Recent Multidisciplinary Approach In Thoraco Pulmonary Ewing Sarcoma, Clinico - Pathological Study, NCI Experience, Cairo

Thesis
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Abstract

**Background:**

Because of the rarity of chest wall ES, most of the literature comes from retrospective subset analyses of large multi-institutional Ewing sarcoma trials.

**Objective:**

To evaluate the multidisciplinary management modalities for chest wall ES/PNET and its outcome.

**Methods:**

This is a retrospective study that will be conducted on all patients of both sexes and definite age groups attending at the outpatient clinic at the National Cancer Institute and with thoracic ES / PNET and candidate for surgical intervention. from January 2000 to December 2014.

**Results:**

A combination of neoadjuvant chemotherapy followed by surgery and radiotherapy resulted in optimal outcome in patients with this tumor.

**Conclusion:**

With extended follow-up, our series demonstrates that upfront interval-compressed systemic multi-agent chemotherapy followed by delayed local control in the form of adequate surgery, alone or combined with radiotherapy, along with concurrent consolidation chemotherapy are the backbone in the treatment of patients with localized chest wall Ewing tumors, decreasing the incidence of both local and systemic relapses and leads to a longer OS and DFS.

**Keywords:**
PNET, Chest wall, Ewing sarcoma, Askin’s Tumor, multidisciplinary, survival.
Introduction

In 1979, Askin and his colleagues[1] described a rare malignant small-cell tumor of the thoracopulmonary region in 20 children and adolescents with a mean age of 14 years, referred to as an Askin tumor. Ewing Sarcoma (ES), Extra-osseous Ewing tumors (EES), Primitive Neuro Ectodermal Tumors (PNET) and Askin tumors (PNET of the chest wall) have been categorized as members of the Ewing sarcoma family of tumors (ESFT). Most commonly seen in children and young adults, these highly malignant tumors of bone and soft tissue are histopathologically described as poorly differentiated "small round cell tumors". ESFT are tumors of neural crest derivation showing varying degrees of neuroectodermal differentiation.[2,3]

Current evidence indicates that ES and PNET represent a single neoplastic entity, differing only in their degree of neural differentiation. Tumors that demonstrate neural differentiation by these analyses have been traditionally named PNETs and those that are undifferentiated have been called Ewing sarcoma.[4]

Though PNETs are well described in the literature, most of them are case reports of tumors located in the chest wall, lung, kidney, urinary bladder, myocardium, pancreas, retro peritoneum and the female genital tract.[5-7]

PNETs should be considered in the differential diagnosis of all chest wall tumors, parenchymal lung nodules and mediastinal tumefactions regardless of age. There were only very few reported cases of PNETs arising as primary tumors of the lung without pleural or chest wall involvement.[8,9]
The treatment of an Askin tumor should aim to control local disease and distant metastasis. Thus, the prevailing treatment of an Askin tumor is a combination of neoadjuvant chemotherapy, radical surgical resection and adjuvant chemotherapy and radiotherapy. Several studies have proved that this aggressive therapy may lead to a longer relapse-free survival.[10,11]

The satisfactory outcomes that have been achieved to date may be attributed to comprehensive treatment. Surgery, as an option in the treatment of an Askin tumor, is crucial for local control due to the removal of the tumor itself, while chemotherapy/radiotherapy are administered as supplementary treatment. According to a study on malignant chest wall tumors in children and young adults by Dang et al.,[12] surgical resection with en bloc removal of adjacent muscles or organs and chest wall reconstruction provided excellent local control of malignant chest wall tumors. According to a study conducted in the Memorial Sloan-Kettering Cancer Center (MSKCC),[13] complete remission was achieved in patients following surgery and chemotherapy rather than chemotherapy alone, thus underlining the importance of surgery.

Based on the grouping of these two diseases into the same WHO classification in 2002, the therapeutic guidelines for Ewing sarcoma may be useful in guiding the treatment of Askin tumors. In certain cases, extended surgery followed by post-operative chemotherapy and radiotherapy is the first choice of treatment. [14] However, no standard therapy is available for the treatment of Askin tumors due to the rarity of this disease and the poor prognosis.
Aim of the Work

This study was designed to evaluate:

1- Frequency of Thoracopulmonary PNET cases among the other chest wall tumors presented to the NCI outpatient clinic.

