Ewing's Sarcoma of Soft Tissues in Childhood: A Report From the Intergroup Rhabdomyosarcoma Study, 1972 to 1991

By R. Beverly Raney, Lina Asmar, William A. Newton, Jr, Charles Bagwell, John C. Breneman, William Crist, Edmund A. Gehan, Bruce Webber, Moody Wharam, Eugene S. Wiener, James R. Anderson, and Harold M. Maurer

Purpose: **One hundred thirty of 2,792 patients (5%) registered on three Intergroup Rhabdomyosarcoma Study clinical trials (IRS-I, -II, and -III) from 1972 to 1991 had an extraosseous Ewing's sarcoma (EOE). We report here the results of multimodality therapy for this tumor.**

Patients and Methods: **The 130 patients were less than 21 years of age; 70 (54%) were males. Primary tumor sites were on the trunk in 41 patients, an extremity in 34, the head/neck in 23, the retroperitoneum/pelvis in 21, and other sites in 11. One hundred fourteen patients had no metastases at diagnosis. In 21 patients, the tumor was completely resected; in 30, the localized or regional tumor was grossly resected, and in 63 patients, grossly visible sarcoma was left behind. Sixteen patients (12%) had distant metastases at diagnosis. All patients were given multiagent chemotherapy and most received irradiation (XRT); none were treated with bone marrow transplantation.**

Results: **One hundred seven patients (82%) achieved a complete response. At 10 years, 62%, 61%, and 77% of the patients were alive after treatment on IRS-I, IRS-II, or IRS-III therapeutic protocols, respectively, similar to figures obtained in all IRS patients. At last follow-up evaluation, 42 patients had died of progressive tumor and one of infection. Survival at 10 years was most likely for patients with tumor that arose in the head and neck, extremities, and trunk, and for those who underwent grossly complete tumor removal before initiation of chemotherapy. For patients with localized, gross residual tumor, adding doxorubicin (DOX) to the combination of vincristine, dactinomycin, cyclophosphamide (VAC), and XRT did not significantly improve survival in 39 patients (62% alive at 10 years) compared with that of 24 patients treated with VAC and XRT without DOX (65% alive at 10 years, $P = .93$).**

Conclusion: **This series indicated that EOE in children is similar to rhabdomyosarcoma (RMS) in its response to multimodal treatment. No benefit was apparent from the addition of DOX to VAC chemotherapy in patients with gross residual EOE.**

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THE INTERGROUP Rhabdomyosarcoma Study Group (IRSG) was formed in 1972 by members of the three pediatric cancer cooperative groups in the United States and Canada. Its primary goal was to improve the knowledge of and treatment results in children with rhabdomyosarcoma (RMS) and undifferentiated soft tissue sarcoma by conducting controlled, therapeutic clinical trials. Early in the first IRS trial (IRS-I, 1972 to 1978), review of surgical specimens by members of the IRS Pathology Subcommittee showed that some patients who were registered with the suspected diagnosis of RMS or undifferentiated sarcoma actually had extraosseous Ewing's sarcoma (EOE).[1,2] Because patients with these tumors had primary lesions that arose in soft tissue, rather than bone, they received the same treatment as those with RMS. The main objective of this report is to review the characteristics and results of treatment of the 130 patients with EOE entered onto IRS-I, -II, and -III during the period from 1972 through 1991. The second objective is to compare the results of treatment in the patients with EOE with both those of all other patients in IRS-I, -II, and -III, and with those of patients with osseous Ewing's sarcoma (OES) in the first Intergroup Ewing's Sarcoma Study (IESS-I).

From the Intergroup Rhabdomyosarcoma Study Committee of the Childrens Cancer Group, Arcadia, CA; Pediatric Intergroup Statistical Office, Washington, DC; Pediatric Oncology Group, Chicago, IL; and Intergroup Rhabdomyosarcoma Study Group Statistical Office, Omaha, NE.

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Address reprint requests to R. Beverly Raney, MD, The University of Texas M.D. Anderson Cancer, Department of Pediatrics, Box 87, 1515 Holcombe Blvd, Houston, TX 77030; Email Graney@pedi01.mdacc.tme.edu.

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PATIENTS AND METHODS

Definition and Pathology.

The members of the IRSG Pathology Subcommittee defined EOE as a tumor "composed uniformly of small undifferentiated cells with immature nuclei and abundant cytoplasmic glycogen . . . indistinguishable from osseous Ewing's sarcoma."[3] Because many of the patients entered the trial before more specific markers of Ewing's sarcoma, such as HBA-71 or 12 E7 antigen immunostaining, became

