Demographic and Treatment Variables Influencing Outcome for Localized Paratesticular Rhabdomyosarcoma: Results From a Pooled Analysis of North American and European Cooperative Groups

David O. Walterhouse, Donald A. Barkauskas, David Hall, Andrea Ferrari, Gian Luca De Salvo, Ewa Koscielniak, Michael C.G. Stevens, Hélène Martelli, Guido Seitz, David A. Rodeberg, Margaret Shnorhavorian, Roshni Dasgupta, John C. Breneman, James R. Anderson, Christophe Bergeron, Gianni Bisogno, William H. Meyer, Douglas S. Hawkins, and Veronique Minard-Colin

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

Published at jco.org on October 23, 2018.

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Corresponding author: David O. Walterhouse, MD, Division of Hematology/Oncology/Stem Cell Transplant, Ann & Robert H. Lurie Children's Hospital of Chicago, 225 E Chicago Ave, Chicago, IL 60611; e-mail: d-walterhouse@northwestern.edu.

© 2018 by American Society of Clinical Oncology

0732-183X/18/3635w-3466w/\$20.00

ABSTRACT

Purpose

Treatment recommendations for localized paratesticular rhabdomyosarcoma (PT RMS) differ in North America and Europe. We conducted a pooled analysis to identify demographic features and treatment choices that affect outcome.

Patients and Methods

We retrospectively analyzed the effect of nine demographic variables and four treatment choices on event-free survival (EFS) and overall survival (OS) from 12 studies conducted by five cooperative groups.

Results

Eight hundred forty-two patients with localized PT RMS who enrolled from 1988 to 2013 were included. Patients age ≥ 10 years were more likely than younger patients to have tumors that were > 5 cm, enlarged nodes (N1), or pathologically involved nodes ($P \leq .05$ each). With a median follow-up of 7.5 years, Kaplan-Meier estimates for 5-year EFS and OS were 87.7% and 94.8%, respectively. Of demographic variables, cooperative group, era of enrollment, age category, tumor size, Intergroup Rhabdomyosarcoma Study group, and T stage affected EFS ($P \leq .05$ each). Surgical assessment of regional nodes, which was performed in 23.5% of patients—usually in those age ≥ 10 years or with suspicious or N1 nodes—was the only treatment variable associated with EFS by univariable and multivariable analyses ($P \leq .05$ each) in patients age ≥ 1 year. A variable selection procedure on a proportional hazards regression model selected era of enrollment, age, tumor size, and surgical assessment of regional nodes as significant ($P \leq .05$ each) in the EFS model, and era of enrollment, age, tumor size, and histology ($P \leq .05$ each) in the OS model.

Conclusion

Localized PT RMS has a favorable prognosis. Age ≥ 10 years at diagnosis and tumor size larger than 5 cm are unfavorable prognostic features. Surgical assessment of regional nodes is important in patients age ≥ 10 years and in those with N1 nodes as it affects EFS.

J Clin Oncol 36:3466-3476. © 2018 by American Society of Clinical Oncology

INTRODUCTION

Patients with localized paratesticular rhabdomyosarcoma (PT RMS) have a favorable prognosis.^{1,2} Unfavorable prognostic features include age ≥ 10 years, tumor size > 5 cm, invasive (T2) or unresectable (group III) tumors, and tumor involvement of retroperitoneal lymph nodes.³⁻⁷ Retroperitoneal lymph node involvement has

been associated with age ≥ 10 years and tumors > 5 cm.⁵⁻¹⁰

Treatment recommendations for localized PT RMS differ on the basis of clinical trials conducted by cooperative groups in North America and Europe.^{5-7,11-18} The recommended surgical approach to the primary tumor has uniformly been complete resection by inguinal orchiectomy with high ligation of the spermatic cord^{19,20}; however, the surgical approach to regional retroperitoneal

ASSOCIATED CONTENT

Appendix
DOI: <https://doi.org/10.1200/JCO.2018.78.9388>

DOI: <https://doi.org/10.1200/JCO.2018.78.9388>

lymph nodes remains controversial.^{7-9,21} Currently, staging ipsilateral retroperitoneal lymph node assessment (RPLNA) is recommended for patients age ≥ 10 years or in younger patients with enlarged nodes (N1) by the North American Children's Oncology Group (COG). This is based on the decreased recognition of involved retroperitoneal lymph nodes with computed tomography evaluation on Intergroup Rhabdomyosarcoma Study (IRS) IV compared with surgical assessment used on IRS-III and a higher rate of regional nodal relapse on IRS-IV.^{8,9}

In contrast, surgical assessment of retroperitoneal lymph nodes has not been routinely recommended as part of staging by European cooperative groups, including the Cooperative Weichteilsarkom Studiengruppe (CWS), the Italian Cooperative Group (ICG), the International Society of Pediatric Oncology Malignant Mesenchymal Tumor Group (MMT), or the European Pediatric Soft Tissue Sarcoma Group (EpSSG), which was more recently established by joining ICG and MMT. These groups have demonstrated no difference in the rate of retroperitoneal nodal involvement or outcome using imaging instead of systematic surgery for the assessment of retroperitoneal nodes.^{5,6,21} They have reserved surgical assessment of retroperitoneal nodes during staging for patients with suspicious nodes on imaging, but have recommend therapeutic lymph node resection only if enlarged lymph nodes persist after induction chemotherapy.^{5,17} However, recent analysis of the MMT-89 and -95 studies demonstrated an increased risk of lymph node relapse in patients with PT RMS who are age ≥ 10 years compared with younger patients using this approach.⁷

Radiotherapy (RT) dose is based on the extent of residual tumor after initial surgical resection or delayed surgical resection with chemotherapy.^{5-7,9,11-18} Specific RT guidelines for involved regional lymph nodes again differ by cooperative group. In COG, ICG, and EpSSG, RT has been administered to regional nodes for

patients who have enlarged nodes at diagnosis or pathologic involvement of regional lymph nodes. In contrast, patients in CWS and MMT studies with enlarged nodes at diagnosis that disappear after induction chemotherapy or who undergo secondary therapeutic nodal resection do not receive RT.

Chemotherapy regimens for localized PT RMS generally include vincristine and dactinomycin (VA). Duration of therapy and use of cyclophosphamide, ifosfamide, doxorubicin, topotecan, irinotecan, or other agents in addition to VA have been studied by the cooperative groups, depending on such features as age, tumor size, IRS group, stage, histology, and nodal involvement.^{5-7,11-18,22-24}

We conducted a pooled analysis to identify demographic features and treatment choices that affect outcome for patients with localized PT RMS. This analysis can contribute to the establishment of standard therapy guidelines that optimize outcome for patients with localized PT RMS.

PATIENTS AND METHODS

Patients were eligible for this analysis if they received a diagnosis of localized PT RMS and were enrolled in one of 12 COG, CWS, EpSSG, ICG, or MMT studies between 1988 and 2013^{5-8,11-19,21,23,24} (Table 1). IRS-IV was included with COG for the analysis. The upper age eligible for the studies differed: 50 years for COG; 21 years for IRS-IV, CWS, EpSSG, and ICG; and 18 years for MMT studies.

