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Local Control and Outcome in Children with Localized Vaginal Rhabdomyosarcoma: A Report from the Soft Tissue Sarcoma Committee of the Children's Oncology Group

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Abstract

Background—The local control approach for girls with non-resected vaginal rhabdomyosarcoma (RMS) enrolled onto Intergroup RMS Study Group (IRSG)/Children's Oncology Group (COG) studies has differed from that used at other primary sites by delaying or eliminating radiotherapy (RT) based on response achieved with chemotherapy and delayed primary resection.

Procedures—We reviewed locoregional treatment and outcome for patients with localized RMS of the vagina on the two most recent COG low-risk RMS studies.

Results—Forty-one patients with localized vaginal RMS were enrolled: 25 onto D9602 and 16 onto Subset 2 of ARST0331. Only four of the 39 with non-resected tumors received RT. The 5-year cumulative incidence of local recurrence was 26% on D9602, and the 2-year cumulative incidence of local recurrence was 43% on ARST0331. Increased local failure rates appeared to correlate with chemotherapy regimens that incorporated lower cumulative doses of cyclophosphamide. Estimated 5-year and 2-year failure free survival rates were 70% (95% CI: 46%, 84%) on D9602 and 42% (95% CI: 11%, 70%) on ARST0331, respectively.

Conclusions—To prevent local recurrence, we recommend a local control approach for patients with non-resected RMS of the vagina that is similar to that used for other primary sites and

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CONFLICT OF INTEREST STATEMENT

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includes RT. We recognize that potential long-term effects of RT are sometimes unacceptable, especially for children less than 24 months of age. However, when making the decision to eliminate RT, the risk of local recurrence must be considered especially when using a chemotherapy regimen with a total cumulative cyclophosphamide dose of 4.8 g/m².

Keywords

rhabdomyosarcoma; female; genitourinary; vagina; radiotherapy

INTRODUCTION

Rhabdomyosarcoma (RMS) arising in the female genital tract is rare, accounting for 3.5% of cases [1]. Approximately half of all cases in the female genital tract arise in the vagina, a site that has been associated with a favorable prognosis [1–4]. However, the optimal locoregional treatment approach for patients with vaginal RMS remains controversial since the tumor usually cannot be surgically resected if organ integrity is to be preserved. Furthermore, most patients present before the age of 2 years, making them especially susceptible to long-term complications of radiotherapy (RT) [1, 3–6].

Intergroup RMS Study Group (IRSG)/Children's Oncology Group (COG) clinical trials have routinely included RT for local control of tumors at most primary sites that are not resected prior to chemotherapy [2, 7]. In contrast, the locoregional treatment paradigm for patients with vaginal RMS has delayed or eliminated RT altogether, if the tumor shrinks with chemotherapy or a complete response is achieved, with or without delayed primary resection [6]. Recently, enrollment onto the COG low-risk RMS study (ARST0331) was suspended for patients with Stage 1, Group III (non-orbit) and Stage 3, Group I or II embryonal RMS because of a high rate of local recurrences, largely accounted for by patients with Group III vaginal tumors. We reviewed locoregional treatment and tumor control as well as outcome for patients with localized RMS of the vagina enrolled on the two most recent COG low-risk RMS studies, D9602 and ARST0331. We report higher local failure rates than expected for patients with Group IIA or III N₀ vaginal RMS enrolled onto D9602 or ARST0331 and recommend modifications to the current treatment approach for these patients.

METHODS

Patients

Between 1997 and 2008, COG conducted two consecutive low-risk RMS studies (D9602: 1997–2004 and ARST0331: 2004–2008), for patient subsets whose 5-year failure free survival (FFS) exceeded 83% in IRS-III or – IV [2,7]. Patients with localized embryonal RMS of the vagina, including the botryoid and spindle cell embryonal variants, were included in the low-risk group in both studies. Pathologists on the COG Soft Tissue Sarcoma (STS) Committee reviewed pathologic material from all patients to confirm diagnosis and histologic subtype, according to the International Classification of Rhabdomyosarcoma [8].

A vaginal primary was defined as a tumor visible on the vaginal surface, which could be biopsied through the vagina. The primary site was evaluated with MRI or CT. Since tumors in the vagina are often poorly visualized with these modalities, examinations under anesthesia (EUA) were also conducted to assess initial extent of disease and response. Pathologic extent of local disease following an initial operation (Group) was determined by surgical report and histologic evaluation [7]. Surgeons on the COG STS Committee confirmed primary site, Group, and Stage for all patients [7].

