients received intermediate dose regime (48%) [67]. The National Cancer Institute International ES Study (NCI INT-0091) conducted in the mid 1990's compared the use of a regimen containing VCR, DOX, CPA (VDC) to a regimen containing IFO and ETO in addition (VDC-IE), in patients with localized ES. The 5-year EFS was significantly higher in patients who received the VDC-IE regimen (69%) compared to 54% in patients who received the VDC regimen [68].

As the addition of IFO and ETO to the VDC regimen has resulted in the best recorded EFS and OS in localized EFT and those with lung metastasis. Nowadays the VDC-IE regimen (or a slightly modified regimen) constitute the standard CTR regimen for treatment of EFT across all the major treatment groups Based on these results, the recently published Children's Oncology Group (COG) AEWS0031 study results have shown that interval compression between the VDC-IE courses from 2 to 3 weeks resulted in further improvement in 3-year EFS, which reached up to 76% for localized EFT patients [9,69,70].

The current 5 - drug conventional CTR regimen seems to have reached the ceiling and further improvement of results using the same medications is not expected. Novel drugs are needed to continue improvement. Newer conventional therapies such as Topotecan (TOP), irinotecan and Aldoxorubicin (ADX), a novel pro-drug of DOX demonstrated good activity against EFT and are being investigated. These drugs have also been incorporated into the therapeutic regimens for newly diagnosed EFT patients, [44,63,71,72].

HD CTR followed by HSC support have been thought to have some survival benefits but its use has been largely limited to relapsed and metastatic EFT patients. Results of studies of HD CTR and HSC support should be taken carefully because of the diversity of the patient population and the absence of randomized clinical studies. In addition there are no published trials of use of HD CTR and HSC support in patients with A-R tumor patients specifically. The Euro-Ewing 99 clinical trial have shown slightly improved outcomes in patients with localized ES and high-risk features by using HD CTR with Busulfan (Bu) and Melphalan (Mel) conditioning followed by HSC support. Patients with pulmonary metastasis especially those who have a single metastatic lesion and those with multiple but unilateral disease have better outcomes compared to those with extrapulmonary disease. The 5-year EFS was between 40% to 45%. Patients who has good histological response to induction CTR seem to have better survival however, complete radiological response does not give survival advantage [57,68,69,71,73,74]. A recent comprehensive review by Tenneti et al. from the University of Arizona, Tucson, AZ, USA included twenty-four studies with total of 345 patients with relapsed EFT that received HD CTR with HSC support showed significantly improved outcomes. The reported EFS at 3 to 5 years ranged between 42% to 47% and the OS ranged between 33% to 77% [75].

The standard-of-care 5-drug conventional CTR regimens has little benefit in patients with metastases EFT, those with CTR refractory disease and those with recurrent disease. Recent developments with the use of targeted therapies are promising. The EWS/FLI1 fusion gene is a transcription factor which is essential for EFT growth and development. Based on the EWS/FLI1 capability to up or down regulate specific target genes and transcription factors, EWS/FLI1 and its target genes can offer a good chance to identify new targeted therapies [76]. Immune therapies (adoptive T-cell therapy, vaccines and immune checkpoint blockade) constitute important targets in some types of cancers such as leukemia and breast cancers. Early results of use of immune and targeted therapies in the treatment of EFT are promising. Recently, several newer drugs (pazopanib, trabectedin, and eribulin) received approval by the USA Food and Drug Administration (FDA) for treatment of metastatic sarcomas. The uses of these agents to date have led to marginal improvement

in the Progression-Free Survival (PFS) and OS but did not yet lead to durable responses [77].

The p53 tumor suppressor gene is one of the major body mechanisms to prevention oncogenesis. Most cancers evade the P53 gene suppression effect by creation of a mutated copy of the TP53 gene. TP53 mutations are infrequent in EFT and most tumors express functional wild type TP53 gene. EFT tumors with point mutation of the TP53 are generally associated with a poor outcome. Recent evidence demonstrating the potential of small molecule p53 activators as a promising therapeutic approach for the treatment in EFT with wild-type p53. The strategy had some success at preclinical level [45,78].

Inhibition of Insulin-like Growth Factor I Receptor (IGF1R) signaling and the mammalian Target of Rapamycin (mTOR) pathways has emerged as potential targets in EFT, with some patients showing dramatic therapeutic responses. Combining IGF1R and mTOR inhibitor-based regimens together with upfront CTR in newly diagnosed high-risk EFT patients may clarify the true benefit [79,80].

Bromodomain and Extra-Terminal domain (BET) proteins are key translators of aberrant acetylomes. BET inhibitors are emerging promising treatments in EFT, BET inhibitors were shown to block transcription of the fusion onco-protein in two independent studies resulting in strong down-regulation of EWS-FLI1 in cell lines of EFT and hence suppress tumor activity [63,81].

At present, nivolumab and pembrolizumab are the only two FDA approved anti- programmed cell death receptor-1 (PD-1 (inhibitors for the treatment of advanced melanoma, non-small cell lung cancer and Hodgkin's Lymphoma (HL). PD-1 and PD-L1 receptors have been detected in various subtypes of bone and soft tissue sarcoma tumor cells and they correlate with poor prognosis. Despite the growing preclinical data, the clinical application of anti-PD-1 receptor blockade in EFT remains largely unexplored and is supported by few clinical reports. However larger clinical trials are underway to clarify its role and applications [12,82].

Histone Deacetylase (HDAC) inhibitors have shown good activity in pre-clinical studies in translocation-associated sarcomas such as SS, LS and EFT. Clinical studies have demonstrated enhanced effect of HDAC inhibitors when given in combination with topoisomerase II inhibitors, such as ATC.

The use of these novel agents, together advances in multimodal approaches (including surgery and RT, in addition to introducing novel therapies in the frontline EFT therapy represent the newer strategies for tackling the challenges [63,83].

Local Control Measures

Despite the use of aggressive surgical management, historically the outcome of treatment of EFT had been relatively poor with OS figures between 40% and 60%. Patients with A-R tumor in particular, have lower EFS and OS figures. Difficulties arise from the aggressive nature of the tumor, the degree of local invasiveness and the sometimes, the presence of distant metastasis. However, and in most occasions, it is the size of the tumor and its invasion into the surrounding vital tissue inside or outside the thoracic cavity that precludes effective surgical resection. Most treatment failures are in fact attributed to local invasiveness and metastatic recurrence. Surgical resection alone or in combination with RT offered cure for many patients but local and metastatic relapses are common. Initially, the median survival after surgery and RT was nearly 1 year. Neoadjuvant CTR was therefore advocated in an attempt to clear systemic micro–metastasis and reduce the tumor size to allow effective surgical resection. Results of randomized trials using CTR in addition to surgical resection (with or without RT) have shown much higher cure rates and reduction in the frequencies of local and systemic relapses. The prognoses after using CTR and RT (without surgical resection) were not as good. The use of CTR for treatment of localized ES in addition to local control is now standard [28,63,64].