We assessed nine demographic characteristics, including cooperative group; era of enrollment; age (either as a categorical or as a continuous variable); size of the primary tumor; IRS group¹¹; T stage¹¹; N stage, defined as clinical status of nodes on the basis of physical examination and imaging¹¹; pathologic status of regional lymph nodes; and histology. We also assessed four treatment choices, including surgical approach to the

Table 1. Clinical Trials Included in This Analysis

Group and Study Name	Years of Enrollment	Type of Phase III Study	No. of Patients (excluded)	Median Age at Enrollment, Years (range)	Median Follow-Up, Years (range)	Reference
COG						
IRS-IV	1991-1998	A, grp I R, grp II, III	133	7.23 (0.45-19.81)	8.66 (0.67-14.73)	Wiener et al ⁸ ; Crist et al ¹¹
D9602	1997-2004	A	138 (1)	7.08 (0.73-18.96)	7.01 (0.02-14.83)	Raney et al ¹²
D9803	1999-2005	R	20	9.74 (0.12-19.84)	5.90 (1.61-9.23)	Arndt et al ¹⁵
ARST0331	2004-2011	A	120	8.72 (0.68-28.30)	7.80 (0.88-12.29)	Walterhouse et al ^{13,14}
ARST0531	2006-2013	R	3	3.59 (1.96-14.85)	6.18 (6.18-6.18)	Hawkins et al ¹⁶
CWS						
CWS-96	1995-2003	A, N0 R, N1	74 (1)	6.39 (0.04-18.91)	7.88 (0.49-12.44)	Ferrari et al ⁵ ; Seitz et al ¹⁷
CWS-2002P	2003-2010	A	32 (2)	6.56 (0.33-18.04)	7.53 (0.02-10.86)	Seitz et al ¹⁷
EpSSG						
EpSSG2005	2005-2011	R, ERMS N1; ARMS N0 A, others	99	11.1 (0.40-21.10)	3.97 (0.54-7.32)	Cecchetto et al ¹⁹ ; Olive et al ²¹ ; Bisogno et al ²³
ICG						
RMS-88	1988-1995	A	20	5.07 (1.71-18.07)	18.12 (13.55-21.52)	Ferrari et al ⁵
RMS-96	1996-2003	A	44	6.16 (1.62-17.71)	11.71 (4.51-18.49)	Ferrari et al ⁵
MMT						
MMT-89	1989-1995	A	69	6.37 (0.30-17.87)	9.19 (4.14-14.97)	Stewart et al ⁶ ; Rogers et al ⁷ ; Stevens et al ¹⁸
MMT-95	1995-2003	A, ERMS R, ARMS	90	5.57 (0.58-17.46)	8.58 (2.97-13.91)	Rogers et al ⁷ ; Oberlin et al ²⁴

Abbreviations: A, assigned; ARMS, alveolar rhabdomyosarcoma; COG, Children's Oncology Group; CWS, Cooperative Weichteilsarkom Studiengruppe; EpSSG, European Pediatric Soft Tissue Sarcoma Group; ERMS, embryonal rhabdomyosarcoma; grp, Intergroup Rhabdomyosarcoma Study group; ICG, Italian Cooperative Group; IRS, Intergroup Rhabdomyosarcoma Study; MMT, International Society of Pediatric Oncology Malignant Mesenchymal Tumor Group; R, randomized.

primary tumor; surgical assessment of regional lymph nodes, either as a staging or therapeutic procedure; chemotherapy regimen; and RT delivered. We assessed the site of recurrence, defined as local if the tumor recurred at the site of primary disease, regional if regional lymph nodes were involved with recurrent disease, or distant if metastatic disease was present at the time of recurrence. Ipsilateral iliac and retroperitoneal nodes up the level of the renal hilum were considered regional nodes. We assessed two outcome measures: event-free survival (EFS) and overall survival (OS).

Statistical Considerations

We checked categorical demographic variables and treatment choices for association using the exact conditional test of proportions.²⁵ Age as a continuous variable was assessed for association with demographic or treatment variables using a *t* test or one-way ANOVA.²⁶ Most of the statistical analysis cited in this work included all patients. Exceptions are comparisons made by age category at enrollment. As a result of the small number of patients who were younger than age 1 year at enrollment (*n* = 20) and the poor prognosis of these patients compared with patients who were age 1 to 9 years at enrollment, patients younger than age 1 year were excluded from analyses that compared patients age ≥ 10 years with younger patients. A logistic regression was conducted with pathologic status of nodes as the response variable and age and tumor size as explanatory variables.¹⁰ *P* values for these multiple comparisons were adjusted using the Tukey-Kramer method.²⁶ EFS and OS of patient groups were estimated using the Kaplan-Meier method.²⁷ Outcomes were observed annually across the studies. Patients who did not experience an event, including relapse, second malignant neoplasm, or death, were censored at the date of last contact. Relative risks for EFS events or death were compared across groups using the log-rank test.²⁷ We conducted multivariable analysis on each treatment variable with demographic variables using a proportional hazards regression model.²⁷ A stepwise variable selection procedure was performed on a proportional hazards regression model starting with all demographic variables except N stage, which was not associated with EFS on univariable analysis (*P* = .47), and treatment choices to identify the best EFS and OS models.²⁷ Analyses were performed using SAS (SAS/STAT User's Guide, Version 9.4; SAS Institute, Cary, NC). A *P* value $\leq .05$ was considered significant.

RESULTS

Patients

Eight hundred forty-six patients with localized PT RMS enrolled in the 12 studies during the 25-year period analyzed. Four patients were excluded with a diagnosis of RMS not otherwise specified, so that 842 patients—414 patients from COG, 106 from CWS, 99 from EpSSG, 64 from ICG, and 159 from MMT—were included in this analysis (Table 1).

Demographic characteristics by cooperative group are listed in Table 2. There was a bimodal age distribution with peaks at age 5 and 15 years (Appendix Fig A1, online only). Analysis of age as a continuous variable demonstrated a significant association in mean age at enrollment and cooperative group, with EpSSG patients older than each of the other cooperative groups' patients and COG patients older than those in MMT: EpSSG: mean age, 11.0 years; standard deviation (SD), 6.0 years; COG: mean age, 9.3 years; SD, 5.7 years; ICG: mean age, 8.5 years; SD, 5.5 years; CWS: mean age, 8.5 years; SD, 5.6 years; or MMT: mean age, 7.2 years; SD, 4.6 years (*P* < .001). In fact, all demographic variables were associated with cooperative group (*P* $\leq .05$ each), which demonstrates differences in patient populations among cooperative

groups presumably on the basis of specific eligibility criteria for each of the studies.

The following demographic variables were significantly associated with age category at enrollment (age ≥ 10 years or 1 to 9 years): tumors larger than 5 cm (192 [62.3%] of 308 *v* 126 [26.0%] of 485, respectively; *P* < .001), enlarged retroperitoneal lymph nodes (N1; 55 [17.5%] of 315 *v* 17 [3.4%] of 493, respectively; *P* < .001), pathologically involved nodes (44 [31.9%] of 138 *v* nine [11.3%] of 80, respectively; *P* < .001), and pathologically involved nonenlarged nodes (21 [18.9%] of 111 *v* four [5.5%] of 73, respectively; *P* = .009). Patients age ≥ 10 years and 1 to 9 years had similar rates of pathologically involved N1 nodes (23 [52.3%] of 44 *v* four [55.6%] of nine, respectively; *P* = .28). Patients with unknown tumor size (*n* = 29), unknown nodal status (Nx; *n* = 14), or who did not undergo pathologic evaluation of nodes (*n* = 604) were excluded from the above respective analyses.

