Prognostic Significance of Tumor Response at the End of Therapy in Group III Rhabdomyosarcoma: A Report From the Children's Oncology Group

David A. Rodeberg, Julie A. Stoner, Andrea Hayes-Jordan, Simon C. Kao, Suzanne L. Wolden, Steve J. Qualman, William H. Meyer, and Douglas S. Hawkins

From the Division of Pediatric Surgery, Children's Hospital of Pittsburgh, Pittsburgh, PA; Department of Biostatistics & Epidemiology, University of Oklahoma Health Sciences Center; Department of Hematology/Oncology, University of Oklahoma Health Sciences Center, Oklahoma City, OK; Department of Surgery, M. D. Anderson Cancer Center, Houston, TX; Department of Radiology, University of Iowa Hospital and Clinics, Iowa City, IA; Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY; Biopathology Center, Children's Hospital, Center for Childhood Cancer, Columbus, OH; and the Department of Hematology/Oncology, Children's Hospital and Regional Medical Center, Seattle, WA.

Submitted October 2, 2008; accepted February 20, 2009; published online ahead of print at www.jco.org on May 26, 2009.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: David A. Rodeberg, MD, University of Pittsburgh School of Medicine, Department of Pediatric Surgery, Children's Hospital of Pittsburgh, 3705 Fifth Ave, Pittsburgh, PA 15213-2585; e-mail: david.rodeberg@chp.edu.

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

© 2009 by American Society of Clinical Oncology

0732-183X/09/2722-3705/\$20.00

DOI: 10.1200/JCO.2008.19.5933

A B S T R A C T

Purpose

Some patients with rhabdomyosarcoma (RMS) achieve less than a complete response (CR) despite receiving all planned therapy. We assessed the impact of best response at the completion of all therapy on patient outcome.

Patients and Methods

We studied 419 clinical group III participants who completed all protocol therapy without developing progressive disease for Intergroup Rhabdomyosarcoma Study (IRS) IV. Response (complete resolution [CR], partial response [PR; $\geq 50\%$ decrease], or no response [NR; $< 50\%$ decrease and $< 25\%$ increase]) was determined by radiographic measurement and categorized by the best response.

Results

At the end of therapy, 341 participants (81%) achieved a best response of CR and 78 (19%) had a best response of PR/NR. Five-year failure-free survival was similar for participants achieving CR (80%) and PR/NR (78%). After adjustment for age, nodal status, primary site, and histology, there was no significant indication of lower risk of failure (hazard ratio [HR], 0.77; 95% CI, 0.46 to 1.27; $P = .3$) nor death (HR, 0.63; 95% CI, 0.36 to 1.09; $P = .1$) for CR versus PR/NR participants. Seventeen participants with a best response of PR/NR had surgical procedures; eight (50%) of 16 with available pathology reports had residual viable tumor and only three achieved a complete resection. Resection of residual masses was not associated with improved outcome.

Conclusion

CR status at the end of protocol therapy in clinical group III participants was not associated with a reduction of disease recurrence and death. Aggressive alternative therapy may not be warranted for RMS patients with a residual mass at the end of planned therapy.

J Clin Oncol 27:3705-3711. © 2009 by American Society of Clinical Oncology

INTRODUCTION

The response of tumors to induction therapy is a prognostic indicator for several pediatric malignancies, including acute lymphoblastic leukemia, Hodgkin's lymphoma, Ewing sarcoma, and osteosarcoma.¹⁻⁶ European rhabdomyosarcoma (RMS) clinical trials use radiographic response to initial therapy to tailor subsequent therapy in an attempt to minimize toxicity yet maximize survival.^{7,8} This treatment philosophy assumes that initial response to therapy is associated with ultimate outcome and can identify chemotherapy-sensitive tumors more likely to be cured with systemic therapy. In contrast, recent analysis of the Intergroup Rhabdomyosarcoma Study (IRS) IV data showed no predictive value of radiographic response after 8 weeks

of induction therapy.⁹ Radiographic imaging is an imperfect method to assess response in soft tissue sarcomas and gastrointestinal stromal tumors in adults.¹⁰