available[4] and before the characteristic t(11;22) chromosomal translocation was demonstrated,[5] these studies could not be applied for most of the patients' specimens included in this report. Electron micrographs were reviewed when possible. The pathologic and immunohistochemical findings in 84 of these 130 patients have been reviewed in an earlier publication from the IRSG.[6] That study showed that many of the EOE lesions, but not the majority, had neural features at the light microscopic, histochemical, and ultrastructural levels. Immunohistochemical analysis of 50 patients' tumors so studied showed that 36 had features of EOE and 14 were primitive neuroectodermal tumors; survival of these two groups of patients was not statistically different. The results of HBA-71 stains in 38 patients showed that 33 (87%) were positive; 28 of the 33 were considered moderately to strongly positive. Earlier analyses indicated that survival of EOE patients given treatment as for RMS was virtually the same as that of patients with embryonal RMS, and therefore patients with EOE continued to be registered through IRS-III, which was closed in 1991. It is recognized that some institutions may have decided to treat patients with EOE in a manner different from the IRS-III approach, based on data from other studies,[7-9] which suggested a worse prognosis for osseous Ewing's tumors with neuroectodermal features. However, this area is controversial, because two recent reports found no difference in survival of more than 315 patients with OES according to the presence or absence of neuroectodermal features.[10,11] Nevertheless, there were no exclusions by the IRSG pathologists from the IRS-I, -II, and -III data base of patients with EOE who showed evidence of neuroectodermal differentiation. In addition, there were no patients with poorly differentiated embryonal RMS in this series. Poorly differentiated RMS only rarely is confused with EOE, because the histologic features of the two disorders are quite separable with light microscopy, which renders electron microscopy nearly always unnecessary.

Patients

One hundred thirty eligible patients with EOE were registered onto the three sequential IRS trials conducted from 1972 through 1991; they represented approximately 5% of the 2,792 patients entered. Of the remaining 2,662 patients, 92% had RMS and 8% had undifferentiated sarcoma. Thus, during that 20-year period, approximately 6.5 patients with EOE were entered each year. Seventy patients were male and 60 were female (male-to-female ratio, 1.2:1). One hundred fourteen patients (88%) were white, five (4%) were black, and 11 (8%) came from other racial or ethnic backgrounds. Their median age at diagnosis was 12 years (range, < 1 to 20). None of the 130 patients had been previously treated. Chemotherapy was initiated within 42 days of the initial surgical procedure or within 21 days of a secondary operation (eg, a primary reexcision planned to remove residual local tumor).

Tumors

The most frequently affected body region was the trunk; the 41 patients (32%) included 25 with paraspinal tumors, 13 with chest-wall tumors, and three with abdominal-wall tumors. Thirty-four lesions (26%) arose in an extremity. Twenty-three (18%) arose in the head and neck, including two in the orbit, 10 cranial parameningeal lesions, five cranial nonparameningeal tumors, and six in the neck. Twenty-one (16%) arose in the retroperitoneum/pelvis and 11 (8%) in other sites. The maximum diameter of the primary tumor was recorded in 105 of 130 cases; the diameter was ≤ 5 cm in 39 patients and greater than 5 cm in 66 (63%).

Table 1. IRS: Clinical Groups and Treatment

Group I:	Localized sarcoma, completely removed with no regional spread or microscopic residual tumor: VCR, AMD ± CPM; no XRT*
Group II:	Localized sarcoma, grossly removed but with regional lymph nodal spread and/or microscopic residual tumor: VCR, AMD ± CPM or DOX; XRT
Group III:	Localized sarcoma with visible tumor remaining after partial removal or biopsy only: VCR, AMD, CPM ± DOX†; XRT
Group IV:	Sarcoma with distant metastases detected at diagnosis: treated as in Group III‡

Abbreviations: VCR, vincristine; AMD, dactinomycin; CPM, cyclophosphamide; DOX, doxorubicin; XRT, radiation therapy.

*Some group I patients in IRS-I received XRT.

†Some group III and IV patients in IRS-III also received cisplatin ± etoposide.

‡Lung metastases were irradiated in all IRS protocols; other metastases (not bone marrow) were irradiated in IRS-II and -III, but not in IRS-I patients.

Clinical Grouping (extent of disease)

Table 1 lists the IRS Clinical Grouping System, in use since 1972, and the types of treatment given the patients. Patients in clinical groups I, II, and III had localized disease, with no metastases detected on chest radiographs (including chest computed tomographic scans, mandatory from 1978 onward), bone scans and/or skeletal surveys, and bone marrow smears and/or biopsies. Patients in clinical group IV had distant metastases at diagnosis that involved one or more of the above regions with or without tumor in a body cavity (pleura or peritoneum), one or more distant lymph nodes, or distant soft tissues.

Localized tumors were found in 114 patients. Of the total 130 patients, 21 (16%) underwent total tumor excision with negative margins on pathologic examination and no evidence of regional lymph node spread (clinical group I). Thirty patients (23%) had microscopic residual and/or extension of tumor into regional lymph nodes, which were grossly excised (clinical group II). Sixty-three patients (49%) had localized tumors with grossly visible residual disease (clinical group III). Only 16 patients (12%) had distant metastases at diagnosis (clinical group IV). Table 2 shows a breakdown of age, primary tumor site, and clinical group in the IRS-I, -II, and -III patients with EOE as compared with all other IRS-I, -II and -III patients.

Treatment

Table 1 also lists the treatment for these patients. Randomized trials were conducted within each clinical group according to the IRS regimens prescribed by protocol at the time of registration.