Disease spread was assessed by CT of the chest, retroperitoneum and liver, bone scan, bilateral bone marrow aspirates and biopsies, and lymph node biopsies of radiographically or clinically enlarged nodes. Eligibility criteria included: age < 50 years old; adequate renal, liver, and bone marrow function; enrollment on study and initiation of protocol treatment within 42 days of the initial surgical procedure or biopsy; availability for periodic follow-up; and signed written informed consent by the patient or guardian according to institutional guidelines with IRB approval according to the declaration of Helsinki.

Local Therapy

Resection of vaginal RMS was recommended at the time of diagnosis and at any delayed operation only if it could be accomplished while preserving organ integrity. In contrast to tumors at other favorable sites, delayed resections and biopsies to assess response for vaginal RMS were postponed until week 28 (D9602) or 24 (ARST0331) for patients with Group IIA or III N₀ vaginal RMS (Table I).

RT dose for non-resected vaginal RMS was based on histologic assessment. Unlike other primary sites, RT was omitted if there was a complete response after chemotherapy with or without surgery (Table I). Recommendations were to start RT at week 12 on D9602 and week 13 on ARST0331 for patients with Group IIB, IIC or III vaginal primaries with clinical involvement of lymph nodes (N₁) (Table I). Radiation oncologists on the COG STS Committee reviewed RT records and portal films for all patients for quality and appropriateness.

Chemotherapy

D9602 and ARST0331 each consisted of two subgroups of low-risk RMS requiring different treatment intensities based on whether an alkylating agent had been included in the regimen that produced a 5-year FFS of 83% or better in IRS-III or -IV [2, 7]. In D9602, patients with grossly resected localized vaginal RMS without evidence of nodal involvement (Stage 1, Group I, IIA) received cycles of vincristine and dactinomycin (VA) over 45 weeks (Table II). Patients with non-resected localized vaginal tumors and/or evidence of nodal involvement (Stage 1, Group IIB, IIC, III) received cycles of vincristine, dactinomycin and cyclophosphamide (VAC) over 45 weeks (Table II). VA and VAC doses changed over the course of D9602 because of concerns relating to the incidence of hepatopathy [9]. In ARST0331, patients with grossly resected vaginal RMS (Stage 1, Group I, II) were enrolled onto Subset 1. Those patients are not included in this report, because the clinical trial remained open for them. Patients with non-resected localized vaginal RMS (Stage 1, Group III) were enrolled onto Subset 2 and received four cycles of VAc with lower-dose cyclophosphamide than on D9602 followed by 12 cycles of VA (VAc/VA) over 45 weeks (Table II).

Response was assessed on D9602 and ARST0331 at weeks 12, 24, 36, and 48 by physical examination and diagnostic imaging. EUAs were conducted at weeks 12 (D9602 and ARST0331), 20 (D9602), 24 (ARST0331), and 28 (D9602) to assess tumor shrinkage and obtain biopsies.

Statistics

FFS was defined as the time from the start of treatment to disease progression, recurrence or death as a first event. Survival was defined as the time from start of treatment to death from any cause. FFS and survival for patients who never experienced the event of interest were censored at the time of the patient's last contact date. FFS and survival curves were calculated by the method of Kaplan and Meier [10]. Confidence intervals (CI) for estimates of time-to-event distributions were calculated using Greenwood's formula [11].

RESULTS

Patient Characteristics

Forty-one patients with localized vaginal RMS were enrolled between September 1997 and May 2008: 25 onto D9602 and 16 onto Subset 2 of ARST0331 (Table III). The median age at diagnosis was 2 years (range < 1 month – 14 years), and 76% were < 3 years of age (n=31). The majority of patients had unresected disease at the time of protocol enrollment (five Group IIA and 34 Group III; 95%). Two patients (5%) had clinical involvement of regional lymph nodes (N₁); neither underwent lymph node biopsy. The tumor extended beyond the vagina (T₂) in seven patients (17%). The site of extension was bladder (n=3), pelvis (n=1) or not specified (n=3). Thirty-nine (95%) patients had embryonal histology; the botryoid variant was most common (n=33, 80%). The histologic subtype could not be determined on central pathology review for two patients. Eight patients enrolled onto D9602 were treated with VA chemotherapy (two Group I, five Group IIA, and one Group III) and 17 with VAC. Group assignment was changed by the treating physician from III to IIA shortly after enrollment for one patient who underwent an initial excisional biopsy on D9602; this patient received VA but was classified as Group III in the study. All 16 patients in this report who were enrolled onto ARST0331 were assigned to VAc/VA given over 45 weeks.

