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Phase III Trial Adding Vincristine-Topotecan-Cyclophosphamide to the Initial Treatment of Patients With Nonmetastatic Ewing Sarcoma: A Children's Oncology Group Report

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PURPOSE The primary aim of this phase III randomized trial was to test whether the addition of vincristine, topotecan, and cyclophosphamide (VTC) to interval compressed chemotherapy improved survival outcomes for patients with previously untreated nonmetastatic Ewing sarcoma.

METHODS Patients were randomly assigned to receive standard five-drug interval compressed chemotherapy (regimen A) for 17 cycles or experimental therapy with five cycles of VTC within the 17 cycles (regimen B). Patients were stratified by age at diagnosis (< 18 years and ≥ 18 years) and tumor site (pelvic bone, nonpelvic bone, and extraosseous). Tumor volume at diagnosis was categorized as < 200 mL or ≥ 200 mL. Local control occurred following six cycles. Histologic response was categorized as no viable or any viable tumor. Event-free survival (EFS) and overall survival (OS) were compared between randomized groups with stratified log-rank tests.

RESULTS Of 642 enrolled patients, 309 eligible patients received standard and 320 received experimental therapy. The 5-year EFS and OS were 78% and 87%, respectively. There was no difference in survival outcomes between randomized groups (5-year EFS regimen A v regimen B, 78% v 79%; $P = .192$; 5-year OS 86% v 88%; $P = .159$). Age and primary site did not affect the risk of an EFS event. However, age ≥ 18 years was associated with an increased risk of death at 5 years (hazard ratio 1.84; 95% CI, 1.15 to 2.96; $P = .009$). The 5-year EFS rates for patients with pelvic, nonpelvic bone, and extraosseous primary tumors were 75%, 78%, and 85%, respectively. Tumor volume ≥ 200 mL was significantly associated with lower EFS.

CONCLUSION While VTC added to five-drug interval compressed chemotherapy did not improve survival, these outcomes represent the best survival estimates to date for patients with previously untreated nonmetastatic Ewing sarcoma.

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ASSOCIATED CONTENT

Data Supplement Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Ewing sarcoma (EWS) represents a rare childhood malignancy for which continued revision of conventional chemotherapy has led to progressively improved outcomes. Most notably, improved patient survival was achieved when the combination of etoposide and ifosfamide was included in a regimen that contained 17 cycles of chemotherapy,¹ and once again achieved with dose intensification through the compression of cycle intervals to 2 weeks in a 14-cycle regimen.² Despite these advances, a substantial proportion of patients with nonmetastatic EWS experience disease recurrence, with low likelihood of cure postrelapse.³

Topotecan with cyclophosphamide (TC) is an effective chemotherapy combination for children with recurrent

or metastatic EWS. TC resulted in a sustained 2- to 21-month complete response or partial response in 35% of heavily pretreated patients with relapsed refractory EWS⁴ and a 33% partial response rate in registry data for an additional $n = 54$ recurrent or refractory patients.⁵ In the frontline setting, TC was also effective for patients with newly diagnosed metastatic EWS, 57% of whom experienced a partial response to TC.⁶ An evaluation of the addition of TC to therapy in the newly diagnosed localized setting was considered a critical question and necessitated 17 chemotherapy cycles in a randomized study maintaining delivery of doxorubicin, ifosfamide, and etoposide consistent with previous phase III trials.^{1,2,7,8} Vincristine was added to TC based on single-agent activity of vincristine in EWS⁹

CONTEXT

Key Objective

To evaluate the impact of the addition of vincristine, topotecan, and cyclophosphamide to interval compressed chemotherapy on the survival of patients with previously untreated nonmetastatic Ewing sarcoma.

Knowledge Generated

Among 642 patients enrolled, of whom 629 were randomly assigned, the experimental therapy did not significantly improve survival outcomes, but the 78% and 87% 5-year event-free and overall survival rates, respectively, are the best reported estimates to date.

Relevance

Clinical and response biomarkers identify patients at risk for an event-free survival event within the context of interval compressed chemotherapy, which is identified as the optimal systemic therapy for previously untreated patients with nonmetastatic Ewing sarcoma.

and synergistic activity with topotecan.¹⁰ The Children's Oncology Group (COG) demonstrated the feasibility of delivering vincristine, topotecan, and cyclophosphamide (VTC) in the context of interval compressed chemotherapy, with no unanticipated toxicity.¹¹

COG conducted AEWS1031 to investigate the effect of adding VTC to five-drug interval compressed chemotherapy for newly diagnosed patients with nonmetastatic EWS of bone and soft tissue. This report provides the primary outcome of this randomized phase III trial, as well as survival outcomes by stratified parameters of age and primary tumor site, and survival outcomes by local control, primary tumor volume (TV), and histologic response to induction therapy.