Chemotherapy

All patients received multiple-agent chemotherapy with vincristine and dactinomycin, and most received cyclophosphamide (collectively called VAC). In general, chemotherapy for patients in groups II, III, and IV became more intensive with each successive IRS trial, while attempts were made to reduce therapy for group I patients, because their likelihood of cure was greatest. Patients who received only vincristine and dactinomycin were treated for 1 year; patients

Table 2. Comparison of EOE Sarcoma Patients With All Other Patients (designated as RMS) Treated on IRS-I, -II, and -III

Variable	EOE	RMS
No. of patients	130	2,662
Male-to-female ratio	1.17	1.46
Age, years (%)		
< 1	5	7
1-5	19	44
6-10	15	21
11-15	46	20
16-20	15	9
Primary tumor site (%)		
Trunk	32	7
Extremity	26	18
Retroperitoneum	16	9
Head and neck	8	9
Orbit	2	10
Parameningeal	8	17
Bladder-prostate	3	11
Genitourinary/not bladder-prostate	1	13
Others	5	5
Clinical group (%)		
I	18	16
II	23	20
III	46	46
IV	12	18

who received three or more drugs were usually treated for 2 years. Drug dosages were determined according to the patients' weight or surface area and were later adjusted as needed to reduce life-threatening toxicity (eg, bacteremia with absolute neutropenia of < 500 polymorphonuclear leukocytes/μL).

Radiation Therapy

Radiation therapy (XRT; 50 to 60 Gy in 5 to 6 weeks, using supervoltage equipment) to the primary tumor bed was randomly assigned to some group I patients in IRS-I, but it was not administered to group I patients in IRS-II and -III, because its benefit had not been established in the randomized IRS-I trial for patients with group I tumors.[12] All group II, III, and IV patients were to receive local XRT. The dose was adjusted in IRS-II and -III according to the clinical group. The dose was 41.4 Gy for all group II patients. The dose varied from 40 to 55 Gy for groups III and IV patients according to patient age and maximum diameter of the primary tumor at diagnosis. Patients less than age 6 years with tumors $\leq$ 5 cm in diameter were to receive 40 to 45 Gy; those older with small ($\leq$ 5 cm) tumors or younger with larger (> 5 cm) tumors received 45 to 50 Gy; and those $\geq$ 6 years with tumors larger than 5 cm in widest diameter received 50 to 55 Gy. Patients in group IV on IRS-I with lung metastases were to receive bilateral lung irradiation to approximately 15 Gy in 2 weeks; in IRS-II and -III, all metastatic sites other than bone marrow were to be treated with XRT provided that no more than 25% of the active marrow would be in the field. These parameters have been reviewed in greater detail in previous publications.[12-14]

Response and Survival

As defined in previous IRS-related reports, complete response signified the disappearance of all detectable tumor deposits; partial response signified shrinkage of measurable tumor or tumors by at least 50% but less than complete disappearance. Patients in clinical groups I and II were considered to be in complete remission status on the first day of chemotherapy, because all measurable tumor had already been removed surgically. Failure-free survival (FFS) was defined as the time from study entry to the first occurrence of progression, relapse after response, or death from any cause. Patients alive without recurrence of disease were censored at their last follow-up date. Survival was defined as the time from study entry to death from any cause. Patients alive were censored at their last follow-up date.

RESULTS

Response

The overall complete response rate in these patients with EOE was 82% (107 of 130). An additional 5% (six patients) achieved at best a partial response. The remaining 13% (17 patients) had less than 50% shrinkage, no response, or increasing tumor growth. These rates are comparable to those for all other patients in the combined series of IRS-I, -II, and -III, in which, overall, 2,121 of 2,662 eligible patients (80%) achieved a complete response and 242 (9%) achieved a partial response.

FFS

The FFS and overall survival rates at 10 years after initiation of chemotherapy are listed in Table 3. Note that the figures in both categories were relatively similar within each study period. Also note a trend toward improving FFS and survival from IRS-I through IRS-III, so that the 10-year FFS and survival rates for EOE patients in IRS-III equaled or exceeded 65%; in IRS-I and -II, 10-year FFS and survival rates for EOE patients were in the range of 55% to 62%. However, these differences were not significant (P = .45 for FFS and .53 for survival). Overall, 43 patients have died as of the date of last contact: 42 of recurrent tumor and one of overwhelming infection.

FFS and Survival by Site of Primary Tumor

Because primary tumor site and the presence or absence of distant metastases at diagnosis correlate highly with eventual outcome for patients on IRS protocols, we examined these factors as well. Figures 1 and 2 show FFS and survival curves for all 130 patients, categorized by primary tumor site. It is apparent that patients with head and neck tumors had the best prognosis, followed by those with extremity and trunk tumors, followed by those with retroperitoneal/pelvic and other tumors (P < .001). The findings were similar, and the outlook for FFS and survival was somewhat improved, when patients with

Table 3. FFS and Survival at 10 Years

	EOE Patients					Other IRS Patients				
		FFS		Survival			FFS		Survival	
Study	No.	%	95% CL	%	95% CL	No.	%	95% CL	%	95% CL
IRS-I	41	55	39-70	62	46-77	674	49	45-53	52	48-55
IRS-II	51	58	44-72	61	46-75	972	53	50-56	59	56-63
IRS-III	38	67	48-86	77	64-91	1,016	58	51-66	65	58-71

Abbreviation: 95% CL, 95% confidence limits.

metastases at diagnosis (group IV) were excluded from the calculations.