Response-Based Local Therapy

Patients with Group IIA or III N₀ RMS on D9602 (n=23) and Group III N₀ RMS on ARST0331 (n=14) were to follow the response-based approach to local therapy that could delay or eliminate RT (n=37) (Table I). Thirty-one of the 37 patients with Group IIA or III N₀ RMS completed protocol therapy (Fig. 1A, B). Of these 31 patients, only four received RT: three received 50.4 Gy and one received 45 Gy. Four patients (two Group I and two Group III N₁) were enrolled for whom the response-based approach that could delay or eliminate RT did not apply (Table I). According to protocol, neither of the patients with Group I tumors received RT. In contrast, neither of the patients with Group III N₁ tumors on ARST0331 followed the protocol specified guidelines for local therapy for N₁ tumors; neither received RT.

Local Tumor Control

Four patients with Group IIA or III N₀ vaginal RMS developed PD before local therapy (two Group IIA on VA and two Group III N₀; one on VA and one on VAc/VA) (Fig. 1A, B). Twenty-three of the 31 patients with Group IIA or III N₀ vaginal RMS who completed protocol therapy, remained disease free with a median follow-up of 5.6 years on D9602 (n=17) and 1 year on ARST0331 (n=6) (Fig. 1A, B). Eight of the 31 patients with Group IIA (n=1) or Group III N₀ (n=7) vaginal RMS who completed protocol therapy developed PD at the primary site (three in D9602; one on VA and two on VAC, and five in ARST0331) after completing local therapy. In addition, one of two patients with Group I RMS developed PD at week 12, and one of two patients with Group III N₁ RMS suffered a simultaneous local and distant recurrence in bone at week 22.

The 5-year cumulative incidence of local recurrence for patients with Group IIA or III N₀ vaginal RMS was 26% on D9602. This compared unfavorably with the 5-year cumulative incidence of local recurrence of 14% for patients with Group IIA or III N₀ low-risk embryonal RMS enrolled onto D9602 at sites other than the vagina. The 2-year cumulative incidence of local recurrence was 43% for patients with Group III N₀ vaginal RMS enrolled onto ARST0331.

Overall, five local recurrences were observed in eight patients treated with VA (62% local failure rate), in two of 17 treated with VAC (12% local failure rate; total cumulative cyclophosphamide dose ranged from 0.86 g/kg to 28.6 g/m² depending on the age of the patient), and in seven of 16 treated with VAc/VA (44% local failure rate; total cumulative cyclophosphamide dose ranged from 0.12 g/kg to 4.8 g/m² depending on the age of the patient). Local recurrence rates for patients with Group IIA or III N₀ that did not receive RT (n=33) were 67% (4/6) on VA, 14% (2/14) on VAC, and 46% (6/13) on VAc/VA.

Outcome

For the 25 patients with vaginal RMS treated on D9602, estimated 2-year and 5-year FFS rates were 80% (95% CI: 58%, 91%), and 70% (95% CI: 46%, 84%), respectively. The 5-year overall survival (OS) rate was 100% with a median follow-up of 5.6 years (Fig. 2). For the 16 patients with Group III vaginal RMS treated on ARST0331, the estimated 2-year FFS and OS rates were 42% (95% CI: 11%, 70%) and 88% (95% CI: 39%, 98%), respectively with a median follow-up of 1 year (Fig. 3).

The estimated 5-year FFS rate for the 23 patients with Group IIA or III N₀ vaginal RMS on D9602 was 71% (95% CI: 46%, 86%). This compared unfavorably with the 5-year FFS rate of 84% (95% CI: 78%, 89%) for 184 patients with Group IIA and III N₀ low-risk embryonal RMS enrolled onto D9602 at sites other than the vagina. In contrast, the estimated 5-year OS rate for patients with Group IIA or III N₀ vaginal RMS on D9602 (100%) was similar to the 5-year OS rate (n=184, 94%, 95% CI, 89%, 97%) for patients with Group IIA or III N₀ low-risk embryonal RMS on D9602 at other sites. The 2-year FFS rate for the 14 patients with Group III N₀ vaginal RMS on ARST0331 was 44% (95% CI: 11%, 74%). The 2-year OS rate for patients with Group III N₀ RMS on ARST0331 was 100%.

