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Ewing Sarcoma

Ewing sarcoma in adults treated with modern radiotherapy techniques

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ABSTRACT

Background and purpose: To evaluate local control and survival outcomes in adults with Ewing sarcoma (ES) treated with radiotherapy (RT).
Material and methods: Retrospective review of all 109 patients age ⩾18 treated for ES with RT to the primary site at Memorial Sloan Kettering Cancer Center between 1990 and 2011. RT was used as the definitive local control modality in 44% of patients, preoperatively for 6%, and postoperatively for 50%.
Results: Median age at diagnosis was 27 years (range, 18–67). The 5-year local failure (LF) was 18%. Differences in LF were not identified when evaluated by modality of local control (RT versus combined surgery and RT), RT dose, fractionation, and RT technique. However, margin status at time of resection significantly predicted LF. The 5-year event-free survival and overall survival rates were 44% and 66% for patients with localized disease, compared with 16% and 26% for metastatic disease ($p = 0.0005$ and 0.0002). Tumor size, histopathologic response to chemotherapy, and treatment on or according to a protocol were also significantly associated with survival.
Conclusions: This series of adults treated with modern chemotherapy and RT had prognostic factors and outcomes similar to adolescents with ES. All adults with ES should be treated with an aggressive, multidisciplinary approach.

The Ewing sarcoma family of tumors consists of a group of related small round cell neoplasms including osseous and extraosseous Ewing sarcoma (ES) and peripheral primitive neuroectodermal tumor. ES occurs most commonly in the second decade of life [1], and accordingly most of the existing literature consists of multidisciplinary trials reporting on outcomes in children and adolescents. Few studies have investigated adult outcomes, and concerning the existing studies, there is an ongoing debate regarding prognosis. In some series, adults have worse outcomes [2–4], while in others, outcomes are similar to those among children and adolescents [5–9]. Additionally, many of the reports on adults are single-institution series with a small number of patients, treated before the era of modern radiotherapy (RT) techniques (for example, intensity-modulated radiotherapy [IMRT]) and the addition of ifosfamide and etoposide to the chemotherapy regimen.

There is also an ongoing debate regarding the optimal modality of local control (LC) for ES. While some studies have reported better LC with surgery than RT [10–12], there is a selection bias in that the more favorable tumors are amenable to surgery. RT patients are often a negatively selected group with tumors in unfavorable locations [12,13]. In practice, the modality of LC is determined on an individual basis, depending on the size and location of the tumor, the response to chemotherapy, and the balance between enhancing LC while minimizing morbidity. Regardless, RT remains an important part of treatment for nonoperable tumors, in the postoperative setting for close or positive margins, and for situations where RT would result in better functionality.

Given the conflicting literature on both adult outcomes and LC achieved with RT, we evaluated prognostic factors, patterns of failure, and outcomes among the adult ES population treated with RT in the modern era.

Methods

Patients

This is a single-institution, retrospectively ascertained cohort of adult patients ⩾18 years of age at diagnosis treated with RT to their primary site at Memorial Sloan Kettering Cancer Center (MSKCC) between 1990 and 2012. Exclusion factors included RT treatment for a recurrence, RT at an outside institution, palliative RT for metastatic disease only, or primary intraoperative RT. Workup for all patients consisted of a computed tomography (CT) scan or magnetic resonance imaging (MRI) of the primary site,

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chest CT, and bone marrow aspirate and biopsy to evaluate for metastatic disease. After treatment, patients were followed with imaging of the primary site and chest every 3 months for the first 2 years; every 6 months from 2 to 5 years; and annually after 5 years.

Radiotherapy

Radiation treatment charts and films were reviewed to determine the dose, fractionation, technique, and field of radiation. All patients had MRI and CT scan-based treatment planning. The gross tumor volume (GTV) consisted of the initial extent of the tumor at diagnosis, but allowing for chemotherapy response at pushing borders such as into the pelvic or thoracic cavity. The clinical target volume (CTV) was obtained by adding a 1 cm margin to the GTV to account for microscopic disease, and the planning target volume was obtained by adding a 0.5 cm margin to the CTV to account for daily variability in set-up. Doses were assigned based on timing and reason for RT (preoperative, postoperative, or definitive), the treatment protocol, patient characteristics, and tumor proximity to critical organs such as the spinal cord. In general, 55.8 Gy was used for definitive RT or gross residual disease in the postoperative setting, 45–50.4 Gy for close (<5 mm) or positive margins and/or poor chemotherapeutic response in the postoperative setting, and 45–50.4 Gy preoperatively. Most patients (59%) were treated with IMRT. Eighty-four percent of patients received daily fractions of 1.8 Gy, while 16% received hyperfractionated RT with 1.5 Gy twice per day (interfractional interval $\geqslant$6 h) as per the institutional P6 protocol [14]. Additionally, 65% of patients with lung metastases received 12–15 Gy whole lung irradiation (n = 15), and 80% of patients with bony metastases received 20–40 Gy RT to the site of bony disease (n = 12). Four patients were treated with 12–15 Gy intraoperative radiotherapy in addition to their external beam RT.