Survival by Clinical Group

Figure 3 lists survival by clinical group for the 130 patients. Group I patients had the best survival rate at 10 years (86%), compared with 78% for group II and 60% for group III. The 5-year survival rate was 25% for group IV patients. Only one of six group I patients who died had experienced a local recurrence; the others had developed distant metastases.

Sites of First Relapse

Among 107 patients who achieved a complete response, nine patients later developed a local recurrence. Primary tumor sites were the pelvis in three patients, and one each in the middle ear, neck, chest wall, pleura, paraspinal region, and bladder-prostate. Thus, the local relapse rate was 8% (nine of 107). Five others had never achieved local control of the tumor, which had arisen in the pelvis (two patients), chest wall, thorax, or inguinal region (one patient each). Altogether, the local control rate was 89% (116 of 130). Thus, the sites of local failure included the pelvis (five patients) and chest wall or thorax (two patients each); other sites of local failure included the bladder-prostate region, inguinal area, middle ear, neck, and paraspinal area in one patient each. Of these 14 patients, two had received no XRT, including one patient who had undergone a complete resection (clinical group I) and another with known microscopic residual tumor (group II). The remaining 12 patients were in clinical groups II (n = 1), III (n = 10), or IV (n = 1). Three had received adequate radiotherapy, defined as ≥ 50 Gy for gross residual disease and 40 Gy for microscopic residual tumors, given to the appropriate volume with no break in delivery of XRT exceeding 10 days in length. XRT was deemed suboptimal upon retrospective review of the other nine patients. Six patients with gross disease had received lower total doses of 40 Gy to less than 50 Gy (three patients), 30 Gy to 40 Gy (two), or 25 Gy (one). Another patient had clearly received an inadequate volume of XRT, and two had had extended breaks in their treatment of more than 10 days.

Other sites of initial tumor regrowth included distant

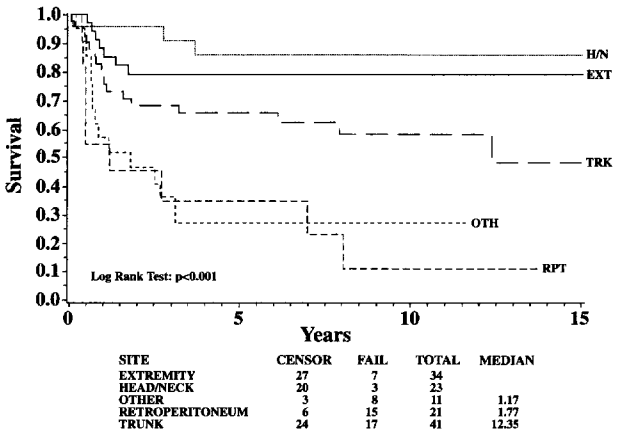

Fig 1. FFS for 130 EOE patients by primary tumor site.

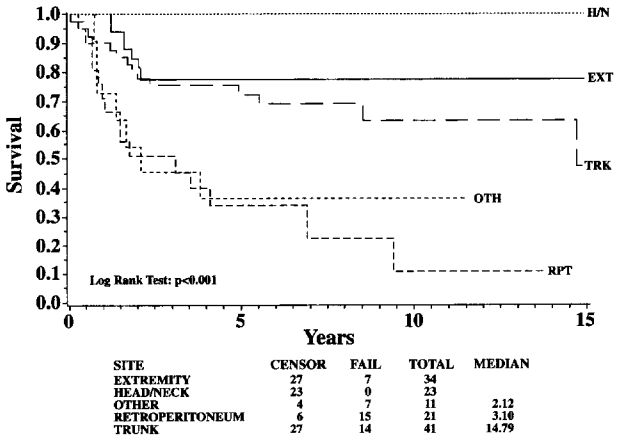

Fig 2. Overall survival of 130 EOE patients.

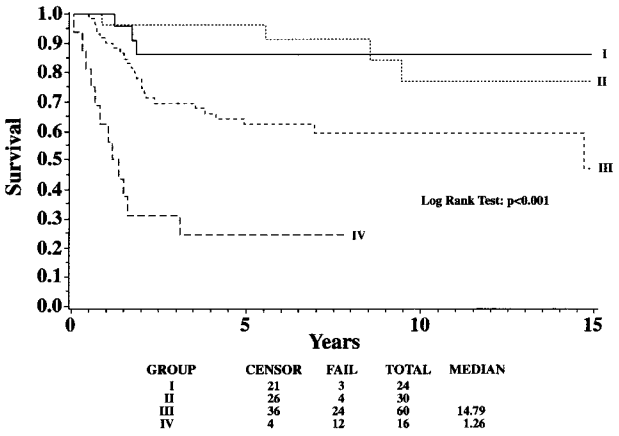

Fig 3. Overall survival of 130 EOE patients by clinical group at diagnosis.

metastases alone in 21 patients, of whom 20 had only one distant site or tissue involved. Eleven of these developed lung metastases, four developed bone metastases, and two were found to have distant soft tissue masses; one each developed a spinal, brain, or liver metastasis. An additional patient was known to have a distant recurrence, but the precise site was unknown. Seven other patients developed tumor spread in more than one distant site simultaneously. In addition, three patients experienced simultaneous local and distant recurrence, and four others had an isolated regional recurrence. Altogether, 49 patients had disease progression (n = 35) or failed to achieve local control (n = 14). As of the date of last contact, four of nine patients who had achieved a complete response and then a local recurrence were still alive (44%). Only three of 21 patients with distant recurrence were still alive (14%); no patient with regional recurrence or with distant plus local recurrence survived.

