EWING SARCOMA OF THE RIB: RESULTS OF AN INTERGROUP STUDY WITH ANALYSIS OF OUTCOME BY TIMING OF RESECTION

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Objective: We sought to establish the outcome and optimal therapeutic sequence for patients with nonmetastatic Ewing sarcoma/primitive neuroectodermal tumor of the chest wall.

Methods: Patients 30 years of age or younger with nonmetastatic Ewing sarcoma/primitive neuroectodermal tumor of the bone were randomly assigned to receive vincristine, doxorubicin, cyclophosphamide, and dactinomycin or those drugs alternating with ifosfamide and etoposide. Local control was obtained with an operation, radiotherapy, or both.

Results: Fifty-three (13.4%) of 393 patients had primary tumors of the chest wall (all rib). Event-free survival at 5 years was 57% for the chest wall compared with 61% for other sites ($P > .2$). Ifosfamide and etoposide improved outcome in the overall group (5-year event-free survival, 68% vs 54%; $P = .002$), and a similar trend occurred in chest wall lesions (5-year event-free survival, 64% vs 51%). Patients with chest wall lesions had more attempts at initial surgical resection (30%) than those with other primary tumor sites (8%, $P < .01$). The attempt at initial resection for chest wall lesions did not correlate with size. Initial resections at other sites were restricted to smaller tumors. Initial resection resulted in negative pathologic margins in 6 of 16 patients, whereas the delayed resection resulted in negative margins in 17 of 24 patients ($P = .05$). Although there was no difference in survival by timing of the operation in rib lesions, a higher percentage of patients with initial surgical resection received radiation than those with resection after initial chemotherapy ($P = .13$).

Conclusions: Although rib primary tumors are significantly larger than tumors found in other sites, their outcome is similar. We favor delayed resection whenever possible to minimize the number of patients requiring radiation therapy. (J Thorac Cardiovasc Surg 2000;119:1154-61)

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Ewing sarcoma is the most frequent chest wall tumor occurring in children and adolescents. It is an extremely aggressive tumor, and management requires intensive local therapy with surgical resection, radiotherapy, or both, as well as adjuvant chemotherapy to prevent or treat metastases. Local recurrence in this tumor has been frequent. An intergroup study with two new agents in the treatment of this tumor recently has been completed. We have reviewed the patients in this study with chest wall tumors because particular consideration is required for treatment of this location. Radiation administered to the chest is less well tolerated than that administered to other sites because of exposure to the heart and lungs. Also, the ribs have often been considered as expendable bones in contrast to the central axial skeleton and certain long bones of the extremities.

Methods

Patients and therapeutic plan. Intergroup study INT-0091 (CCG 7881, POG 8850) was opened to all member institutions of the Children's Cancer Group and the Pediatric Oncology Group in December 1988 and closed in November 1992. Patients accrued to this study were 30 years of age or less at diagnosis, with a primary bone tumor that had a histologic diagnosis of Ewing sarcoma, peripheral neuroectodermal tumor, or primitive sarcoma of bone. Prior anticancer therapy other than an operation to obtain a diagnosis was not allowed. To retain eligibility, protocol chemotherapy had to start within 1 month of the diagnostic biopsy. Patients, guardians, or both had to give informed written consent according to institutional guidelines to participate.

Patients were randomized at study entry to receive standard chemotherapy with doxorubicin, vincristine, cyclophosphamide, and dactinomycin or to receive the experimental therapy consisting of those 4 drugs alternating with courses of ifosfamide and etoposide. Randomization was stratified into groups according to the presence of metastases. Details of the chemotherapy regimens are presented elsewhere.¹ This report is restricted to patients without metastatic disease at diagnosis.

Local control measures consisted of either radiation therapy, an operation, or both. The protocol called for delivery of local control at 12 weeks. The treating physicians decided which local control modality to use in each case, and this factor was not a randomized variable; the protocol allowed an operation for tumors deemed to be resectable. For patients receiving radiotherapy alone, the initial tumor volume (soft tissue and osseous extent of tumor) with a 3-cm margin was treated to 4500 cGy. This was followed by a reduction in treatment volume to the postchemotherapy, preradiotherapy extent of tumor for an additional 1080 cGy, resulting in a total dose of 5580 cGy. Patients with residual tumor after an operation also were irradiated after these dose-volume guidelines

for gross residual disease and 4500 cGy with a 1-cm margin for microscopic disease. The protocol allowed for attempted surgical resection before the start of chemotherapy and after consultation with the study chair and surgical members of the study committee.

