Management of Ewing Sarcoma: Current Management and the Role of Radiation Therapy

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Abstract

The management of Ewing sarcoma has evolved over the last few decades with successive improvement in survival rates. Multidisciplinary management is the key to successful outcomes. Dose intensity of chemotherapy is of vital importance. Local control can be effectively achieved with surgery, radiation therapy or a combination of the two. The choice of appropriate local therapy should be individualized and depends on various factors such as site, size, resectability, expected morbidity, long term effects etc. Metastatic disease remains a significant challenge and optimal therapeutic strategies still need to be defined. Current management and the role of radiation therapy in Ewing sarcoma are reviewed.

Keywords: Ewing sarcoma, radiation therapy, management

Introduction:

Ewing sarcoma family of tumors (ESFT) are a group of small round cell tumors showing varying degrees of neuroectodermal differentiation with Ewing sarcoma being the least differentiated. Primitive neuroectodermal tumors (PNET) show neuroectodermal differentiation by light microscopy, immune histochemistry (IHC) or electron microscopy [1]. According to WHO classification of bone and soft tissue tumors, Ewings sarcoma/PNET is synonymous with Ewing tumor, peripheral neuroepithelioma, peripheral neuroblastoma and Askin tumor [1]. In most of the patients, a chromosomal translocation leads to the expression of the EWS-FLI1 chimeric transcription factor which is the major oncogene in this pathology [2].

Epidemiology:

Ewing sarcoma is the second most common primary bone tumor of childhood and it most commonly occurs in the second decade of life with a slight male preponderance. The incidence of Ewing sarcoma has been reported to be low in Asian population as compared to Caucasians[3]. Data from Indian population show that it is not so uncommon[4]. The common sites of primary Ewing sarcoma are the long bones of the lower extremities (41%), pelvic bones (26%), and bones of the chest wall (16%)[5]. Extraosseous Ewing sarcoma is more commonly axial in location involving the trunk (32%), extremities (26%), head and neck (18%), the retroperitoneum (16%) etc[6]. Approximately 20-25% of patients present with metastasis at diagnosis. Common sites of metastases include lungs, bones and bone marrow.

Diagnostic Evaluation:

Typical presenting symptoms include pain and swelling with occasional constitutional symptoms like fever, fatigue and loss of weight. Patients should be evaluated and managed by a multidisciplinary team of experts including pediatric oncologists, orthopedic surgeons, radiologists, pathologists and rehabilitation specialists. A biopsy should be performed in a way such that the track and scar can be included in the subsequent resection or radiation portal. Biopsy should be from soft tissue as often as possible to avoid increasing the risk of fracture and should be through rather than between muscle compartments avoiding the neurovascular bundles. A skilled pathologist should be available onsite to confirm adequacy of the material and review the frozen sections. A needle biopsy may be adequate if sufficient tissue can be obtained for histological, cytogenetic and molecular studies. The risk of diagnostic errors and complications increases by as much as 12-fold when the biopsy is improperly done [7]. Ewing sarcoma/PNETs usually strongly express the cell surface glycoprotein MIC2 (CD99) and this can be helpful in diagnosis of small blue round cell tumors. CD99 is however not exclusively specific for ES/PNET and is found in other tumors such as synovial sarcoma, NHL, GIST etc [8]. Approximately 85% patients have expression of EWS-FLI1 chimeric transcription factor resulting from translocation between EWS and FLI-1 gene t(11;22)(q24;q12) [9]. In most of the remaining patients, alternative translocations between EWS and another ETS- family member (ERG, FEV, ETV1, E1AF) are detected [2]. Molecular analysis for EWS-FLI 1 should be considered. The prognostic value of the same remains inconclusive until now[10]. This is being evaluated as potential therapeutic target [11]. Local imaging with MRI with or without CT scan is recommended.

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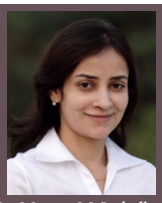
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Conventional staging evaluation includes bilateral bone marrow aspiration and biopsy or MRI of spine and pelvis, bone scan and CT scan of the chest. Serum LDH is an important prognostic marker. Positron emission tomography (PET) combined with conventional imaging is a valuable tool in staging and restaging ESFT with a sensitivity of 96% and specificity of 92% [12]. FDG-PET can also serve as a non-invasive method to predict response to chemotherapy which is a useful prognostic marker.13 Whole-body MRI can be a useful radiation-free modality to detect metastatic lesions with a higher sensitivity than bone scintigraphy [14,15]. Fertility consultation should be done for patients desiring future child bearing before starting therapy.