The estimated percent pathologic nodal involvement by patient age and tumor size on the basis of logistic regression was 3.4% (95% CI, 0.8% to 12.6%) for patients age 1 to 9 years with tumors ≤ 5 cm compared with 31.6% (95% CI, 14.9% to 54.8%; odds ratio [OR], 13.2; *P* = .017) for patients age 1 to 9 with tumors larger than 5 cm, 31.5% (95% CI, 20.6% to 44.9%; OR, 13.1; *P* = .005) for patients age ≥ 10 years with tumors ≤ 5 cm, and 34.2% (95% CI, 24.5% to 45.5%; OR, 13.1; *P* = .005) for patients age ≥ 10 years with tumors > 5 cm. For patients age ≥ 10 years, tumor size was not found to be a significant predictor of pathologic nodal involvement (*P* = .99).

Treatment choices by cooperative group are listed in Table 3. Treatment choices differed by cooperative group (*P* $\leq .05$ each). Patients most commonly underwent inguinal resection (*n* = 685 [81.4%]), did not undergo surgical assessment of regional nodes (*n* = 587 [69.7%]), or RT (*n* = 708 [84.1%]) and were treated with VA (*n* = 414 [49.2%]).

Outcome

With a median follow-up of 7.5 years, 738 patients did not experience an event (87.6%; Table 3). The most common event was relapse (*n* = 97; 93.3% of events). Local only recurrence was less common (*n* = 17; 17.5% of recurrences) than regional lymph node (*n* = 41; 42.3% of recurrences) or distant recurrences (*n* = 37; 38.1% of recurrences). EFS was univariably significantly associated with the following demographic features: cooperative group (*P* = .044), era of enrollment (*P* = .009), age category at enrollment (*P* < .001), tumor size (*P* < .001), IRS group (*P* = .005), and T stage (*P* < .001; Table 4 and Appendix Fig A2, online only). Histology (*P* = .060) was marginally associated with EFS.

When analyzing patients by the known prognostic factors age (≥ 10 years *v* 1 to 9 years) and tumor size (> 5 cm *v* ≤ 5 cm), proportional hazards regression for age and tumor size combined showed that patients who were age ≥ 10 years and had tumors larger than 5 cm had significantly worse EFS and OS than did patients who had neither or only one of these two unfavorable characteristics (*P* < .001; Table 4 and Fig 1). Of the treatment variables, only surgical assessment of regional nodes was associated with EFS on stratified univariable (*P* = .004) and multivariable (*P* = .023) analyses using all demographic variables except N stage for patients age ≥ 1 year. When analyzed by age category and tumor size, the effect of surgical assessment of regional nodes on EFS was only

Table 2. Demographic Characteristics of Patients by Cooperative Group

Demographic	Cooperative Group					Total
	COG	CWS	EpSSG	ICG	MMT	
Era of initial enrollment						
≤ 2002	255 (61.6)	75 (70.8)		51 (79.7)	157 (98.7)	538 (63.9)
≥ 2003	159 (38.4)	31 (29.2)	99 (100.0)	13 (20.3)	2 (1.3)	304 (36.1)
Age category at enrollment, years						
< 1	7 (1.7)	6 (5.7)	1 (1.0)		6 (3.8)	20 (2.4)
1–9	236 (57.0)	64 (60.4)	47 (47.5)	42 (65.6)	114 (71.7)	503 (59.7)
≥ 10	171 (41.3)	36 (34.0)	51 (51.5)	22 (34.4)	39 (24.5)	319 (37.9)
Size of primary tumor, cm						
≤ 5	229 (55.3)	66 (62.3)	50 (50.5)	45 (70.3)	102 (64.2)	492 (58.4)
> 5	172 (41.5)	35 (33.0)	47 (47.5)	19 (29.7)	48 (30.2)	321 (38.1)
Unknown	13 (3.1)	5 (4.7)	2 (2.0)		9 (5.7)	29 (3.4)
IRS group*						
I	318 (76.8)	75 (70.8)	69 (69.7)	60 (93.8)	111 (69.8)	633 (75.2)
Ila	37 (8.9)	17 (16.0)	10 (10.1)	4 (6.3)	36 (22.6)	104 (12.4)
Ilb	36 (8.7)		4 (4.0)		5 (3.1)	45 (5.3)
IIc	16 (3.9)	3 (2.8)	7 (7.1)		7 (4.4)	33 (3.9)
III	7 (1.7)	6 (5.7)	9 (9.1)			22 (2.6)
Unknown		5 (4.7)				5 (0.6)
T stage†						
T1	373 (90.1)	74 (69.8)	74 (74.7)	49 (76.6)	135 (84.9)	705 (83.7)
T2	41 (9.9)	30 (28.3)	22 (22.2)	15 (23.4)	21 (13.2)	129 (15.3)
Unknown		2 (1.9)	3 (3.0)		3 (1.9)	8 (1.0)
N stage‡						
N0	373 (90.1)	94 (88.7)	79 (79.8)	64 (100.0)	146 (91.8)	756 (89.8)
N1	38 (9.2)	4 (3.8)	19 (19.2)		11 (6.9)	72 (8.6)
Nx	3 (0.7)	8 (7.5)	1 (1.0)		2 (1.3)	14 (1.7)
Pathologic status of regional lymph nodes						
Not involved	112 (27.1)	26 (24.5)	8 (8.1)	12 (18.8)	9 (5.7)	167 (19.8)
Involved	49 (11.8)		2 (2.0)		2 (1.3)	53 (6.3)
Not evaluated	253 (61.1)	80 (75.5)	89 (89.9)	52 (81.3)	148 (93.1)	622 (73.9)
Histology						
Embryonal	277 (66.9)	102 (96.2)	82 (82.8)	47 (73.4)	108 (67.9)	616 (73.2)
Spindle cell	121 (29.2)		5 (5.1)	6 (9.4)	11 (6.9)	143 (17.0)
Alveolar	16 (3.9)	4 (3.8)	12 (12.1)	11 (17.2)	40 (25.2)	83 (9.9)

NOTE. Data are given as No. (%).

Abbreviations: COG, Children's Oncology Group; CWS, Cooperative Weichteilsarkom Studiengruppe; EpSSG, European Pediatric Soft Tissue Sarcoma Group; ICG, Italian Cooperative Group; IRS, Intergroup Rhabdomyosarcoma Study; MMT, International Society of Pediatric Oncology Malignant Mesenchymal Tumor Group.

*IRS group: I, localized disease, completely excised, no microscopic residual; Ila, gross resection with evidence of microscopic local residual; Ilb, regional disease with involved lymph nodes, completely resected with no microscopic residual; Ilc, microscopic local disease and involved regional nodes, completely resected; III, incomplete resection or biopsy with gross residual.

†T stage: T1, confined to the organ of origin; T2, extension or fixation to surrounding tissue.

‡N stage: N0, regional nodes not clinically involved; N1, regional nodes clinically involved with neoplasm; or Nx, clinical status of regional nodes unknown

significant in patients age ≥ 10 years with tumors larger than 5 cm ($P = .012$; Table 4 and Figs 2A and 2B). Patients age ≥ 10 years with tumors larger than 5 cm who underwent RPLNA had superior outcome compared with those who did not undergo surgical assessment of lymph nodes. Furthermore, patients age ≥ 10 years with tumors larger than 5 cm who received RT had superior EFS compared with those who did not receive RT ($P = .002$; Table 4 and Figs 2C and 2D).

For EFS, starting with all demographic variables except N stage and all treatment variables, a proportional hazards regression stepwise selection process chose era of enrollment, age category, tumor size, and surgical assessment of regional lymph nodes as statistically significant ($P \leq .05$ each; Table 4). Patients who enrolled in 2003 and after, those age 1 to 9 years, those with tumors ≤ 5 cm, or those who underwent surgical assessment of regional lymph nodes had better EFS. When analyzing only patients age 10 years or older with tumors greater than 5 cm, the proportional hazards regression stepwise selection process for EFS chose the univariable model with only RT delivered as a predictor variable (Table 4 and

Figs 2C and 2D). Patients with these characteristics who received RT had superior EFS.