The persistence of radiographic masses at the end of RMS therapy is well known, but their biologic potential is uncertain. RMS can undergo progressive cytodifferentiation to rhabdomyoblasts and stromal scarring after chemotherapy and radiation therapy, as observed in small retrospective series.^{11,12} Persisting masses are often seen in malignant germ cell tumors after treatment with chemotherapy, although surgical resection usually reveals necrotic tumor or benign teratoma rather than residual malignancy.¹³ The frequency of residual masses after RMS treatment and the impact on ultimate outcome are unknown. Using data from IRS-IV, we

determined the prognostic significance of best response by the end of therapy and described the results of surgery to evaluate persistent masses.

PATIENTS AND METHODS

Patient Population

We studied 419 clinical group III IRS-IV participants enrolled from 1991 to 1997 who completed all protocol therapy without developing progressive disease. At the time of data analysis, median follow-up for these patients was 8.4 years (range, 0.9 to 13.2). The population evaluated included eligible IRS-IV participants who were assigned to one of three chemotherapy arms and were clinical group III (biopsy only or gross residual disease after resection without distant metastases) at study enrollment. Clinical group III participants all had measurable primary tumors at study entry and therefore were assessable for radiographic response. The study was restricted to participants who completed four phases of therapy without disease progression. Details of the chemotherapy treatment have been previously published.¹⁴ All treatment arms were combined for our analysis because there was no significant difference in outcome by chemotherapy regimen. Radiotherapy was the predominant method of local control by study design. Participants received either conventional daily fractionation or twice daily hyperfractionation as previously described.¹⁵ Because there was no difference in outcome by radiotherapy fractionation, all participants were evaluated as a combined group. The suggested protocol for surgical resection emphasized initial complete resection when feasible but for those that were clinical group III after initial resection then subsequent surgical resection was discouraged since the studies primary local control question was designed to evaluate standard versus hyperfractionation radiotherapy.

Definition of End Points

Response was categorized by the best response achieved by the end of therapy and was determined by radiographic measurement of tumor. Complete response (CR; complete resolution of disease), partial response (PR; $\geq 50\%$ decrease in the sum of the products of the maximum perpendicular diameters of measurable lesions), or no response (NR; $< 50\%$ decrease or $< 25\%$ increase in the sum of the products of the maximum perpendicular diameters of measurable lesions) was determined by local institutions without central imaging review. Failure-free survival (FFS) is defined as the time from the start of treatment to disease progression or death. This end point reflects the percentage of participants who remained alive in the study without relapse, progressive disease, or a fatal event from any cause. Overall survival (OS) was defined as the time from the start of treatment to death from any cause. FFS and survival for participants who had not experienced the event of interest were censored at the patient's last contact date.

Statistical Analysis Methods

The Kaplan-Meier method was used to estimate the FFS and OS distributions.¹⁶ Differences between survival curves were analyzed by the log-rank test.¹⁷ A Cox proportional hazards regression model was used to adjust comparisons of time-to-event distributions between patient groups for possible confounding factors including age, histology, nodal status, and primary site.¹⁸ The distributions of categorical participant characteristics were compared between the groups using a χ^2 test or Fisher's exact test. Analyses were based on data available by July 2005. *P* values lower than .05 were considered statistically significant. The site of first recurrence was defined as local if the tumor recurred only at the site of primary disease; as regional if regional lymph nodes were involved, with or without local recurrence; and as distant if any metastatic disease was present at recurrence. The cumulative incidence of local, regional, and distant failures at 5 years was estimated.