The choices of local control in metastatic EFT include surgery, RT or both. Patients with isolated lung metastasis has a relatively better outcomes than patients with bone or BM metastasis [84-86].

Surgical Management

Complete surgical resection is always the goal in A-R tumor. However, in many occasions local invasiveness of the tumor precludes effective primary surgical resection. The available date generally favor radical surgical resection over RT. Surgical strategy should include radical resection of the tumor, including the rib levels involved in addition to the adjacent inferior and superior ribs, muscle and all the adherent soft tissue, targeting a tumor - free margins of 3 cm to 4 cm. difficulties arise in smaller children where there is no enough normal tissue to remove from around the tumor and supplementary RT may then become necessary. Chest wall reconstruction is then undertaken using muscle flaps or muscular tissue. When the lung parenchyma is involved, a lobectomy or pneumonectomy should then be performed [28]. As long as the tumor shows good response to neoadjuvant CTR and the surgical resection was complete, the pre-treatment tumor size has not been shown to have significant effect on the final outcome. Complete surgical resection improves the chances of local control and prolongs DFS in localized A-R tumor. However, the chances for development of local recurrences although small, remain a threat. Patients who respond well to neoadjuvant CTR usually have the best outcomes following surgery. Because of the risk of long-term complications and especially when planning surgery for smaller children, it is important for the surgeon to plan for the potential child growth following the surgery [87-89].

Patients with isolated lung metastasis generally have better outcomes than patients with bone and BM metastasis. Therefore, complete surgical resection of the local tumor and depending on the number and location of the lung lesions surgical resection is performed. When the lung lesions are numerous, RT is applied instead. RT dose of 14 Gy to 18 Gy is very effective in controlling metastatic lung lesions. Patients who received lung RT had better outcomes than those who did not however; there is significant risk of long-term lung complications. Despite the known poor prognosis of metastatic EFT, surgical resection of the primary tumor has been shown to improve OS. Patients who present with metastasis to the other bones and BM have low OS figures of 10% to 15% at 3-years. Although few retrospective studies have shown slightly better outcomes with complete surgical resection of the primary tumor, local control is practically limited to RT and in most occasions the aim will be palliation rather than cure [88,89]. Ren et al. from the Department of Orthopedics, The Affiliated Yangming Hospital of Ningbo University, Yuyao People's Hospital of Zhejiang Province, Yuyao, Zhejiang, P.R. China used the Surveillance, Epidemiology, and End Results SEER database to identify 643 patients with metastatic EFT of the bone between 1973 to 2015. The OS and Cancer-Specific Survival (CSS) rates at 5-years were 33.1% and 34.3%, respectively. Surgical

resection of the primary tumor and age <20 years were significantly associated with improved OS. RT used as definite therapy alone was associated with significantly reduced OS and CSS compared with complete surgical resection alone. Combined surgery and RT of the primary tumor did not show any improvement in the OS compared with surgery alone [86].

Chest Wall Reconstruction

Extensive surgical resection in cases of locally invasive A-R tumor increases surgical morbidity and mortality and result in large thoracic wall full thickness tissue defects and hence increase the chances for infections. Reconstruction of the excised tumor site is therefore an important part of the surgical care. Gap coverage using soft tissue flaps is determined by the quality of soft tissue available and the status of the vascular pedicle supplying the flaps [90-92].

The main goals of chest wall reconstruction after surgery are tight closure of the chest cavity and good stability. The first choice for use is pedicled muscular and musculocutaneous flaps such as latissimus dorsi, pectoralis and vertical or transverse rectus abdominis muscles. Large chest wall defects have been successfully reconstructed using combination of latissimus dorsi muscle flaps in addition to a biomaterial. A free flap (tensor fascia latae, anterolateral thigh, transverse rectus abdominis, omental and deep epigastric perforator) reconstruction may be rarely used if local options are not reliable. Pure artificial biomaterial meshes may sometimes be used to cover large surgical defects and give the necessary stability. Methyl methacrylate cement embedded between two layers of mesh, or one or two rib grafts fixed to the mesh may also be added to grant stability and prevent paradoxical chest movements [93,94]. Girelli et al. retrospectively analyzed the outcomes of 30 pediatric and adolescent patients (21 males and 9 females) who underwent chest wall reconstruction for malignant tumors at Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy, over a period of 30-year. The endpoints were survival, recurrences, and long-term outcomes. The median age was 13.7 years. Eleven patients (37%) presented with a chest wall mass and 26 (87%) of them had EFT. Twenty-eight (94%) received neoadjuvant CTR after histologic diagnosis. One rib was resected in 13 cases (43%); 2 or 3 contiguous ribs in 8 cases (26.6%). The rate of complications was 40% but no postoperative mortality was observed. Relapse occurred in 7 patients (23%). The OS and DFS at 5-years were 85.2% and 82% years [95].

Radiation Therapy

EFT's are very sensitive to RT. RT doses ranging between 36 Gy and 60 Gy were initially used as the sole treatment to control the disease. Despite the ability of such doses to eradicate viable tumor cells, local and metastatic relapses were common. The introduction of adjuvant CTR regimens coupled with improvement in RT and surgical techniques improved outcomes significantly. The European Ewing's Sarcoma CESS 8 and 86 and the Pediatric Oncology Group (POG) 8,346 studies have shown that the effectiveness of RT is significantly enhanced by the quality of RT planning and delivery techniques. Current standard RT techniques involve the use of linear accelerators to deliver external beam RT in 1.8 Gy fractions via conformal or intensity modulated or less commonly interstitial brachytherapy techniques. RT field and volume are decided based on the pre-treatment CT and MRI scans. The treatment should involve a standard RT dose to the pre-treatment tumor bed with a 1 cm to 2 cm margin and a boost to the post-treatment tumor size. Patients receiving definitive RT will usually receive a dose of 45 Gy to the pre-treatment volume. Patients with larger tumors (>8 cm) receive an approximate dose of 65 Gy and patients with smaller tumors (<8 cm) receive a dose of 55.8 Gy directed to the post-treatment volume. Brachytherapy is commonly delivered in a dose of 15 Gy to 20 Gy. When brachytherapy and external beam RT are used in combination, a total cumulative RT dose of 45 Gy to 60 Gy is given [87,96].

The use of RT as the sole method for local control for A-R tumor is rare and requires careful consideration. RT is only used as definite treatment when surgical resection is deemed totally unsafe due to big tumor size and deep tissue invasiveness or if the aim of the treatment is palliative. Several international randomized trials have shown inferior outcomes with higher local relapse rates when RT was used as the sole local control measure compared to complete surgical resection or combined surgery and RT (local failure rates exceeding 30%). RT however, is currently mainly employed to treat patients with very extensive tumors that cannot be removed with save margins, and in situations where tumor response to neoadjuvant CTR was suboptimal (necrosis <90%) [97,98].