METHODS

AEWS1031 was a phase III randomized trial of the addition of VTC to five-drug interval compressed chemotherapy in the treatment of patients with newly diagnosed nonmetastatic EWS (ClinicalTrials.gov identifier: [NCT01231906](https://clinicaltrials.gov/ct2/show/study/NCT01231906)).

Eligibility

Patients were eligible if they were younger than 50 years old at the time of a biopsy-confirmed new diagnosis of extracranial nonmetastatic EWS or primitive neuroectodermal tumor of bone or soft tissue. The diagnosis of EWS was established by an institutional pathologist, and central review was not required. Molecular confirmation of *EWSR1* gene rearrangement was recommended, but not required. Primary site required three-dimensional radiographic imaging. Staging studies included chest computed tomography, whole-body bone scan, and bilateral bone marrow aspirate and biopsies. Computed tomography with positron emission tomography was recommended. Eligibility necessitated protocol-defined adequate renal, liver, and cardiac function. No prior chemotherapy or radiation therapy was permitted. Patients with a chest wall primary and ipsilateral pleural effusions, ipsilateral positive pleural

cytology, or ipsilateral pleural-based secondary tumor nodules were eligible, as were patients with regional lymph node involvement. Exclusion criteria included distant metastases including solitary pulmonary nodules > 0.5 cm, or multiple pulmonary nodules > 0.3 cm unless biopsy-proven otherwise; EWS as a second malignant neoplasm (SNM); patients with dural or intradural tumors; and pregnancy or breastfeeding. All patients and or their parents or legal guardians signed a written informed consent approved by institutional review board, and all institutional, US Food and Drug Administration, and National Cancer Institute requirements for human studies were met.

Study Design and Treatment

Patients were randomly assigned at the time of study entry to standard five-drug interval compressed chemotherapy (regimen A [the standard arm]) for 17 cycles or to experimental therapy with five cycles of VTC within the 17 cycles (regimen B [the experimental arm]). All patients received six cycles of induction therapy (12 weeks) and 11 cycles of consolidation therapy (22 weeks). Patients assigned to regimen A received five cycles of vincristine, doxorubicin, and cyclophosphamide, four cycles of vincristine and cyclophosphamide, and eight cycles of ifosfamide and etoposide. Patients assigned to regimen B received five cycles of VTC, five cycles of vincristine, doxorubicin, and cyclophosphamide, and seven cycles of ifosfamide and etoposide. Chemotherapy schedule and dose information are listed in [Table 1](#).

Dexrazoxane was administered only during the last two doxorubicin-containing cycles. All patients received myeloid growth factor support. Although granulocyte macrophage colony-stimulating factor was not permitted, the selection of myeloid growth factor was otherwise at the treating physicians' discretion.

Local tumor control was to take place upon recovery from induction chemotherapy typically at chronologic protocol week 13, whereas the mode of local control was

TABLE 1. Treatment Regimens

Chemotherapy (intravenous for all agents) ^a	Day(s)	Induction (six cycles)		Continuation (11 cycles)		Cumulative Recommended Doses	
		Regimen A	Regimen B	Regimen A	Regimen B	Regimen A	Regimen B
		Weeks (1-12)		Weeks (1-22)			
Vincristine ^b 1.5 mg/m ² /dose	1	1, 2, 5, 6, 9, 10	1, 2, 5, 6, 9-12	1, 2, 7-10, 13, 14, 17, 18, 21, 22	1, 2, 7-10, 13-16, 19, 20	27 mg/m ²	30 mg/m ²
Doxorubicin ^c 37.5 mg/m ² /dose	1, 2	1, 5, 9	5, 11	1, 9	9, 13, 19	375 mg/m ²	375 mg/m ²
Cyclophosphamide 1,200 mg/m ² /dose	1	1, 5, 9	5, 11	1, 7, 9, 13, 17, 21	9, 13, 19	10.8 g/m ²	12.25 g/m ²
Ifosfamide 1800 mg/m ² /dose	1-5	3, 7, 11	3, 7	3, 5, 11, 15, 19	3, 5, 11, 17, 21	72 g/m ²	63 g/m ²
Etoposide 100 mg/m ² /dose	1-5	3, 7, 11	3, 7	3, 5, 11, 15, 19	3, 5, 11, 17, 21	4 g/m ²	3.5 g/m ²
Topotecan 0.75 mg/m ² /dose	1-5	NA	1, 9	NA	1, 7, 15	—	18.75 mg/m ²
Cyclophosphamide 250 mg/m ² /dose	1-5	NA	1, 9	NA	1, 7, 15	—	—

Abbreviation: NA, not administered.

^aAll doses were given once per day on the day(s) administered.

^bMaximum dose 2 mg.