RESULTS

Patient Demographics and Disease Characteristics

A total of 419 participants were eligible for evaluation, including 341 participants (81%) who achieved a CR and 78 participants (19%) who achieved a PR/NR. The distribution of disease characteristics by best response is presented in Table 1. Participants who achieved CR were more likely to have disease in a favorable site ($P = .05$), have a lower stage at presentation ($P = .1$), and have smaller tumors ($P = .08$) that are not locally invasive ($P = .001$). In addition, other prognostic factors, such as patient age, nodal status, and tumor histology, were not different between groups. Second look operations were not responsible for the final response to therapy after completion of all standard therapy to any significant degree. Among the 419 study participants, 47 subjects (11%) underwent a second look operation. Among the 341 CR patients, 30 (9%) underwent a second look operation (23 underwent biopsy, four underwent a complete resection, and three underwent an incomplete resection). Among the 78 PR/NR

Table 1. Participant Demographics Based on Response Status

Primary Site	CR (n = 341)		PR/NR (n = 78)		<i>P</i> (χ^2 or Fisher's Exact Test)
	No.	%	No.	%	
Unfavorable	252	74	66	85	
Extremity	33	10	3	4	
GU B/P	49	14	6	8	
PM	115	34	46	59	
Other	55	16	11	14	
Favorable	89	26	12	15	
GU non-B/P	31	9	0		
Orbit	41	12	9	12	
Head and neck	17	5	3	4	
Age, years					.6
< 1	11	3	3	4	
1-9	248	73	52	67	
10+	82	24	23	29	
Stage					.1
1	88	26	12	15	
2	74	22	14	18	
3	178	52	52	67	
4	1	< 1	0		
Tumor size, cm					.08
≤ 5	159	47	28	36	
> 5	180	53	50	64	
T stage					.001
T1	125	37	14	18	
T2	214	63	64	82	
Nodal status					.6
N0	256	76	63	81	
N1	69	20	12	15	
NX	14	4	3	4	
Histology					.3
Alveolar/Undif	84	25	14	18	
Embryonal/Spl/Bot	237	70	57	73	
Other	20	6	7	9	

NOTE. $P = .05$ (favorable v unfavorable).

Abbreviations: PM, parameningeal primary site; GU, genitourinary primary site; B/P, bladder/prostate; CR, complete response; PR, partial response; NR, no response.

patients, 17 (22%) underwent a second look operation (five underwent biopsy, four underwent a complete resection, and eight underwent an incomplete resection).

FFS Based on Best Therapeutic Response

There were no statistical differences in FFS between participants who achieved a best response of CR and those who achieved a PR/NR (CR 5-year FFS 80% *v* PR/NR 78%; $P = .4$; Fig 1A). Since the majority of the PR/NR participants had a parameningeal (PM) primary site, we analyzed the PM and non-PM populations separately. There were no PR/NR participants with genitourinary (GU), nonbladder/prostate (non-B/P) primary sites. Participants with GU, non-B/P primary sites were excluded from the non-PM analysis. Again, there were no significant differences in FFS for participants with PM or non-PM disease comparing CR versus PR/NR (Table 2). To adjust for differences in clinical prognostic factors between the CR and PR/NR groups, including age, histology, primary site, and nodal status, we performed a Cox proportional hazards regression analysis. Similar to the unadjusted comparison, FFS was not significantly different between participants that achieved CR versus PR/NR for all participants and when separated by PM or non-PM sites of disease (Table 2). To determine if there were differences in outcome associated with degree of tumor response for large tumors we performed an analysis for tumors larger than 5 cm. Among the 50 subjects with maximum tumor diameter

Fig 1. (A) Failure-free survival (FFS) of participants who achieved a best response of complete response (CR) and those who only achieved a partial response/no response (PR/NR; CR 5-year FFS 80% *v* PR/NR 78%; $P = .4$). (B) Overall survival (OS) of participants who achieved a best response of CR and those who only achieved a PR/NR (CR 5-year OS 85% *v* PR/NR 80%; $P = .2$).