Neoadjuvant RT is sometimes employed to boost the effect of CTR and reduce tumor size allowing for complete surgical resection. Neo-adjuvant RT is given in an approximate dose of 46 Gy to 50.5 Gy delivered to the pre-treatment tumor volume. In patients with lung metastasis, RT dose of 14 Gy to 18 Gy is very effective in controlling lung lesions. Patients with bone metastasis and depending on the site may require doses up to 50 Gy to effectively control the disease [89,96]. Wilkins et al. from the Luke's Medical Center, Denver, CO, USA, reported a 5-year EFS rate of only 27% of patients that received RT alone for local control whereas patients treated with surgery and RT had 5-year EFS of 72% [99].

Disease Relapse

Less than 2/3 of patients with A-R tumor are cured of the disease. However, at least 40% of patients with localized disease will still develop local or metastatic recurrence at variable time intervals and die as a result of the disease. Common findings at relapse are local chest wall masses, lung infiltrates, and enlarged paratracheal and mediastinum LN. Metastasis to the bone, BM, liver, adrenal glands, or the retroperitoneal space can rarely occur. Published data on the long-term outcome of non-metastatic EFT report a time range of 2 to 10 years between commencing treatment and the development of recurrence [63,100].

Treatment of localized late A-R tumor relapse (>2 years since initial diagnosis) involves the use of second line CTR in addition to local control measures. Aggressive treatment steps may not be suitable for patients with metastatic relapse or those with early (<2 years) local relapse and second line CTR and RT may be enough to slow down the disease and control symptoms [71].

The combination of Gemcitabine (GEM), Docetaxel (DCT) has shown good activity against metastatic and relapsed soft tissue sarcoma. The potency has been further enhanced by the addition of the antiangiogenic agent bevacizumab. The PFS was reported in one study to be 76% at 3 months however, survival figures has declined steadily thereafter. TOP was tested in Phase II trials against relapsed EFT. Various schedules of administration have been evaluated, including the continuous 24-h infusion for 72 h. The best results were achieved when TOP was used as daily 30-min infusion for 5 days together with CPA. Results of studies of use of HD CTR and HSC

support for treatment of relapsed EFT have shown some promise for selected patients especially those with late local relapse and those with isolated lung metastasis with slightly improved EFS and OS figures. Late local or metastatic recurrence still occurs in some cases of EFT even after very long time of completing therapy [R. Tenneti P, Dancsok AR]. Hanna et al. from Royal National Orthopedic Hospital, Stanmore, Middlesex, UK, reported 2 cases of localized EFT who relapsed 16 and 19 years after receiving CMT. When the CMT (CTR, surgery, RT) fail, there are few - if any-effective salvage options available [101]. Repeated surgical resection may also be undertaken for local relapses especially when the patient's general health is maintained. Intraoperative RT has been used for treatment of recurrent A - R tumor with relatively good results [102,103].

Prognosis

Survival data of pediatric patients with A-R tumor is scarce. Most results are extrapolated from small size case series retrospective reports therefore, the outcomes are very variable. Some case series report poor outcomes but some others surprisingly report outcomes that exceed the outcomes known for EFT affecting other body sites. Over the past three decades, the outcome of treatment of EFT patients who are non-metastatic at presentation has improved considerably mainly as a result of proper use of CMT. Outcomes of treatment of EFT are considerably worse for those with pelvic bone involvement, large size tumors, poor tumor response to CTR, metastatic disease and those patients with disease recurrence [12,104]. The overall 5-year DFS for localized ES treated with surgery, RT, and multi-agent CTR is approximately 70%. In contrast, patients with metastases have a 5-year DFS rate of approximately 20% to 30% [105]. Laskar et al. from TATA Memorial Hospital, Mumbai, India, reported the treatment results of their 72 patients of A-R tumor treated between 1995 and 2003. Male to female ratio 2.3:1. All patients received CTR and local therapy; surgery alone, radical RT alone, or a combination of surgery and RT. A total of 32 patients (40%) received all three modalities, 21 (27%) received CTR and RT, and 19 (24%) received CTR followed by surgery only. Distant metastasis was diagnosed in 25% of patient. After a median follow-up of 28 months, local control, DFS, and OS rates were 67%, 36%, and 45%, respectively. The median time to relapse was 25 months; the median survival was 76 months. Multivariate analysis revealed that poor response to induction CTR, the presence of pleural effusion and age ≥ 18 years as indicators of inferior survival. Patients with metastatic disease at presentation had EFS and OS of 4% and 14% at 5-years, respectively. CMT with neoadjuvant CTR, surgery, and RT gave the best treatment results [26].

Before the introduction of CTR in the early 1970's, the median EFT patient survival was 8 months. Using the current 5 - drug regimen has improved the 5-year EFS into between 60% and 70%. Compression of the interval of administration of the same 5 - drug regimen courses from 3 to 2 weeks resulted in further improvement in 3-year EFS, which reached up to 76% for patients with localized disease [69,106]. Fathalla from the National Cancer Institute, Cairo University, Egypt reported a case series of 30 A-R tumor patients treated between 2011 and 2015. There were 19 males and 11 females, all were <18 years of age. The disease affected the ribs in 22 scapula 5, clavicle 2 and sternum 1. Metastasis was diagnosed in 7 patients and 23 had localized disease. All patients received neoadjuvant CTR followed by surgery (17 patients), radical RT (3 patients) or both (9 patients). One patient with lung metastasis received no local control. The OS at 5 years was 45.6% and the DFS was 40.6% at 5 years [107].

The prognostic significance of tumor volume, tumor site (pelvic/non pelvic, axial/extremity, bone/soft tissue), tumor response to CTR and choice of local treatment option) in localized EFT has been recognized long ago. These factors still carry the same significance to dates and that was proved in the recent clinical trials [108-111]. Sirivella, from the Newark Beth Israel Medical Center, University of Medicine and Dentistry of New Jersey, Newark, NJ, USA reported the outcome of the 23 patients (median age 29.5 years) with PNET (15 chest wall, 4 lung, 3 costovertebral sulcus and 1 anterior mediastinum) treated in their hospital between 1980 and 2010. The 19 patients with localized disease were treated with surgical resection and adjuvant CTR and RT. The 4 patients with metastasis were treated with CTR and RT only. The tumor recurred in 4 patients. The DFS for the whole group was 82 %. At 5 and 64% tat 10 years. Patients with stage I disease has DFS of 86% compared to patients with stage III disease who have DFS of 63% at 10 years [112]. Saenz, from the From the Departments of Surgery and Pediatrics, Memorial Sloan Kettering Cancer Center, New York, NY reported their experience with 20 patients with A-R tumor (median age 12 years) treated between 1979 and 1998. All patients were treated according to an institutional multi-agent CTR protocol. Twelve (12) patients had surgery with varying degree of chest wall resection. A total of 15 patients received adjuvant RT. Eleven patients were alive and free of disease after a follow up period of 7-years giving an EFS of 55% [113].