With a median follow-up of 7.7 years, 795 patients were alive (94.5%; Table 3). The most common cause of death was relapse ($n = 40$; 85.1% of deaths). Using univariable analysis, the following demographic variables were significantly associated with OS: age category at enrollment ($P < .001$), tumor size ($P < .001$), IRS group ($P < .001$), T stage ($P = .009$), and histology ($P < .001$; Appendix Fig A2). OS was not associated with cooperative group ($P = .499$). None of the treatment variables was significantly associated with OS on univariable and multivariable analysis in patients age ≥ 1 year when era of enrollment, age category at enrollment, tumor size, and histology were already in the survival proportional hazards regression model.

For OS, starting with all demographic variables except N stage and all treatment variables, a proportional hazards regression stepwise selection process chose era of enrollment, age category, tumor size, and histology as statistically significant ($P \leq .05$ each;

Table 3. Treatment Choices and Outcome by Cooperative Group

Analysis Variable	Cooperative Group					Total
	COG	CWS	EpSSG	ICG	MMT	
Surgical approach to primary tumor						
Inguinal resection	362 (87.4)	66 (62.3)	87 (87.9)	51 (79.7)	119 (74.8)	685 (81.4)
Trans-scrotal resection	21 (5.1)	13 (12.3)	12 (12.1)	4 (6.3)	15 (9.4)	65 (7.7)
Biopsy only	3 (0.7)				1 (0.6)	4 (0.5)
Unknown	22 (5.3)	4 (3.8)		9 (14.1)		35 (4.2)
Tumorectomy (unknown approach)	2 (0.5)	23 (21.7)			17 (10.7)	42 (5.0)
Trans-scrotal orchidectomy and inguinal excision of cord during the same procedure	4 (1.0)				7 (4.4)	11 (1.3)
Surgical assessment of regional lymph nodes						
Not done	244 (58.9)	57 (53.8)	86 (86.9)	52 (81.3)	148 (93.1)	587 (69.7)
RPLNA	120 (29.0)	4 (3.8)	1 (1.0)	4 (6.3)	2 (1.3)	131 (15.6)
Biopsy	9 (2.2)	2 (1.9)	8 (8.1)	8 (12.5)	8 (5.0)	35 (4.2)
Other	14 (3.4)	14 (13.2)	3 (3.0)		1 (0.6)	32 (3.8)
Unknown	27 (6.5)	29 (27.4)	1 (1.0)			57 (6.8)
Chemotherapy regimen assigned						
VA	228 (55.1)	54 (50.9)	23 (23.2)	38 (59.4)	71 (44.7)	414 (49.2)
IVA		40 (37.7)	23 (23.2)	17 (26.6)	70 (44.0)	150 (17.8)
VAC/IVA + VA	120 (29.0)		41 (41.4)			161 (19.1)
IVA/VAC + Do		8 (7.5)	12 (12.1)	5 (7.8)		25 (3.0)
VAC ± T/I	58 (14.0)					58 (6.9)
Other	8 (1.9)	3 (2.8)		4 (6.3)	18 (11.3)	33 (3.9)
Unknown		1 (0.9)				1 (0.1)
RT delivered						
Yes	90 (21.7)	7 (6.6)	19 (19.2)	2 (3.1)	4 (2.5)	122 (14.5)
No	324 (78.3)	88 (83.0)	80 (80.8)	62 (96.9)	154 (96.9)	708 (84.1)
Unknown		11 (10.4)			1 (0.6)	12 (1.4)
Site of recurrence*						
Local only	8 (19.5)	2 (15.4)	1 (10.0)	3 (50.0)	3 (11.1)	17 (17.5)
Regional ± local, not distant	15 (36.6)	5 (38.5)	1 (10.0)	1 (16.7)	19 (70.4)	41 (42.3)
Distant ± regional ± local	17 (41.5)	5 (38.5)	8 (80.0)	2 (33.3)	5 (18.5)	37 (38.1)
Unknown	1 (2.4)	1 (7.7)				2 (2.1)
EFS event, No.						
No event	371	92	89	58	128	738
Relapse	41	13	10	6	27	97
SMN	2	1			3	6
Death					1	1
Life status, No.						
Alive	392	101	93	62	148	796
Dead	22	5	6	2	11	46
Cause of death						
Disease	20 (87.0)	5 (100)	6 (100)	2 (100)	7 (63.6)	40 (85.1)
Toxicity	1 (4.3)				3 (27.3)	4 (8.5)
SMN	1 (4.3)				1 (9.1)	2 (4.3)
Other reason, unrelated to disease or treatment	1 (4.3)					1 (2.1)

NOTE. Data are given as No. (%) unless otherwise noted.

Abbreviations: COG, Children's Oncology Group; CWS, Cooperative Weichteilsarkom Studiengruppe; EFS, event-free survival; EpSSG, European Pediatric Soft Tissue Sarcoma Group; ICG, Italian Cooperative Group; IRS, Intergroup Rhabdomyosarcoma Study; IVA, ifosfamide plus vincristine plus dactinomycin; IVA/VAC + Do, ifosfamide plus vincristine plus dactinomycin plus doxorubicin or vincristine plus dactinomycin plus cyclophosphamide plus doxorubicin; MMT, International Society of Pediatric Oncology Malignant Mesenchymal Tumor Group; RPLNA, retroperitoneal lymph node assessment; RT, radiotherapy; SMN, secondary malignant neoplasm; VA, vincristine plus dactinomycin; VAC/IVA + VA, vincristine plus dactinomycin plus lower-dose cyclophosphamide (total cumulative cyclophosphamide 4.8 g/m²) or lower-dose ifosfamide (total cumulative ifosfamide 24 g/m²) followed by vincristine plus dactinomycin; VAC ± T/I, vincristine plus dactinomycin plus cyclophosphamide with or without topotecan or irinotecan.

*Site of recurrence: local, primary site; regional, retroperitoneal lymph nodes; distant, metastatic site.

Table 4). Patients who enrolled in 2003 and after, those age 1 to 9 years, those with tumors 5 cm or smaller, or those with embryonal RMS or spindle-cell RMS had better OS.

DISCUSSION

Our analysis combines a 25-year experience of 842 patients with localized PT RMS from five cooperative groups in North America

and Europe. Some of these cooperative groups may not conduct additional clinical trials for patients with localized PT RMS on the basis of their favorable outcome. Instead, standard therapy guidelines will be developed on the basis of completed trials. Therefore, our goal was to identify demographic variables and treatment choices that affect outcome in patients with localized PT RMS to guide the development of standard therapy guidelines.