^cDexrazoxane 375 mg/m²/dose administered pre-doxorubicin intravenously during continuation weeks 1 and 9 for regimen A and weeks 13 and 19 for regimen B.

determined by treating physicians. If surgery was performed for local control, consolidation therapy was to begin 1-2 weeks postoperatively allowing time for wound healing. For patients who received definitive radiation alone for local control, or who received preoperative radiation or as adjuvant for positive surgical margins, radiation and chemotherapy were given concurrently. If a combined modality approach was planned, preoperative radiation was recommended during weeks 1-4 of consolidation, with surgery as soon as possible thereafter. Further local control guidelines for rare tumor sites are included in the Data Supplement (online only).

Statistical Design

Outcome measures. The primary outcome measure was event-free survival (EFS) defined as time from enrollment to (1) disease progression; (2) diagnosis of SMN; (3) death regardless of cause; or (4) date of last contact, whichever came first. Patients whose EFS follow-up was terminated because of reasons (1)-(3) were considered to have experienced an event; otherwise, the patient was censored at the time of last contact. Overall survival (OS) was defined as time from enrollment to death regardless of cause or date of last patient contact, whichever came first. Patients whose OS follow-up was terminated because of death were considered to have experienced an event; otherwise, the patient was censored at last contact.

Secondary objectives reported in this manuscript include survival outcomes by stratified parameters, by local control type, by TV, and response to chemotherapy at local control.

Patients who completed induction according to protocol therapy and subsequently received surgery or radiation to the site of the primary tumor were considered for the analysis of the types and outcomes of local control modalities. EFS or OS after local control was calculated as EFS or OS as defined above minus the number of days from enrollment to local control surgery or the start of radiation therapy, whichever was later. The definitions of EFS event and OS event after local control were as defined above for EFS and OS. The analytical methodology used was identical to that used for EFS and OS.

Patients considered for the histologic assessment of tumor response (assessed as amount of viable tumor in the resection specimen) were those included in the analysis of local control modality who had surgery only or who had surgery followed by radiation therapy. EFS after surgery was calculated as above for EFS after local control, whereas the definitions of EFS event after surgery were as defined above for EFS. The analytical methodology used was identical to that used for EFS.

Study design. The study was designed to enroll 630 eligible patients, which was estimated to take over 4.5 years. The first analysis was to occur 12 months after the last patient was enrolled. Random assignment was stratified according to age at enrollment (< 18 years *v* ≥ 18 years) and site of tumor (pelvic bone *v* nonpelvic bone *v* extraosseous). The study was designed to have 80% power to detect a relative hazard rate (RHR) of 0.63 associated with regimen B, using a 1-sided test of size 0.05. Detailed statistical properties of