Table 2. Risk of Treatment Failure, Defined by Relapse, Disease Progression, or Death, Utilizing Cox Proportional Hazards Regression Modeling to Adjust Comparison for Potential Confounding Variables

Patient Subset and Regression Model	Hazard Ratio (CR:PR/NR)	95% CI	P
All participants, N = 419			
Unadjusted	0.80	0.49 to 1.30	.4
Adjusted*	0.77	0.46 to 1.27	.3
PM only, n = 161			
Unadjusted	0.65	0.32 to 1.30	.2
Adjusted	0.63	0.30 to 1.29	.2
Not PM (excluding GU non B/P), n = 227			
Unadjusted	0.98	0.46 to 2.08	> .9
Adjusted	0.93	0.43 to 1.97	.8

Abbreviations: PM, parameningeal primary site; GU, genitourinary primary site; B/P, bladder/prostate; CR, complete response; PR, partial response; NR, no response.

*Regression models were adjusted for age, nodal status, histology, and primary site (only for models not stratified by PM site).

larger than 5 cm and a best response of PR/NR, the 5-year event-free survival probability was 71% (95% CI, 56% to 82%). Among the 180 subjects with maximum tumor diameter larger than 5 cm and a best response of CR, the 5-year event-free survival probability was 75% (95% CI, 68% to 80%). Among subjects with a maximum tumor diameter larger than 5 cm, the event-free survival distributions did not differ significantly between subjects with a best response of CR and subjects with a best response of PR/NR ($P = .3$).

OS Based on Best Therapeutic Response

OS is usually higher than FFS due to the potential for curative second-line therapy after disease recurrence. It is possible that OS due to curative second-line therapy may have been different when evaluated in relation to end of therapy response status. The OS distribution for all participants was similar between CR and PR/NR participants (CR 5-year OS 85% *v* PR/NR 80%; $P = .2$; Fig 1B). Cox regression analysis adjusted for differences in prognostic characteristics between CR and PR/NR participants, including age, histology, primary site, and nodal status, demonstrated a similar lack of statistically significant

Table 3. Risk of Death Utilizing Cox Proportional Hazards Regression Modeling to Adjust Comparison for Potential Confounding Variables

Patient Subset and Regression Model	Hazard Ratio (CR:NR/PR)	95% CI	P
All participants, N = 419			
Unadjusted	0.68	0.40 to 1.16	.2
Adjusted*	0.63	0.36 to 1.09	.1
PM only, n = 161			
Unadjusted	0.72	0.34 to 1.54	.4
Adjusted	0.67	0.30 to 1.49	.3
Not PM (excluding GU non B/P), n = 227			
Unadjusted	0.71	0.33 to 1.54	.4
Adjusted	0.62	0.28 to 1.36	.2

Abbreviations: PM, parameningeal primary site; GU, genitourinary primary site; B/P, bladder/prostate; CR, complete response; PR, partial response; NR, no response.

*Regression models were adjusted for age, nodal status, histology, and primary site (only for models not stratified by PM site).

difference between participants with CR versus PR/NR (hazard ratio [HR], 0.63; 95% CI, 0.36 to 1.09; $P = .1$; Table 3). No OS difference was observed when we analyzed the PM versus non-PM participants separately (Table 3).

Pattern of First Recurrence

To determine whether best response by the end of therapy influenced the pattern of initial disease recurrence, we analyzed the site of first failure. Disease progression occurred in 20% of participants who achieved CR and 22% of PR/NR participants by 5 years. Comparing CR versus PR/NR, the 5-year local failure rates (13.5% ν 13.5%, respectively), regional failure rates (2.7% ν 2.6%), and distant failure rates (6.0% ν 8.0%) were similar.

Surgical Resection of Residual Mass at the Completion of Therapy

To determine the effect of surgical resection after the completion of all planned therapy, we analyzed 17 participants with a best re-

sponse of PR/NR who had some form of surgical resection (complete resection, incomplete resection, or biopsy). Patient characteristics defined by the type of surgical procedure are presented in Table 4. There are minor differences in disease characteristics between patients that had second look procedures versus those that were observed. Some of these differences reflect primary sites that were likely more accessible to resection (such as GU, B/P) than others (such as PM). Participants who underwent resection of a residual mass at the end of therapy had similar FFS and OS as participants who did not (5-year FFS 71% ν 80%; 5-year OS 71% ν 83%). Formal comparisons between groups were not made given the limited sample sizes and time-varying nature of the surgical exposure.