We observed differences in median age at the time of enrollment among patients enrolled in trials conducted by the

Variables Influencing Outcome of Localized PT RMS

Table 4. Regression Models for EFS and OS

Variable	Hazard Ratio (95% CI)	P
EFS, univariable analysis, all patients		
Cooperative group		
CWS v COG (n = 106 v n = 414)	1.31 (0.72 to 2.39)	.044
EpSSG v COG (n = 99 v n = 414)	1.00 (0.50 to 1.98)	
ICG v COG (n = 64 v n = 414)	0.85 (0.36 to 2.00)	
MMT v COG (n = 159 v n = 414)	1.93 (1.22 to 3.07)	
Era of enrollment		
2003 and later v 2002 and earlier (n = 304 v n = 538)	0.55 (0.35 to 0.87)	.009
Age, years		
< 1 v ≥ 10 (n = 20 v n = 319)	1.40 (0.56 to 3.49)	< .001
1-9 v ≥ 10 (n = 503 v n = 319)	0.36 (0.24 to 0.54)	
Tumor size, cm		
> 5 v ≤ 5 (n = 321 v n = 492)	2.72 (1.81 to 4.09)	< .001
Unknown v ≤ 5 (n = 29 v n = 492)	2.40 (0.94 to 6.10)	
IRS group		
I v IIb (n = 633 v n = 45)	1.04 (0.42 to 2.58)	.005
IIa v IIb (n = 104 v n = 45)	1.29 (0.47 to 3.54)	
IIc v IIb (n = 33 v n = 45)	0.51 (0.10 to 2.62)	
III v IIb (n = 22 v n = 45)	3.88 (1.27 to 11.87)	
Unknown v IIb (n = 5 v n = 45)	0.00 (0.00 to —)*	
T stage		
T2 v T1 (n = 129 v n = 705)	2.26 (1.47 to 3.48)	< .001
Unknown v T1 (n = 8 v n = 705)	1.33 (0.19 to 9.58)	
EFS, multivariable analysis, all patients		
Era of enrollment		
2003 and later v 2002 and earlier (n = 304 v n = 538)	0.48 (0.30 to 0.76)	.002
Age, years		
< 1 v ≥ 10 (n = 20 v n = 319)	1.86 (0.71 to 4.89)	< .001
1-9 v ≥ 10 (n = 503 v n = 319)	0.37 (0.24 to 0.58)	
Tumor size, cm		
> 5 v ≤ 5 (n = 321 v n = 492)	2.42 (1.54 to 3.81)	< .001
Unknown v ≤ 5 (n = 29 v n = 492)	2.50 (0.96 to 6.51)	
Surgical assessment of lymph nodes		
RPLNA v not done (n = 131 v n = 587)	0.30 (0.14 to 0.64)	.017
Biopsy v not done (n = 35 v n = 587)	1.03 (0.37 to 2.85)	
Other v not done (n = 32 v n = 587)	0.39 (0.10 to 1.61)	
Unknown v not done (n = 57 v n = 587)	1.17 (0.60 to 2.32)	
EFS, multivariable analysis, patients age ≥ 1 year		
Era of initial enrollment		
2003 and later v 2002 and earlier (n = 283 v n = 510)	0.46 (0.28 to 0.76)	.002
Age, years		
1-9 v ≥ 10 (n = 474 v n = 279)	0.34 (0.22 to 0.54)	< .001
Tumor size, cm		
> 5 v ≤ 5 (n = 288 v n = 465)	2.17 (1.38 to 3.42)	< .001
Surgical assessment of lymph nodes		
RPLNA v not done (n = 127 v n = 555)	0.30 (0.14 to 0.64)	.023
Biopsy v not done (n = 34 v n = 555)	0.72 (0.22 to 2.31)	
Other v not done (n = 32 v n = 555)	0.38 (0.09 to 1.55)	
Unknown v not done (n = 45 v n = 555)	0.89 (0.38 to 2.06)	
EFS, univariable analysis, patients age ≥ 1 year		
Age category and tumor size (Figs 1A and 1B; all hazard ratios v 1-9 years, ≤ 5 cm)		
1-9 years, > 5 cm (n = 126 v n = 359)	0.59 (0.30 to 1.17)	< .001
≥ 10 years, ≤ 5 cm (n = 116 v n = 359)	1.05 (0.48 to 2.31)	
≥ 10 years, > 5 cm (n = 192 v n = 359)	2.64 (1.43 to 4.89)	
EFS, univariable analysis, patients age ≥ 10 years, tumor size > 5 cm		
Surgical assessment of lymph nodes (Figs 2A and 2B)		
RPLNA v not done (n = 58 v n = 110)	0.23 (0.09 to 0.60)	.012
Biopsy v not done (n = 4 v n = 110)	1.87 (0.45 to 7.81)	
Other v not done (n = 7 v n = 110)	0.46 (0.06 to 3.32)	
Unknown v not done (n = 13 v n = 110)	0.92 (0.33 to 2.60)	
RT delivered (Figs 2C and 2D)		
Yes v no (n = 55 v n = 135)	0.32 (0.14 to 0.76)	.002
Unknown v no (n = 2 v n = 135)	5.37 (0.72 to 40.27)	

(continued on following page)

Table 4. Regression Models for EFS and OS (continued)

Variable	Hazard Ratio (95% CI)	P
OS, univariable analysis, all patients		
Age, years		
< 1 v ≥ 10 (n = 20 v n = 319)	2.12 (0.75 to 6.02)	< .001
1-9 v ≥ 10 (n = 503 v n = 319)	0.23 (0.12 to 0.44)	
Tumor size, cm		
> 5 v ≤ 5 (n = 321 v n = 492)	4.41 (2.27 to 8.58)	< .001
Unknown v ≤ 5 (n = 29 v n = 492)	2.94 (0.66 to 13.19)	
IRS group		
I v IIb (n = 633 v n = 45)	0.90 (0.21 to 3.78)	< .001
IIa v IIb (n = 104 v n = 45)	1.91 (0.41 to 8.84)	
IIc v IIb (n = 33 v n = 45)	0.65 (0.06 to 7.19)	
III v IIb (n = 22 v n = 45)	7.53 (1.52 to 37.35)	
Unknown v IIb (n = 5 v n = 45)	0.00 (0.00 to —)*	
T stage		
T2 v T1 (n = 129 v n = 705)	2.52 (1.35 to 4.73)	.009
Unknown v T ₁ (n = 8 v n = 705)	0.00 (0.00 to —)*	
Histology		
Spindle cell v embryonal (n = 143 v n = 616)	0.24 (0.06 to 1.00)	< .001
Alveolar v embryonal (n = 83 v n = 616)	2.48 (1.26 to 4.91)	
OS, multivariable analysis, all patients		
Era of enrollment		
2003 and later v 2002 and earlier (n = 304 v n = 538)	0.47 (0.23 to 0.97)	.040
Age, years		
< 1 v ≥ 10 (n = 20 v n = 319)	4.02 (1.31 to 12.38)	< .001
1-9 v ≥ 10 (n = 503 v n = 319)	0.31 (0.16 to 0.64)	
Tumor size, cm		
> 5 v ≤ 5 (n = 321 v n = 492)	3.60 (1.76 to 7.39)	.002
Unknown v ≤ 5 (n = 29 v n = 492)	3.44 (0.75 to 15.80)	
Histology		
Spindle cell v embryonal (n = 143 v n = 616)	0.28 (0.07 to 1.18)	.005
Alveolar v embryonal (n = 83 v n = 616)	2.45 (1.21 to 4.96)	
OS, univariable analysis, patients age ≥ 1 year		
Age category and tumor size (Figs 1C and 1D; all hazard ratios v 1-9 years, ≤ 5 cm)		
1-9 years, > 5 cm (n = 126 v n = 359)	0.41 (0.13 to 1.35)	< .001
≥ 10 years, ≤ 5 cm (n = 116 v n = 359)	0.93 (0.25 to 3.48)	
≤ 10 years, > 5 cm (n = 192 v n = 359)	3.78 (1.45 to 9.88)	

Abbreviations: COG, Children's Oncology Group; CWS, Cooperative Weichteilsarkom Studiengruppe; EFS, event-free survival; EpSSG, European Pediatric Soft Tissue Sarcoma Group; ICG, Italian Cooperative Group; IRS, Intergroup Rhabdomyosarcoma Study; MMT, International Society of Pediatric Oncology Malignant Mesenchymal Tumor Group; OS, overall survival; RPLNA, retroperitoneal lymph node assessment; RT, radiotherapy.