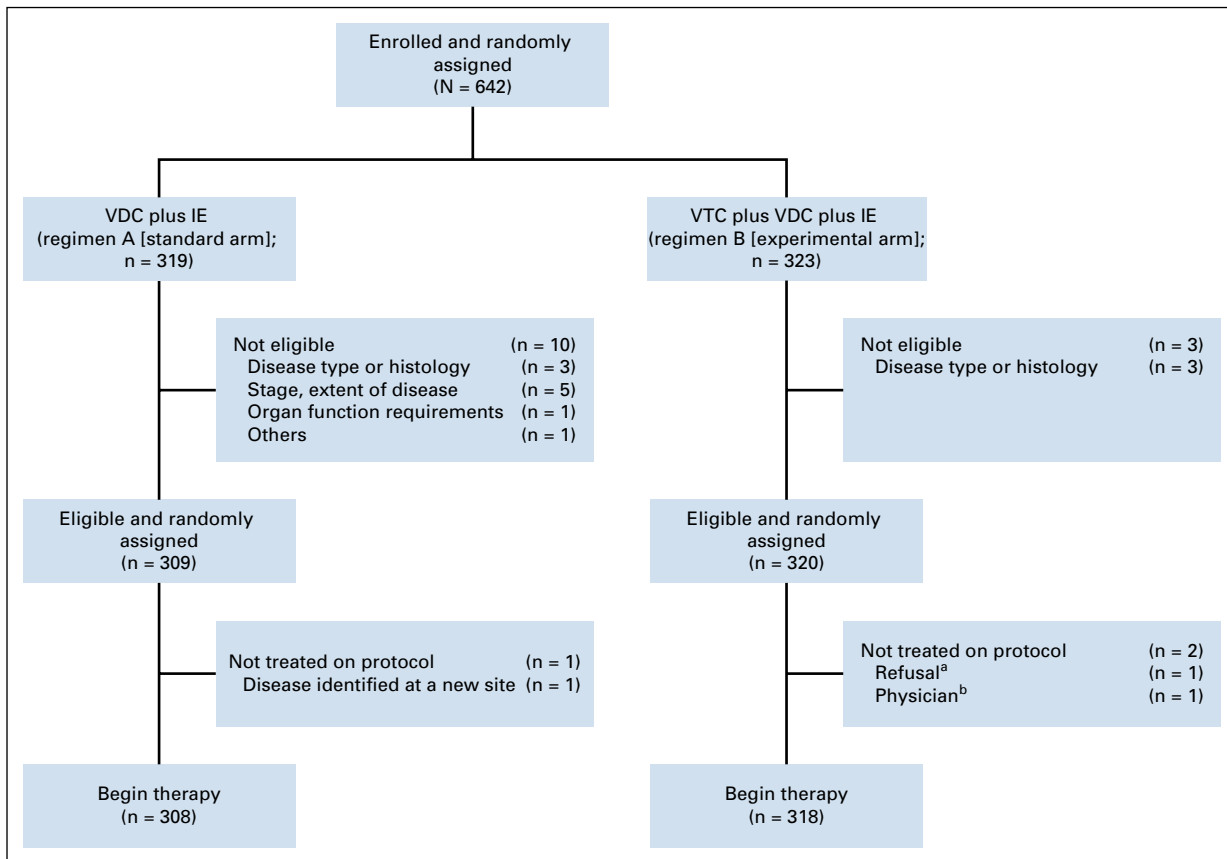


FIG 1. AEWS1031 CONSORT diagram. ^aRefusal of protocol therapy by patient, parent, or guardian. ^bPhysician considered administration of protocol therapy to not be in the patient's best interests. IE, ifosfamide and etoposide; VDC, vincristine, doxorubicin, and cyclophosphamide; VTC, vincristine, topotecan, and cyclophosphamide.

the design, interim monitoring, and analytical methods are described in the Data Supplement.

All statistical analyses were performed using SAS 9.4 (Cary, NC) or STATA 16.1 (College Station, TX). Except as specified by the study design, two-sided *P* values of .05 or less were considered statistically significant.

RESULTS

The study activated November 22, 2010, and was closed to patient accrual January 4, 2016. Data were released by the Data Safety and Monitoring Committee in March 2019, and data current to September 30, 2020, were used for this analysis.

Patient Characteristics

A total of 642 patients were enrolled, of whom 13 were considered ineligible (Fig 1). Of 629 eligible patients, 309 were randomly assigned to regimen A and 320 were randomly assigned to regimen B. Three patients did not receive any protocol therapy.

Patient characteristics were well balanced between randomized groups (Table 2). Eighty-three percent of patients were age < 18 years, 18% had pelvic primary tumors, and

18% had extraosseous primary tumors. Three hundred twenty-seven patients underwent surgery alone for local control, 159 patients received definitive radiation, and 108 patients had both (Table 3).

Survival Outcomes

One hundred forty-three events were reported: 112 recurrences, 27 SNMs, and four deaths as a first event (Table 3). Estimated EFS and OS rates at 5 years for all eligible patients were 78% (95% CI, 75 to 81) and 87% (95% CI, 84 to 90), respectively (Data Supplement).

The 5-year EFS for patients randomly assigned to regimen A was 78% (95% CI, 72 to 82) compared with 79% (95% CI, 74 to 83) for regimen B (Fig 2A). The EFS treatment effect of the experimental arm (regimen B) compared with the standard arm (regimen A) was estimated as an RHR 0.86 (95% CI, 0.62 to 1.2; one-sided *P* value = .192). The 5-year OS for patients randomly assigned to regimen A was 86% (95% CI, 82 to 90) compared with 88% (95% CI, 84 to 91) for regimen B (Fig 2B). The OS treatment effect of the experimental arm compared with the standard arm was estimated as an RHR of 0.81 (95% CI, 0.54 to 1.2; one-sided *P* value = .159).

TABLE 2. Patient Characteristics

Demographic or Clinical Characteristic	VDC Plus IE (regimen A) (n = 309)	VTC Plus VDC Plus IE (regimen B) (n = 320)	All Eligible Patients (n = 629)
Age as stratified, years			
< 18, No. (%)	255 (83)	265 (83)	520 (83)
≥ 18, No. (%)	54 (17)	55 (17)	109 (17)
Median age, years	13	13	13
Range age, years	0-32	0-34	0-34
Sex, No. (%)			
Male	166 (54)	191 (60)	357 (57)
Female	143 (46)	129 (40)	272 (43)
Race, No. (%)			
White	260 (84)	278 (87)	538 (86)
African American	10 (3)	4 (1)	14 (2)
American Indian	0 (0)	3 (1)	3 (0)
Asian	10 (3)	6 (2)	16 (3)
Pacific Islander	3 (1)	2 (1)	5 (1)
Not reported	26 (8)	27 (8)	53 (8)
Ethnicity, No. (%)			
Non-Hispanic	260 (84)	273 (85)	533 (85)
Hispanic	44 (14)	43 (13)	87 (14)
Not reported	5 (2)	4 (1)	9 (1)
Primary tumor site (by stratum), No. (%)			
Extraosseous	59 (19)	57 (18)	116 (18)
Nonpelvic	196 (63)	203 (63)	399 (63)
Pelvic	54 (17)	60 (19)	114 (18)
Primary tumor site, No. (%)			
Skull	17 (6)	13 (4)	30 (5)
Spine	24 (8)	20 (6)	44 (7)
Ribs	39 (13)	32 (10)	71 (11)
Sternum, scapula, and clavicle	15 (5)	19 (6)	34 (5)
Humerus	15 (5)	28 (9)	43 (7)
Radius, ulna, or bone of the hand	4 (1)	6 (2)	10 (2)
Pelvis	54 (17)	60 (19)	114 (18)
Femur	31 (10)	38 (12)	69 (11)
Tibia, fibula, patella, or bone of the foot	46 (15)	45 (14)	91 (14)
Soft tissue	60 (19)	59 (18)	119 (19)
Other nonpelvic bone	4 (1)	0 (0)	4 (1)