Estimation of size of tumor at diagnosis. The 3 largest perpendicular measures of the patient's primary tumor, as determined by computed tomography, were to be supplied at the time of study entry. For patients for whom all 3 measurements were reported, tumor volume was estimated by the product of the 3 perpendicular measures. If one or more of the measurements were not available, the tumor volume was not estimated.

Statistical analysis. Adverse event-free survival (EFS) was defined to be the time from study entry until disease progression, diagnosis of a second malignant neoplasm, death, or last patient contact when an event was considered to have occurred, whichever came first. Otherwise, the patient was censored at the date of last contact. Data current to December 1997 were used in the analysis.

For a patient to be considered capable for evaluation for local control, the individual must have started maintenance after all local interventions were completed. Adverse EFS after local control was defined to be the time from the start of maintenance therapy until disease progression, diagnosis of a second malignant neoplasm, death, or last patient contact, whichever came first. If the patient experienced disease progression, diagnosis of a second malignant neoplasm or death after an event was considered to have occurred. Otherwise, the patient was censored at the date of last contact.

The survivor functions for EFS and EFS after local control were estimated by the method of Kaplan and Meier.² Risk for adverse event was compared across groups defined by treatment or prognostic factors by the log-rank statistic.² The patient's randomized treatment assignment was used in all comparisons involving regimen. Hazard ratios (HRs) and associated confidence intervals (CIs) were estimated by the proportional hazards regression model.²

The proportional hazards regression model was used to determine, for patients with rib primary tumors, which factors were independently prognostic for outcome. All factors that were significant at the .10 level in univariate analyses, as well as the randomized regimen, were selected for inclusion in a backward stepwise model. Age and tumor volume were selected by this screening process. The absolute value of age and tumor volume were used. Modifying these effects with quadratic terms did not significantly improve fit. A multiplicative interaction term for age and tumor volume was included in the regression model used to start the backward stepwise procedure. Terms that were significant at the .05 level or less in the final model were considered independently prognostic for risk of adverse events.

Qualitative characteristics were compared across subgroups by means of the exact conditional test of proportions.³ In particular, tumor size was classified as above or below median and compared across groups defined by site of primary tumor.

Table I. Size of primary tumors by site (calculated volume)

Tumor volume	Site of primary tumor			
	Rib	Pelvis	Humerus, femur, or both	Other
<240 cm ³	11 (32%)	17 (31%)	25 (43%)	55 (69%)
≥240 cm ³	23 (68%)	37 (69%)	33 (57%)	25 (31%)

Rib and pelvic tumors are similar in size, and both are significantly larger than tumors at sites other than the pelvis or ribs ($P < .001$). Values in parentheses represent the percentage of patients with primary tumors at a particular location for each volume category.

Table II. Relationship of primary tumor site and size by largest tumor dimension to likelihood of initial attempt at resection

Primary site	<8 cm	≥8 cm
Ribs	5/14* (36%)	9/33 (27%)
Other	18/102 (18%)	4/173 (2%)

Size did not correlate with initial attempt at resection for rib primary tumors ($P = .9$) in contrast to other sites, where initial resection was attempted significantly less often in tumors with a maximum dimension of 8 cm or larger ($P < .001$).

*The first entry represents the number of patients for whom a resection was attempted. The second entry is the total number of patients in the tumor dimension category.

Results

Three hundred ninety-three eligible patients with nonmetastatic Ewing sarcoma were entered on the study. Fifty-three patients had a primary tumor located in the ribs, and 340 had primary tumors located at other sites. There were no sternal primary tumors.

Two hundred twenty-six patients had sufficient data submitted to estimate tumor volume. Patients without tumor volume calculated were distributed similarly across the various primary tumor sites when compared with patients with known volumes. Rib lesions were significantly larger than tumors at some other sites and most closely resembled pelvic tumors in volume (Table I).

