Management Head and Neck Ewing’s Sarcoma Family of Tumors: Experience of the National Cancer Institute, Cairo University

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ABSTRACT

Background: Ewing’s sarcoma accounts for 4-6% of primary malignant bone tumors and it affects the head and neck in only 1-4% of cases. The purpose of this study was to review the NCI experience with Ewing’s sarcoma of the head and neck in children.

Patients and Methods: A retrospective analysis of patient files with head and neck Ewing’s sarcoma treated at the National Cancer Institute, Cairo University, Egypt, during the period from 1997 to 2008 was done. Files were reviewed and data for patients, tumor and treatment profile were extracted.

Results: Twenty patients out of 280 with Ewing’s sarcoma were identified during an 11-year period. Patients had a median age of 11.5 years (range 5 months - 22 years) with a male to female ratio of 1:1. The most common tumor site was in the mandible (9/20, 45%) followed by a neck mass (4/20, 20%) and a clavicular mass (3/20, 15%). Six patients (30%) were metastatic at presentation. Most of the patients (19/20, 95%) received chemotherapy. Local therapy was in the form of radical radiotherapy for 8 patients (40%), 2 patients (10%) had surgery alone, while five patients (25%) had surgical resection and postoperative radiotherapy. Overall survival ranged from 1 to 128 months, with a median of 36 months. At the end of the study, 9 patients (45%) were alive in CR, 6 (30%) were lost to FU in disease progression, while 5 patients died from disease progression.

Conclusion: Ewing’s sarcoma of the head and neck is a disease of a rare incidence with debate about the optimum local therapy. Small non-metastatic tumors with good response to chemotherapy have better outcome.

Key Words: Ewing’s sarcoma – Head and neck – Management.

INTRODUCTION

Ewing’s sarcoma (ES) is the second most common primary bone tumor in childhood after osteosarcoma. It accounts for 4-6% of primary malignant bone tumors, peaks in the second decade of life, slightly more common in males, and affects the head and neck in only 1-4% of cases [1].

The term Ewing Sarcoma Family of Tumors (ESFT) defines a group of small round cell neoplasms of neuroectodermal origin, that manifests as a continuum of neurogenic differentiation, with Ewing sarcoma of bone representing the least differentiated, and primitive neuroectodermal tumor and peripheral neuroepithelioma the most differentiated forms. More than 50% of the tumors arise from axial bones, with the pelvis being the most commonly involved (23-27%) [2].

Approximately 20-25% of cases have clinically apparent metastatic disease at the time of diagnosis. Isolated lung disease, usually bilateral, occurs in 25-45% of the cases; the majority of patients (50-60%) have extrapulmonary disease (usually bone and bone marrow) [3].

Treatment of ESFT is aimed to achieve two major goals, local control and eradication of the systemic disease. To achieve this goal, most protocols consider 3 phases: a- Induction chemotherapy to achieve rapid initial cytoreduction and facilitate local control, b- Local control, using surgery, irradiation, or both, usually after 10-12 weeks of chemotherapy, and c- Continuation therapy, with the same chemotherapeutic...
agents. All patients with ESFT require local therapy for cure, however the most appropriate local therapy modality remains to be defined for any specific patient group [4].

The most favorable group of patients has small localized tumors that are amenable to surgical resection or local radiation therapy. The volume or size of the tumor has been noted as a prognostic factor for event-free survival but its effect on local control rates is less clear [5-8]. Post-operative, and more recently, pre-operative irradiation, have been applied to patients with marginally resected or poorly responding tumors [9].

The aim of the present study is to explore the clinicopathological features of this disease, different treatment modalities (including chemotherapy, surgery, and radiation therapy), as well as the patterns of failure.

PATIENTS AND METHODS

A retrospective analysis of the data available from the medical records of patients with head and neck Ewing’s sarcoma (ES) treated at the National Cancer Institute, Cairo University, Egypt, during the period from January 1997 to December 2008 was done. A total of 20 patients with head and neck ES/PNET were identified out of 280 patients with the ES pathology during the same time period. Patients under 24 years of age, with pathologically proven ES by internal pathologist slide revision and/or biopsy, and normal hematopoeitic, renal, hepatic and cardiac functions were included in the study. Initial work-up included pathological confirmation, local CT/MRI, bone scan, C-T scan of the chest, bone marrow aspirate and biopsy.