Abbreviations: IE, ifosfamide and etoposide; VDC, vincristine, doxorubicin, and cyclophosphamide; VTC, vincristine, topotecan, and cyclophosphamide.

Adverse Events

There were no differences in toxicities observed between treatment regimens (data not shown). Four patients experienced death as a first event (two each on regimens A and B). Fourteen SMN events occurred in patients on regimen A, whereas 13 SMN events occurred in patients treated on regimen B (Data Supplement).

Impact of Stratification Factors and Local Control

The 5-year EFS rates for patients < 18 years versus ≥ 18 years were 79% (95% CI, 75 to 82) and 75% (95% CI, 65 to 82), respectively (Fig 3A). Age ≥ 18 years was associated with an RHR for EFS event of 1.25 (95% CI, 0.82 to 1.9; $P = .294$). The 5-year OS rates for patients < 18 years versus 18+ years were 89% (95% CI, 86 to 91) and 78%

TABLE 3. First Event by Local Control Modality

Event Type (n = 626)	Local Control Modality (n = 626)			
	Surgery (n = 327), No.	Radiation (n = 159), No.	Surgery Plus Radiation (n = 108), No.	None (n = 32), No.
Isolated local relapse (n = 33)	13	12	4	4
Isolated systemic relapse (n = 68)	37	11	15	5
Local and systemic relapse (n = 11)	7	1	3	0
SNM (n = 27)	13	6	7	1
Death as a first event (n = 4)	2	1	1	0
No event (n = 483)	255	128	78	22

NOTE. Data represent the number of patients in each category. No event-free survival events were reported among the three eligible patients who were randomly assigned, but who did not receive protocol therapy.

Abbreviation: SNM, second malignant neoplasm.

(95% CI, 68 to 85), respectively (Fig 3B). Age ≥ 18 years was associated with an increased risk of death at 5-years with an RHR of 1.84 (95% CI, 1.15 to 2.96; *P* = .00993).

The 5-year EFS rates for patients with pelvic bone, non-pelvic bone, and extraosseous primary sites were 75% (95% CI, 65 to 82), 78% (95% CI, 73 to 81), and 85% (95% CI, 76 to 90), respectively (Fig 3C). Relative to pelvic bone primary tumors, the RHR for an EFS event associated with bone nonpelvic sites was 0.84 (95% CI, 0.56 to 1.26) and associated with extraosseous sites was 0.58 (95% CI, 0.33 to 1.03), with a global *P* = .124. The 5-year OS rates for patients with pelvic, nonpelvic bone, and extraosseous primary sites were 87% (95% CI, 79 to 92), 85% (95% CI, 82 to 89), and 92% (95% CI, 84 to 96), respectively (Fig 3D). Relative to pelvic bone primary tumors, the RHR for death for bone nonpelvic sites was 1.03 (95% CI, 0.61 to

1.73) and for extraosseous was 0.61 (95% CI, 0.29 to 1.29), with a global *P* = .205.

Local control was completed according to protocol recommendations for 594 patients (Table 3). No significant differences in postinduction survival were identified based on local control modality (Data Supplement). The 5-year EFS rates for patients who had surgery, radiation, or combined local control were 79% (95% CI, 74 to 83), 82% (95% CI, 75 to 87), and 74% (95% CI, 60 to 78), respectively (*P* = .3). Event types by local control are shown in Table 3.

Tumor Biomarkers

Institutional investigators reported three tumor dimensions in 587 of the 629 eligible patients who were considered in the analysis of TV. The 5-year EFS rates for patients with TV < 200 mL and ≥ 200 mL were 81% (95% CI, 2 to 85)