Despite aggressive CMT, results of treatment of metastatic EFT are poor with DFS rates ranging between 20% to 30%. The outcome is even worse for those who relapse within two years of diagnosis. Local recurrence and remote metastases are common in A-R tumors. Recurrent disease generally carries poor prognosis and the likelihood of long-term survival is less than 20%.

The TP53 gene mutation was proved by Huang et al to represent the strongest independent prognostic marker in EFT. Using a combined immunohistochemistry, Genechip and sequencing techniques, he studied 60 EFT to detect TP53 mutations and analyzed it using multivariate analysis. TP53 mutations were detected in 8 of the 60 cases (13.3%). All eight patients expressing mutant p53 gene died within 21 months of diagnosis. The mean survival after diagnosis was 11 months, as compared to a mean survival of 99 months for patients with wild-type p53 mutation [78].

Treatment Related Complication

Treatment of A-R tumor is often long and complicated. Successful management requires the use of substantial amount of multiagent CTR in addition to local control measures. As a result, the treatment is associated with numerous potential severe short- and long-term side effects. Complications may develop early with the introduction of CTR. Myelosuppression places the patient at increased risk of infection, anemia and bleeding tendency. After administration of several cycles of CTR, specific organ toxicity such as cardiac, liver and renal impairment may start to appear.

ATC induced cardiac toxicity is a potential major side effects that can severely adversely affect the patient quality of life. Regular screening with echocardiogram and Electrocardiograms (ECG) must be performed at regular intervals. VCR neurotoxicity manifests as ptosis, foot drop, or even motor polyneuropathy. In addition to severe myelosuppression, CPA and IFO therapy may result in hemorrhagic cystitis and encephalitis [114,115].

Patients with A-R tumor require regular follow-up in order to detect long-term complications. There is clear association between therapeutic exposures and specific long-term complications such as cardiac, pulmonary, endocrine, growth impairment, reduced fertility musculoskeletal complications and Second Malignant Neoplasms (SMN). Patients are in danger of developing acute leukemia's and lymphomas especially after administration of alkylators such as CPA, IFO and ETO [9,114].

Radical surgical resection and reconstruction for the treatment of A-R tumor can be lifesaving. Surgical resection may result in wider tissue removal from the thoracic bones, muscles, pleura or even lung tissue. The consequences of such surgeries may be tremendous on the patient's quality of life afterwards especially if RT is added. Whether used alone or as an adjunct to CTR and surgery, RT remains an important factor for improving cure rates and long-term survival. Despite its efficacy, RT is associated with several short and long-term complications; osteopenia, pathological fractures and osteoradionecrosis. RT-induced SMN such as OSS, RMS, EFT and USS is rare, but serious complications [92,116,117].

Future Prospects

The A-R tumor is a very aggressive malignancy with modest survival rates. For any chance of long-term survival, the tumor should be treated aggressively. The outcome of therapy is modest. Patients with relapsed and metastatic A-R tumor has very poor outcomes. Further improvement in the outcomes is not expected with the currently available therapies. The currently available conventional CTR combinations are potentially associated with severe organ toxicity that limits use. Phase II therapies targeting the newly discovered biological and genetic pathways are the only hope in making the breakthrough and improve survivals [80].

Biological studies of EFT have been started long years ago and all the developments reached are in fact related to the extensive studies performed. Over the last 3 decades, the COG has created successive EFT biology studies and tissue banking protocols in which they collect high quality tumor specimens that were subsequently distributed to researchers to perform basic science investigation [118]. FLI1 is the most common translocation partner of EWSR1, the oncogenic fusion protein driving EFT development and progression. For full recovery, FL11 requires binding to transcriptional cofactor RNA helicase A. YK-4-279, a small molecule that blocks the interaction between FLI1 and the RNA helicase A, was tested in EFT cell line xenograft and resulted in significant tumor regression when given in daily doses [119,120]. Enhancing the TP53 suppression pathway, silencing of EWS-FLI1 gene expression and the TWIST1 gene fusion and targeting them with the appropriate medication are possible promising treatment mechanisms. Exploring the potential effect of the Nutlin-3a small molecules antitumor activity and IGF-1 receptor inhibition seems to have the most promising future prospects in improving the outcome of treatment of EFT [45,105,121].

Conclusion

The A-R tumor is a rare member of the EFT that affects the thoracopulmonary region. The diagnosis is obvious in most occasions however it may rarely be mysterious. Radiological tests such as plain radiographs, CT, MRI, Bone scan and FDG-PET scan play an important role is suspecting the diagnosis and precisely identify the extent of local invasiveness and metastasis. The combination of morphology, immunohistochemistry, and more recently molecular genetics has very much improved the diagnostic yield. The best treatment results are achieved with CMT using CTR, surgery and/or RT. The outcomes after complete surgical resection are clearly superior to RT. The prognosis is generally poor however most published data is extrapolated from variable size case series. Variable results were reported by different authors with the wide-range of OS and DFS figures ranging between 45% to 60% and 60% to 85%. Results for metastatic and relapsed disease and tumors that show poor response to induction CTR remains very poor with DFS rates of around 10% to 15% at 3-years. HD CTR followed by HSC support showed marginal benefits in patients with localized disease and those with lung relapse. Results with conventional CTR seem to have plateaued. Very little progress has been made in the outcomes. Grouping patients into randomized controlled trials provides optimal study environment. More refined CTR combinations, better surgical approaches and newer RT modalities and the use of new targeted medications may improve the outcomes. Early studies are showing some promise in cell lines and animal models however human trials is yet to be concluded.