**Chemotherapy:** The treatment protocol consisted of 3 phases: Induction, local control and maintenance. Induction phase consisted of two courses of ifosfamide and etoposide alternating with one course of vincristine, adriamycin and cyclophosphamide. Maintenance therapy consisted of courses of ifosfamide and vepeside alternated with vincristine, adriamycin and cyclophosphamide until the end of chemotherapy. Adriamycin was replaced by Actinomycin D starting from week 36 until the end of chemotherapy (Table 1).

**Local therapy of the primary tumor** was due at week 9 from the start of chemotherapy after radiological re-evaluation. It consisted of surgery and/or radiotherapy. The choice of the type of local therapy was made on an individual basis and was dependent on the primary site, tumor resectability with chemotherapy given concomitantly.

### Table (1): Applied treatment protocol for Ewing’s sarcoma at NCI-Egypt.

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<th>Induction (Phase 1)</th>
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I = Ifosfamide 1.8g/m² IV over 1 hour infusion/day x 5 days with MESNA.
E = Etoposide 100mg/m² IV over 1 hour infusion/day x 5 days.
V = Vincristine 2mg/m² (2mg max) IV push.
Adr = Adriamycin 75mg/m² IV over 15 minutes (total cumulative dose 375mg/m²).
D = Actinomycin D 1.25mg/m² IV push.
C = Cyclofosamide 1200mg/m² IV over 30min with MESNA.
* = Evaluation.

**Statistical analysis:**

The SPSS package for Windows, version 15 (SPSS Inc., Chicago, Illinois, USA) was used. Chi-square test (Fisher’s exact test) was used to detect association between qualitative variables. For survival time analyses, times from the date of definitive biopsy to the time of first event, or of last examination, were calculated.
The outcome associated with local control, however, was assessed using the time of local treatment completion, which was available for all patients who received any local therapy. For estimation of event-free survival, relapse (local recurrence and/or metastatic disease), measurable local progression of disease, and death irrespective of its cause were counted as an event. In the overall survival (OAS) curves, only death was regarded as an event. The functions for both the overall survival and the event-free survival were estimated using the Kaplan-Meier product limit method [10].

**RESULTS**

According to the NCI, Cairo University, records, a total of 20 patients out of 280 (7%) patients were recorded to have ES of the head and neck during the period from January 1997 to December 2008.

The median age of the patients was 11.5 years (range 5 months - 22 years) with equal numbers of males and females in the study. A painful swelling was the most common presentation found in 17/20 of patients. The mandibular ramus was the most common site of presentation seen in 9/20 patients (45%), followed by a neck mass in 4 (20%), clavicular mass in 3 (15%), and a parapharyngeal mass in 2/20 patients (10%).

Locally advanced tumors were documented in 9/20 (45%) of the patients. This was in the form of infiltration of critical structures in 6/20 patients (30%), or large size (>8cm) in 3/20 (15%) patients. Metastasis at initial presentation was found in 6/20 (30%) of the patients; 2 had isolated brain deposits, 2 had brain and pulmonary metastasis, while the last 2 patients had isolated bony lesions (maxilla and neck of femur).

The majority of patients, 18/20 (90%), did not receive any anticancer treatment before being admitted to our institution, while two patients (10%) received prior chemotherapy, one of the them received NHL-like chemotherapy. Almost all patients 19/20 (95%) received chemotherapy, although 9 patients did not complete their treatment. At week 9, and following induction chemotherapy, locoregional CT/MRI was done to assess response and to decide the modality of local therapy.

Radical treatment was feasible for 15 (75%) patients, 8 with radical radiotherapy (40%), surgery alone in 2 (10%), and surgery and post-operative radiotherapy in 5 (25%) patients. Two patients had palliative radiotherapy with disease progression. Three patients (15%) did not receive any local therapy as they were lost for follow-up before the due time for local treatment.