Chemotherapy

All patients received multiagent chemotherapy. Seven patients treated in the 1990s received vincristine, doxorubicin, and cyclophosphamide. The other 102 patients were treated with vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide, 19 of which were on the P6 protocol [14]. Overall, 77 of the 109 patients were treated on or according to a pediatric protocol. Ten patients received irinotecan and temozolomide in addition to the typical 5-drug regimen per an ongoing Phase II trial. Additionally, seven patients with neurological symptoms at diagnosis from spinal tumors were treated without vincristine, and nine patients had a shortened course of chemotherapy due to toxicity.

Statistics

Event-free survival (EFS) was calculated as the time from initiation of treatment to the first event. Events were defined as local and/or distant failure or progression, treatment-related malignancy, or death. A local failure was defined as relapse in the primary tumor bed or disease progression at the primary site. Treatment plans and imaging at the time of failure were reviewed to determine if the local failure occurred within the RT field. Overall survival (OS) was calculated as the time from initiation of treatment to death from any cause. Patients without an event were censored at the time of last follow-up. The Kaplan–Meier method was used to assess the EFS and OS, and a competing-risks analysis was used to assess the cumulative incidence of local and distant failures. Survival curves among different subgroups of patients were compared with the Mantel log-rank test. Cumulative incidence curves were compared with Gray's method. A Cox proportional hazards model with forward stepwise selection was used for multivariate analysis (MVA) to assess for independent prognostic factors for survival; variables with $p < 0.10$ on univariate analysis (UVA) were included in the MVA, except histopathologic response to chemotherapy due to the incomplete data set. $p \leqslant 0.05$ was considered significant. All statistical analyses were performed using XLSTAT, version 16.1.01, Addinsoft®.

Results

Patient and tumor characteristics (Table 1)

Median age at diagnosis was 27 years (range, 18–67), with 20 patients $\geqslant$40 years. Seventy percent of patients had localized disease while 30% had metastatic disease. Given that all of our patients received RT, the majority of tumors (85%) were centrally located, the most common primary sites being the pelvis (30%) and spine (22%). Fifty-six percent were $\geqslant$8 cm in maximum dimension at diagnosis. Among the 34 patients with metastatic disease, 41% had distant disease only in the lungs. Median follow-up length for the surviving patients was 4.8 years (range, 1.0–17.5).

Treatment

The median time from initiation of chemotherapy to RT was 15.6 weeks (range, 0–42 weeks, with one patient receiving RT on day 0 due to spinal cord compression). Forty-four percent of patients received definitive RT, 50% postoperative RT, and 6% preoperative RT. The median dose for the entire cohort was 55.8 Gy (range, 27–66 Gy). Median dose was 55.8 Gy (range, 36–63 Gy) for definitive RT; 50.4 Gy (range, 27–66 Gy) for postoperative RT, and 50.2 Gy (range, 45–54 Gy) for preoperative RT. Three patients did not receive their prescribed dose: 1 patient planned for 45 Gy only received 27 Gy due to thrombocytopenia, and 2 patients were

Table 1
Patient and tumor characteristics.

	Patients with localized disease (n = 76)	Patients with metastatic disease (n = 33)	Total patients (n = 109)
Gender			
Female	25 (33%)	8 (24%)	33 (30%)
Male	51 (67%)	25 (76%)	76 (70%)
Site			
Extremity	11 (14%)	5 (15%)	16 (15%)
Pelvis	15 (20%)	18 (55%)	33 (30%)
Spine	18 (24%)	6 (18%)	24 (22%)
Head and Neck	15 (20%)	0 (0%)	15 (14%)
Chest Wall	9 (12%)	3 (9%)	12 (11%)
Other*	8 (11%)	1 (3%)	9 (8%)
Primary tumor origin			
Osseous	30 (39%)	22 (67%)	52 (48%)
Non-osseous	46 (61%)	11 (33%)	57 (52%)
Tumor size			
<8 cm	36 (50%)	10 (31%)	46 (44%)
$\geqslant$8 cm	36 (40%)	22 (69%)	58 (56%)
Metastases			
Lung only	–	14 (42%)	14 (42%)
Other	–	19 (58%)	19 (58%)
Modality of LC			
Definitive RT	27 (36%)	21 (64%)	48 (44%)
Surgery + postoperative RT	43 (57%)	11 (33%)	54 (50%)
Surgery + preoperative RT	6 (8%)	1 (3%)	7 (6%)

* Other = abdomen, mediastinum, supraclavicular fossa.