References

1. Watt AJ. Chest wall lesions. Paediatr Respir Rev. 2002;3(4):328-38.
2. Carter BW, Benveniste MF, Betancourt SL, de Groot PM, Lichtenberger JP, Amini B, et al. Imaging evaluation of malignant chest wall neoplasms. Radiographics. 2016;36(5):1285-306.
3. Tazi I, Zafad S, Madani A, Harif M, Quessar A, Benchekroun S. Askin tumor: A case report with literature review. Cancer Radiother. 2009;13(8):771-4.
4. Mohandas KM, Chinoy RF, Merchant NH, Lotliker RG, Desai PB. Malignant small cell tumour (Askin -Rosai) of the pericardium. Postgrad Med J. 1992;68(796):140-2.
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(6):2438-51.
6. Ewing J. Diffuse endothelioma of bone. Proceedings of the New York Pathology Society. 1921;21:17-24. CA Cancer J Clin. 1972;22(2):95-8.
7. Seemayer TA, Theimo WL, Bolande RF, Wiglesworth FW. Peripheral neuroectodermal tumor. Perspect pediatr Pathol. 1975;2:151-72.
8. Hameed M. Small round cell tumors of bone. Arch Pathol Lab Med. 2007;131(2):192-204.
9. Ozaki T. Diagnosis and treatment of Ewing sarcoma of the bone: A review article. J Orthop Sci. 2015;20(2):250-63.
10. Shamberger RC, LaQuaglia MP, Gebhardt MC, Neff JR, Tarbell NJ, Marcus KC, et al. Ewing sarcoma/primitive neuroectodermal tumor of the chest wall: Impact of initial versus delayed resection on tumor margins, survival, and use of radiation therapy. Ann Surg. 2003;238(4):563-8.
11. Saenz NC, Hass DJ, Meyers P, Wollner N, Gollamudi S, Bains M, et al. Pediatric chest wall Ewing's sarcoma. J Pediatr Surg. 2000;35(4):550-5.
12. Thanindratarn P, Dean DC, Nelson SD, Hornicek FJ, Duan Z. Advances in immune checkpoint inhibitors for bone sarcoma therapy. J Bone Oncol. 2019;15:100221.
13. Casaroto AR, Sampieri MB, Soares CT, Santos PS, Yaedu RY, Damante JH, et al. Ewing's sarcoma family tumors in the jaws: Case report, immunohistochemical analysis and literature review. *In Vivo*. 2017;31(3):481-91.
14. Fiorentino A, Chiumento C, Caivano R, Fusco V. Ewing sarcoma of the thoracic wall in a 54-year-old man. Tumori. 2012;98(1):e10-2.

15. Takagi-Takahashi Y, Shijubo N, Yamada G, Saitoh E, Sawada K, Ohnishi T, et al. Peripheral primitive neuroectodermal tumor of the chest wall of a 69-year-old man. Intern Med. 2004;43(7):578-81.

16. Gedik GK, Sari O, Altinock T, Tavli L, Kaya B. Askin's tumor in an adult: Case report and findings on 18FDG PET/CT. Case Reports Medicine. 2009.

17. Tanveer N, Kaur N, Mishra K, Wadhwa N, Singh N. Is it Askin Tumour? A question you must ask even in elderly. J Clin Diagn Res. 2014;8(10):FD21-3.

18. Gogna S, Parshad S, Karwasra RK, Goyal P, Gogna S. Bilateral synchronus Askin's Tumor - case report & review of literature. Indian J Surg Oncol. 2016;7(1):124-6.

19. Fletcher CD, Hogendoorn P, Mertens F, Bridge J. WHO Classification of Tumors of Soft Tissue and Bone. 4th ed. Lyon, France: IARC Press; 2013.

20. Doyle LA. Sarcoma classification: An update based on the 2013 World Health Organization classification of tumors of soft tissue and bone. Cancer. 2014;120(12):1763-74.

21. Tateishi U, Gladish GW, Kusumoto M, Hasegawa T, Yokoyama R, Tsuchiya R, et al. Chest wall tumors: Radiological findings and pathological correlation. Radiographics. 2003;23(6):1491-508.

22. Shishikura V, Ushigome S, Shimoda T. Primitive neuroectodermal tumors of bone and soft tissue: Histological subclassification and clinicopathologic correlations. Acta Pathol Jpn. 1993;43(4):176-86.

23. Laine M, Ghorfi IA, Lambatten D, Kettani F, Abid A. Rapidly fatal Askin's tumor: A case report and literature review. Pan Afr Med J. 2014;18:104.

24. Parikh PM, Charak BS, Banavali SD, Advani SH, Saikia TK, Gopal R, et al. Treatment of Askin Rosai tumor - need for a more aggressive approach. J Surg Oncol. 1988;39(2):126-8.

25. Dickinson J, Watts AC, Robb JE. Extra-osseous Ewing's sarcoma. J Bone Joint Surg. 2009;91-B (Suppl 11):215.

26. Laskar V, Nair C, Mallik S, Bahl G, Pai S, Shet T, et al. Prognostic factors and outcome in Askin-Rosai tumor: A review of 104 patients. Int J Radiat Oncol Biol Phys. 2011;79(1):202-7.

27. Patterson FR, Basra SK. Ewing's sarcoma. In: Schwartz HS, editor. Orthopaedic knowledge update: musculoskeletal tumors 2. Rosemont: American Academy of Orthopedic Surgeons. 2007:175-83.

28. Demir A, Gunluoglu MZ, Dagoglu N, Turna A, Dizdar Y, Kaynak K, et al. Surgical treatment and prognosis of primitive neuroectodermal tumors of the thorax. J Thorac Oncol. 2009;4(2):185-92.

29. Györke T, Zajic T, Lange A, Schäfer O, Moser E, Makó E, et al. Impact of FDG PET for staging of Ewing sarcomas and primitive neuroectodermal tumours. Nucl Med Commun. 2006;27(1):17-24.

30. Gulati D, Bahal A, Dhar AK, Chakravorty N, Muttagikar MP, Lakhtakia R. Askin Rosai Tumour. Med J Armed Forces India. 2007;63(3):284-5.

31. Winer-Muram HT, Kauffman WM, Gronemeyer SA, Jennings SG. Primitive neuroectodermal tumors of the chest wall (Askin tumors): CT and MR findings. Am J Roentgenol. 1993;161(2):265-8.

32. Folpe AL, Goldblum JR, Rubin BP, Shehata BM, Liu W, Dei Tos AP, et al. Morphologic and immunophenotypic diversity in Ewing family tumors: A study of 66 genetically confirmed cases. Am J Surg Pathol. 2005;29(8):1025-33.

33. Noguera R, Triche TJ, Navarro S, Tsokos M, Llombart-Bosch A. Dynamic model of differentiation in Ewing's sarcoma cells. Comparative analysis of morphologic, immunocytochemical, and oncogene expression parameters. Lab Invest. 1992;66(2):143-51.

34. Llombart-Bosch A, Machado I, Navarro S, Bertoni F, Bacchini P, Alberghini M, et al. Histological heterogeneity of Ewing's sarcoma/PNET: An immunohistochemical analysis of 415 genetically confirmed cases with clinical support. Virchows Arch. 2009;455(5):397-411.

35. Parham DM, Hijazi Y, Steinberg SM, Meyer WH, Horowitz M, Tzen CY, et al. Neuroectodermal differentiation in Ewing's sarcoma family of tumors does not predict tumor behavior. Hum Pathol. 1999;30(8):911-8.