*As no one experienced an event, there is no upper estimate for the hazard ratio CI.

different cooperative groups. Age ≥ 10 years has been recognized as an unfavorable prognostic feature for patients with localized PT RMS and has been associated with tumor size > 5 cm and retroperitoneal lymph node involvement.⁵⁻¹⁰ Here, we observed a bimodal age distribution at the time of enrollment across clinical trials, which may support underlying biologic differences between PT RMS in younger children and adolescents.

Age and tumor size were confirmed as prognostic features for EFS and OS. Using the stepwise logistic selection procedure, histology was also selected in the OS model. Although patients with alveolar RMS generally have inferior outcome compared with patients with ERMS, this result should be interpreted with caution as the histologic definition of alveolar RMS changed in the years during which these patients were enrolled.^{28,29} Histology was not rereviewed at the time of this analysis. IRS group (completeness of initial resection) and T stage (invasiveness) were also confirmed as prognostic factors on univariable analysis.

The most controversial aspect of the management of localized PT RMS may be whether surgical assessment of retroperitoneal lymph nodes is necessary as part of the staging evaluation if imaging does not show nodal enlargement. We provide risks for pathologic nodal involvement that differ by age and tumor size and support the existing literature from the cooperative groups.^{5,7,8}

Although the risk of pathologic nodal involvement was significantly higher for patients age 1 to 9 years with tumors > 5 cm than for patients age 1 to 9 years with tumors ≤ 5 cm, the rate of pathologically involved nonenlarged nodes in this age group is low (5.5%). Given the favorable outcome for patients age 1 to 9 years with current treatment approaches in the cooperative groups (5-year EFS, 92.7%), which included surgical assessment of nodes in only 15.3% of patients, we believe that staging on the basis of imaging is justified for most patients younger than age 10 years. Surgical assessment of nodes may be indicated for patients age 1 to 9 years with either suspicious or N1 nodes (Fig 1 and Appendix Fig A2C).

Fig 1. Event-free survival (EFS) and overall survival (OS) analysis by age category at enrollment and tumor size. (A) For EFS hazard ratios (HRs), 95% CIs were done for all age category and tumor size pairwise comparisons (1 to 9 years and ≤ 5 cm, 1 to 9 years and > 5 cm, ≥ 10 years and ≤ 5 cm, or ≥ 10 years and > 5 cm). Intervals are displayed on the log scale with a $\log(\text{HR}) = 0$ indicating no difference in HR. (B) EFS by age category and tumor size (1 to 9 years and ≤ 5 cm, 1 to 9 years and > 5 cm, ≥ 10 years and ≤ 5 cm, or ≥ 10 years and > 5 cm). (C) For OS HRs, 95% CIs were done for all age category and tumor size pairwise comparisons (1 to 9 years and ≤ 5 cm, 1 to 9 years and > 5 cm, ≥ 10 years and ≤ 5 cm, or ≥ 10 years and > 5 cm). Intervals are displayed on the log scale with a $\log(\text{HR}) = 0$ indicating no difference in HR. (D) OS by age category and tumor size (1 to 9 years and ≤ 5 cm, 1 to 9 years and > 5 cm, ≥ 10 years and ≤ 5 cm, or ≥ 10 years and > 5 cm). *Data are given as percent. LCL, lower confidence limit; UCL, upper confidence limit.

The only treatment choice that was associated with EFS in patients age ≥ 1 year on stratified univariable and multivariable analyses was surgical assessment of nodes, which had been performed routinely as a part of staging in patients age ≥ 10 years in COG and in some patients with either suspicious or N1 nodes in the cooperative groups. Thirty-one percent of the study population from all cooperative groups age ≥ 10 years underwent RPLNA. The proportional hazards regression stepwise selection process for EFS also chose surgical assessment of nodes as statistically significant. On subset analysis, the impact of surgical assessment of nodes on EFS was significant on univariable analysis in patients age ≥ 10 years with tumors > 5 cm. Of note, the proportional hazards regression stepwise selection process for EFS also chose a univariable model with RT delivered as a predictor variable in

patients age ≥ 10 years with tumors > 5 cm. Therefore, surgical assessment of nodes may most accurately identify patients with nodal involvement who benefit from RT.⁹ It should be recognized that our pooled analysis is retrospective and is not randomized. Given these inherent limitations in design, uncontrollable confounding may affect conclusions with regard to outcome.

On subset analysis, surgical assessment of nodes was not associated with EFS in patients age ≥ 10 years with tumors ≤ 5 cm; however, the small number of events in this subset limited the power of the analysis. As tumor size was not found to be significant in predicting nodal involvement in patients age ≥ 10 years, taken together we believe that a uniform approach that includes surgical assessment of regional nodes during staging may be warranted for patients age ≥ 10 years.

Fig 2. Event-free survival (EFS) analysis by age category at enrollment and size of primary tumor for surgical assessment of regional lymph nodes and radiotherapy (RT) delivered. (A) For EFS hazard ratios (HRs), 95% CIs were done for all estimable pairwise comparisons of surgical assessment of regional lymph nodes (not done, retroperitoneal lymph node assessment [RPLNA], biopsy, other, or unknown) performed within all age category and tumor size categories (1 to 9 years and ≤ 5 cm, 1 to 9 years and > 5 cm, ≥ 10 years and ≤ 5 cm, or ≥ 10 years and > 5 cm). Intervals are displayed on the log scale with a $\log(\text{HR}) = 0$ indicating no difference in HR. (B) EFS by surgical assessment of regional lymph nodes (not done, RPLNA, biopsy, other, or unknown) for patients age ≥ 10 years at enrollment and size of primary tumor larger than 5 cm only. (C) For EFS HRs, 95% CIs were done for all estimable pairwise comparisons of RT delivered (no, yes, unknown) performed within all age category and tumor size categories (1 to 9 years and ≤ 5 cm, 1 to 9 years and > 5 cm, ≥ 10 years and ≤ 5 cm, or ≥ 10 years and > 5 cm). Intervals are displayed on the log scale with a $\log(\text{HR}) = 0$ indicating no difference in HR. (D) EFS by RT delivered (no, yes, unknown) for patients age ≥ 10 years at enrollment and size of primary tumor larger than 5 cm only. Pairwise comparisons not displayed were those which were not estimable as a result of at least one category containing no events. (*) Data are given as percent. (†) 5-year time point estimate is longer than the longest follow-up time. LCL, lower confidence limit; UCL, upper confidence limit.