2- Patients Demographics with regard to age and sex.

3- Anatomical site within the thoracopulmonary region.

4- Treatment modalities in NCI.

5- Short term relapse and survival.

To compare our results with the observations of other trials and intergroup studies across the world and to recommend the best approach for the treatment.
Review of the Literature

Natural history of the chest wall tumors (CWTs):

Patients with chest wall tumors present diagnostic and therapeutic challenges. The differential diagnosis of these tumors is broad, because they can represent a heterogeneous spectrum of diseases from primary benign or malignant tumors to metastases; local extension of adjacent tumors of the lung, mediastinum, pleura or breast; non-neoplastic infectious or inflammatory conditions; or even local manifestations of systemic disease.

Primary chest wall tumors are best classified according to their tissue of origin, bone or soft tissue, and further sub classified according to whether or not they are benign or malignant. Most of these tumors are uncommon, with information garnered from individual case reports or institutional case series.

Approximately 60% of primary chest wall tumors are malignant. Although primary chest wall tumors are diagnosed in every age group, they are more likely malignant in the extremes of age: in the young and the elderly. Certain tumors present predominantly in one age group.\textsuperscript{[15]}

Chest wall tumors in children and adolescents are also rare with an incidence of 1/1,000,000.\textsuperscript{[3]} They can be caused by a wide range of benign and malignant diseases. About 1/5 of the thoracic tumors occurring in childhood originate from the chest wall. In children, Ewing's sarcoma is the most common chest wall tumor\textsuperscript{[3]} and second most common sarcoma in children and young adults.\textsuperscript{[16]}
Ewing Sarcoma Family of tumors (ESFT) / Primitive Neuro ectodermal tumors (PNET):

Ewing sarcoma and Primitive Neuro- Ectodermal Tumors (PNETs) were originally described as distinct clinic-pathologic entities: in 1918, Stout described a tumor of the ulnar nerve composed of small round cells focally arranged as rosettes; this entity was subsequently designated neuroepithelioma, and then PNET.

Later, in 1921, Ewing sarcoma was described as an undifferentiated tumor involving the diaphysis of long bones. It was also reported to arise in soft tissue (extra-osseous Ewing sarcoma). As Sir James Ewing was the first to describe it as non-osteogenic primary tumor of the bone characterized by the presence of small round cells which he termed as "Endotheliomyeloma of bone" (Ewing, 1922).

Recently, PNETs and Ewing sarcoma have been categorized into a group known as the Ewing family of tumors because of their immunohistochemical, ultrastructural, and molecular similarities. Or by other words, because of their genotypic and phenotypic appearance. And it has become clear, over the last three decades, that these entities comprise the same spectrum of neoplastic diseases known as the Ewing sarcoma family of tumors, which also includes malignant small cell tumor of the chest wall and atypical Ewing sarcoma.

It is rare, highly malignant disease found in children, adolescents, and young adults. Median age at diagnosis is 15 years. Approximately 10% of all Ewing's Sarcoma cases arise from the ribs. Ewing's Sarcoma in the Thoraco pulmonary region was called as Askin's tumor.
Introduction to thoraco pulmonary Ewing Sarcoma / Askin tumor:

In small round cell sarcomas of bone and soft tissue, there is a distinct clinicopathologic entity, proposed by Askin et al. in 1979 and termed "malignant small round cell tumor (MSRCT) of the thoraco pulmonary region," present in both children and young adults. This tumor arises in the periosteum, soft tissue, and extra pulmonary fields of the thoracic wall and in the lung, with or without rib involvement. Histologically, it contains homogeneous small round-to-spindle cells, growing in compact sheets on pseudo lobules and is mostly devoid of any particular microscopic differentiation. However, rosette-like figures of Homer-Wright type occasionally are seen. Back then, the precise histogenesis of this entity has not been established, there is evidence to support its derivation from a primitive pluripotential cell, expressing a neuroectodermal phenotype.

Until an identical molecular signature revealed a common origin, ESs of the chest wall have also been referred to as Askin's tumors. This malignancy is also considered as a primitive neuro ectodermal tumor (PNET) probably arising from embryonic migrating cells of the neural crest and located exclusively in the thoracopulmonary region.