The disease characteristics and outcomes were also evaluated based on the type of surgical procedure that the patient underwent. Formal statistical comparisons were not made given the limited sample sizes. The surgical procedure groups differed descriptively in respect to primary site of disease, age, stage, tumor size, tumor invasiveness, and nodal status. For each of these disease characteristics the

Table 4. Demographic Characteristics for Participants With a Best Response of PR/NR ($n = 78$) Who Had SLO Procedures

Table 1. Demographic Characteristics for Participants With a Best Response of PR/CR (n = 75) Who Had CSF Procedures											
Parameter	No SLO (n = 61)		SLO (n = 17)		P (SLO v no SLO)	Type of SLO					
	No.	%	No.	%		Biopsy (n = 5)		Complete Excision (n = 4)		Incomplete Excision (n = 8)	
						No.	%	No.	%	No.	%
Primary site					0.06, favorable v unfavorable						
Unfavorable	49	80	17	100							
Extremity	2	3	1	6		0		0		1	13
GU B/P	3	5	3	18		1	20	1	25	1	13
PM	38	62	8	47		4	80	2	50	2	25
Other	6	10	5	29		0		1	25	4	50
Favorable	12	20	0								
Orbit	9	15	0			0		0		0	
Head and neck	3	5	0			0		0		0	
Age, years					.9						
< 1	2	3	1	6		0		0		1	13
1-9	41	67	11	65		4	80	1	25	6	75
10+	18	30	5	29		1	20	3	75	1	13
Stage					.07						
1	12	20	0			0		0		0	
2	12	20	2	12		1	20	0		1	13
3	37	61	15	88		4	80	4	100	7	88
Tumor size, cm					.08						
≤ 5	25	41	3	18		2	40	0		1	13
> 5	36	59	14	82		3	60	4	100	7	88
T stage					.3						
T1	13	21	1	6		0		0		1	13
T2	48	79	16	94		5	100	4	100	7	88
Nodal status					.3						
N0	47	77	16	94		4	80	4	100	8	100
N1	11	18	1	6		1	20	0		0	
NX	3	5	0			0		0		0	
Histology					.3						
Alveolar/Undif	11	18	3	18		1	20	0		2	25
Embryonal/Spl/Bot	43	70	14	82		4	80	4	100	6	75
Other	7	11	0			0		0		0	

Abbreviations: PR, partial response; NR, no response; SLO, second look operative; PM, parameningeal primary site; GU, genitourinary primary site; B/P, bladder/prostate; CR, complete response; Undif, undifferentiated; Spl, spindle cell; Bot, botryoid.

worse prognosis is associated with those participants that underwent some form of excision compared to those that only underwent biopsy. FFS and OS were evaluated comparing participants that had undergone some form of resection compared to biopsy. Five-year FFS rates were reduced for participants that had undergone resection compared to those who had undergone biopsy (58% v 100%, respectively) and similarly for OS (58% v 100%; Fig 2). Five-year FFS estimates were similar when comparing participants that had undergone a complete resection versus those that had an incomplete resection of their masses (50% v 63%) and likewise, for OS (50% v 63%).

Among participants with a best response of PR/NR, the end of therapy masses that underwent a second look procedure had a median size of 3.25 cm (range, < 1 to 15 cm). The surgical procedures resulted in the resection of vital structures in none of the biopsy participants and 58% of resection participants. Only two of seven participants who had resection of a vital structure had a complete resection of the tumor. Pathologic specimens (available for only 16 participants) revealed that only eight (50%) of 16 patients had viable tumors and only three of eight with viable tumors were completely resected.

DISCUSSION

To our knowledge, this is the first report to describe the prognostic significance of response at the end of therapy in children with clinical group III RMS. It also describes the results of late surgical evaluations

of residual masses at the primary site. Several important conclusions can be drawn from these data. A residual mass (best response of PR/NR) occurs in 19% of clinical group III patients at the completion of all standard therapy. Radiographic determination of best response to therapy is not predicted by disease characteristics at presentation for this population, with the exception of primary site and T stage. The presence of a residual mass at the end of therapy does not lead to lower FFS or OS, even after adjusting for other prognostic clinical characteristics. Only 50% of pathologic specimens from end of therapy masses among participants with a best response of PR/NR demonstrated viable tumor. The pattern of recurrence was not related to response status. Finally, surgical resection of end of therapy masses rarely resulted in complete tumor removal without significant morbidity and did not improve outcome.