Role of DOX in Clinical Groups III and IV Patients

The contribution of DOX to FFS and survival in patients with advanced disease (clinical groups III and IV) was examined by comparing those who were treated with XRT and VAC without DOX to those treated with XRT and VAC plus DOX. We undertook this analysis because of the finding in IESS-I that the addition of DOX to XRT and VAC in a randomized fashion improved the relapse-free survival rate from 24% (n = 74 patients treated without DOX) to 60% (n = 148 patients treated with DOX) ($P < .001$).[15] Patients in groups III and IV with EOE were also randomized on the IRS to receive XRT and VAC with or without DOX. The dose-intensity was somewhat similar in that the IESS-I and IRS protocols used 60 mg/m^2 of DOX given every 8 to 12 weeks by bolus injection. The total cumulative dose of DOX in IESS-I was 420 mg/m^2 from November 1973 to August 1976, given every 12 weeks; after August 1976, the total cumulative dose was 540 mg/m^2, given every 9 weeks. The total cumulative dose of DOX was 300 mg/m^2 in IRS-I, given every 12 weeks, and 480 mg/m^2 in IRS-II and IRS-III, given every 8 weeks. In both IRS-I and -II, patients in groups III and IV received XRT and VAC with or without DOX. In IRS-III, patients who received XRT and VAC plus DOX also received cisplatin (90 mg/m^2 intravenously every 3 weeks for four doses), and half of them also received etoposide (100 mg/m^2/d for five doses) at weeks 3, 6, and 9. The comparison group of patients received XRT and VAC only.

Sixty-three patients with group III EOE tumors were treated in IRS-I (19 patients), IRS-II (22), and IRS-III (22). Figure 4A shows that at 10 years, 54% of the VAC group (n = 24) were failure-free survivors as compared with 56% of the VAC plus DOX group (n = 39; P = .70). At 10 years, 65% of the VAC group were alive as compared with 62% of the VAC plus DOX group (P = .93). Fifty-one of 63 patients with group III EOE received acceptable XRT; the other 12 included five who received no XRT, five who were rejected for major protocol violations, and two who were not reviewable. Thirty-one of 51 assessable patients received XRT plus VAC plus DOX; 20 received only XRT plus VAC. Figure 4B shows that at 10 years, 55% of the VAC group (n = 20) were failure-free survivors as compared with 56% of the VAC plus DOX group (n = 31; P = .81). At 10 years, 61% of the VAC group were alive as compared with 62% of the VAC plus DOX group (P = .98).

We analyzed the 51 assessable group III patients further to ascertain whether the absence of difference in outcome could be explained. There was no major disparity in distribution of primary tumor sites. While 25% of VAC patients had a pelvic primary tumor (relatively unfavorable) compared with only 16% of VAC plus DOX patients, that difference was counterbalanced by the fact that 25% of the VAC group had trunk or intrathoracic tumors (somewhat more favorable) compared with only 9% of the VAC plus DOX group. For the components of VAC, the percentages of drug dose delivered were within 10% in both groups: for vincristine, 88% and 79%; for dactinomycin, 96% and 94%; and for cyclophosphamide, 94% and 85% in the VAC alone versus VAC plus DOX groups, respectively; the patients treated with DOX re-

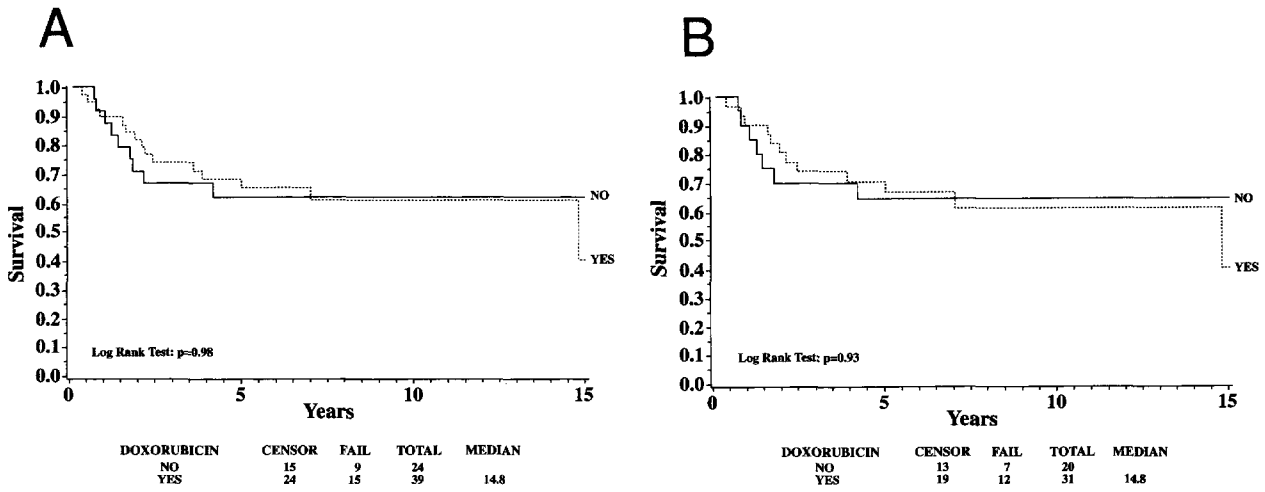

Fig 4. (A) Survival of 63 EOE patients in clinical group III, 39 of whom received XRT and VAC plus DOX and 24, XRT and VAC without DOX. (B) Survival of 51 assessable EOE patients in clinical group III, 31 of whom received XRT and VAC plus DOX and 20, XRT and VAC without DOX.