Two patients did not have any data submitted to describe the surgical procedures performed as part of protocol therapy. These individuals are excluded from subsequent analyses.

Sixteen patients with rib primary tumors had an attempt to resect the tumor before the start of chemotherapy. Patients with rib primary tumors were significantly more likely to have initial surgical excision attempted when compared with patients with tumors of other sites (30% vs 8%, $P < .01$). Attempts at initial resection for chest wall lesions were not associated with size of tumor, as assessed by largest diameter in contrast to tumors at other sites, where initial resections were done only rarely in large tumors (Table II).

Table III. Final local control method segregated by initial surgical intervention

	Operation as the only local method used	Local control included radiation therapy
Initial attempt at resection	4*	11
Initial biopsy	17	17†

The P value for independence of the chance of receiving radiation therapy as part of local control and initial attempted complete resection was .13.

*Includes 1 patient who had a second resection after induction chemotherapy.

†Includes 5 patients who had radiation therapy only as the local control method.

Data from the local pathologist were available for 16 of the initial resections. Sixty-two percent (10/16) were determined to have tumor at the margin of resection. Data from the local pathologist was available for 24 of the 30 patients who underwent an operation after induction therapy. Tumor was found at the margin of resection in 7 (29%) of these patients ($P = .05$).

The type of local therapy delivered after induction as it relates to initial local therapy is demonstrated in Table III. Patients who had an initial resection were more likely to receive radiation therapy than those who had resections after initial chemotherapy, although this was not significant at the .05 level ($P = .13$).

The 5-year EFS for all 393 patients with nonmetastatic disease was 61% (95% CI, 55%-66%; Fig 1). EFS at 5 years was 57% for the chest wall compared with 61% at all other sites (HR for chest wall tumor, 0.88; 95% CI, 0.56-1.4; $P = .6$). Ifosfamide and etoposide significantly improved outcome in the overall group (5-year EFS, 68% vs 54% for standard chemotherapy; HR, 0.61; 95% CI, 0.44-0.84; $P = .002$); the same trend was seen for chest wall lesions but did not reach statistical significance (5-year EFS, 64% vs 51% for standard chemotherapy; HR, 0.61; 95% CI, 0.27-1.4; $P = .2$). The site of the primary tumor was associated with risk for adverse event. Patients with rib primary tumors had outcomes comparable with those of patients with primary tumors in the femur or humerus and outcomes superior to those of patients with pelvic primary tumors (Fig 2; HR for femur or humerus primary tumor, 0.84; HR for pelvic primary tumor, 1.3; HR for any other site, 0.69; $P = .03$). Patients with rib lesions of volume greater than the median for this site were at increased risk for an adverse event (Fig 3; HR, 3.3; 95% CI, 1.0-11), as were older patients (Fig 4; HR for patients 10-17 years of age, 2.4; HR for patients 18 years or older, 7.8; $P = .03$). Risk for an adverse event was not related to an initial attempt at resection (Fig 5; HR, 0.72; 95% CI, 0.28-1.8; $P = .5$). The type of local

Fig 1. Kaplan-Meier estimate of EFS for all patients with nonmetastatic disease at study entry (n = 393).

Fig 2. Kaplan-Meier estimates of EFS for patients with nonmetastatic disease at study entry according to site of primary tumor ($P = .03$): ribs (n = 53), humerus or femur (n = 100), pelvis (n = 93), or other site (n = 147).

control measures also was not related to EFS after local control (Fig 6; HR for operation, 0.35; HR for operation plus radiation therapy, 0.48; $P = .3$).

The backward stepwise model demonstrated that both increased tumor volume and increased age were factors independently associated with elevated risk for

adverse events in patients with rib primary tumors. There was no evidence of an interaction between the two factors.

Complete data regarding the surgical resection was available on 34 patients. The magnitude of chest wall resection is shown in Table IV. Prosthetic mesh was

Fig 3. Kaplan-Meier estimates of EFS for patients with nonmetastatic rib primary tumors according to estimated tumor volume ($P = .03$): 419 cm^3 or less or greater than 420 cm^3 .