This disease was originally reported in 20 white children and adolescents (average age, 14 years) which is a rare disease in the pediatric group, and even rarer in adults.

Due to the rarity of Ewing Sarcoma (ES) of the chest wall, only a limited number of patient series have been published. These patient cohorts were generally too small to allow detailed conclusions to be drawn; therefore, most publications are derived from retrospective subset analyses of large multi-institutional ES trials.
Today, there is an agreement in the literature that an aggressive multimodal approach after primary biopsy is the optimal way to proceed with the treatment\cite{31-34} as Askin tumors are highly aggressive and metastasize rapidly with poor prognosis.\cite{26}

The age of the patients has been demonstrated to be an important factor in the determination of prognosis. Younger patients have an improved survival compared to older patients\cite{20,35} and Caucasian ethnic group is clearly predominant.\cite{20}

The ribs are the most common site of presentation for ES of the chest wall.\cite{36} but paravertebral, sternal and scapular localizations have been reported.\cite{26}

**Challenges in the diagnosis of chest wall Ewing sarcoma:**

Its diagnosis approach is complex and requires a multidisciplinary team. Given the rarity of this entity, no regimen has been validated in the literature\cite{37} and hence Ewing's sarcoma is one of commonest chest wall malignant tumors, Physicians & Orthopaedicians have found it challenging in diagnosing this condition early, which could affect the prognosis of the patient.\cite{22}

A successful approach includes a thorough assessment of the patient and the lesion, an adequate biopsy to confirm tissue diagnosis, and a well-established treatment plan.\cite{37}

The metastasis sites include lung, mediastinal and retroperitoneal lymph nodes, extra thoracic skeleton, liver, adrenal glands, and sympathetic nerve chain. Nevertheless, the radiologic characteristics of Askin tumors are not specific,\cite{38-40} but imaging can be useful for evaluating the extent of the tumor, the response to treatment and local recurrence or distant metastasis. It is also valuable for guiding the biopsy route and determining whether the tumor has been completely resected. Askin tumor is in differential diagnosis with neoplasms that can show a
mass of chest wall at computed tomography (CT) scan, including neuroblastoma, rhabdomyosarcoma, non-Hodgkin lymphoma and Langerhans cell histiocytosis. Neuroblastomas occur before 5 years of age, and characteristically present invasion through neural foramina giving a dumbbell appearance. Rhabdomyosarcoma and Askin tumor at CT imaging, can present similar characteristics, so a biopsy is necessary for diagnosis. Non-Hodgkin lymphoma usually shows nodular thickening of the pleura and rarely isolated chest wall masses. It is important to exclude non-Hodgkin lymphoma as its treatment does not include surgery. Imaging features of Langerhans cell histiocytosis are bony lytic lesions with or without soft tissue masses, with multi-systemic involvement such as brain, lung and abdominal organs. So, the CT images show similar characteristics between Askin tumor and others neoplasms that appear as a mass of chest wall. The differential diagnosis need to include also this rare tumor occurring in children because a prompt treatment and an early evaluation of prognosis should be employed.\cite

**Imaging**

CT with intravenous injection of contrast media represents a useful imaging technique for suspected neoplastic diagnosis and differential diagnosis of thoracic masses in children. Askin tumor is an uncommon malignant neoplasm in children and CT study can be used as a problem-solving tool.\cite
Factors Associated with Poor Prognosis of chest wall Ewing sarcoma:

Askin's tumor occurs in young Caucasian adults and is usually associated with poor prognosis. In EFT, several factors have been considered to be of prognostic importance (stage, primary tumor site, size, age, and response to therapy).