ceived an average of 85% of the scheduled DOX. Neutropenia (< 500/μL) occurred in 45% of the VAC group and 80% of the VAC plus DOX group, which suggests that the VAC group was not treated more heavily than the VAC plus DOX group. Sites of relapse were similar in the VAC and VAC plus DOX groups: local recurrence in 25% versus 27%, distant metastases in 50% versus 55%, and other sites in the remaining 25% versus 18%, respectively. Thus, there were no data that suggested the VAC plus DOX group constituted a particularly unfavorable group of patients compared with the VAC-alone group.

There were few patients with metastatic disease at diagnosis (group IV) for whom similar comparisons could be made. Initially, 16 patients were entered with group IV EOE; 12 received XRT satisfactorily, including eight given VAC plus DOX and four given VAC without DOX. None of four in the VAC group survived and all died within 2 years after study entry. By contrast, three of eight (38%) in the VAC plus DOX group survived (P = .14). These numbers are so small that no meaningful conclusion can be drawn.

Toxicity

As in previous studies of IRS patients,[12-14] the major form of hematologic toxicity was leukopenia with associated neutropenia; the major form of nonhematologic toxicity was infection, usually related to the presence of neutropenia. One patient in this series actually died of neutropenic bacteremia (one of 130, 0.77%).

Cardiotoxicity that might be attributed to DOX administration was reported in seven of 58 patients (12%) who received DOX. Since there were no guidelines for diagnosing and managing suspected DOX cardiotoxicity in IRS-I, -II, and -III, assessments of severity and subsequent administration of DOX were made on an individual basis. The seven patients so reported were in clinical groups II (one patient), III (five), and IV (one). The cardiotoxicity was considered mild or moderate in five of seven patients, each of whom received DOX subsequently without apparent difficulty. Two patients' cardiotoxicity was considered severe; one had decreased left ventricular function and the other had a transient ventricular tachyarrhythmia. Both recovered within 6 months.

DISCUSSION

The initial description of EOE is generally attributed to Tefft et al,[16] who in 1969 reported four cases of children with paravertebral "round cell" soft tissue sarcomas. Two larger series of patients were reported in the 1970s. Angervall and Enzinger[1] described 39 patients, 38 of whose cases they studied at the Armed Forces Institute of Pathology. The pathologic appearance of the tumors was indistinguishable from Ewing's sarcoma of bone, with prominent intracellular glycogen. These patients ranged in age at diagnosis from 20 months to 63 years (median, 20). The youngest had had a paravertebral tumor since birth. Eighty-five percent of the tumors occurred by age 30. Most patients presented with an enlarging mass, which was associated with pain or tenderness in half of

the cases and was usually deep-seated. The most frequent primary tumor sites were the paravertebral region, lower extremity, retroperitoneum-pelvis, and chest wall. The disease often spread to the lungs (17 cases), bone (seven), and elsewhere. Just over half of the patients had died with metastases at the time of the report in 1975.[1] Three years later, Soule et al[2] reported 26 cases of patients entered onto IRS-I, which represented 8% of the 314 cases initially reviewed by the IRS Pathology Subcommittee. The most frequent primary tumor sites were the extremities, followed by the pelvis; metastases were most often detected in lungs and bone. Sixty-five percent of these patients were alive and free of detectable tumor, which suggested that chemotherapy and XRT were often effective in preventing recurrent disease.

More recently, 84 patients with EOE entered onto the IRS-I and -II were reviewed by Shimada et al[6] in 1988. They examined 14 patients' tumors by immunohistochemical and ultrastructural studies. They noted, as have others,[7-9] that with immunohistochemical techniques, some EOE tumors show evidence of neural differentiation as manifested by positive neuron-specific enolase and/or S-100 stains, indicating neuroblastic or Schwannian cell differentiation. Sometimes neurosecretory granules can be seen on electron microscopy. Ultrastructural studies can sometimes be useful to distinguish primitive RMS from EOE.[17] The IRS cases so studied were few, but the presence or absence of one or more neural markers produced no obvious difference in outcome. The similarity in therapeutic outcome to that of the much greater number of IRS cases with embryonal RMS was noteworthy.[6] However, there is a suggestion that patients entered onto the IRS-I and -II with paraspinal embryonal RMS had a worse prognosis than those with paraspinal EOE.[18] But patients with spinal epidural EOE had a relatively poor prognosis in another series, with 10 of 16 dead of tumor within 4 years after diagnosis.[19]