All of the 13 patients who suffered an isolated local recurrence survived (seven in D9602 and six in ARST0331). The only patient who died had Group III N₁ disease and suffered a combined local and distant recurrence. Limited information concerning therapy at the time of recurrence was available: it included further chemotherapy not otherwise specified (n=4); intensified chemotherapy, including doxorubicin, cyclophosphamide, ifosfamide, etoposide with or without irinotecan (n=4); surgery not otherwise specified (n=5); radical surgery (n=3); and RT (n=2). Therefore, the majority of the patients responded to salvage therapy, sometimes including intensified chemotherapy, radical surgery, and/or RT.

DISCUSSION

We observed a higher local failure rate than expected in patients with Group IIA or III N₀ vaginal RMS, using a response-based approach that could delay or eliminate RT on D9602 and ARST0331. Only four of the 37 patients enrolled onto these studies with Group IIA or III N₀ vaginal RMS received RT. For D9602, the cumulative incidence of local recurrence in patients with vaginal RMS was higher than that seen in comparable patients with Group IIA and III N₀ RMS at other primary sites who received the same chemotherapy as patients with vaginal RMS but also received RT. Local failures accounted for 5-year and 2-year FFS rates on D9602 and ARST0331, respectively that were significantly lower than expected for patients in the low-risk category [2, 7]. The high rate of local failures appears related to the attempt to delay or avoid local RT in those patients with non-resected vaginal RMS who also received either a lower dose of cyclophosphamide (VAc/VA) than D9602 VAC or no cyclophosphamide at all (VA). The goal of the vaginal-specific response-adjusted RT guidelines and the cyclophosphamide dose reductions was to maintain excellent FFS yet minimize long-term complications associated with therapy. The increased local recurrence rates and suboptimal FFS for these patients raise concern about continuing this approach to

locoregional tumor control for girls with vaginal RMS along with VA or VAc/VA chemotherapy.

In contrast, OS was excellent for these patients, likely based on the fact that most recurred locally, had not been previously exposed to RT, and could receive intensified chemotherapy. Details regarding the extent of salvage therapy at the time of recurrence were not always available, but in a significant proportion of these patients subsequent treatment included intensified chemotherapy, radical surgery, and RT. These patients are ultimately at risk for long-term complications associated with intensified therapy.

Similar to the results reported here, results of the IRS-II – IV studies for girls with RMS of the genital tract suggested a relatively high local failure rate with favorable OS [1]. Nine of 44 girls with Group II/III vaginal RMS had local recurrences in IRS-III – IV. Only one of the nine received RT, whereas 14 of the remaining 35 patients received RT. Only two patients received neither cyclophosphamide nor RT in IRS-III; both recurred locally. The International Society of Pediatric Oncology (SIOP) Malignant Mesenchymal Tumor (MMT) 84 and 89 studies used a comparable approach to local therapy for these patients and reported locoregional recurrences in seven of 38 patients (18%), but once again the 5-year OS rate was favorable (91% $\pm$ 6%) [3]. Three patients received vincristine and dactinomycin in MMT 89, and the remaining patients in MMT 84 or 89 received three to ten courses of ifosfamide (6 g/m² per course) with vincristine and dactinomycin. Based on the results of these studies, it was felt that the vaginal-specific response-based approach to local therapy provided a strong enough possibility of cure to support its use. However, firm conclusions based on the IRS-II – IV experience were limited because protocol guidelines for the use of RT were often not followed [1].

The IRSG and COG have historically used FFS as the primary endpoint and have administered RT to patients with non-resected RMS at sites other than the vagina in order to optimize outcome and to avoid relapse and subsequent exposure to salvage therapy [7, 12]. In contrast, SIOP has attempted to reduce systematic use of local therapy for RMS at most primary sites on the MMT studies based on response to chemotherapy. OS thus becomes the primary end point, while accepting the possibility of poorer FFS and the necessity of salvage therapy for those who relapse [13]. The response-based approach used on D9602 and ARST0331 exclusively for patients with vaginal RMS that delayed or eliminated RT for Group IIA and III N₀ patients resembled the approach to local therapy used more widely by SIOP. Comparison of IRS-IV 5-year data with MMT 89 for other primary sites revealed that IRS-IV therapy produced superior FFS and somewhat better OS than MMT 89 therapy [12]. Therefore, different cooperative groups may reach conflicting conclusions regarding the data presented here.