36. Suh CH, Ordóñez NG, Hicks J, Mackay B. Ultrastructure of the Ewing's sarcoma family of tumors. Ultrastruct Pathol. 2002;26(2):67-76.

37. Franchi A, Pasquinelli G, Cenacchi G, Rocca CD, Gambini C, Bisceglia M, et al. Immunohistochemical and ultrastructural investigation of neural differentiation in Ewing sarcoma/PNET of bone and soft tissues. Ultrastruct Pathol. 2001;25(3):219-25.

38. Lucas DR, Bentley G, Dan ME, Tabaczka P, Poulik JM, Mott MP. Ewing sarcoma *vs.* lymphoblastic lymphoma. A comparative immunohistochemical study. Am J Clin Pathol. 2001;115(1):11-7.

39. Gu M, Antonescu CR, Guiter G, Huvos AG, Ladanyi M, Zakowski MF. Cytokeratin immunoreactivity in Ewing's sarcoma: Prevalence in 50 cases confirmed by molecular diagnostic studies. Am J Surg Pathol. 2000;24(3):410-6.

40. Sawin RS, Conrad U, Park JR, Waldhausen JHT. Pre-resection chemotherapy improves survival for children with Askin tumor. Arch Surg. 1996;131(8):877-80.

41. Mansoori H, Moiz B. Extensive marrow infiltration in epidural Ewing sarcoma. Blood Res. 2016;51(3):156.

42. Chauhan K, Jain M, Grover S, Shukla P, Rusia U, Grover RK. Bone marrow metastasis in nonhematologic malignancies: Data from a cancer hospital. Clin Cancer Invest J. 2016;5(2):103-9.

43. Özpolat HT, Yilmaz E, Goksoy HS, Özpolat S, Dogan O, Unal SN, et al. Detection of bone marrow involvement with FDG PET/CT in patients with newly diagnosed lymphoma. Blood Res. 2018;53(4):281-7.

44. Bailey K, Cost C, Davis I, Glade-Bender J, Grohar P, Houghton P, et al. Emerging novel agents for patients with advanced Ewing sarcoma: A report from the Children's Oncology Group (COG) new agents for Ewing sarcoma task force. F1000Res. 2019;8:F1000 Faculty Rev-493.

45. Neilsen PM, Pishas KI, Callen DF, Thomas DM. Targeting the p53 pathway in Ewing sarcoma. Sarcoma. 2011;2011:746939.

46. Delattre O, Zucman J, Plougastel B, Desmaze C, Melot T, Peter M, et al. Gene fusion with an ETS DNA-binding domain caused by chromosome translocation in human tumours. Nature. 1992;359(6391):162-5.

47. Turc-Carel C, Philip I, Berger MP, Philip T, Lenoir G. Chromosomal translocation (11; 22) in cell lines of Ewing's sarcoma. C R Seances Acad Sci III. 1983;296(23):1101-3.

48. Ladanyi M. EWS-FLI1 and Ewing's sarcoma: Recent molecular data and new insights. Cancer Biol Ther. 2002;1(4):330-6.

49. de Alava E, Pardo J. Ewing tumour: Tumour biology and clinical applications. Int J Surg Pathol. 2001;9(1):7-17.

50. Bridge RS, Rajaram V, Dehner LP, Pfeifer JD, Perry A. Molecular diagnosis of Ewing sarcoma/primitive neuroectodermal tumor in routinely processed tissue: A comparison of two FISH strategies and RT-PCR in malignant round cell tumors. Mod Pathol. 2006;19(1):1-8.

51. Xu Q, Xu K, Yang C, Zhang X, Meng Y, Quan Q. Askin tumor: Four case reports and a review of the literature. Cancer Imaging. 2011;11(1):184-8.

52. Gaspar N, Di Giannatale A, Geoerger B, Redini F, Corradini N, Enz-Werle N, et al. Bone sarcomas: From biology to targeted therapies. Sarcoma. 2012;2012:301975.

53. Kabiri E, Al Bouzidi A, Kabiri M. Askin tumor mimicking a hydatid cyst of the lung in children: Case report. Pan Afr Med J. 2014;17:131.

54. Liang C, Mao H, Tan J, Ji Y, Sun F, Dou W, et al. Synovial sarcoma: Magnetic resonance and computed tomography imaging features and differential diagnostic considerations. Oncol Lett. 2015;9(2):661-6.

55. Guan YB, Zhang WD, Zeng QS, Chen GQ, He JX. CT and MRI findings of thoracic ganglioneuroma. Br J Radiol. 2012;85(1016):e365-72.

56. Kolb EA, Kushner BH, Gorlick R, Laverdiere C, Healey JH, LaQuaglia MP, et al. Long-term event free survival after intensive chemotherapy for Ewing family of tumors in children and young adults. J Clin Oncol. 2003;21(18):3423-30.

57. Miser JS, Krailo MD, Tarbell NJ, Link MP, Fryer CJH, Pritchard DJ, et al. Treatment of metastatic Ewing's sarcoma or primitive neuroectodermal tumor of bone: Evaluation of combination of ifosfamide and etoposide - A children's cancer group and Pediatric Oncology group study. J Clin Oncol. 2004;22(14):2873-6.

58. Tanaka K, Ozaki T. New TNM classification (AJCC eighth edition) of bone and soft tissue sarcomas: JCOG bone and soft tissue tumor study group. Jpn J Clin Oncol. 2019;49(2):103-7.

59. Cates JMM. The AJCC 8th edition staging system for soft tissue sarcoma of the extremities or trunk: A cohort study of the SEER database. J Natl Compr Canc Netw. 2018;16(2):144-52.

60. Coindre JM. Grading of soft tissue sarcomas, review and update. Arch Pathol Lab Med. 2006;130(10):1448-53.

61. Khoury JD, Coffin CM, Spunt SL, Anderson JR, Meyer WH, Parham DM. Grading of non-rhabdomyosarcoma soft tissue sarcoma in children and adolescents: A comparison of parameters used for the FNCLCC and POG systems. Cancer. 2010;116(9):2266-74.

62. Christiansen S, Semik M, Dockhorn-Dworniczak B, Rötker J, Thomas M, Schmidt C, et al. Diagnosis, treatment and outcome of patients with Askin tumors. Thorac Cardiovasc Surg. 2000;48(5):311-5.

63. Dancsok AR, Asleh-Aburaya K, Nielsen TO. Advances in sarcoma diagnostics and treatment. Oncotarget. 2017;8(4):7068-93.

64. Schöffski P, Cornillie J, Wozniak A, Li H, Hompes D. Soft tissue sarcoma: An update on systemic treatment options for patients with advanced disease. Oncol Res Treat. 2014;37(6):355-62.

65. Veronesi G, Spaggiari L, De Pas T, Solli PG, De Braud F, Catalano GP, et al. Preoperative chemotherapy is essential for conservative surgery in Askin's tumor. J Thorac Cardiovas Surg. 2003;125(2):428-9.