Prognostic factors:

5-year event free survival approaches around 70% with standard multimodality approach in localized disease [16]. Favorable prognostic factors include extremity tumors, tumor volume <100ml, normal LDH and absence of metastases at presentation. Common adverse prognostic factors include metastatic disease at presentation, extra skeletal presentation, pelvis as the primary site and poor response to induction chemotherapy. Metastatic disease is the most significant adverse prognostic factor. Those with isolated pulmonary metastasis have a slightly better outcome than those with bone or bone marrow metastasis [17]. Survival depends on the site and number of metastases and the tumor burden with 5 year survival rates ranging from approximately 30% with isolated lung metastasis to less than 20% with multiple bone metastases. Older patients do worse than patients younger than 15 years.18 Poor histologic response to chemotherapy is associated with worse outcomes in patients with localized disease [19].

Treatment:

Treatment of Ewing sarcoma has evolved following evidence from large multinational trials over the past few decades with successive improvement in outcomes. Multimodality approach is the key in the management of nonmetastatic Ewing sarcoma.

Chemotherapy:

The prognosis in Ewing sarcoma remained very poor until 1960s in spite of good initial response to local treatment. The introduction of chemotherapy into the treatment regimen dramatically improved the response rates and thus the cure rates. Patients are started on induction chemotherapy for 3-4 cycles followed by local therapy at 12weeks. Restaging should be done with a chest imaging and MRI of the local part before local therapy. Further adjuvant chemotherapy is continued for total treatment duration of about 10-12 months. Chemotherapy with Vincristine, Adriamycin/Actinomycin D, cyclophosphamide, (VAC) alternating with Ifosfamide and Etoposide (IE) administered at a three weekly fashion is the standard regimen. Maintaining adequate dose intensity of chemotherapy is of utmost importance. Interval compressed or dose dense chemotherapy improves DFS and has the potential to improve overall survival [20].

Local therapy:

Local therapy is delivered at the completion of 3-4 cycles of chemotherapy at 12 weeks and comprises of surgery or radiotherapy or both. There are no randomized trials comparing the two modalities. The choice of local therapy depends on the site of the disease, age of the patient, expected functional outcomes and concern over the late morbidities. Although retrospective institutional series suggest superior local control and survival with surgery rather than radiation therapy, most of these studies are compromised by selection bias. A North American intergroup trial showed no difference in local control or survival based on local treatment modality - surgery, radiation therapy, or both [21]. In patients with localized Ewing sarcoma treated in cooperative intergroup studies there was no significant effect of local control modality (surgery, RT, or surgery plus RT) on OS or EFS rates. In the CESS 86 trial, although radical surgery and resection plus RT resulted in better local control rates (100% and 95%, respectively) than definitive RT (86%), there was no improvement in relapse free survival and overall survival [22]. Preoperative radiation therapy can achieve tumor shrinkage and surgical resection with negative margins in cases with borderline resectability and can potentially allow smaller fields and lower radiation doses [23].

Definitive Radiotherapy:

Ewing sarcoma was described by James Ewing in 1921 as "diffuse endothelioma of bone", a distinct entity from osteosarcoma due to its high response to radiation therapy. In the current scenario, definitive radiotherapy remains an effective local therapy strategy for patients with tumors in sites not amenable for surgical resection and in cases where resection is likely to result in unacceptable morbidity. Advances in imaging, tumor delineation, treatment planning and delivery is now allowing greater precision and sparing of normal tissues. Historically, patients were treated with whole bone irradiation. With the POG 8346 trial, adequate involved field RT with MRI based planning became the standard. Current guidelines recommend 1.5 to 2 cm margin from the gross tumor volume. A randomized study of 40 patients with Ewing sarcoma using 55.8 Gy to the prechemotherapy tumor extent with a 2 cm margin compared with the same total-tumor dose after 39.6 Gy to the entire bone showed no difference in local control or EFS [24]. Initial treatment volume include the pre-chemotherapy volume with margin up to a dose of 45Gy, further boost is delivered to the post chemotherapy volume upto a total dose of 55.8Gy to 60Gy. Tumor size and RT dose have been shown to be predictive of local control rates in patients with non-metastatic Ewing sarcoma treated with chemotherapy and definitive RT [25]. Role of hyperfractionated radiotherapy in management of Ewing sarcoma has been evaluated in the CESS 86 trial [22]. No significant advantage has been demonstrated over the standard fractionation and dose. Recent reports suggest that Proton beam therapy can potentially spare more amount of normal tissue but longer follow up is needed to determine its impact on morbidity and cure rates [26]. Radiation therapy is associated with the development of second malignant neoplasms. In a retrospective analysis, the incidence of second malignancy was 20% in patients who received doses of 60 Gy or more and 5% in those who received 48 Gy

to 60 Gy. Those who received < 48 Gy did not develop a second malignancy [27]

Postoperative RT:

Postoperative radiation (PORT) is recommended in cases of intralesional or marginal resection, intraoperative spill and poor pathological response to chemotherapy and is usually initiated at 6-8 weeks following surgery. Current Children's Oncology Group (COG) protocols have more specifically defined adequate margin status. Complete resection is defined as a minimum of 1 cm margin and ideally 2–5 cm around the involved bone. The minimum soft tissue margin for fat or muscle planes is at least 5 mm and for fascial planes at least 2 mm. The Intergroup Ewing Sarcoma Study (INT-0091) recommends 45 Gy to the original disease site plus a 10.8 Gy boost for patients with gross residual disease and 45 Gy plus a 5.4 Gy boost for patients with microscopic residual disease. In the absence of gross residual disease there seems to be no clear benefit to doses over 45 Gy [28]. No radiation therapy is recommended for those who have no evidence of microscopic residual disease following surgical resection. Although not statistically significant, local relapse was least in the combined arm (10.5%) compared with 25% for either surgery or radiotherapy alone [21]. EICESS 92 evaluated the role of postoperative RT in patients with poor pathological response to induction chemotherapy (<90% necrosis). In their analysis there was reduction in local failures (5% vs.12%) in the poor responders if they received PORT [29 In the CESS and EICESS trials, the local failure rate for central primaries was reduced by 50% with PORT. However the role of adjuvant radiotherapy in poor responders and central tumors needs to be clearly defined and the benefits need to be balanced against potential risks of long term effects and second malignancies. For extraskeletal ES, PORT is generally recommended except in good prognosis superficial tumors [30].

Management of metastatic disease:

Standard treatment guidelines for metastatic Ewing sarcoma recommend treatment similar to localized disease [30]. Different chemotherapy agents used are Vincristine, Adriamycin, Cyclophosphamide, Ifosphamide and Etoposide. Addition of IE to VAC does not seem to have additional benefit in this subset of patients [31]. Dose-intense treatment approach with high dose chemotherapy and autologous stem cell transplantation (HDT/SCT) was evaluated in the nonrandomized Euro-EWING 99 R3 study [32]. Even though this may have a potential to improve outcome, it has not become the standard of therapy. Following induction chemotherapy, patients are reassessed with local and chest imaging and previously abnormal investigations are repeated. A progressive disease is treated with palliative intent and the good responders are managed with treatment of primary disease and metastatic sites. Timing of local therapy for both primary site and metastatic sites remain unclear.

Radiotherapy in metastatic disease:

Whole lung irradiation (WLI) in patients with lung-only metastases has shown improved disease free and overall survival in various trials. Patients with lung metastasis should be considered for whole lung irradiation even after complete resolution following chemotherapy [33] Doses of 12 to 21 Gy have been used and are usually well tolerated [34]. Hemithoracic irradiation is recommended in patients with chest wall tumor with pleural nodules, pleural effusion or positive pleural cytology. Bone metastases in Ewing sarcoma should be treated with similar doses as the primary site. They may be treated simultaneously or following completion of chemotherapy depending on the risk of marrow suppression. In the phase II POG/CCG trial which evaluated the role of intensive chemotherapy, local treatment for primary disease was done after completion of 21weeks of chemotherapy and that of metastatic disease was done after week 39 chemotherapy [35]. With the emergence of stereotactic body radiotherapy (SBRT), it is now possible to deliver ablative doses to sites of bone metastases with excellent sparing of normal tissues. SBRT delivered in one to five fractions can also minimize interruptions of systemic therapy.

Treatment of relapse:

Outlook of patients who relapse remain unfavorable. Late onset relapse (>2years) and strictly localized disease has a favorable outcome [36]. Chemotherapy regimens in relapse settings are not standard. Two phase II studies have demonstrated upto 33% partial responses in relapsed refractory Ewing's sarcoma with the combination of Topotecan and Cyclophosphamide [37]. The combination of Irinotecan and Temozolomide has demonstrated clinical responses.38 Gemcitabine in combination with Docetaxel has shown modest activity [39]. Newer drugs and targeted therapies are being evaluated. Radiotherapy and/or surgery may play a role in improving control rates.

Indian Data:

There is paucity of data from Indian population. In a retrospective analysis, symptom duration >4 months, tumor diameter >8cm and baseline WBC >11×10(9)/L were predictive of poorer outcomes [40]. Optimal surgical margin in extra skeletal Ewing sarcoma in children was evaluated by Laskar et al who concluded that clear margins of resection correlated with local control irrespective of margin size[41] Survival rates in India remain dismal in spite of the advancement seen in the western world [42]. Patients tend to present with advanced stage disease and often default treatment due to socioeconomic factors.

Conclusions

The management of Ewing sarcoma has significantly evolved over the last few decades with consequent improvements in survival and functional outcomes. Treatment mandates multidisciplinary co-ordination involving Medical, Surgical and Radiation Oncologists, Orthopedic surgeons, Rehabilitation specialists, Pediatricians and others. Dose intensity of chemotherapy and optimal timing and modality of local therapy appear to significantly influence outcomes and survival rates. Metastatic disease represents a major challenge and optimal treatment strategies still need to be defined.

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