The clinical details already outlined are essentially the same in two other series of cases, 11 from the Pediatric Oncology Branch of the National Cancer Institute[20] and 49 from the Mayo Clinic.[21] Tumors at extremity and truncal primary sites predominated; treatment with chemotherapy, plus XRT for patients with residual tumor, was moderately successful, with survival rates in the range of 48% to 64% at 3 to 5 years. In particular, the Mayo Clinic experience indicated that the 5-year survival rate improved from 28% before 1970 to 48% afterward, when coordinated multimodal therapy that included chemotherapy was used for the majority of patients.[21] Multimodal therapy with surgery, XRT, and chemotherapy in the Dana-Farber Cancer Center series produced six survivors among 10 children with localized chest-wall sarcoma (Ewing's/primitive neuroectodermal tumors), but none of their five patients with distant metastases at diagnosis survived.[22]

The results of this review indicate that EOE is a relatively rare form of soft tissue sarcoma in children and adolescents, which represents only 5% of all IRS eligible patients accrued from 1972 through 1991. Some differences and similarities among these patients with EOE and those with RMS and undifferentiated sarcoma (hereinafter considered together as RMS) deserve emphasis. First, as shown in Table 2, EOE tends to occur in children who are somewhat older than those with RMS, whose median age at diagnosis is approximately 5 years. Also, the primary tumor sites in patients with EOE differ from those with RMS: EOE tends to arise on the trunk or an extremity (in 58% of the patients in this series), with only 18% arising in the head and neck; in RMS, approximately 36% of the tumors arise in the head and neck and only 25% in the trunk and extremities; an additional 24% occur in the genitourinary tract. The male-to-female ratio in EOE is near unity (1.17:1 in this series), compared with 1.5:1 in RMS; perhaps the difference is attributable to a relatively large number of patients with paratesticular and prostatic RMS. Yet the response to therapy and outlook for survival of patients with EOE appear similar overall to those of patients with RMS: approximately 80% respond completely to modern therapeutic strategies, and 70% to 75% become survivors at 5 years and beyond.

On the other hand, patients with EOE share some similarities with patients with OES: the median age at diagnosis in the second decade of life, the predominance of truncal and extremity primary tumors, and the relative preponderance of white as opposed to black patients in both diseases. The relative paucity of blacks with EOE and OES does not occur in other predominantly pediatric forms of childhood cancer.[23]

There are several reasons to consider EOE and OES in children and adolescents as nearly identical diseases. In addition to the demographic similarities just listed, a characteristic chromosomal translocation can be demonstrated in tumor tissue from the overwhelming majority of patients with OES.[5] This translocation, denoted as t(11;22)(q 24;q 12), creates a fusion between part of the EWS and the FLI-1 genes; the identical translocation has been reported in several patients with EOE.[5,24,25] Identity of cytogenetic and molecular genetic abnormality suggests identity of the pathologic process in both EOE and OES. However, it is possible that other genetic abnormali-

ties are necessary for malignant transformation, and that other molecular differences between EOE and OES will be found.

Settling this issue will have to await further investigation, likely at a molecular-biologic level, as further patients are accrued and studied carefully. But the assumption that children with EOE should be treated with the same chemotherapeutic agents as those with OES should not be made lightly. There is no question that the addition of DOX in the IESS clearly improved the outlook for patients with localized OES.[15] If OES and EOE were really the same disease at slightly different locations, one might expect to see a similar difference in group III EOE patients, in favor of those who received DOX along with XRT and VAC. Group III EOE patients would be most comparable to localized OES patients, because surgical therapy for the latter, if undertaken at all, is usually not performed until after several weeks of chemotherapy, typically at week 9. But the results of this review show no advantage for group III EOE patients who received DOX compared with those who did not. The situation in group IV patients is uncertain, and larger numbers of group IV patients treated with or without DOX would be needed to examine the efficacy of DOX for patients who have EOE and distant metastases at diagnosis. It is unfortunate that a direct comparison of actual dose-intensity of DOX in IESS-I patients and IRS patients is not possible, because the IESS-I records are no longer available.

Until the situation can be clarified further, it seems prudent to recommend the following approaches to the management of future patients with EOE. Provided that a nonmutilative operation can be accomplished, patients with EOE sarcoma should undergo tumor removal first and then begin chemotherapy with VAC. If not, delayed primary tumor removal can be considered after tumor size has diminished following chemotherapy.[22] The results reported here indicate that the addition of DOX is not worthwhile in group III patients. Appropriate XRT seems to play an important role in achieving local tumor control in patients with microscopic or gross disease following surgery. We hope that future studies will clarify the histogenesis of EOE, the effect of hitherto undefined molecular-genetic changes on tumor evolution, and the optimal use of multiagent chemotherapeutic and radiotherapeutic protocols for patients with EOE.

APPENDIX

The following IRS members participated in this study: Richard Andrassy, MD, W. Archie Bleyer, MD, Sarah Donaldson, MD, Christopher Fryer, MD, Ruth Heyn, MD, Michael Link, MD, Thom Lobe, MD, Sharon Murphy, MD, Jorge Ortega, MD, Frederick Ruymann, MD, Melvin Tefft, MD, Timothy Triche, MD, PhD, and Teresa Vietti, MD.