The local failure rate for patients with Group II or III N₀ RMS who did not receive RT was lowest for patients who received D9602 VAC. The high dose of cyclophosphamide per course (36 mg/kg for patients < 1 year of age, 73 mg/kg for patients 1 - < 3 years of age, and 2.2 g/m² for patients $\geq$ 3 years of age) and high total cumulative dose (0.95 g/kg for patients 1 - < 3 years of age, and 28.6 g/m² for patients $\geq$ 3 years of age) has been associated with significant acute and long-term toxicity, including myelosuppression in > 90% of patients per treatment course, infectious complications, hepatopathy, infertility, and second malignancies [7, 14, 15]. Based in part on this toxicity profile, COG is testing lower dose cyclophosphamide (0.16 g/kg total cumulative dose for patients < 3 years of age, and 4.8 g/m² for patients $\geq$ 3 years of age) in patients with low-risk RMS in the ARST0331 trial. Since outcome did not improve for patients with intermediate-risk RMS with increasing cyclophosphamide dose intensity from IRS-III – V [2, 7, 16], COG is also using a lower cyclophosphamide dose (40 mg/kg for patients < 3 years of age, and 1.2 g/m² for patients

3 years of age) per course and total cumulative dose (0.56 g/kg for patients < 3 years of age, and 16.8 g/m² for patients ≥ 3 years of age) compared with D9602 VAC in the current intermediate-risk RMS trial. It is possible that higher cyclophosphamide dose-intensity contributed to improved local control in the absence of RT for non-resected vaginal RMS. However, given the toxicity, limited number of patients in this report, and uncertainty regarding the role of cyclophosphamide in local control for RMS, we are reluctant to uniformly recommend D9602 VAC with the vaginal-specific response-based local control approach for patients with non-resected vaginal RMS.

Another factor that appeared to complicate local management for vaginal RMS was uncertainty regarding the extent of disease following the initial biopsy or resection, particularly for patients with Group I or II tumors. Re-evaluation at week 11–13 raised the question of whether evidence of disease represented PD or residual tumor with incorrect initial Group assignment. Uncertainty surrounding initial Group assignment for Group I or II tumors also limits conclusions surrounding the role of cyclophosphamide in reducing local failure for vaginal RMS, since three of five recurrences on VA represented cases of early PD. We believe that the risk of local recurrence increases when using a response-based approach that delays or eliminates local RT for girls with Group IIA or III N₀ vaginal RMS using VA or VAc/VA chemotherapy regimens.

We have therefore amended local therapy guidelines on ARST0331 for this site to include RT for patients with Group II or III vaginal RMS in a manner similar to that for other primary sites. However, we also recognize that the long-term toxicity of RT may be considerable, particularly in children less than 24 months old. Potential long-term complications associated with external beam RT for vaginal RMS include vaginal stenosis and fistulas, uterine growth and functional abnormalities, ovarian failure, musculoskeletal hypoplasia and psychologic disorders [5, 17–20]. Therefore, COG RMS protocols permit omission of RT for children less than 24 months with Group II or III RMS if the potential toxicity is considered unacceptable. However, when making the decision to eliminate local RT, physicians should recognize the associated increased risk of local recurrence, whether the tumor arises in the vagina or another primary site, especially in the setting of VA or VAc/VA chemotherapy. Alternative RT approaches, such as intracavitary brachytherapy with individually tailored mold vaginal applicators or proton radiation, may play a role in decreasing toxicity for some patients in the future [3, 6, 18].

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Local control approach and outcome for patients with Group IIA and III N₀ vaginal RMS on D9602 (n=23; median follow-up 5.6 years) **(A)** and for patients with Group III N₀ vaginal RMS on ARST0331 (n=14; median follow-up 1 year) **(B)**. For **(A)**: CR, complete response; PR, partial response (decrease in the product of the maximum perpendicular diameters of the tumor of ≥ 50%); SD, stable disease (decrease in the product of the maximum perpendicular diameters of the tumor of < 50% and not qualifying as progressive disease); PD, progressive disease (increase of ≥ 25% in the product of the maximum perpendicular diameters of the tumor); Neg, negative for RMS; Pos, positive for RMS; NED, no evidence of disease. For **(B)**: Abbreviations as in **(A)** except; PR, partial response (decrease in tumor volume of ≥ 64%); SD, stable disease (decrease in tumor volume < 64% and not qualifying as progressive disease); PD, progressive disease (increase in tumor volume ≥ 40%). *Timing of the response assessment varied based on the timing of the definitive biopsy or delayed primary resection. **Uncertain based on available records.