66. Nesbitt KA, Vidone RA. Primitive neuroectodermal tumor (neuroblastoma) arising in sciatic nerve of a child. Cancer. 1976;37(3):1562-70.

67. Burgert EO Jr, Nesbit ME, Garnsey LA, Gehan EA, Herrmann J, Vietti TJ, et al. Multimodal therapy for the management of nonpelvic, localized Ewing's sarcoma of bone: Intergroup study IESS-II. J Clin Oncol. 1990;8(9):1514-24.

68. Grier HE, Krailo MD, Tarbell NJ, Link MP, Fryer CJH, 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(8):694-701.

69. Womer RB, West DC, Krailo MD, Dickman PS, Pawel B. Randomized comparison of every-two-week *vs.* every three-week chemotherapy in Ewing sarcoma family tumors (ESFT). J Clini Oncol. 2008;26(15):10504.

70. Le Deley MC, Paulussen M, Lewis I, Brennan B, Ranft A, Whelan J, et al. Cyclophosphamide compared with ifosfamide in consolidation treatment of standard-risk Ewing sarcoma: Results of the randomized noninferiority Euro-EWING99-R1 trial. J Clin Oncol. 2014;32(23):2440-8.

71. Wagner LM. Fifteen years of irinotecan therapy for pediatric sarcoma: where to next? Clin Sarcoma Res. 2015;5:20.

72. Chawla SP, Papai Z, Mukhametshina G, Sankhala K, Vasylyev L, Fedenko A, et al. First-line aldoxorubicin *vs.* doxorubicin in metastatic or locally advanced unresectable soft-tissue sarcoma: A phase 2b randomized clinical trial. JAMA Oncol. 2015;1(9):1272-80.

73. Granowetter L, Womer R, Devidas M, Krailo M, Wang C, Bernstein M, et al. Dose intensified compared with standard chemotherapy for non-metastatic Ewing sarcoma family of tumors: A children's oncology group study. J Clin Oncol. 2009;27(15):2536-41.

74. Ladenstein R, Hartmann O, Pincerton R, Dalloroso G, Burdach S, Jurgens H, et al. A multivariate and matched pair analysis on high-risk Ewing tumors patients treated by megatherapy and stem cell reinfusion in Europe. Proc Annu Meet Am Soc Clin Oncol. 1999;18:555(Abstract).

75. Tenneti P, Zahid U, Iftikhar A, Yun S, Sohail A, Warraich Z, et al. Role of high-dose chemotherapy and autologous hematopoietic cell transplantation for children and young adults with relapsed Ewing's sarcoma: A systematic review. Sarcoma. 2018;2018:2640674.

76. Cidre-Aranaz F, Alonso J. EWS/FLI1 target genes and therapeutic opportunities in Ewing sarcoma. Front Oncol. 2015;5:162.

77. Nathenson MJ, Conley AP, Sausville E. Immunotherapy: A new (and old) approach to treatment of soft tissue and bone sarcomas. Oncologist. 2018;23(1):71-83.

78. Huang HY, Illei PB, Zhao Z, Mazumdar M, Huvos AG, Healey JH, et al. Ewing sarcomas with p53 mutation or p16/p14ARF homozygous deletion: A highly lethal subset associated with poor chemoresponse. J Clin Oncol. 2005;23(3):548-58.

79. Olmos D, Martins AS, Jones RL, Alam S, Scurr M, Judson IR. Targeting the insulin-like growth factor 1 receptor in Ewing's sarcoma: Reality and expectations. Sarcoma. 2011;2011:402508.

80. Subbiah V, Kurzrock R. Ewing's sarcoma: Overcoming the therapeutic plateau. Discov Med. 2012;13(73):405-15.

81. Hensel T, Giorgi C, Schmidt O, Calzada-Wack J, Neff F, Buch T, et al. Targeting the EWS-ETS transcriptional program by BET bromodomain inhibition in Ewing sarcoma. Oncotarget. 2016;7(2):1451-63.

82. Machado I, Noguera R, Mateos EA, Calabuig-Fariñas S, López FIA, Martínez A, et al. The many faces of atypical Ewing's sarcoma. A true entity mimicking sarcomas, carcinomas and lymphomas. Virchows Arch. 2011;458(3):281-90.

83. Thomas S, Aggarwal R, Jahan T, Ryan C, Troung T, Cripps AM, et al. A phase I trial of panobinostat and epirubicin in solid tumors with a dose expansion in patients with sarcoma. Ann Oncol. 2016;27(5):947-52.

84. Paulussen M, Ahrens S, Burdach S, Craft A, Dockhorn-Dworniczak B, Dunst J, et al. Primary metastatic (stage IV) Ewing tumor: Survival analysis of 171 patients from the EICESS studies. European intergroup cooperative Ewing sarcoma studies. Ann Oncol. 1998;9(3):275-81.

85. Bölling T, Schuck A, Paulussen M, Dirksen U, Ranft A, Könemann S, et al. Whole lung irradiation in patients with exclusively pulmonary metastases of Ewing tumors. Toxicity analysis and treatment results of the EICESS-92 trial. Strahlenther Onkol. 2008;184(4):193-7.

86. Ren Y, Zhang Z, Shang L, You X. Surgical resection of primary Ewing's sarcoma of bone improves overall survival in patients presenting with metastasis. Med Sci Monit. 2019;25:1254-62.

87. Talleur AC, Navid F, Spunt SL, McCarville MB, Wu J, Mao S, et al. Limited margin radiotherapy for children and young adults with Ewing's sarcoma achieves high rate of local tumor control. Int J Radiat Oncol Biol Phys. 2016;96(1):119-26.

88. Houdek MT, Griffin AM, Ferguson PC, Wunder JS. Morbid obesity increases the risk of postoperative wound complications, infection, and repeat surgical procedures following upper extremity limb salvage surgery for soft tissue sarcoma. Hand (N Y). 2019;14(1):114-120.

89. Ozaki T, Hillmann A, Hoffmann C, Rübe C, Blasius S, Dunst J, et al. Significance of surgical margin on the prognosis of patients with Ewing's sarcoma. A report from the cooperative Ewing's sarcoma study. Cancer. 1996;78(4):892-900.

90. Tsuchiya H, Wan SL, Sakayama K, Yamamoto N, Nishida H, Tomita K.

Reconstruction using an autograft containing tumour treated by liquid nitrogen. J Bone Joint Surg Br. 2005;87(2):218-25.

91. Murakami H, Demura S, Kato S, Nishida H, Yoshioka K, Hayashi H, et al. Increase of IL-12 following reconstruction for total en bloc spondylectomy using frozen autografts treated with liquid nitrogen. PLoS One. 2013;8(5):e64818.