Our results demonstrate that a residual mass at the completion of all standard therapy is commonly encountered in clinical group III RMS patients. Interestingly pathology results suggest that only 50% of residual masses, among patients with a best response of PR/NR, have viable tumor. It is possible that the mass at the end of therapy is mostly reactive in nature or that it is comprised of nonmalignant rhabdomyoblasts that occur as a result of differentiation of RMS cells secondary to therapy. Rhabdomyoblasts are commonly present at the end of therapy, do not appear to have malignant potential, and are not an indication for additional therapy.¹² A similar clinical scenario is encountered in patients with metastatic testicular cancer.^{19,20} In this malignancy, up to 80% of patients have a residual mass at the completion of therapy; however, viable tumor is present in only 10% to 20% of these masses. These findings have prompted a paradigm of radiographic and tumor marker surveillance for many patients with an incomplete response and a residual mass at the end of therapy.

It is unclear why radiographic response to therapy was not a better predictor of outcome. The assessment of response to therapy for solid tumors can be determined using several techniques. Response to therapy is routinely determined utilizing anatomic imaging methods for patients with RMS. Functional imaging techniques have also been utilized to assess treatment response for other tumors. Examples include metaiodobenzylguanidine (MIBG) in neuroblastoma and changes in glucose uptake determined by fluorodeoxyglucose positron emission tomography (FDG PET) in soft tissue sarcomas and bone tumors.^{10,21,22} FDG PET has been incorporated into the current Children's Oncology Group intermediate-risk RMS treatment protocol (ARST0531) to determine its utility in assessing early response to therapy.

Early response to therapy, as determined by anatomic imaging, after 8 weeks of therapy is also not predictive of outcome in the same IRS-IV cohort.⁹ It is possible that week 8 was not the optimal time to determine early response to therapy. However, our own results would suggest that response to therapy may not be an accurate predictor of outcome at anytime during therapy. The Appendix (online only) contains a more complete discussion of response to induction therapy as a predictor of outcome. Although radiographic imaging is the standard method to determine response to therapy in RMS, it may lack the ability to distinguish necrotic tissue from residual active tumor and therefore may not be a reliable predictor of response to therapy. Our evaluation of late surgery also supports this hypothesis. The pathologic finding of viable tumor in only 50% of radiographic positive masses among patients with a best response of PR/NR indicates the lack of specificity for current anatomic imaging techniques

Fig 2. (A) Failure-free survival rates at 5 years for participants that had undergone resection compared to those who had undergone biopsy (58% v 100%, respectively). (B) Overall survival rates at 5 years for participants that had undergone resection compared to those who had undergone biopsy (58% v 100%, respectively).

for RMS. For osteosarcoma and Ewing sarcoma, determining response to therapy by imaging with computed tomography (CT) and magnetic resonance (MRI) is less effective than direct assessment of tumor necrosis by pathology in predicting outcomes.^{4,23-25} These results support our own finding that imaging with CT or MRI may not be an effective way to predict response to therapy and predict outcome in pediatric RMS. Functional imaging with FDG PET may be more accurate in assessing response to therapy to determine which residual masses harbor viable tumor and would therefore potentially benefit from alternative chemotherapy or operative resection.