Radical surgery was done for 7 patients. It was in the form of segmental mandibular resection with soft tissue margin in 4 patients, two patients had clavicular resection and 1 patient had orbital excentration. Four patients (57%) had negative surgical margin, while 3 (43%) patients had positive margins. Reconstruction was done for two patients with mandibular tumors; a free fibular vascularized graft was done as a second setting while a plate was used as a spacer. One patient had dental osteo-integration as a staged procedure. One patient had prosthetic rehabilitation after total maxillectomy.

**Radiation-therapy:** Eight (40%) patients received radical radiotherapy as local treatment, while 5 (25%) patients received postoperative radiation-therapy. All of them completed their radiotherapy schedule. It was delivered in 180-200cGy dose per fraction, with 6MV linear accelerator. The total radiation dose ranged from 45-54Gy (median = 50.38).

The overall survival period ranged from 1 month to 128 months, with median of 36 months (Fig. 1). Nine patients (45%) were alive free from disease, 5 (25%) patients died during the treatment period from progressive disease, while 6 (30%) patients were lost for follow-up in progressive disease condition (Figs. 2,3). The 3-year overall survival (OS) and progression-free survival (PFS) rates were 50% and 67%, respectively (Figs. 1,3). OS rate for those with metastases at presentation was 14% compared to 69% for localized non-metastatic disease, \( p=0.007 \) (Fig. 3). Studying the effect of prognostic factors in Ewing’s sarcoma in other sites was not applicable due to the small number of patients.
DISCUSSION

Ewing’s sarcoma of the head and neck is a rare disease [11] with lower survival for adolescents compared to children [12]. When the tumor involves the head and neck region, the mandible and skull base are the two most common primary sites [1], followed by the orbit, and nasal cavity with or without the paranasal sinuses [13]. In our study, the mandibular ramus was found to be the most common primary tumor site followed by neck and clavicular masses. A total of 20 patients out of 280 (7%) patients were found to have ES of the head and neck during an 11 year-period at the NCI, Cairo University. The same incidence was reported by other researchers [14,15].

In our study, the age ranged from 5 months to 22 years, with a mean of 11.5 years, a much wider range than reported in the literature [14,15]. Although there are no pathognomonic clinical findings for Ewing’s tumors in the head and neck region, the most common manifestations are due to the mass effect of the tumor. The mass is slowly growing, hard, with associated mild tenderness or dull aching pain. Other signs and symptoms are often associated with mandibular involvement, including loose teeth, local paresthesia or otitis media [14]. In our study, the most common mode of presentation was a painful swelling, as report by other authors [13-15].

Being a rare disease at that region, the clinical differential diagnosis is biased towards more common diseases, mainly lymphoma. In our study, 4/20 patients (20%) were initially misdiagnosed as having lymphoma but the pathological diagnosis was changed when reviewed or rebiopsied at NCI. Lymphoblastic lymphoma and anaplastic large cell lymphomas are known issues in the differential diagnosis of Ewing’s sarcoma [16,17]. Other differential diagnoses of intracranial round cell tumor should include rhabdomyosarcoma, and metastatic neuroblastoma [17,18].

Tumors with a maximal diameter larger than 8cm were reported to have a poorer outcome than those with smaller tumors [19]. Tumor volume has been shown to be an important prognostic factor in most studies. Cutoffs of 100ml [19], 150ml [20] or 200ml [21] have been found prognostic. Whether this concept could
be applied in head and neck tumor, should be prospectively evaluated. In our study, tumor size and volume was not much considered as nearly 50% of our cases were locally advanced and/or surgically irresectable.

Chemotherapy:

Chemotherapy controls both micrometastasis as well as local residual disease. Chemotherapeutic agents active against ES include doxorubicin, dactinomycin, cyclophosphamide, and vincristine [22]. The addition of ifosfamide and etoposide to the treatment regimens had further increased the 5-year event-free survival from the previously 50-60% to the current 60-80% [23].

From the present study, we could detect causes that made the final outcome of our patients (45%) worse than the international figures, including late presentation to the treatment centers as well as poor patient compliance to chemotherapy (9/20 patients did not complete their chemotherapy protocols).

The most common location for metastases in ES is the lungs, followed by bones and the bone marrow. The presence of metastasis is the main adverse prognostic factor and is associated with significantly worse relapse-free survival and only about 20% long term survivors [24]. In our study, 6 of our patients were metastatic at presentation, mainly to the brain with or without other sites and most of them had fatal outcome, except for one patient who received cranial irradiation followed by second line chemotherapy and remained in CCR for 84 months from the end of treatment. For the rest of the patients, all died from disease progression while on chemotherapy.