REFERENCES

1. Angervall L, Enzinger FM: Extraskeletal neoplasm resembling Ewing's sarcoma. Cancer 36:240-251, 1975

2. Soule EH, Newton W Jr, Moon TE, et al: Extraskeletal Ewing's sarcoma: A preliminary review of 26 cases encountered in the Intergroup Rhabdomyosarcoma Study. Cancer 42:259-264, 1978

3. Newton WA Jr, Soule EH, Hamoudi AB, et al: Histopathology of childhood sarcomas, Intergroup Rhabdomyosarcoma Studies I and II: Clinicopathologic correlation. J Clin Oncol 6:67-75, 1988

4. Ambros IM, Ambros PF, Strehl S, et al: MIC2 is a specific marker for Ewing's sarcoma and peripheral primitive neuroectodermal tumors: Evidence for a common histogenesis of Ewing's sarcoma and peripheral primitive neuroectodermal tumors from MIC2 expression and specific chromosome aberration. Cancer 67:1886-1893, 1991

5. Turc-Carel C, Aurias A, Mugneret F, et al: Chromosomes in Ewing's sarcoma. I. An evaluation of 85 cases and remarkable consistency of t(11;22) (q24;q12). Cancer Genet Cytogenet 32:229-238, 1988

6. Shimada H, Newton WA Jr, Soule EH, et al: Pathologic features of extraosseous Ewing's sarcoma: A report from the Intergroup Rhabdomyosarcoma Study. Hum Pathol 19:442-453, 1988

7. Schmidt D, Herrmann C, Jürgens H et al: Malignant peripheral neuroectodermal tumor and its necessary distinction from Ewing's sarcoma: A report from the Kiel Pediatric Tumor Registry. Cancer 68:2251-2259, 1991

8. Stephenson C, Bridge JA, Sandberg AA: Cytogenetic and pathologic aspects of Ewing's sarcoma and neuroectodermal tumors. Hum Pathol 23:1270-1277, 1992

9. Dehner LP: Primitive neuroectodermal tumor and Ewing's sarcoma. Am J Surg Pathol 17:1-13, 1993

10. Terrier P, Henry-Amar M, Triche TJ, et al: Is neuro-ectodermal differentiation of Ewing's sarcoma of bone associated with an unfavorable prognosis? Eur J Cancer 31A:307-314, 1995

11. Hijazi Y, Tsokos M, Steinberg S, et al: Neuroectodermal differentiation does not play a role in the prognosis of Ewing's sarcoma (ES) versus primitive neuroectodermal tumor (PNET). Mod Pathol 9:7A, 1996 (abstr 21)

12. Maurer HM, Beltangady M, Gehan EA, et al: The Intergroup Rhabdomyosarcoma Study-I: A final report. Cancer 61:209-220, 1988

13. Maurer HM, Gehan EA, Beltangady M, et al: The Intergroup Rhabdomyosarcoma Study-II. Cancer 71:1904-1922, 1993

14. Crist W, Gehan EA, Ragab AH, et al: The Third Intergroup Rhabdomyosarcoma Study. J Clin Oncol 13:610-630, 1995

15. Nesbit ME Jr, Gehan EA, Burgert EO, et al: Multimodal

therapy for the management of primary, nonmetastatic Ewing's sarcoma of bone: A long-term follow-up of the first Intergroup Study. J Clin Oncol 8:1664-1674, 1990

16. Tefft M, Vawter GF, Mitus A: Paravertebral "round cell" tumors in children. Radiology 92:1501-1509, 1969

17. Dickman PS, Triche TJ: Extraosseous Ewing's sarcoma versus primitive rhabdomyosarcoma: Diagnostic criteria and clinical correlation. Hum Pathol 17:881-893, 1986

18. Ortega JA, Wharam M, Gehan EA, et al: Clinical features and results of therapy for children with paraspinal soft tissue sarcoma: A report of the Intergroup Rhabdomyosarcoma Study. J Clin Oncol 9:796-801, 1991

19. Kaspers G-J JL, Kamphorst W, van de Graaff M, et al: Primary spinal epidural extraosseous Ewing's sarcoma. Cancer 68:648-654, 1991

20. Kinsella TJ, Triche TJ, Dickman PS et al: Extraskeletal Ewing's sarcoma: Results of combined modality treatment. J Clin Oncol 1:489-495, 1983

21. Rud NP, Reiman HM, Pritchard DJ, et al: Extraosseous Ewing's sarcoma: A study of 42 cases. Cancer 64:1548-1553, 1989

22. Shamberger RC, Tarbell NJ, Perez-Atayde AR, et al: Malignant small round cell tumor (Ewing's-PNET) of the chest wall in children. J Pediatr Surg 29:179-185, 1994

23. Young JL Jr, Ries LG, Silverberg E, et al: Cancer incidence, survival, and mortality for children younger than age 15 years. Cancer 58:598-602, 1986

24. Becroft DMO, Pearson A, Shaw RL, et al: Chromosome translocation in extraskeletal Ewing's tumour. Lancet 2:400, 1984 (letter)

25. Casorzo L, Fessia L, Sapino A, et al: Extraskeletal Ewing's tumor with translocation t(11;22) in a patient with Down syndrome. Cancer Genet Cytogenet 37:79-84, 1989