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CLINICAL INVESTIGATION **Sarcoma**

RADIATION THERAPY FOR EWING'S SARCOMA: RESULTS FROM MEMORIAL SLOAN-KETTERING IN THE MODERN ERA

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Purpose: To evaluate the outcomes of patients with Ewing's sarcoma family of tumors (ESFT) treated with modern radiotherapy techniques with MRI along with optimal chemotherapy.

Methods and Materials: The records of all 60 patients with ESFT who received radiation to the primary site between 1990 and 2004 were reviewed. All patients received chemotherapy, including vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide. Radiation was used as the sole modality for local control in 31 patients and was given either before ($n = 3$) or after surgical resection ($n = 26$) in the remainder. All patients had MRI and CT scan–based treatment planning, and 43% received intensity-modulated radiation therapy. Radiation doses ranged from 30 Gy to 60 Gy (median, 51 Gy), and 35% received hyperfractionated radiotherapy.

Results: Median age was 16 years (range, 2–40 years). Because of selection bias for radiotherapy, the majority of primary tumors were centrally located (72%): spine ($n = 18$), pelvis ($n = 15$), extremities ($n = 12$), chest wall ($n = 5$), head and neck ($n = 5$), and other ($n = 5$). Thirty-eight percent of patients presented with metastatic disease, and 52% of primary tumors were ≥8 cm. Actuarial 3-year local control was 77%. The presence of metastases at diagnosis was an adverse prognostic factor for local control (84% vs. 61%, $p = 0.036$). No other predictive factors for local failure were identified. In patients without metastatic disease, 3-year disease-free and overall survival rates were 70% and 86%, respectively, whereas in patients with metastases they were both 21%. Follow-up of surviving patients was 6–178 months (median, 41 months).

Conclusion: In this unfavorable cohort of ESFT patients, radiation therapy was an effective modality for local control, especially for patients without metastases. The presence of metastases at diagnosis is a predictive factor not only for death but also for local failure. © 2006 Elsevier Inc.

Ewing's sarcoma, Radiotherapy, Local control.

INTRODUCTION

The Ewing's sarcoma family of tumors (ESFT) is a spectrum of small round-cell neoplasms that includes osseous and extraosseous Ewing's sarcoma (ES), peripheral primitive neuroectodermal tumor, and Askin's tumor of the chest wall. Advances in the multidisciplinary management of ESFT over the last several decades have markedly improved the survival rates of children with ESFT, with long-term survival reaching 80% in patients with nonmetastatic ES (1–3). Results from large cooperative trials conducted by the Intergroup Ewing's Sarcoma Study and the European Cooperative Ewing's Sarcoma Study (CESS) Group have guided the multiagent systemic therapy regimens currently used in the management of ESFT (4–7). Meanwhile, the decision regarding the optimal modality for achieving local tumor control—surgery, radiation therapy (RT), or both—remains unclear. The issues of balancing long-term local disease control with long-term functional results (including the risks of late fracture and second malignant neoplasms) have become more important with the improvement in prognosis and long-term survival.

Some retrospective studies that have evaluated the efficacy of these local therapy modalities have suggested that patients treated with surgery have higher rates of local tumor control and survival, but the patients treated with RT typically represented a prognostically unfavorable population in terms of tumor site (8–14). As a result, current treatment is tailored to the individual patient, with the goal of maximizing local tumor control while minimizing treatment-related morbidities.

In the past, radical surgical techniques led to poor functional outcomes, and patients often received RT for local tumor control (15). Although the trend is now shifting toward surgery because of advances in surgical techniques

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and limb-sparing procedures, as well as concerns regarding RT-induced secondary malignancies, RT remains a necessary procedure for patients with nonoperable tumors, such as those in the pelvis or spine, for patients with close or positive margins postoperatively, in cases in which RT provides markedly improved functional outcomes, or in skeletally immature patients for whom nonablative surgical options might be limited (16, 17). Therefore, it is important to analyze the efficacy of RT in achieving local control, to evaluate prognostic factors for local control, and to determine long-term functional outcomes after RT, including the incidence of secondary malignancies. On the basis of recent data collected from patients treated with definitive and postoperative RT for ESFT at Memorial Sloan-Kettering Cancer Center (MSKCC), we report outcomes and patterns of local failure.

METHODS AND MATERIALS

A retrospective chart review was conducted for all 60 ESFT patients treated with RT to the primary site in the Department of Radiation Oncology at MSKCC between January 1990 and August 2004. All patients were previously untreated and had a diagnosis of ES, extraosseous ES, or primitive neuroectodermal tumor, as proven by pathology reports. Exclusion factors included previous RT treatment, RT treatment at another institution, primary intraoperative RT, and RT treatment for a recurrence.