Somewhat surprisingly, late operative procedures, whether biopsy or resection, did not impact outcome and resection of masses did not appear to be any better than biopsy alone. Even complete resection, which improves outcome when performed before chemotherapy,²⁶ did not improve outcome for participants resected at the end of therapy. Given the small number of participants, we could not adjust for confounding disease characteristics that would influence prognosis, and the results should be interpreted with caution. Nonetheless, the data clearly show that resection did not improve outcome. There are possible explanations for these results. The low frequency of viable tumor in the resected specimens indicates that resection of the tumor at best would only be beneficial 50% of the time among patients with a best response of PR/NR. Disease characteristics that adversely affected prognosis (primary site of disease, age, stage, tumor size, tumor invasiveness, and nodal status)²⁶ were more commonly associated with patients that underwent resection compared to biopsy alone.

The high frequency of morbidity (58% resection of vital structures) and permanent loss of organ function illustrate the cost of end of therapy resection. Even with the loss of vital structures, only 29% had complete resection of the tumor. Given the minimal benefit and high risk/morbidity of resection, there appears to be little justification to attempt resection of residual masses present at the end of therapy.

In summary, residual masses (best response PR/NR) occur in 19% of clinical group III participants treated on IRS-IV and the response to therapy was not predictive of outcome. This may reflect current limitations in anatomic imaging utilizing CT and MRI and may support the use of FDG PET to evaluate response to therapy and the presence of residual viable tumors. Restricting operative procedures only to patients with viable tumors could potentially lead to improved outcomes associated with resection of masses. Given the low frequency of viable tumor in the end of therapy masses, aggressive surgical resection, radiotherapy, or alternative chemotherapy are probably not warranted.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: David A. Rodeberg, Julie A. Stoner, Suzanne L. Wolden, Douglas S. Hawkins

Administrative support: William H. Meyer

Provision of study materials or patients: Andrea Hayes-Jordan, Suzanne L. Wolden, Steve J. Qualman, William H. Meyer

Collection and assembly of data: David A. Rodeberg, Andrea Hayes-Jordan, Steve J. Qualman, Douglas S. Hawkins

Data analysis and interpretation: David A. Rodeberg, Julie A. Stoner, Andrea Hayes-Jordan, Steve J. Qualman, William H. Meyer, Douglas S. Hawkins

Manuscript writing: David A. Rodeberg, Andrea Hayes-Jordan, Simon C. Kao, Steve J. Qualman, Douglas S. Hawkins

Final approval of manuscript: David A. Rodeberg, Julie A. Stoner, Andrea Hayes-Jordan, Simon C. Kao, Suzanne L. Wolden, Steve J. Qualman, William H. Meyer, Douglas S. Hawkins