Fig 4. Kaplan-Meier estimates of EFS for patients with nonmetastatic rib primary tumors according to age at study entry ($P = .01$): 10 years or younger ($n = 19$), 10 to 17 years ($n = 30$), or older than 17 years ($n = 4$).

used for reconstruction in 19 children (polytetrafluoroethylene,* 9 children; Marlex mesh [Bard Implants, Billerica, Mass], 6 children; Prolene mesh [Ethicon, Inc, Somerville, NJ], 2 children; Vicryl mesh [Ethicon],

2 children; and dural graft, 1 child). In 1 child a prosthetic sandwich reconstruction was performed, and in another child a frozen rib allograft was placed. A lung was adherent to the mass in 18 patients, and a wedge resection was performed in 15 patients. Adherent diaphragm was resected in 9 patients, and in all cases primary closure was possible. Muscle flap rotation was

*Gore-Tex mesh, registered trademark of W. L. Gore & Associates, Inc, Flagstaff, Ariz)

Fig 5. Kaplan-Meier estimates of EFS for patients with nonmetastatic rib primary tumors according to whether the operation was conducted before the start of systemic chemotherapy ($P = .5$): yes ($n = 16$) versus no ($n = 35$).

performed in 4 patients (pectoral muscle, 1 patient; latissimus dorsi muscle, 3 patients).

Few complications were reported. Only 2 were reported in the 16 attempted resections before chemotherapy. Both patients had intraoperative hemorrhage. There was 1 incident of intraoperative hemorrhage and 1 incident of delayed wound healing among the resections attempted after induction chemotherapy.

Discussion

In this large study of primitive neuroectodermal tumor and Ewing sarcoma of bone, rib primary tumors did as well or better than primary tumors of similar size at other sites. As in other sites, outcome correlated with size and age, as well as whether the patient received the experimental therapy, although the latter did not reach statistical significance for the rib lesions. Surgeons are more likely to attempt an initial resection for patients with rib primary tumors. In contrast to other sites, initial resection of the ribs was attempted, even with very large primary tumors.

Should one attempt initial resection in Ewing sarcoma/primitive neuroectodermal tumor of the ribs? We found no difference in eventual outcome for patients who had initial resection compared with those who had initial biopsy only, but the numbers are limited in this study. Importantly, however, more patients with an initial attempt at resection required eventual radiation therapy than those patients who had their resection

Table IV. Definitive chest wall resections

No. of ribs resected	No. of patients	Patients with prosthetic graft	Patients with muscle flap
1	8	2	1
2	9	5	
3	18	8	1
4	6	5	2
Total	41	20	4

after initial shrinkage of the tumor with chemotherapy. Radiation therapy has special side effects in the chest, where large volumes of lung may be damaged with the required high doses of radiation therapy.⁴ In addition, the heart may be in the field, and radiation to the heart is believed to add toxicity to the damage caused by an essential chemotherapeutic agent for this disease, doxorubicin.^{5,6} Finally, the risk of second malignant neoplasms after radiation therapy in Ewing sarcoma is quite high (10%-30%).⁷⁻⁹

We therefore agree with Rao and others, who believe that initial attempts at resection should rarely be done in Ewing sarcoma/primitive neuroectodermal tumor of the chest wall.¹⁰⁻¹² After initial chemotherapy, the tumors are generally smaller and the margins of involvement are better defined, resulting in an increased proportion of resections with negative microscopic margins, as was found in this study. A limited number of children will require radi-

Fig 6. Kaplan-Meier estimates of EFS after local control ($P = .3$): radiation therapy ($n = 14$), an operation ($n = 18$), or radiation therapy and an operation ($n = 12$).

ation therapy because of paravertebral involvement, size of the lesion, apical location of the tumor, or incomplete resection of the tumor at a delayed operation. EFS for patients without metastases now is nearly 60%, regardless of the form of local treatment. Any therapy that might lead to long-term side effects, such as radiation, should be avoided if possible, and this can best be achieved by use of initial chemotherapy before attempted resection.