All patients in this study underwent routine systemic workup and disease evaluation that included CT or MRI of the primary tumor site, CT of the chest, and bone marrow aspirates and biopsy for evaluation of metastatic disease. All patients received multiagent chemotherapy, with the majority of the patients receiving chemotherapy according to the MSKCC institutional protocol P6 (18). Thirty-one patients were treated on the P6 protocol, which consisted of vincristine, adriamycin, cyclophosphamide, ifosfamide, and etoposide. The 7 most recently treated patients were treated according to a modified version of this same protocol, with a higher dose of ifosfamide and celecoxib as an antiangiogenic agent. The remaining 22 patients were treated with regimens using similar chemotherapeutic drugs on or according to national protocols, including Children's Cancer Group (CCG) 7942, CCG 7951, Children's Oncology Group (COG) AEWS 0031, and COG 7881.

All patients had biopsy confirmation of disease, and 26 patients underwent partial or total surgical resection before receiving RT. Of these 26 patients, 14 had surgery at the time of diagnosis, and the remaining 12 had surgery after three to four cycles of neoadjuvant chemotherapy. All postoperative RT patients had either incomplete resection or histologically close or involved surgical margins. A close margin was defined as <5 mm. The amount of residual tumor before RT was determined by reviewing the most recent imaging before initiation of RT and physicians' notes, as well as pathology and operative reports for postoperative patients. Three patients received preoperative RT to achieve more conservative resections.

Specific characteristics of RT treatment, including dose, fractionation, and technique, were determined by reviewing radiation treatment charts and films. The planning target volume consisted of the initial extent of the tumor plus a 2-cm margin, except in cases in which this would result in overdosing of an adjacent critical structure (e.g., epiphysis, spinal cord, ovary). The dose was prescribed to the isodose line that completely encompassed the planning target volume. Doses varied according to whether the RT was preoperative, definitive, or postoperative; the proximity to critical organs (e.g., the spinal cord); individual patient characteristics; and the treatment protocol, although the standard full-dose of RT for definitive treatment was 55.8 Gy delivered in 1.8-Gy daily fractions. Twenty-one patients were treated with a hyperfractionated regimen according to an institutional protocol at that time. The target doses were 54 Gy in cases of gross residual disease ($n = 8$) and 45 Gy for microscopic residual disease ($n = 11$) delivered in 1.5-Gy fractions twice per day, and the target volume consisted of the initial extent of the tumor plus a 3-cm margin (19).

Local failure in definitive RT cases was defined as growth of the residual abnormality or recurrence of the lesion after complete resolution on imaging and clinically. Sites of distant metastases (lung and bone) were also routinely irradiated. Five patients with metastatic disease received total body irradiation in rapid sequence to local RT according to stem cell transplant protocols. Of these 5 patients, 4 received 15 Gy in 1.25-Gy fractions three times per day, and the last patient received 12 Gy in 2-Gy fractions twice per day.

The Kaplan-Meier method was used to calculate actuarial rates of local control, disease-free survival, and overall survival from the first date of chemotherapy (20). Potential differences in actuarial outcomes between groups of patients were evaluated with the Mantel log–rank test for censored data (21).

RESULTS

Patient and tumor characteristics

The age range at diagnosis for these 60 patients was 2–40 years (median, 16 years); 58% were aged $\leq$18 years. Minimum follow-up of patients was 2 months and ranged to a maximum of 14.9 years, with a median follow-up for surviving patients of 41 months. Fourteen of the patients (23%) were followed for more than 5 years and therefore were potentially at risk for radiation-associated secondary malignant neoplasms. There were 31 male and 29 female patients. The primary sites are detailed in Table 1; 72% of patients had centrally located primary tumors in the chest ($n = 5$), pelvis ($n = 15$), spine ($n = 18$), and other sites, including the scapula and abdomen ($n = 5$).

Additional tumor characteristics, such as presence of metastases at diagnosis and size of primary tumor, are detailed in Table 1. Thirty-eight percent of the patients presented with metastatic disease, and 52% of all primary tumors had a maximum diameter of $\geq$8 cm at diagnosis. Therefore, this series represents a group of patients with generally poor prognostic factors for local control and survival.

Treatment characteristics

All patients included in this study were treated with a combination of chemotherapy and preoperative, postoperative, or definitive RT. Forty-three percent of patients received postoperative RT for partial resections or close or positive margins, whereas 52% received definitive and 5% received preoperative RT. Twenty-six of the more recent patients were treated with intensity-modulated RT (IMRT).