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Local Control With Reduced-Dose Radiotherapy for Low-Risk Rhabdomyosarcoma: A Report From the Children's Oncology Group D9602 Study

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Summary

In summary, this study supports the use of reduced RT doses for local control of RMS in lymph node–negative, low-risk patients with orbital primary tumors or microscopic tumor after resection. Cyclophosphamide-containing regimens are associated with lower rates of local failure for these patients.

Purpose: To analyze the effect of reduced-dose radiotherapy on local control in children with low-risk rhabdomyosarcoma (RMS) treated in the Children's Oncology Group D9602 study.

Methods and Materials: Patients with low-risk RMS were nonrandomly assigned to receive radiotherapy doses dependent on the completeness of surgical resection of the primary tumor (clinical group) and the presence of involved regional lymph nodes. After resection, most patients with microscopic residual and uninvolved nodes received 36 Gy, those with involved nodes received 41.4 to 50.4 Gy, and those with orbital primary tumors received 45 Gy. All patients received vincristine and dactinomycin, with cyclophosphamide added for patient subsets with a higher risk of relapse in Intergroup Rhabdomyosarcoma Study Group III and IV studies.

Results: Three hundred forty-two patients were eligible for analysis; 172 received radiotherapy as part of their treatment. The cumulative incidence of local/regional failure was 15% in patients with microscopic involved margins when cyclophosphamide was not part of the treatment regimen and 0% when cyclophosphamide was included. The cumulative incidence of local/

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Nonbladder genitourinary primary sites in girls do not seem to confer any special favorable biologic feature that would permit the omission of RT, and therefore these children should receive RT/brachytherapy as part of their treatment regimen. The current COG RMS protocols continue the use of these reduced RT doses, with the addition of a moderate cumulative dose of cyclophosphamide.

regional failure was 14% in patients with orbital tumors. Protocol-specified omission of radiotherapy in girls with Group IIA vaginal tumors ($n = 5$) resulted in three failures for this group. **Conclusions:** In comparison with Intergroup Rhabdomyosarcoma Study Group III and IV results, reduced-dose radiotherapy does not compromise local control for patients with microscopic tumor after surgical resection or with orbital primary tumors when cyclophosphamide is added to the treatment program. Girls with unresected nonbladder genitourinary tumors require radiotherapy for postsurgical residual tumor for optimal local control to be achieved.

Keywords: Rhabdomyosarcoma, Radiotherapy, Low risk, Local control

Introduction

The prospect of cure for children with rhabdomyosarcoma (RMS) has improved over the past three decades. Currently, children with favorable risk factors have a 5-year failure free survival (FFS) rate greater than 85% (1). However, therapy for RMS is intensive, requiring multimodality treatment with chemotherapy and surgery and/or radiotherapy (RT). Before this current study was undertaken, the Intergroup Rhabdomyosarcoma Study Group (IRSG) studies focused primarily on exploring therapies to improve FFS. This recently completed generation of studies (D-series: D9602, D9802, and D9803) focused on risk-adapted therapy: investigating new treatment agents and strategies for those with average and high-risk disease, and minimizing therapy while maintaining good outcomes for those with low-risk disease. Previous IRSG protocols had typically used radiation doses of 41.4 Gy for patients with microscopic residual tumor after initial resection of the primary tumor, and 50.4 Gy or more for patients with gross residual tumor. The excellent results obtained in these trials in certain "low-risk" patient populations (defined below) presented the opportunity to investigate selectively decreasing the intensity of therapy for patients with favorable risk factors. Additionally, single-institution reports suggested that RT doses for microscopic residual RMS might be reduced without compromising local control (2, 3). In the Children's Oncology Group (COG) low-risk study, D9602, a major objective was to decrease the dose of RT without compromising FFS in comparison with the results from the IRS III and IRS IV studies. This report details the results of this strategy on local control in children with low-risk RMS.

Methods and Materials

Patients with RMS were categorized according to the IRSG pretreatment staging system and the IRSG surgicopathologic group classification as detailed in Table 1 (4). Low-risk patients eligible for D9602 included all children with nonmetastatic RMS in a "favorable" site (orbit, nonparameningeal head and neck, nonbladder/prostate genitourinary and biliary tract) and children with nonmetastatic RMS in an "unfavorable" site (bladder/prostate, extremity, parameningeal, or other not specifically listed as a favorable site) who had undergone a gross total resection of all tumor (Group I or Group II) at the time of diagnosis (Figure). When first opened in September 1997, D9602 included previously untreated patients under 21 years old with a histologic diagnosis of embryonal RMS, ectomesenchymoma, alveolar RMS, or undifferentiated sarcoma. After September 1999, the eligibility criteria were changed to exclude patients with alveolar and undifferentiated histologic features and to move them to the "intermediate-risk" study, D9803. The patients with embryonal RMS form the study population for this report. Clinical staging of regional lymph nodes was accepted for all patients initially, but beginning in July 1999, regional lymph node sampling was required for all patients with extremity primary sites. Beginning March 2000, children 10 years old or older with paratesticular primary tumors and normal staging computed tomography images of the abdomen and pelvis were required to have a staging ipsilateral retroperitoneal lymph node dissection before entry into the study (5). Eligible patients were further stratified into two subgroups, A and B, based on anticipated prognosis (Figure). Patients were required to start protocol therapy within 6 weeks of their initial surgical procedure.

Local therapy

An initial surgical procedure was performed in all cases to obtain a histologic diagnosis. A more aggressive surgical procedure was performed if there was thought to be a chance of achieving a gross total resection without compromising function or cosmesis. Group I patients received no further local therapy. Group II patients and Group III patients with orbital tumors received RT beginning at Week 3. Patients with nonorbital Group III tumors were reevaluated for second-look operation (SLO) at Week 12. Children with Group III, lymph node−negative primary vaginal tumors responding to chemotherapy by Week 12 were reevaluated at Weeks 20 and 28 for continued response. If biopsy and clinical examination at those times showed a complete response, then no local therapy was given. If tumor persisted, SLO was considered. Postoperative RT was given only for postoperative residual gross or microscopic tumor. For other Group III patients with nonorbital