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Appendix 1. Participating Pediatric Oncology Group and Children's Cancer Group institutions

<i>Institution</i>	<i>Grant No.</i>	<i>Institution</i>	<i>Grant No.</i>
Alberta Children's Hospital		Nemours Children's Clinic	
Cross Cancer Institute		University of Kansas	
Baylor	CA-03161	St Mary's Hospital	
Hackensack Medical Center		University of Miami	
Boston Floating Hospital		University of Rochester	
Children's Hospital Greenville System	CA-69177	UC/Davis	
Medical University of South Carolina	CA-69177	UC/San Diego	CA-28439
Presbyterian Hospital	CA-69177	Naval Medical Center, Portsmouth	
Children's Hospital Michigan	CA-29691	Tripler Army Medical Center	
Hurley Medical Center	CA-29691	Walter Reed Army Medical	
St Johns Hospital	CA-29691	San Antonio MPC & BDC	
Children's Memorial Hospital (Chicago)	CA-07431	UT/San Antonio	
Dana-Farber Cancer Institute/Children's Hospital	CA-41573	University of South Alabama	
Maine Children's	CA-41573	Wake Forest University School of Medicine	CA-53128
Duke University	CA-15525	Washington University	CA-05587
West Virginia University, Morgantown	CA-15525	Nemours/Orlando	
Mount Sinai Medical School (NY)	CA-69428	SUNY/Syracuse	
Yale University	CA-69428	Children's Hospital San Diego	CA-28439
Emory University	CA-20549	Via Christi Regional Medical Center	
All Children's Hospital		CCG Group Operations Center	CA-13539
Puerto Rico POG		University of Michigan Medical Center	CA-02971
San Jorge Children's Hospital		University of California Medical Center	CA-17829
Tampa Children's Hospital		University of Wisconsin Hospital, Madison	CA-05436
Cancer Center of Hawaii		Children's Hospital & Medical Center	CA-10382
Hospital for Sick Children		Rainbow Babies & Children's Hospital	CA-20320
Farifax Hospital	CA-28476	Children's National Medical Center	CA-03888
Johns Hopkins University	CA-28476	Children's Hospital of Los Angeles	CA-02649
Children's Hospital New Orleans/LSU CCOP		Children's Hospital of Columbus	CA-03750
Children's East Ontario	CA-33587	Columbia Presbyterian College of Physicians & Surgeons	CA-03526
McGill University	CA-33587	Children's Hospital of Pittsburgh	CA-36015
Medical College Virginia		Vanderbilt University School of Medicine	CA-26270
Miami Children's Hospital		Doernbecher Memorial Hospital for Children	CA-26044
Midwest Children's Cancer Center	CA-32053	University of Minnesota Health Sciences Center	CA-07306
Dartmouth Hitchcock	CA-29293	Children's Hospital of Philadelphia	CA-11796
Massachusetts General Hospital	CA-29293	Memorial Sloan-Kettering Cancer Center	CA-42764
Rhode Island Hospital	CA-29293	James Whitcomb Riley Hospital for Children	CA-13809
University of Vermont	CA-29293	University of Utah Medical Center	CA-10198
Ochsner Clinic		University of British Columbia	CA-29013
Oklahoma University	CA-11233	Children's Hospital Medical Center	CA-26126
University of New Mexico		Harbor/UCLA & Miller Children's Medical Center	CA-14560
Operations Office	CA-30969	University of California Medical Center/UCLA	CA-27678
Roswell Park Cancer Institute	CA-28383	University of Iowa Hospitals and Clinics	CA-29314
Sainte-Justine		Children's Hospital of Denver	CA-28851
SPOG Bern		Mayo Clinic and Foundation	CA-28882
SPOG Lausanne		Izaak Walton Killam Hospital for Children	
Kaiser/Santa Clara	CA-33603	University of North Carolina	
Stanford University	CA-33603	University of Medicine & Dentistry of New Jersey	
University of Arizona	CA-33603	Children's Mercy Hospital	
Cook-Ft. Worth Children's Medical Center	CA-33625	University of Nebraska Medical Center	
Southwestern Medical School	CA-33625	Wyler Children's Hospital	
Statistical Office	CA-29139	M.D. Anderson Cancer Center	
University of Alabama	CA-25408	Princess Margaret Hospital	
University of Arkansas			