The prognosis of Askin's tumor was very poor. Askin reported that 14 of 18 patients with known prognosis died four to forty-four months after diagnosis, and the mean survival period was eight months. Local recurrences are very common. Furthermore, metastases are already present at diagnosis in 10% of cases. Yet, over the past three decades, the outcome of Ewing sarcoma family tumor (ESFT) patients who are non-metastatic at presentation has improved considerably. The prognosis of patients with metastatic disease at the time of diagnosis and recurrence after therapy remains dismal. The risk of local recurrence is associated with the status of the resection margins. Long-term survival in Askin tumor is possible even in cases with primary metastatic lesions or malignant effusion by an aggressive approach, which includes neoadjuvant and adjuvant chemotherapy and radical surgery. Careful long-term follow-up is necessary, since even a late relapse after 9 years are described in the literature. Utilization of biomaterials is easy and favorable, which leads to satisfactory results in many patients. In addition, coverage of the prosthetic material by autologous soft tissue, preferably by adjacent thoracic or abdominal muscle flaps, improves the respiratory stability of the chest wall and minimizes the risk of infection. Multidisciplinary management has improved the 5-year survival of patients with localized disease to rates of 60–70 % and higher. Multimodal therapy includes systemic therapy as well as surgery and/or radiotherapy (RT).

Negative Predictive Factors
Several factors were investigated as predictors of relapse and survival. Histological response, tumor volume, and age at diagnosis were negative predictive factors in a univariate analysis. Multivariate analysis was performed including the univariate significant factors, and revealed large tumor volume and poor histological responses significant factors.\textsuperscript{[34]}

**Recent approaches in treatment of chest wall Ewing sarcoma and therapeutic targets:**

The ultimate aim of all the research into any tumor is to find a therapeutic agent. The EWS-FLI1 fusion is present only in EFT cells and does not exist in any normal cell of the body. Thus, EFT contains a unique protein generated by tumor-specific translocation with a potential for molecular target, but so far nothing has reached the clinics. This might be due to EWS-FLI1 being a very difficult molecule to analyze directly in vitro due to its poor solubility.\textsuperscript{[34]}

As IGF-1 is associated with EFT growth, monoclonal antibodies against this potential target are being tried.\textsuperscript{[37]} Other conceivable candidates include phospholipase D2 (PLD2)\textsuperscript{[38]} and protein tyrosine phosphatase I (PTPL1),\textsuperscript{[39]} both of which are highly expressed in EFT.

**Patients and Methods**
**Study population:**

This is a retrospective study that will be conducted on all patients of both sexes and definite age groups attending at the outpatient clinic at the National Cancer Institute and with thoracic ES / PNET and candidate for surgical intervention.

- **Sampling:** all cases fulfilling the inclusion criteria will be included in the study.
- **Baseline demographics and short-term outcome,** will be analyzed.

**Inclusion criteria:**

Patients will be included in the study if they present to NCI with:

- Recent radiological and tissue diagnosis of ES / PNET in the thoracic region.
- From January 2000 to December 2014.
- They haven’t received prior treatment neither surgery, chemotherapy nor radiotherapy.
- CT chest with soft tissue mass and rib involvement.
- Pathology and Immunohistochemistry for PNET / Ewing Sarcoma.

All the patients have completed their work-up in the form of (High resolution CT chest, bone scan, BMA and BMB).

**Exclusion criteria:**

- Progressive local disease after neoadjuvant Chemotherapy.
- Uncontrolled metastasis after neoadjuvant Chemotherapy.
Methodology

- Type of study: A retrospective study.
- Follow up: will be completed within 36 months.

Treatment protocol:

Upfront neoadjuvant systemic chemotherapy followed by local control in the form of surgery with adequate rigid and soft tissue reconstruction, alone or combined with radiotherapy in selected patients, along with concomitant chemotherapy. Thereafter the patient receives adjuvant chemotherapy.
**Chemotherapy:**
Systemic treatment was received every 3 weeks in the first arm of the study and every 2 weeks in the second arm i.e. interval compression. Chemotherapy may be interrupted due to symptoms of toxicity such as nausea, vomiting, myelosuppression and febrile neutropenia. Hence, G-CSF, 5 micrograms/kg/day may be used 24-36 hours after completion of chemotherapy to help interval compression.

**Surgery:**
Complete full thickness chest wall surgical excision was performed for all cases of the study followed by immediate reconstruction for defects larger than 5 cm and not covered with posterior scapula as follows:

- Skeletal stabilization was performed using methyl methacrylate sandwiched between 2 layers of polypropylene mesh.
- Soft tissue reconstruction using latissimus dorsi or Pectoralis Major myocutaneous flaps were added for large defects.