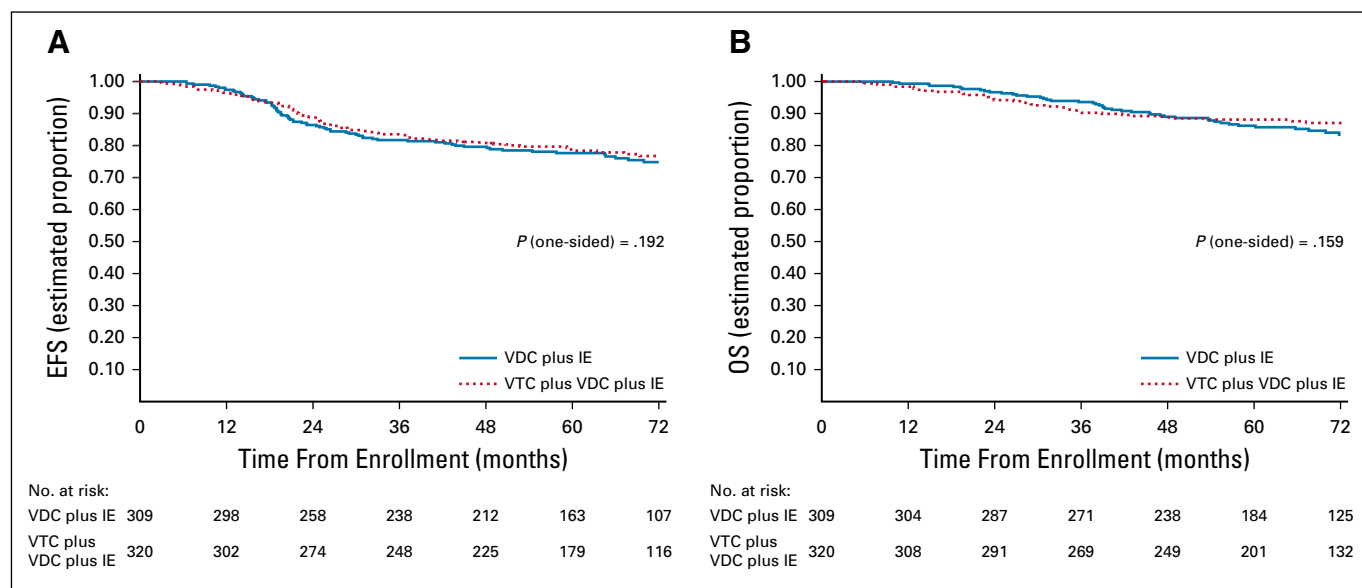


FIG 2. (A) EFS and (B) OS according to randomized treatment arm. Regimen A = VDC plus IE; regimen B = VTC plus VDC plus IE. EFS, event-free survival; IE, ifosfamide and etoposide; OS, overall survival; VDC, vincristine, doxorubicin, and cyclophosphamide; VTC, vincristine, topotecan, and cyclophosphamide.