Potential morbidity has accounted for reluctance to perform staging RPLNA by some^{6,8,30}; however, recent use of nerve-sparing lymphadenectomy or minimally invasive laparoscopic techniques has been associated with less morbidity.³¹ Debate continues surrounding the optimal number of nodes to sample, which cannot be addressed by our data.^{5,9} In addition, the impact of [¹⁸F]fluorodeoxy-D-glucose positron emission tomography imaging on the need for staging RPLNA remains to be determined.^{32,33}

We conclude that patients with localized PT RMS have a favorable outcome, which improved over the course of the study period. Age ≥ 10 years and tumor size > 5 cm represent important prognostic features for EFS and OS. Surgical assessment of retroperitoneal lymph nodes, which was most commonly performed in those age ≥ 10 years or those with suspicious or N1 nodes, is important as it affects EFS, likely by more accurately identifying those patients who require RT. This analysis can contribute to the establishment of standard therapy guidelines for patients with localized PT RMS.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: David O. Walterhouse, Donald A. Barkauskas, Guido Seitz, David A. Rodeberg, Roshni Dasgupta, James R. Anderson, Douglas S. Hawkins
Provision of study materials or patients: Ewa Koscielniak, Hélène Martelli

Collection and assembly of data: David O. Walterhouse, Donald A. Barkauskas, David Hall, Andrea Ferrari, Gian Luca De Salvo, Ewa Koscielniak, Michael C.G. Stevens, Hélène Martelli, Guido Seitz, David A. Rodeberg, Margaret Shnorhavorian, Roshni Dasgupta, John C. Breneman, James R. Anderson, Douglas S. Hawkins, Veronique Minard-Colin

Data analysis and interpretation: David O. Walterhouse, Donald A. Barkauskas, David Hall, Andrea Ferrari, Ewa Koscielniak, David A. Rodeberg, Margaret Shnorhavorian, Roshni Dasgupta, John C. Breneman, Christophe Bergeron, Gianni Bisogno, William H. Meyer, Douglas S. Hawkins, Veronique Minard-Colin

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

REFERENCES

1. Raney RB Jr, Tefft M, Lawrence W Jr, et al: Paratesticular sarcoma in childhood and adolescence. A report from the Intergroup Rhabdomyosarcoma Studies I and II, 1973-1983. *Cancer* 60: 2337-2343, 1987
2. Cecchetto G, Grotto P, De Bernardi B, et al: Paratesticular rhabdomyosarcoma in childhood: Experience of the Italian Cooperative Study. *Tumori* 74: 645-647, 1988
3. LaQuaglia MP, Ghavimi F, Heller G, et al: Mortality in pediatric paratesticular rhabdomyosarcoma: A multivariate analysis. *J Urol* 142:473-478, discussion 489, 1989
4. Wiener ES, Lawrence W, Hays D, et al: Retroperitoneal node biopsy in paratesticular rhabdomyosarcoma. *J Pediatr Surg* 29:171-177, discussion 178, 1994
5. Ferrari A, Bisogno G, Casanova M, et al: Paratesticular rhabdomyosarcoma: Report from the Italian and German Cooperative Group. *J Clin Oncol* 20:449-455, 2002
6. Stewart RJ, Martelli H, Oberlin O, et al: Treatment of children with nonmetastatic paratesticular rhabdomyosarcoma: Results of the Malignant Mesenchymal Tumors studies (MMT 84 and MMT 89) of the International Society of Pediatric Oncology. *J Clin Oncol* 21:793-798, 2003
7. Rogers T, Minard-Colin V, Cozic N, et al: Paratesticular rhabdomyosarcoma in children and adolescents: Outcome and patterns of relapse when utilizing a nonsurgical strategy for lymph node staging—Report from the International Society of Paediatric Oncology (SIOP) Malignant Mesenchymal Tumour 89 and 95 studies. *Pediatr Blood Cancer* 64:e26486, 2017
8. Wiener ES, Anderson JR, Ojimba JI, et al: Controversies in the management of paratesticular rhabdomyosarcoma: Is staging retroperitoneal lymph node dissection necessary for adolescents with resected paratesticular rhabdomyosarcoma? *Semin Pediatr Surg* 10:146-152, 2001
9. Dang ND, Dang PT, Samuelian J, et al: Lymph node management in patients with paratesticular rhabdomyosarcoma: A population-based analysis. *Cancer* 119:3228-3233, 2013
10. Alanee S, Holland B, Dynda D, et al: Primary tumor size predicts pathologic findings in the retroperitoneal lymph nodes in patients with paratesticular rhabdomyosarcoma. *Virchows Arch* 465:697-701, 2014
11. Crist WM, Anderson JR, Meza JL, et al: Intergroup Rhabdomyosarcoma Study-IV: Results for patients with nonmetastatic disease. *J Clin Oncol* 19: 3091-3102, 2001
12. Raney RB, Walterhouse DO, Meza JL, et al: Results of the Intergroup Rhabdomyosarcoma Study Group D9602 protocol, using vincristine and dactinomycin with or without cyclophosphamide and radiation therapy, for newly diagnosed patients with low-risk embryonal rhabdomyosarcoma: A report from the Soft Tissue Sarcoma Committee of the Children's Oncology Group. *J Clin Oncol* 29: 1312-1318, 2011
13. Walterhouse DO, Pappo AS, Meza JL, et al: Shorter-duration therapy using vincristine, dactinomycin, and lower-dose cyclophosphamide with or without radiotherapy for patients with newly diagnosed low-risk rhabdomyosarcoma: A report from the Soft Tissue Sarcoma Committee of the Children's Oncology Group. *J Clin Oncol* 32:3547-3552, 2014
14. Walterhouse DO, Pappo AS, Meza JL, et al: Reduction of cyclophosphamide dose for patients with subset 2 low-risk rhabdomyosarcoma is associated with an increased risk of recurrence: A report from the Soft Tissue Sarcoma Committee of the Children's Oncology Group. *Cancer* 123:2368-2375, 2017
15. Arndt CA, Stoner JA, Hawkins DS, et al: Vincristine, actinomycin, and cyclophosphamide compared with vincristine, actinomycin, and cyclophosphamide alternating with vincristine, topotecan, and cyclophosphamide for intermediate-risk rhabdomyosarcoma: Children's Oncology Group study D9803. *J Clin Oncol* 27:5182-5188, 2009
16. Hawkins DS, Yueh-Yin C, Anderson JR, et al: Addition of vincristine and irinotecan to vincristine, dactinomycin, and cyclophosphamide does not improve outcome for intermediate-risk rhabdomyosarcoma: A report from the Children's Oncology Group. *J Clin Oncol* 36:2770-2777, 2018
17. Seitz G, Fuchs J, Martus P, et al: Outcome, treatment, and treatment failures in patients suffering localized embryonal paratesticular rhabdomyosarcoma: Results from the "Cooperative Weichteilsarkom Studiengruppe" trials CWS-86, -91, -96, and -2002P. *Ann Surg* 264:1148-1155, 2016
18. Stevens MC, Rey A, Bouvet N, et al: Treatment of nonmetastatic rhabdomyosarcoma in childhood and adolescence: Third study of the International Society of Paediatric Oncology—SIOP Malignant Mesenchymal Tumour 89. *J Clin Oncol* 23:2618-2628, 2005
19. Cecchetto G, De Corti F, Rogers T, et al: Surgical compliance with guidelines for paratesticular rhabdomyosarcoma (RMS). Data from the European Study on non-metastatic RMS. *J Pediatr Surg* 47: 2161-2162, 2012
20. Seitz G, Dantonello TM, Kosztyla D, et al: Impact of hemiscrotectomy on outcome of patients with embryonal paratesticular rhabdomyosarcoma: Results from the Cooperative Soft Tissue Sarcoma Group Studies CWS-86, 91, 96 and 2002P. *J Urol* 192:902-907, 2014
21. Olive D, Flamant F, Zucker JM, et al: Para-aortic lymphadenectomy is not necessary in the treatment of localized paratesticular rhabdomyosarcoma. *Cancer* 54:1283-1287, 1984
22. Ferrari A, Bisogno G, Casanova M, et al: Is alveolar histotype a prognostic factor in paratesticular rhabdomyosarcoma? The experience of Italian and German Soft Tissue Sarcoma Cooperative Group. *Pediatr Blood Cancer* 42:134-138, 2004
23. Bisogno G, Jenney M, Bergeron C, et al: Addition of dose-intensified doxorubicin to standard chemotherapy for rhabdomyosarcoma (EpSSG RMS 2005): A multicenter, open-label randomised controlled, phase 3 trial. *Lancet Oncol* 19:1061-1071, 2018
24. Oberlin O, Rey A, Sanchez de Toledo J, et al: Randomized comparison of intensified six-drug versus standard three-drug chemotherapy for high-risk non-metastatic rhabdomyosarcoma and other chemotherapy-sensitive childhood soft tissue sarcomas: Long-term results from the International Society of Pediatric Oncology MMT95 study. *J Clin Oncol* 30:2457-2465, 2012
25. Bishop S, Feinberg SE, Holland YMM: Discrete Multivariate Analysis: Theory and Practice (ed 1). Cambridge, MA, MIT Press, 1975
26. Kutner MH, Nachtsheim CJ, Neter J, et al: Applied Linear Statistical Models (ed 4). New York, NY, McGraw-Hill/Irwin, 2005
27. Kalbfleisch JD, Prentice RL: The Statistical Analysis of Failure Time Data (ed 2). New York, NY, John Wiley and Sons, 2002
28. Newton WA Jr, Gehan EA, Webber BL, et al: Classification of rhabdomyosarcomas and related sarcomas. Pathologic aspects and proposal for a new classification: An Intergroup Rhabdomyosarcoma Study. *Cancer* 76:1073-1085, 1995
29. Rudzinski ER, Teot LA, Anderson JR, et al: Dense pattern of embryonal rhabdomyosarcoma, a lesion easily confused with alveolar rhabdomyosarcoma: A report from the Soft Tissue Sarcoma Committee of the Children's Oncology Group. *Am J Clin Pathol* 140:82-90, 2013
30. Heyn R, Raney RB Jr, Hays DM, et al: Late effects of therapy in patients with paratesticular rhabdomyosarcoma. *J Clin Oncol* 10:614-623, 1992
31. Stephenson AJ, Klein EA: Surgical management of low-stage nonseminomatous germ cell testicular cancer. *BJU Int* 104:1362-1368, 2009
32. Burnette JO, Klaassen Z, Hatley RM, et al: Staging paratesticular rhabdomyosarcoma in the "as low as reasonably achievable" age: The case for PET-CT. *Urology* 82:220-223, 2013
33. Norman G, Fayter D, Lewis-Light K, et al: An emerging evidence base for PET-CT in the management of childhood rhabdomyosarcoma: Systematic review. *BMJ Open* 5:e006030, 2015