Fig. 2.
FFS and OS for the 25 patients with vaginal RMS on D9602.

Fig. 3.
FFS and OS for the 16 patients with Group III vaginal RMS on ARST0331.

TABLE I

Local Control Paradigms

Local control paradigm for sites other than the vagina			
Group I	No RT		
Group IIA	36 Gy beginning at week 3 (D9602) or 13 (ARST0331)		
Group IIB, IIC	41.4 Gy beginning at week 3 (D9602) or 13 (ARST0331)		
Group III	If RT alone, 50.4 Gy (45 Gy if orbit) beginning at week 3 (D9602; unless the primary site was vulva, uterus, biliary tract, or a superficial non-parameningeal head and neck site for which RT started at week 12) or 13 (ARST0331)		
	If delayed primary resection at week 12 (D9602) or 13 (ARST0331) followed by RT		
	Margin	Nodes	RT dose
	Negative	N ₀	36 Gy
	Negative	N ₁	41.4 Gy 36 Gy
	Microscopic residual	N ₀	
	Microscopic residual	N ₁	41.4 Gy
	Gross residual	N ₀ or N ₁	50.4 Gy
Local control paradigm for Group IIA or III vaginal RMS on D9602 and Group III vaginal RMS on ARST0331 without lymph node involvement (N ₀ or N _X)			
Group I	No RT		
Group II, III	Reassess with imaging/EUA at week 12; if tumor shrinking or undetectable at week 12, reassess with imaging/EUA and biopsy at week 28 (D9602) or 24 (ARST0331) with or without delayed primary resection		
	Histologic Response	RT dose	
	Complete response	0 Gy	
	Microscopic residual	36 Gy	
	Gross residual	50.4 Gy	
Local control paradigm for Group IIB, IIC or III vaginal RMS on D9602 and Group III vaginal RMS on ARST0331 with lymph node involvement (N ₁)			
Group II, III	Reassess with EUA/biopsy at week 12; RT started after biopsy or delayed primary resection at week 12 (D9602) or 13 (ARST0331)		
	Histologic Response	RT to primary	RT to nodes
	Complete response	0 Gy	41.4 Gy
	Microscopic residual	36 Gy	41.4 Gy
	Gross residual	50.4 Gy	50.4 Gy

TABLE II

Treatment regimens

D9602 Subgroup A													
Week	0	1	2	3	4	5	6	7	8	9	10	11	12**
V	V	V	V	V	V	V	V	V	V	-	-	-	Eval
A	-	-	A	-	-	A*	-	-	-	A	-	-	
RT (if Group IIA or III non-vaginal)													
12	13	14	15	16	17	18	19	20***	21	22	23	24	24**
V	V	V	V	V	V	V	V	V	-	-	-	-	Eval
A	-	-	A	-	-	A	-	-	A	-	-	-	
24	25	26	27	28***	29	30	31	32	33	34	35	36	36**
V	V	V	V	V	V	V	V	V	-	-	-	-	Eval
A	-	-	A	-	-	A*	-	-	A*	-	-	-	
RT (if indicated for vaginal Group IIA)													
36	37	38	39	40	41	42	43	44	45	46	47	48	48**
V	V	V	V	V	V	V	V	V	-	-	-	-	Eval
A	-	-	A	-	-	A	-	-	A	-	-	-	
D9602 Subgroup B													
Week	0	1	2	3	4	5	6	7	8	9	10	11	12**
V	V	V	V	V	V	V	V	V	V	-	-	-	Eval
A	-	-	A	-	-	A*	-	-	A	-	-	-	
C	-	-	C	-	-	C	-	-	C	-	-	-	
RT (if Group IIB, C or III non-vaginal)													
12	13	14	15	16	17	18	19	20***	21	22	23	24	24**
V	V	V	V	V	V	V	V	V	-	-	-	-	Eval
A	-	-	A*	-	-	A*	-	-	A	-	-	-	
C	-	-	C	-	-	C	-	-	C	-	-	-	
RT (if indicated following delayed primary resection or vaginal N ₁)													
12	13	14	15	16	17	18	19	20***	21	22	23	24	24**
V	V	V	V	V	V	V	V	V	-	-	-	-	Eval
A	-	-	A*	-	-	A*	-	-	A	-	-	-	
C	-	-	C	-	-	C	-	-	C	-	-	-	