92. Raz DJ, Clancy SL, Erhunmwunsee LJ. Surgical management of the radiated chest wall and its complications. Thorac Surg Clin. 2017;27(2):171-9.

93. Tukiainen E. Chest wall reconstruction after oncological resections. Scand J Surg. 2013;102(1):9-13.

94. Basharkhah A, Pansy J, Urban C, Höllwarth ME. Outcomes after interdisciplinary management of 7 patients with Askin tumor. Pediatr Surg Int. 2013;29(5):431-6.

95. Girelli L, Luksch R, Podda MG, Meazza C, Puma N, Scanagatta P, et al. Surgical approach to primary tumors of the chest wall in children and adolescents: 30 years of mono-institutional experience. Tumori. 2016;102(1):89-95.

96. Dunst J, Sauer R, Burgers JM, Hawliczek R, Kürten R, Winkelmann W, et al. Radiation therapy as local treatment in Ewing's sarcoma. Results of the cooperative Ewing's sarcoma studies CESS 81 and CESS 86. Cancer. 1991;67(11):2818-25.

97. Krasin MJ, Rodriguez-Galindo C, Davidoff AM, Billups CA, Fuller CE, Neel MD, et al. Efficacy of combined surgery and irradiation for localized Ewing's sarcoma family of tumors. Pediatr Blood Cancer. 2004;43(3):229-36.

98. Schuck A, Ahrens S, Paulussen M, Kuhlen M, Könemann S, Rübe C, et al. Local therapy in localized Ewing tumors: Results of 1058 patients treated in the CESS 81, CESS 86, and EICESS 92 trials. Int J Radiat Oncol Biol Phys. 2003;55(1):168-77.

99. Wilkins RM, Pritchard DJ, Burgert EO Jr, Unni KK. Ewing's sarcoma of bone. Experience with 140 patients. Cancer. 1986;58(11):2551-5.

100. Sallustio G, Pirronti T, Lasorella A, Natale L, Bray A, Marano P, et al. Diagnostic imaging of primitive neuroectodermal tumour of the chest wall (Askin tumour). Pediatr Radiol. 1998;28:697-702.

101. Hanna SA, David LA, Gikas PD, Tindall AJ, Cannon SR, Briggs TWR. Very late local recurrence of Ewing's sarcoma - can you ever say 'cured'? A report of two cases and literature review. Ann R Coll Surg Engl. 2008;90(7):W12-5.

102. Yeste L, Sierra A, Cañon R, Aristu J, Torre W. Successful use of intraoperative radiotherapy for local control of an Askin's tumor recurrence. J Cardiovasc Surg (Torino). 2001;42(1):143-5.

103. Takanami I, Imamura T, Naruke M, Kodaira S. Long-term survival after repeated resections of Askin tumor recurrences. Eur J Cardiothorac Surg. 1998;13(3):313-5.

104. Pinto A, Dickman P, Parham D. Pathobiologic markers of the Ewing sarcoma family of tumors: State of the art and prediction of behaviour. Sarcoma. 2011;2011:856190.

105. Choo S, Wang P, Newbury R, Roberts W, Yang J. Reactivation of TWIST1 contributes to Ewing sarcoma metastasis. Pediatr Blood Cancer. 2018;65(1):10.1002/pbc.26721.

106. Singh A, Abhinay A, Kumar A, Prasad R, Ghosh A, Mishra OP. Askin tumor. A rare neoplasm of thoracopulmonary region. Lung India. 2016;33(2):196-8.

107. Fathalla AE, Ahmed BE. Askin Tumor in Egyptian Patients; 5 Years Experience at the National Cancer Institute. Cairo University. J Cancer Therapy. 2016;7:216-22.

108. Terrier P, Llombart-Bosch A, Contesso G. Small round blue cell tumor in bone: Prognostic factors correlated to Ewing's sarcoma and neuroectodermal tumors. Semin Diagn Pathol. 1996;13(3):250-7.

109. Saeter G, Elomaa I, Wahlqvist Y, Alvegård TA, Wiebe T, Monge O, et al. Prognostic factors in bone sarcomas. Acta Orthop Scand Suppl. 1997;273:156-60.

110. Mendenhall CM, Marcos RB, Enneking WF, Springfield DS, Thar TL, Million RR. The prognostic significance of soft tissue extension in Ewing's sarcoma. Cancer. 1983;51:913-7.

111. Pan HY, Morani A, Wang WL, Hess KR, Paulino AC, Ludwig JA, et al. Prognostic factors and patterns of relapse in Ewing sarcoma patients treated with chemotherapy and r0 resection. Int J Radiat Oncol Biol Phys. 2015;92(2):349-57.

112. Sirivella S, Gielchinsky I. Treatment outcomes in 23 thoracic primitive neuroectodermal tumours: A retrospective study. Interact Cardiovasc Thorac Surg. 2013;17(2):273-9.

113. Saenz NC, Hass DJ, Meyers P, Wollner N, Gollamudi S, Bains M, et al. Pediatric chest wall Ewing's sarcoma. J Pediatr Surg. 2000;35(4):550-5.

114. Landier W, Armenian S, Bhatia S. Late effects of childhood cancer and its treatment. Pediatr Clin North Am. 2015;62(1):275-300.

115. Hussain AE, Blakley BW, Nicolas M, Balderston J. Assessment of the protective effects of amifostine against cisplatin-induced toxicity. J Otolaryngol. 2003;32(5):294-7.

116. Wood J, Ver Halen J, Samant S, Florendo N. Radiation-induced sarcoma masquerading as osteoradionecrosis: Case report and literature review. J Laryngol Otol. 2015;129(3):279-82.

117. Mitchell MJ, Logan PM. Radiation-induced changes in bone. Radiographics. 1998;18(5):1125-36.

118. Borinstein SC, Beeler N, Block JJ, Gorlick R, Grohar P, Jedlicka P, et al. A decade in banking Ewing sarcoma: A report from the children's Oncology group. Front Oncol. 2013;3:57.

119. Lamhamedi-Cherradi SE, Menegaz BA, Ramamoorthy V, Aiyer RA, Maywald RL, Buford AS, et al. An oral formulation of YK-4-279: Preclinical efficacy and acquired resistance patterns in Ewing sarcoma. Mol Cancer Ther. 2015;14(7):1591-604.

120. Wilky BA, Kim C, McCarty G, Montgomery EA, Kammers K, DeVine LR, et al. RNA helicase DDX3: a novel therapeutic target in Ewing sarcoma. Oncogene. 2016;35:2574-83.

121. Wiles ET, Bell R, Thomas D, Beckerle M, Lessnick SL. ZEB2 represses the epithelial phenotype and facilitates metastasis in Ewing sarcoma. Genes Cancer. 2013;4(11-12):486-500.