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Clinical Investigation

Intraoperative Electron-Beam Radiation Therapy for Pediatric Ewing Sarcomas and Rhabdomyosarcomas: Long-Term Outcomes

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Summary

With advancements in multimodal treatment for pediatric patients with Ewing sarcomas and rhabdomyosarcomas, intraoperative radiation therapy has emerged to minimize treatment morbidity. These mature clinical data add support that intraoperative radiation therapy promotes high local control in the context of an innovative multimodality approach.

Purpose: To assess long-term outcomes and toxicity of intraoperative electron-beam radiation therapy (IOERT) in the management of pediatric patients with Ewing sarcomas (EWS) and rhabdomyosarcomas (RMS).

Methods and Materials: Seventy-one sarcoma (EWS n = 37, 52%; RMS n = 34, 48%) patients underwent IOERT for primary (n = 46, 65%) or locally recurrent sarcomas (n = 25, 35%) from May 1983 to November 2012. Local control (LC), overall survival (OS), and disease-free survival were estimated using Kaplan-Meier methods. For survival outcomes, potential associations were assessed in univariate and multivariate analyses using the Cox proportional hazards model.

Results: After a median follow-up of 72 months (range, 4-310 months), 10-year LC, disease-free survival, and OS was 74%, 57%, and 68%, respectively. In multivariate analysis after adjustment for other covariates, disease status ($P = .04$ and $P = .05$) and R1 margin status ($P < .01$ and $P = .04$) remained significantly associated with LC and OS. Nine patients (13%) reported severe chronic toxicity events (all grade 3).

Conclusions: A multimodal IOERT-containing approach is a well-tolerated component of treatment for pediatric EWS and RMS patients, allowing reduction or

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substitution of external beam radiation exposure while maintaining high local control rates.

Introduction

Pediatric sarcomas form a heterogeneous group of mesenchymal skeletal and extraskeletal malignancies (1). Over the last few decades a multimodal treatment approach has improved dramatically the prognosis for children with localized Ewing sarcomas (EWS) and rhabdomyosarcomas (RMS) (65%-70% event-free survival rate) (2, 3). Although EWS and RMS are considered radiosensitive, the proportion of patients whose primary tumors are treated with external beam radiation therapy (EBRT) alone has steadily declined over the past 30 years (4). Increased awareness of the late effects of radiation therapy (particularly second malignancies and growth disturbances) and advances in imaging and orthopedic surgery has increased the use of surgical management for these tumors (5). Because complete resection is often difficult or morbid to perform, adjuvant EBRT still plays an important role in local control (LC) promotion (2, 3). The challenge of achieving LC with a suitable therapeutic ratio is especially demanding in the pediatric population and results in a very narrow therapeutic window in which to balance benefits and late effects. The known detrimental effects of irradiating large volumes with EBRT prompted clinicians to explore limited radiation therapy alternatives, such us intraoperative radiation therapy (IORT) as an adapted technical opportunity to be explored in innovative practice (6). Several collaborative groups are trying to determine the optimal radiation therapy dose and volume necessary to further improve (intensification [reduce the EBRT dose and add an IORT boost]) and/or maintain (de-escalation [substitution of IORT for the entire EBRT dose]) current clinical outcomes and minimize treatment morbidity (7-11). In this complex clinical scenario we conducted a joint analysis of multi-institutional data (3 Spanish institutions), to investigate on a large and mature cohort of patients evidence of the contribution of an intraoperative electron-beam radiation therapy (IOERT)-containing multimodality approach in promoting LC with acceptable tolerance.

Methods and Materials

Patient characteristics and staging evaluation

The IORT Spanish multicentric database was searched for pediatric patients (aged <21 years) with pathologically confirmed primary or locally recurrent RMS and EWS without evidence of distant metastasis (head and neck, n=9 [12%]; extremity/trunk, n=46 [65%]; pelvis, n=16 [23%]). Patients with primary tumors treated locally (n=46, 65%) with combined reduced-dose EBRT (in whom EBRT doses after surgery would exceed expected normal tissue tolerance levels), surgery, plus an IOERT boost, and patients with locally recurrent (n=25, 35%) tumors treated with surgery and IOERT for local relapse (LR) were eligible. Treatment for the initial primary tumor in patients with local recurrence was induction chemotherapy (CT) followed by surgery (n=10, 40%), EBRT (n=11, 44%), or surgery plus EBRT (n=4, 16%). Data were prospectively collected and retrospectively analyzed at the time of scheduled follow-up. From June 1983 to September 2012, 71 patients were identified (RMS, n=34; Ewing sarcoma of the bone, n=21; extraskeletal Ewing sarcoma, n=16). Patient and treatment characteristics are listed in Table 1; there were no significant differences in baseline variables between patients in the RMS and EWS groups. Pretreatment evaluation consisted of a complete history and physical examination, complete blood count, renal and liver function tests, chest X ray, and computed tomography or magnetic resonance imaging of the tumor site and chest. The protocol followed the recommendations of the Declaration of Helsinki. The multi-institutional ethics committee approved the protocol, and written informed consent was obtained from all patients.

Treatment characteristics

Details of the EBRT technique, IOERT, and adjuvant CT followed standards previously described (11). A range of multiagent CT protocols was used because of the wide treatment period included in this study. Most commonly used agents consisted of vincristine, actinomycin D, and cyclophosphamide (use of agents such as doxorubicin and iphosfamide was based on institutional protocol recommendations). The goal of surgery was gross total resection and was subsequently confirmed on postoperative imaging in all cases. Because a conservative approach was preferred, a wide resection was possible in 73% (n=52) and marginal resection in 27% (n=19) (12). Twenty percent of the patients (n=14) after a prior excision, excisional biopsy, or an intralesional surgical procedure underwent a tumor bed re-excision. A single attempt for definitive resection after incisional or core needle biopsy was done for the remaining 80% of the patients (n=57). In patients who had more than 1 procedure, the most radical approach is listed. The IOERT program was performed in a nondedicated linear accelerator with outpatient radiation therapy activity by the 3 institutions. Before surgical reconstruction and after resection, a median dose of 10 Gy (range, 7.5-20 Gy) was delivered in a single fraction to a 1-field (n=48, 68%) or 2-field (n=23, 32%) surgical bed volume, using a median energy of 9 MeV (range,