Defects covered with posterior scapula was reconstructed using only polypropylene mesh to prevent Scapula impaction.

**Radiotherapy:**
Post-operative radiotherapy was received in the following conditions:

- Inadequate surgical margins (i.e. positive margins).
- Patients with pleural effusion or pneumothorax.
- Patients with poor pathologic response to chemotherapy i.e. tumor necrosis is 90% or less.
Conclusion

With extended follow-up, the best practice for the patients with chest wall Ewing sarcoma according to our series demonstrates that upfront interval-compressed systemic multi-agent chemotherapy followed by local control in the form of adequate surgery, alone or combined with radiotherapy, along with concomitant chemotherapy followed by adjuvant chemotherapy are the backbone in the treatment of patients with chest wall Ewing tumors, decreasing the incidence of both local and systemic relapses and leads to a longer overall survival and disease free survival. In a select group of favorable patients, if there is no pleural effusion or pneumothorax, surgery with negative margins and good pathologic response to neoadjuvant chemotherapy i.e. more than 90 % tumor necrosis alone with rigid and soft tissue reconstruction in a specialized center is a reasonable alternative of radiotherapy. Because of anatomy, any local treatment has the potential for serious toxicity, and new strategies are needed to minimize this risk. The correct choice of management needs to be evaluated on an individual patient basis by a multidisciplinary group to decrease the exposure of critical normal tissues. As a community, we need to continue improving our treatment techniques and report the long-term toxicity and survival associated with our management decisions.
ملخص الرسالة

خلفية عامة:
أورام إيوبنج بالصدر هي أورام نادرة، فهي أورام خبيثة ونسب البقاء والشفاء محل دراسة وتحسين بشكل دائم ومستمر.

الهدف من البحث:
هي دراسة استعادية، على المرضى الذين يعانون من أورام إيوبنج بالصدر، والذين خضعوا للأساليب المختلفة للعلاج في المعهد القومي للسرطان بجامعة القاهرة من يناير 2000 حتى ديسمبر 2014 خلال فترة متابعة للمرضى تتراوح من 36 شهرًا إلى 17 عاما بعد تلقي العلاج.

المريض وطرق البحث:
خلال فترة الدراسة، شملت دراستنا 20 مريضاً يعانون من أورام إيوبنج بالصدر تلقوا العلاج بالمعهد القومي للأورام، جامعة القاهرة. البيانات تم جمعها من قسم الإحصاء الطبي ووبائيات السرطان والاتصال بالهاتف في حالة فقد المتابعة الدورية.

النتائج:
كانت هناك غلبة في نسبة الإناث (16 مريضة، 52,3%) مقارنة بالذكور (14 مريضاً، 47,7%). وبشكل عام، على مدى متوسط فترة المتابعة، كانت نسب البقاء على قيد الحياة العامة للمجموعة كلها في 36 شهراً (أي 3 سنوات) 28,8%.

الخلاصة:
أورام إيوبنج بالصدر تمتلك تحديات تشخيصية وعلاجية هامة. للكثير من المرضى، اتباع نهج متعدد الطرق ضروري لنتائج أفضل من حيث صلة بوفيات السرطان ووظيفة القفص الصدري على المدى الطويل. ويمكن الحصول على نتائج ممتازة للمريض مع الاستئصال الجراحي الكامل بحري أمان واسع وإعادة البناء المناسب. العلاج الكيميائي الاستباقي المضغوط ما قبل وبعد العلاج الموضعي المتمثل في الاستئصال الجراحي مع إعادة البناء مع أو بدون العلاج الإشعاعي ساعد في تحسين نسب البقاء وتقليل نسبة الوفاة لمرضى أورام إيوبنج بالصدر، كما أن النهج متعدد الطرق الحديث لعلاج أورام إيوبنج بالصدر ساعد في تحسين نسب الشفاء وتقليل احتمالية ارتداع الورم موضعياً وتقليل الثانويات.

كلمات البحث:
أورام إيوبنج بالصدر، معدلات الإصابة، طرق البقاء، البقاء على قيد الحياة.
النهج متعدد التخصصات الحديث لأورام إيوينج بالصدر،
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