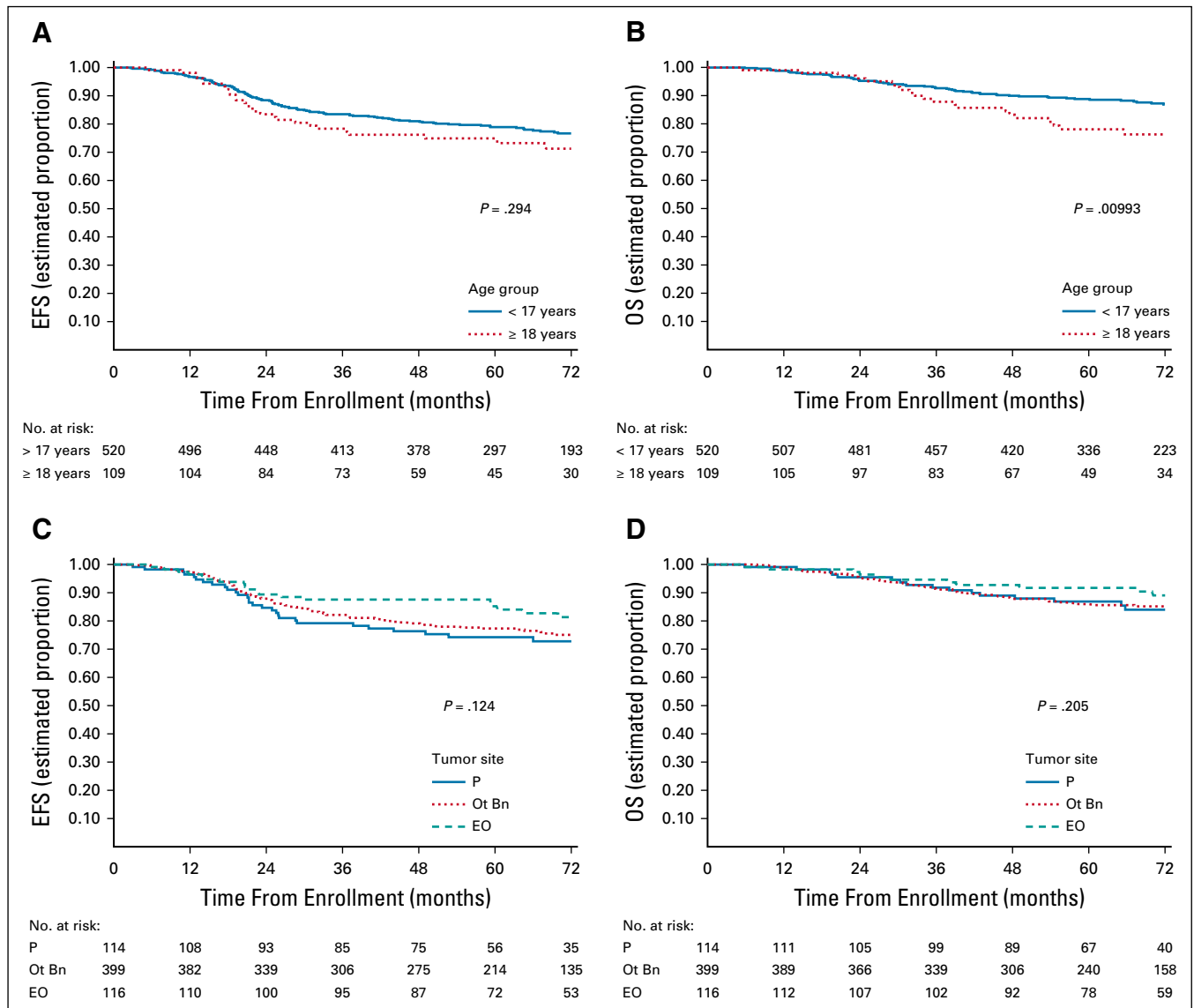


FIG 3. (A) EFS and (B) OS according to age; (C) EFS and (D) OS by primary site. EFS, event-free survival; EO, extrasosseous; Ot Bn, nonpelvic bone; OS, overall survival; P, pelvic bone.

and 71% (95% CI, 4 to 77), respectively (Fig 4A). TV \geq 200 mL was associated with an RHR for an EFS event of 1.63 (95% CI, 1.16 to 2.31; $P = .005$).

Three hundred twenty-three (323) patients contributed to an analysis of impact of viable tumor at local control. Two-hundred fifty patients were not evaluable for this analysis because: (1) 34 patients experienced an EFS event before any local control intervention; (2) 209 patients did not have surgery as a local control modality; and (3) seven patients had radiation therapy before surgical resection as local control. Data on the amount of viable tumor in the resection specimen were not available for an additional 56 patients. The 5-year EFS rates for patients with no viable tumor versus any viable tumor at the time of local control were 81% (95% CI, 3 to 87) and 75% (95% CI, 4 to 81), respectively (Fig 4B).

Presence of any viable tumor was associated with an RHR for an EFS event of 1.57 (95% CI, 0.99 to 2.51; $P = .055$).

DISCUSSION

The addition of VTC to five-drug interval compressed chemotherapy did not improve EFS or OS for the study population. However, the 5-year EFS and OS in this trial represent the best reported outcomes for patients with previously untreated nonmetastatic EWS to date.

This trial further validates excellent patient outcomes with interval compressed chemotherapy, a finding also seen in preliminary results comparing interval compressed therapy with a prior European standard combining vincristine, ifosfamide, doxorubicin and etoposide.^{7,12} This study achieved further dose intensification to interval compression by the