REFERENCES

- Visser JH, Wessels G, Hesseling PB, et al: Prognostic value of day 14 blast percentage and the absolute blast index in bone marrow of children with acute lymphoblastic leukemia. *Pediatr Hematol Oncol* 18:187-191, 2001
- Gaynon PS, Bleyer WA, Steinherz PG, et al: Day 7 marrow response and outcome for children with acute lymphoblastic leukemia and unfavorable presenting features. *Med Pediatr Oncol* 18:273-279, 1990
- Weiner MA, Leventhal B, Brecher ML, et al: Randomized study of intensive MOPP-ABVD with or without low-dose total-nodal radiation therapy in the treatment of stages IIB, IIIA2, IIB, and IV Hodgkin's disease in pediatric patients: A Pediatric Oncology Group study. *J Clin Oncol* 15:2769-2779, 1997
- Picci P, Rougraff BT, Bacci G, et al: Prognostic significance of histopathologic response to chemotherapy in nonmetastatic Ewing's sarcoma of the extremities. *J Clin Oncol* 11:1763-1769, 1993
- Wunder JS, Paulian G, Huvois AG, et al: The histological response to chemotherapy as a predictor of the oncological outcome of operative treatment of Ewing sarcoma. *J Bone Joint Surg Am* 80:1020-1033, 1998
- Rosen G, Caparros B, Groshen S, et al: Primary osteogenic sarcoma of the femur: A model for the use of preoperative chemotherapy in high risk malignant tumors. *Cancer Invest* 2:181-192, 1984
- Koscielniak E, Jurgens H, Winkler K, et al: Treatment of soft tissue sarcoma in childhood and adolescence: A report of the German Cooperative Soft Tissue Sarcoma Study. *Cancer* 70:2557-2567, 1992
- Flamant F, Rodary C, Rey A, et al: Treatment of non-metastatic rhabdomyosarcomas in childhood and adolescence: Results of the second study of the International Society of Paediatric Oncology: MMT84. *Eur J Cancer* 34:1050-1062, 1998
- Burke M, Anderson JR, Kao SC, et al: Assessment of response to induction therapy and its influence on 5-year failure-free survival in group III rhabdomyosarcoma: The Intergroup Rhabdomyosarcoma Study-IV experience—a report from the Soft Tissue Sarcoma Committee of the Children's Oncology Group. *J Clin Oncol* 25:4909-4913, 2007
- Schuetze SM: Imaging and response in soft tissue sarcomas. *Hematol Oncol Clin North Am* 19:471-487, vi, 2005
- Arndt CA, Hammond S, Rodeberg D, et al: Significance of persistent mature rhabdomyoblasts in bladder/prostate rhabdomyosarcoma: Results from IRS IV. *J Pediatr Hematol Oncol* 28:563-567, 2006
- Ortega JA, Rowland J, Monforte H, et al: Presence of well-differentiated rhabdomyoblasts at the end of therapy for pelvic rhabdomyosarcoma: Implications for the outcome. *J Pediatr Hematol Oncol* 22:106-111, 2000
- Quek ML, Stein JP, Nichols PV, et al: Prognostic significance of lymphovascular invasion of bladder cancer treated with radical cystectomy. *J Urol* 174:103-106, 2005
- 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
- Donaldson SS, Meza J, Breneman JC, et al: Results from the IRS-IV randomized trial of hyperfractionated radiotherapy in children with rhabdomyosarcoma—a report from the IRSG. *Int J Radiat Oncol Biol Phys* 51:718-728, 2001
- Kaplan GL, Meier P: Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 53:457-481, 1958
- Peto R, Pike MC, Armitage P, et al: Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II: Analysis and examples. *Br J Cancer* 35:1-39, 1977
- Cox DR: Regression models and life-tables. *J R Stat Soc Series B* 34:187-220, 1972
- Quek ML, Simma-Chiang V, Stein JP, et al: Postchemotherapy residual masses in advanced seminoma: Current management and outcomes. *Expert Rev Anticancer Ther* 5:869-874, 2005
- Flechon A, Bompas E, Biron P, et al: Management of post-chemotherapy residual masses

in advanced seminoma. *J Urol* 168:1975-1979, 2002

21. Katzenstein HM, Cohn SL, Shore RM, et al: Scintigraphic response by ¹²³I-metaiodobenzylguanidine scan correlates with event-free survival in high-risk neuroblastoma. *J Clin Oncol* 22:3909-3915, 2004

22. Hawkins DS, Rajendran JG, Conrad EU 3rd, et al: Evaluation of chemotherapy response in pediatric bone sarcomas by [¹⁸F]-fluorodeoxy-D-glucose positron emission tomography. *Cancer* 94:

3277-3284, 2002

23. Bredella MA, Caputo GR, Steinbach LS: Value of FDG positron emission tomography in conjunction with MR imaging for evaluating therapy response in patients with musculoskeletal sarcomas. *Am J Roentgenol* 179:1145-1150, 2002

24. Reinus WR, Gilula LA, Donaldson S, et al: Prognostic features of Ewing sarcoma on plain radiograph and computed tomography scan after initial treatment. A Pediatric Oncology Group study (8346). *Cancer* 72:2503-2510, 1993

25. Bacci G, Longhi A, Versari M, et al: Prognostic factors for osteosarcoma of the extremity treated with neoadjuvant chemotherapy: 15-year experience in 789 patients treated at a single institution. *Cancer* 106:1154-1161, 2006

26. Meza JL, Anderson J, Pappo AS, et al: Analysis of prognostic factors in patients with nonmetastatic rhabdomyosarcoma treated on intergroup rhabdomyosarcoma studies III and IV: The Children's Oncology Group. *J Clin Oncol* 24:3844-3851, 2006