24	25	26	27	28	29	30	31	32	33	34	35	36
V	V	V	V	V	V	V	V	V	-	-	-	Eval
A	-	-	A	-	-	A*	-	-	A*	-	-	-
C	-	-	C	-	-	C	-	-	-	-	-	-
RT (if indicated for vaginal N ₀)												
36	37	38	39	40	41	42	43	44	45	46	47	48
V	V	V	V	V	V	V	V	V	-	-	-	Eval
A	-	-	A	-	-	A	-	-	A	-	-	-
C	-	-	C	-	-	C	-	-	-	-	-	-
ARST0331 Subset 2												
Week												
1	2	3	4	5	6	7	8	9	10	11	12	**
V	V	V	V	V	V	V	V	V	-	-	-	Eval
A	-	-	A	-	-	A	-	-	A	-	-	-
c	-	-	c	-	-	c	-	-	c	-	-	-
13	14	15	16	17	18	19	20	21	22	23	24	**
V	V	V	V	V	V	V	V	V	-	-	-	Eval
A	-	-	A*	-	-	A*	-	-	A	-	-	-
RT (Group II or III or vaginal N ₁)												
25	26	27	28	29	30	31	32	33	34	35	36	**
V	V	V	V	V	V	V	V	V	-	-	-	Eval
A*	-	-	A*	-	-	A	-	-	A	-	-	-
37	38	39	40	41	42	43	44	45	46	47	48	**
V	V	V	V	V	V	V	V	V	-	-	-	Eval
A	-	-	A	-	-	A	-	-	A	-	-	-

V, vincristine (dose before August 2002 on D9602, age < 1 year: 0.75 mg/m², 1 year: 1.5 mg/m² [maximum dose 2 mg]; dose after December 2002 on D9602 and on ARST0331, age < 1 yr: 0.025 mg/kg, age 1 - < 3 yr: 0.05 mg/kg, age 3 yr: 1.5 mg/m² [maximum dose 2 mg]); A, dactinomycin (dose before August 2002 on D9602, age < 1 year: 0.025 mg/kg, age 1 year and 30 kg: 0.045 mg/kg, age > 1 year and > 30 kg: 1.5 mg/m² [maximum dose 2.5 mg]; dose after December 2002 on D9602 and on ARST0331, age < 1 yr: 0.025 mg/kg, age 1 yr: 0.045 mg/kg [maximum dose 2.5 mg]); C, cyclophosphamide (dose before August 2002 on D9602, age < 1 year: 1.1 g/m², age > 1 year: 2.2 g/m²; dose after December 2002 on D9602, age < 1 yr: 36 mg/kg, age 1 - < 3 yr: 73 mg/kg, age 3 yr: 2.2 g/m²); c, cyclophosphamide (dose on ARST0331, age < 3 yr: 40 mg/kg, age 3 yr: 1.2 g/m²).

* Omitted during RT.

*** Evaluation for all patients, including those with vaginal primaries.

*** Evaluation for patients with vaginal primaries.

TABLE III

Characteristics of Patients with Vaginal RMS on D9602 and ARST0331

	D9602 n=25	ARST0331 n=16	All Patients n=41
Age (years)			
2	16	15	31
3–9	7	0	7
10–14	2	1	3
15	0	0	0
Race			
White	19	10	29
Black	4	2	6
Other	1	4	5
Unknown	1	0	1
Group			
I	2	0	2
IIA	5	0	5
III	18	16	34
Tumor size			
5 cm	13	10	23
> 5 cm	12	6	18
Nodal status			
N ₀	25	14	39
N ₁	0	2	2
N _x	0	0	0
Invasiveness			
T1	20	14	34
T2	5	2	7
Histology			
Embryonal	3	3	6
Botryoid	20	13	33
RMS, NOS	2	0	2
Treatment			
D9602 VA	8	NA	8
D9602 VAC	17	NA	17
ARST0331 VAc/VA	NA	16	16

N₀, no regional lymph nodal involvement; N₁, regional lymph nodes involved by tumor; N_x, regional lymph nodal status unknown; T1, noninvasive; T2, invasive; NOS, not otherwise specified.