Affiliations

David O. Walterhouse, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL; **Donald A. Barkauskas**, University of Southern California, Los Angeles; **David Hall**, Children's Oncology Group, Monrovia, CA; **Andrea Ferrari**, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Istituto Nazionale Tumori, Milan; **Gian Luca De Salvo**, Istituto Oncologico Veneto Istituto di Ricovero e Cura a Carattere Scientifico, Padua; **Gianni Bisogno**, University of Padua, Padova, Italy; **Ewa Koscielniak**, Olgahospital, Stuttgart; **Guido Seitz**, University Hospital, Marburg, Germany; **Michael C.G. Stevens**, Royal Hospital for Children, Bristol, United Kingdom; **Hélène Martelli**, Assistance Publique-Hôpitaux de Paris, Hôpital Bicêtre, Le Kremlin-Bicêtre; **Christophe Bergeron**, Centre Léon Bérard, Lyon; **Veronique Minard-Colin**, Gustave Roussy, Villejuif, France; **David A. Rodeberg**, East Carolina University, Greenville, NC; **Margarett Shnorhavorian** and **Douglas S. Hawkins**, Seattle Children's Hospital, University of Washington; **Douglas S. Hawkins**, Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA; **Roshni Dasgupta** and **John C. Breneman**, Cincinnati Children's Hospital Medical Center, Cincinnati, OH; **James R. Anderson**, Merck Research Laboratories, North Wales, PA; and **William H. Meyer**, University of Oklahoma School of Medicine, Oklahoma City, OK.

Support

Supported in part by Grants No. U10-CA180886, U10-CA098543, U10-CA180899, U10-CA098413, and U24-CA114766 from the National Cancer Institute; St Baldrick's Foundation; and a grant from the WWW (QuadW) Foundation to the Children's Oncology Group.

Prior Presentation

Presented in part at the 51st Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, May 31, 2015.

Get the *Managing the Cost of Cancer Care* Booklets for Your Practice

Do your patients have financial questions about cancer care? Cancer.Net's *Managing the Cost of Cancer Care* booklet provides tools and resources that can help your patients answer these questions and plan for costs before, during, and after treatment. Order copies of the booklet for your patients through the ASCO University Bookstore at cancer.net/estore. ASCO members receive a 20% discount. Free domestic shipping! The booklet is also available as a downloadable PDF in English and Spanish at cancer.net/managingcostofcare.

Cancer.Net

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Demographic and Treatment Variables Influencing Outcome for Localized Paratesticular Rhabdomyosarcoma: Results From a Pooled Analysis of North American and European Cooperative Groups

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

David O. Walterhouse

No relationship to disclose

Donald A. Barkauskas

No relationship to disclose

David Hall

No relationship to disclose

Andrea Ferrari

No relationship to disclose

Gian Luca De Salvo

Travel, Accommodations, Expenses: Bayer

Ewa Koscielniak

No relationship to disclose

Michael C.G. Stevens

No relationship to disclose

Hélène Martelli

No relationship to disclose

Guido Seitz

No relationship to disclose

David A. Rodeberg

No relationship to disclose

Margarett Shnorhavorian

No relationship to disclose

Roshni Dasgupta

No relationship to disclose

John C. Breneman

No relationship to disclose

James R. Anderson

Employment: Merck Sharp & Dohme

Christophe Bergeron

No relationship to disclose

Gianni Bisogno

Consulting or Advisory Role: Clinigen Group, Genentech

Travel, Accommodations, Expenses: Jazz Pharmaceuticals

William H. Meyer

No relationship to disclose

Douglas S. Hawkins

Travel, Accommodations, Expenses: Loxo, Bayer, Bristol-Myers Squibb, Celgene

Veronique Minard-Colin

No relationship to disclose

Appendix

Fig A1. Age distribution of patients at the time of enrollment. Histogram shows the percentage of patients by age in years at the time of enrollment in the clinical trials combined (N = 842). The first quartile (Q1), median, and third quartile (Q3) ages are shown in the right upper corner.

Variables Influencing Outcome of Localized PT RMS

Fig A2. Demographic and treatment variables associated with event-free survival (EFS; A-F) and overall survival (OS; G-K). (A) EFS by cooperative group (Children's Oncology Group [COG], Cooperative Weichteilsarkom Studiengruppe [CWS], the Italian Cooperative Group [ICG], the International Society of Pediatric Oncology Malignant Mesenchymal Tumor Group [IMMT], or the European Pediatric Soft Tissue Sarcoma Group [EpSSG]). (B) EFS by era of enrollment (2002 and earlier or 2003 and later). (C) EFS by age category (age < 1 year, 1 to 9 years, or ≥ 10 years). (D) EFS by tumor size (≤ 5 cm, > 5 cm, or unknown). (E) EFS by Intergroup Rhabdomyosarcoma Study (IRS) group (I, IIa, IIb, IIc, III, or unknown). (F) EFS by T stage (T1, T2, or unknown). (G) OS by age category (age < 1 year, 1 to 9 years, or ≥ 10 years). (H) OS by tumor size (≤ 5 cm, > 5 cm, or unknown). (I) OS by IRS group (I, IIa, IIb, IIc, III, or unknown). (J) OS by T stage (T1, T2, or unknown). (K) OS by histology (embryonal, spindle cell, or alveolar). *Data are given as percent. LCL, lower confidence limit; UCL, upper confidence limit.

Fig A2. (Continued).