Local therapy:

The head and neck region imposes both diagnostic and therapeutic problems when involved by Ewing’s sarcoma. The debate whether radiotherapy or surgery is the best local control modality has been long going. For extremities, surgery has proved to have a slightly better outcome, but this issue remains obscure for head and neck tumors, as there are obviously other factors than in extremity tumors that limit both surgery and radiotherapy.

In our study, most of the patients, 15/20 (75%), received radiotherapy either as the sole line of local control, 10/20 (50%), or postoperatively, 5/20 (25%). Seven patients had radical surgical resection, 4/7 had positive surgical margins and 3/20 had negative margin.

The role of surgical resection (with or without radiotherapy) has been shown to be superior to radiotherapy alone in the local control of Ewing’s sarcoma of the extremities, however this difference is not clear regarding overall survival [25,26]. This is probably attributed to selection bias of surgical cases. The same results are not studied in the literature for head and neck Ewing’s sarcoma and we do not think that the superiority of surgery could be extrapolated to encompass the head and neck region where the luxury of obtaining a generous margin is missing. Patients who received definitive radiotherapy were those with irresectable tumors and/or positive surgical margins, or those with progressive disease on chemotherapy. After the initial chemotherapy, the choice of local treatment should be individualized. The trend for local management of ES has changed recently toward surgical resection whenever feasible, based on retrospective reports [27,28].

It should be noted that the medial margin (infratemporal fossa) for mandibular tumors was the most compromised, making medial extension a sign of locally advanced disease in the mandibular region. We also remark that in all patients with mandibular Ewing’s sarcoma, the tumor occurred in the ramus and the posterior part of the body of the mandible, while none had a central tumor. Reconstruction after resection of mandibular tumors in a growing child is challenging; vascularized and non vascularized [26,27] bone grafts have been described as well as non osseous vascularized grafts [16]. In our series, major soft tissue component resection limited the use of a free non vascularized graft and left the primary choice for free vascularized fibular graft. Free vascularized fibular graft was performed in 2 patients and in one patient dental osteo-integration was done as a third stage. On the other hand, patients with Ewing’s sarcoma of the clavicle did not require reconstruction after claviculectomy and he functional outcome was adequate. The same approach and outcome for clavicular tumors were described on a very limited number of patients by Rodriguez-Galindo and colleagues [4].

According to the surgical highlights from the European Ewing Tumour Working Initiative
of National Groups – 99 section (EURO-E.W.I.N.G. 99 COG), in the patients with poor radiographic and clinical response to induction chemotherapy, one should consider preoperative radiotherapy and delayed surgery should be done after the end of chemotherapy. When radical surgery would be a mutilating one, radiotherapy should be the treatment of choice [29]. However, radical radiotherapy in the pediatric age group is not without complications. The use of high doses of radiation for tumors in the head and neck region may produce functional squeal and local complications, including fibrosis, contractures, anklyosis of the temporomandibular joint, as well as second malignancy. Combining surgery and postoperative radiotherapy in fact, exposes the patients to the sequel of both treatments.

The use of combined modality (surgery and radiotherapy) in our series (25%) may reflect resection difficulties to achieve an adequate negative margin in the very confined space of the head and neck region. Due to the limited number of patients, we were unable to draw statistical evaluation of the margin status and its relation to local recurrence and survival.

The European Intergroup Cooperative Ewing’s Sarcoma Studies (EI CESS-studies) defined narrow surgical margins and/or poor histologic response in the surgical specimen as criteria for postoperative radiotherapy [30-32].

In conclusion, Ewing’s sarcoma of the head and neck is a rare neoplasm that imposes surgical difficulties that are different from that of the more common type of the extremities. Although the chemotherapy treatment protocol is not different from that for extremity tumors, the main issues are local treatment at this region. Surgical resection should be carried out to achieve maximal local control, with a negative margin whenever possible, and should not be hindered by the presence of metastatic disease. Radiotherapy should be given as adjuvant treatment for virtually all patients and as a definitive local treatment for those with unresectable disease.

REFERENCES