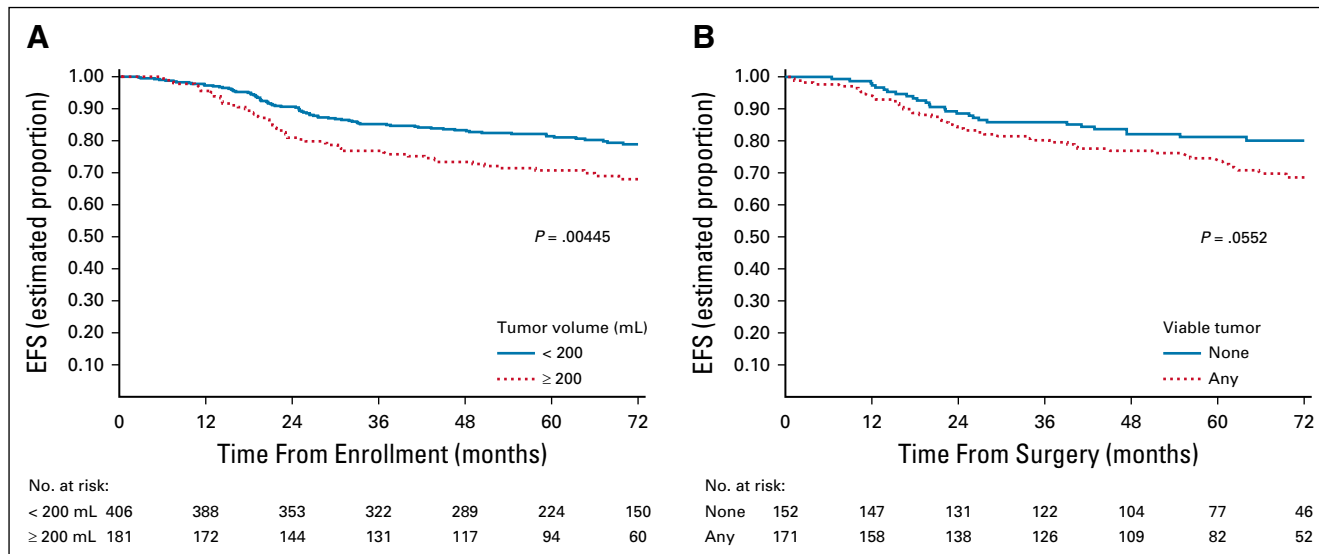


FIG 4. (A) EFS by tumor volume and (B) EFS by amount of viable tumor at time of local control surgery. EFS, event-free survival.

addition of a novel chemotherapy cassette in the experimental arm, which has recently been identified as one of the two more effective regimens in a randomized trial in recurrent or refractory EWS.¹³ Intensification was also achieved by increasing vincristine exposure and by administration of 17 cycles of chemotherapy.^{1,8} These results compare favorably to the 73% and 83% EFS and OS rates, respectively, with 14 cycles of interval compressed chemotherapy reported by Womer et al.² Direct comparison of these sequential trials is limited by possible differences in patient populations, approaches to local control, and supportive care. Consequently, there remains an opportunity to determine whether interval compressed 17 cycles with higher cumulative vincristine doses are superior to 14 cycles.

Older patients (≥ 18 years) experienced a significantly worse OS in this study but age was not a significant stratification parameter for EFS. We enrolled more patients ≥ 18 years compared with each of three sequential preceding COG cooperative group trials (17% of patients v 10%,¹ 14%,⁸ and 11%²) and report the highest EFS for this age group, 75% at 5 years compared with 47% and 63% in two of the aforementioned preceding studies.^{2,8} The improvement in EFS in this group is considered to reflect the numerical overall improvement in EFS for all patients in this study and appears consistent with observations in Euro-Ewing studies.^{14,15} The inferior OS in older patients may relate to differences in access to off-study health care for older patients versus younger patients remains largely unexplained.

We report a 75% 5-year EFS for patients with pelvic bone primary site, but we identified no significant association between risk for EFS event or death and primary tumor site. The association between tumor site and survival outcome, specifically pelvic primary and unfavorable outcome, is inconsistent in reported studies.^{2,8,14-17} In this study, 18%

of patients had pelvic tumors, for whom local control was surgery in 32%, radiation in 56%, and the combination in 12%. The absence of an outcome effect of primary tumor site as a stratified parameter in our data remains unexplained but may reflect the numerical improvement in EFS for all patients or changes in local control, given nominal differences in local control therapy reported by Womer et al.² for the same cohort of patients (27%, 45%, and 28% surgery, radiation, and combination, respectively).

We also examined the influence of TV and histologic response to induction chemotherapy on EFS, previously unexplored prognostic factors in the context of interval compressed chemotherapy. Consistent with prior reports in patients treated with other chemotherapy regimens, patients with a TV ≥ 200 mL experienced a greater risk of an EFS event.¹⁸ Patients with any viable tumor had an increased risk of an EFS event (RHR 1.57) that did not meet statistical significance (*P* = .055). Notably, histologic response was unavailable for 15% of surgical patients, and the lack of central review for histologic response likely impedes a uniform assessment of this biomarker.

Patients enrolled on this study experienced 27 (4.3%) SMN events. This is numerically higher than previous North American cooperative group studies with similar patient accrual (7 [1.4%] SMN events reported by Grier et al,¹ 19 [4.0%] SMN events reported by Granowetter et al,⁸ and 16 [2.8%] SMN events reported by Womer et al²). No significant difference was noted in SMN events between the randomized arms of the current study, suggesting that VTC did not influence SMN risk. Alkylator equivalent dosing on the standard arm of this study was the same as that in two prior studies,^{1,8} yet the predominance of hematopoietic malignancies draws attention to systemic therapy as opposed to radiation therapy as the main etiology for these cases.

In conclusion, although the addition of VTC to interval compressed chemotherapy did not improve EFS in patients with previously untreated nonmetastatic EWS, this study reports the best outcomes to date. Furthermore, we report the first prospective evaluation of age, tumor site and volume, and response to therapy as potentially important

prognostic factors in the context of interval compressed therapy. Newer approaches are needed to further improve outcome by decreasing reliance on cytotoxic agents and relying on international collaboration, while incorporating novel agents in biomarker or risk-stratified patients with newly diagnosed EWS.

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DISCLAIMER

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PRIOR PRESENTATION

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Phase III Trial Adding Vincristine-Topotecan-Cyclophosphamide to the Initial Treatment of Patients With Nonmetastatic Ewing Sarcoma: A Children's Oncology Group Report**

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